# Treatments for Anemia in Chronic Kidney Disease: Effectiveness and Value

**Supplemental Materials**

**November 30, 2020**

**Prepared for**

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# A. Background: Supplemental Information

## A1. Definitions

Anemia is defined as "a condition in which the number of red blood cells or their oxygen-carrying capacity is insufficient to meet physiological needs."[1] In anemia, insufficient numbers of circulating red blood cells or inadequate quantities of iron or functional hemoglobin (Hb) are available to transport and release oxygen to tissues. The World Health Organization (WHO) and the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines define anemia as a Hb level of <12 g/dL in females and <13 g/dL in adult males. However, this definition does not provide goals of treatment for different patients' groups.[2,3]

Chronic kidney disease (CKD) is a condition characterized by a gradual loss of kidney function over time. The definition and classification of CKD guidelines were established and endorsed by the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) and the international KDIGO guideline group.[4-7] CKD is defined by the presence of kidney damage or decreased kidney function for three or more months.[8] Decreased kidney function refers to a decreased in glomerular filtration rate (GFR), which is usually estimated (eGFR) using serum creatinine and one of several available equations.[9-11] Patients who are diagnosed with CKD can be categorized into different stages according to the cause, their GFR (six G-stages; G-I: ≥90 ml/min per 1.73 $m^2$, G-II: 60-89, G-IIIa: 45-59, G-IIIb: 30-44, G-IV: 15-29, G-V: <15 ml/min per 1.73 $m^2$), and the amount of albumin or protein in the urine (three A-stages; A-1: <30, A-2: 30-299, and A-3: ≤300 mg/g). Additionally, patients with CKD can advance from being dialysis independent (DI-CKD) to renal failure (also known as end-stage kidney disease [ESKD]), which is defined as severely reduced kidney function or treatment with dialysis (dialysis dependent [DD-CKD]) or transplantation. Risk factors for CKD include genetic or sociodemographic predisposition, or the presence of diseases that can initiate and propagate kidney disease.

## A2. Potential Cost-Saving Measures

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). These services are ones that would not be directly affected by roxadustat (e.g., reduction in blood transfusion), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of CKD beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for

patients with CKD that could be reduced, eliminated, or made more efficient. No suggestions were received.

# B. Patient Perspectives: Supplemental Information

## B1. Methods

ICER engaged with patients with CKD (DI-CKD, DD-CKD, and post-transplant), caregivers, representatives from professional and advocacy organizations, and clinical experts to understand the specific challenges associated with ongoing management of anemia in CKD from the patient perspective. ICER engaged with these groups using different platforms including webinars, one-on-one meetings, group meetings, and written communication.

# C. Clinical Guidelines

Multiple organizations have issued guidelines about management of anemia in CKD. However, most of these guidelines are out of date and do not include roxadustat or any other HIF-PH inhibitors as potential treatment options.

## Kidney Disease: Improving Global Outcomes

In 2012, KDIGO issued an anemia guideline, providing recommendations on treatment including the use of iron agents and ESAs.[12] Since then, KDIGO convened a Controversy Conference in December 2019 and had been planning a second one in 2020. These conferences aim to review the latest evidence and assess change implications for the 2012 KDIGO anemia guideline. Given that studies of the effects of HIF-PH inhibitors were still in progress, the first conference was focused on iron and target iron therapeutic agents. The second conference will be focused on ESAs and HIF-PH inhibitors; however, the conference has been postponed indefinitely due to the COVID-19 pandemic.

## National Institute for Health and Care Excellence (NICE)

In 2015, NICE published their guidelines about anemia management in CKD, which did not include guidance about HIF-PH inhibitors.[13] Since then, NICE has conducted an update of the evidence in 2017 and concluded that there was no new evidence to issue recommendations about HIF-PH inhibitors as larger trials were underway. NICE was planning a scoping workshop in preparation for conducting an appraisal about roxadustat in March 2020, which was cancelled due to updates about the timing of the regulatory review.

# D. Comparative Clinical Effectiveness: Supplemental Information

## D1. Detailed Methods

### Population, Intervention, Comparators, Outcomes, Timing, and Settings Framework (PICOTS)

#### Populations

The population of focus for this review is adults with anemia associated with CKD. We considered evidence across two relevant populations of patients:

1. Patients with DI-CKD
    - In population one, where data were available, we examined subgroups of patients defined by stages of CKD: G-stages III, IV, and V.
2. Patients with DD-CKD
    - In population two, we evaluated a subgroup of patients newly initiated on dialysis (incident DD-CKD).

We also considered other subgroups of interest defined according to iron status, inflammation status and ESA-hyporesponsiveness, presence of cardiovascular disease, or cancer.

#### Interventions

The intervention of interest is roxadustat (AstraZeneca).

#### Comparators

We sought evidence to compare roxadustat to:

- Darbepoetin alfa (Aranesp®, Amgen)
- Epoetin alfa (Epogen®, Amgen; Procrit®, Janssen)
- Methoxy polyethylene glycol-epoetin beta (Mircera®, Roche)
- Usual care (estimated by placebo arms of clinical trials)

#### Outcomes

We looked for evidence on the following outcomes of interest:

- Patient-important outcomes
    - All-cause mortality

    - Cardiovascular mortality
    - Stroke
    - Myocardial infarction (MI)
    - Unstable angina
    - Heart failure
    - Hospitalization
    - Blood transfusion
    - Rescue therapy
    - End-stage kidney disease (ESKD)
    - Health-related quality of life (HRQoL)
    - Improvement in symptoms or function (e.g., fatigue, dyspnea)
    - Adverse events, including:
        - Serious adverse events
        - Treatment-emergent adverse events (TEAEs)
        - Adverse events leading to treatment discontinuation
- Other outcomes
    - Anemia (as assessed by Hb and/or hematocrit)
    - Measures of iron storage and availability
    - Measures of inflammation
    - Lipid levels
    - CKD progression (as assessed by eGFR)

**Timing**

Evidence on intervention effectiveness and evidence on harms was derived from studies of any duration.

**Settings**

All relevant settings were considered, with a focus on outpatient settings in the United States (US).

## Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on roxadustat for anemia in CKD followed established best research methods.[14,15] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] The PRISMA guidelines include a checklist of 27 items described further in Table D1.

**Table D1. PRISMA 2009 Checklist**

| Checklist Items | | |
|---|---|---|
| **TITLE** | | |
| **Title** | 1 | Identify the report as a systematic review, meta-analysis, or both. |
| **ABSTRACT** | | |
| **Structured Summary** | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. |
| **INTRODUCTION** | | |
| **Rationale** | 3 | Describe the rationale for the review in the context of what is already known. |
| **Objectives** | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). |
| **METHODS** | | |
| **Protocol and Registration** | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. |
| **Eligibility Criteria** | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. |
| **Information Sources** | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. |
| **Search** | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. |
| **Study Selection** | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). |
| **Data Collection Process** | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. |
| **Data Items** | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. |
| **Risk of Bias in Individual Studies** | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. |
| **Summary Measures** | 13 | State the principal summary measures (e.g., risk ratio, difference in means). |
| **Synthesis of Results** | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. |
| **Risk of Bias Across Studies** | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). |
| **Additional Analyses** | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. |
| **RESULTS** | | |
| **Study Selection** | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. |
| **Study Characteristics** | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. |
| **Risk of Bias Within Studies** | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). |

| Checklist Items | | |
|---|---|---|
| **Results of Individual Studies** | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. |
| **Synthesis of Results** | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. |
| **Risk of Bias Across Studies** | 22 | Present results of any assessment of risk of bias across studies (see Item 15). |
| **Additional Analysis** | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). |
| **DISCUSSION** | | |
| **Summary of Evidence** | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers). |
| **Limitations** | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). |
| **Conclusions** | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. |
| **FUNDING** | | |
| **Funding** | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. |

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

We searched MEDLINE and EMBASE for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/grey-literature-policy/).

**Table D2. Search Strategy of MEDLINE via Ovid* for Roxadustat**

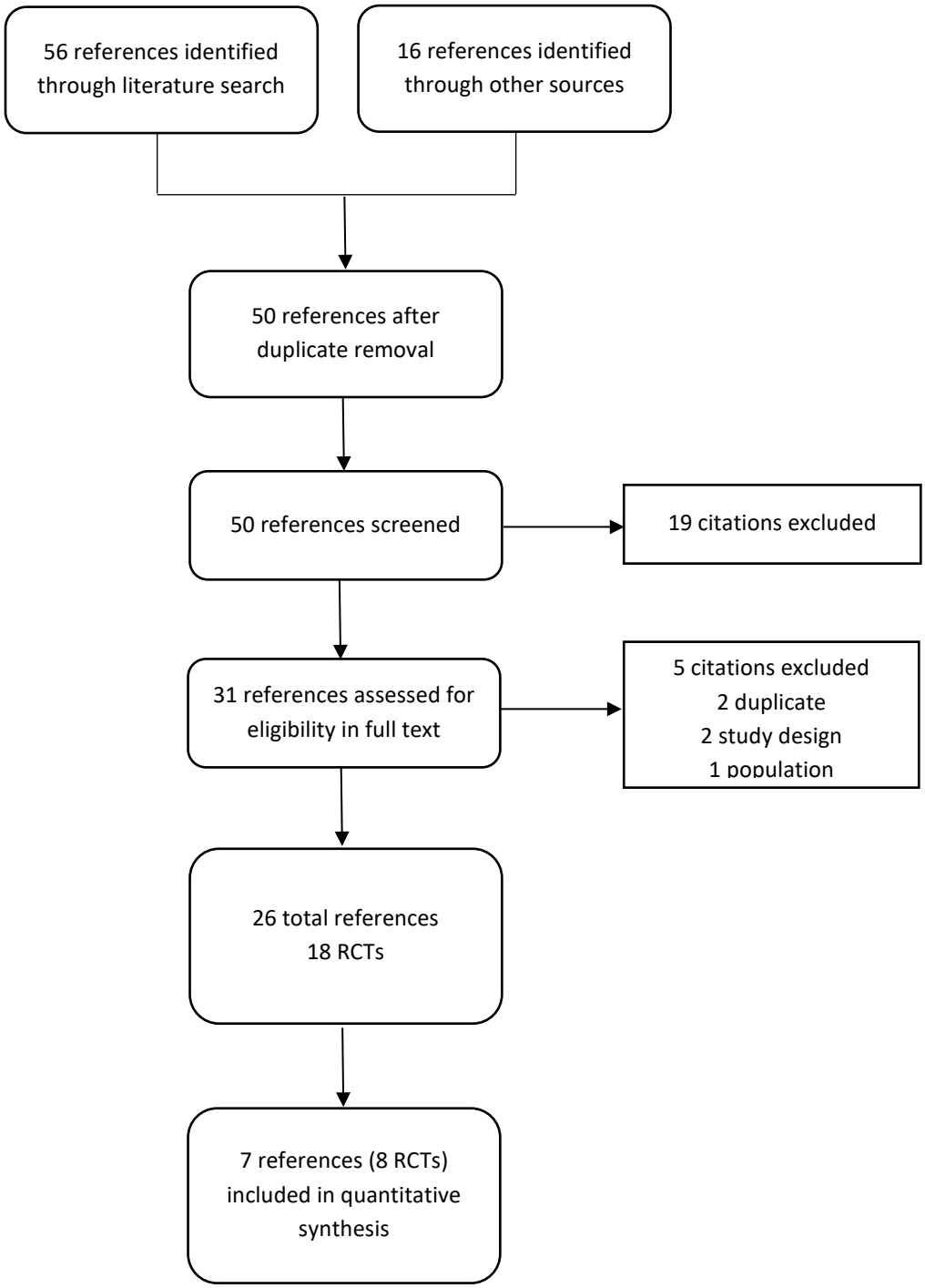
| | |
|---|---|
| 1 | exp Anemia/ OR exp Anemia, Hypochromic/ OR exp Anemia, Refractory/ |
| 2 | (an?emi* OR chronic anemia).ti,ab. |
| 3 | 1 OR 2 |
| 4 | exp Renal Insufficiency, Chronic/ |
| 5 | (chronic kidney disease OR end*stage kidney disease OR end*stage kidney failure OR ESKD OR chronic renal disease OR end*stage renal dysfunction OR end*stage renal failure OR ESRD or stage 5 renal disease).ti,ab. |
| 6 | 4 OR 5 |
| 7 | 3 AND 6 |
| 8 | (roxadustat OR roxa OR FG-4592 OR FG4592 OR FG 4592 ASP-1517 OR ASP1517 OR ASP 1517 OR AZD-9941 OR AZD9941 OR AZD 9941 OR ai rui zhuo OR evrenzo).ti,ab. |
| 9 | 7 AND 8 |
| 10 | (addresses OR autobiography OR bibliography OR biography OR clinical trial, phase I OR comment OR congresses OR consensus development conference OR duplicate publication OR editorial OR guideline OR in vitro OR interview OR lecture OR legal cases OR legislation OR letter OR news OR newspaper article OR patient education handout OR periodical index OR personal narratives OR portraits OR practice guideline OR review OR video audio media).pt. |
| 11 | 9 NOT 10 |
| 12 | (exp animals/ OR exp animal/ OR exp nonhuman/ OR exp animal experiment/ OR animal model/ OR animal tissue/ OR non human/ OR (rat OR rats OR mice OR mouse OR swine OR porcine OR murine OR sheep OR lambs OR pigs OR piglets OR rabbit OR rabbits OR cat OR cats OR dog OR dogs OR cattle OR bovine OR monkey OR monkeys OR trout OR marmoset$1 OR basic research OR cell lines OR in vitro OR animal model OR canine).tw.) NOT (humans/ OR human/ OR human experiment/ OR (human* OR men OR women OR patients OR subjects).tw.) |
| 13 | 11 NOT 12 |
| 14 | limit 13 to english language |
| 15 | remove duplicates from 14 |

*Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present.

**Table D3. Search Strategy of EMBASE for Roxadustat**

| | |
|---|---|
| #1 | 'anemia'/exp OR 'iron deficiency anemia'/exp OR 'refractory anemia'/exp OR 'refractory anemia with excess blasts'/exp |
| #2 | 'an?emi*':ti,ab OR 'chronic anemia':ti,ab |
| #3 | #1 OR #2 |
| #4 | 'chronic kidney failure'/exp OR 'end stage renal disease'/exp |
| #5 | 'chronic kidney disease':ti,ab OR 'end*stage kidney disease':ti,ab OR 'end*stage kidney failure':ti,ab OR 'ESKD':ti,ab OR 'chronic renal disease':ti,ab OR 'end*stage renal dysfunction':ti,ab OR 'end*stage renal failure':ti,ab OR 'ESRD':ti,ab OR 'stage 5 renal disease':ti,ab |
| #6 | #4 OR #5 |
| #7 | #3 AND #6 |
| #8 | 'roxadustat'/exp |
| #9 | 'roxadustat':ti,ab OR 'roxa':ti,ab OR 'fg-4592':ti,ab OR 'fg4592':ti,ab OR 'fg 4592':ti,ab OR 'asp-1517':ti,ab OR 'asp1517':ti,ab OR 'asp 1517':ti,ab OR 'azd-9941':ti,ab OR 'azd9941':ti,ab OR 'azd 9941':ti,ab OR 'ai rui rhuo':ti,ab OR 'evrenzo':ti,ab |
| #10 | #8 OR #9 |
| #11 | #7 AND #10 |
| #12 | ('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp |
| #13 | #11 NOT #12 |
| #14 | ('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it) |
| #15 | #13 NOT #14 |
| #16 | #15 AND [english]/lim |

**Figure D1. PRISMA Flow Chart Showing Results of Literature Search for Roxadustat**



## Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all abstracts identified through electronic searches using DistillerSR (Evidence Partners, Ottawa, Canada) according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. We retrieved the citations that were accepted during abstract-level screening for full-text appraisal. Two investigators reviewed full papers and provided justification for the exclusion of each excluded study.

## Data Extraction and Quality Assessment

Two reviewers extracted key information from the full set of accepted trials. We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials, using the categories "good," "fair," or "poor."[17] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

***Good:*** *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.*

***Fair:*** *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention-to-treat analysis is done for RCTs.*

***Poor:*** *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention-to-treat analysis is lacking.*

Note that case series are not considered under this rating system—because of the lack of comparator, these are generally considered to be of poor quality.

## Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[18,19]

## Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for roxadustat using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published.

## Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in Evidence Tables and synthesized quantitatively and qualitatively in the body of the review. We evaluated the feasibility of conducting a quantitative synthesis by exploring the differences in study populations, study design, analytic methods, and outcome assessment for each outcome of interest. Based on the data availability from at least two sufficiently similar RCTs, we conducted random effect pairwise meta-analyses (MAs) on the following outcomes: MI, stroke, heart failure, all-cause mortality, Short Form (SF)-36 Health Survey, Hb, any TEAE, serious TEAE, and discontinuation due to adverse events. Effect sizes for continuous outcomes (e.g., Hb) were expressed as mean difference (MD) and 95% confidence intervals (95% CIs). For binary outcomes (e.g., all-cause mortality), we calculated risk ratios (RRs) and 95% CIs. We assessed heterogeneity used the Cochran q test and the $I^2$ statistic. To explore heterogeneity across studies, we examined differences in the distribution of key characteristics across studies, such as enrolled patients and baseline Hb. Due to inconsistent or limited reporting of data, other outcomes are described narratively only.

# D2. Supplemental Results

## Assessment of Bias

As described above, we searched for studies completed more than two years ago that would have met our inclusion criteria, and for which no findings have been published. For this review, we did not find any evidence for publication bias for completed trials of roxadustat. However, we identified seven Phase III RCTs (NCT01750190, NCT01887600, NCT02174627, NCT02052310, NCT02174731, NCT02278341, and NCT02780726) and one Phase II RCT (NCT01888445) with interim results that have not been published in a peer-reviewed journal. Further, at the time of this report, only interim data for the key trials of roxadustat are available, and these results have not been published in a peer-reviewed journal.

## Study Selection

Our literature search identified 70 potentially relevant references (see Figure D1), of which 16 references relating to 18 RCTs (eight publications, three clinical trial reports, two conference presentations, one conference abstract, one investor presentation, and one pre-approval Academy of Managed Care Pharmacy [AMCP] dossier) and 17 references relating to pooled analyses of key Phase III RCTs (six conferences presentations, five conference posters, five conference abstracts, and one pre-approval AMCP dossier) met our inclusion criteria. The reasons for study exclusion were duplication, study type (non-comparative trial), and study population outside of our scope. Of the 31 included references, 16 references represented 18 RCTs of roxadustat, and 16 references represented pooled analyses of the key Phase III RCTs. One reference, the pre-approval AMCP dossier, represented both individual RCTs and pooled analyses in both populations. Additionally, results for OLYMPUS, PYRENEES, and ROCKIES were also obtained from the clinicaltrials.gov database. Key trial details, including patient characteristics and clinical benefits, are presented below.

***DI-CKD***

A total of nine references relating to two RCTs comparing roxadustat to darbepoetin alfa[20,21] and eight RCTs comparing roxadustat to placebo[22-28] met our inclusion criteria.

***DD-CKD***

A total of seven references (four publications, two clinical trial reports, and one pre-approval ACMP dossier) relating to one key Phase III RCT,[24,29] two additional Phase III RCTs,[30,31] and three Phase II RCTs met our inclusion criteria.[27,32,33] A total of two references (one investor presentation and one pre-approval AMCP dossier) relating to two key Phase III RCTs comparing roxadustat to epoetin alfa in ID- and stable DD-CKD patients met our inclusion criteria.[23,24] A total of two references (one conference presentation and one pre-approval AMCP dossier) relating to one key Phase III RCT comparing roxadustat to epoetin alfa met our inclusion criteria.[24,34]

## Quality of Individual Studies

We used the USPSTF criteria to rate the quality of the included RCTs.[17] Of note, we did not rate DOLOMITES, ALPS, ANDES, OLYMPUS, and the 1517-CL-0310 RCT in the DI-CKD population and HIMALAYAS, PYRENEES, ROCKIES, SIERRAS, and the 1517-CL-0304 RCT in the DD-CKD population as they were only available in grey literature with limited reporting of details prohibiting evaluation of studies' quality.

In the DI-CKD population, Chen 2019 and Chen 2017 were rated "good," and Besarab 2015 and Akizawa 2019 were rated "poor" due to lack of intention-to-treat (ITT) analysis (see Table D5). In

the DD-CKD population, Chen 2019 was rated “fair” while Akizawa 2020, Provenzano 2016, and Chen 2017 were rated “poor” due to a lack of ITT analysis (see Table D4 on the following page).

**Table D4. Study Quality of Included Trials**

| Trial | Comp. Groups | Non-Differential Lost to Follow-Up | Patient/ Investigator Blinding (Double-Blind) | Clear Def. of Intervention | Clear Def. of Outcomes | Selective Outcome Reporting | Measurements Valid | ITT Analysis | Approach to Missing Data | USPSTF Rating |
|---|---|---|---|---|---|---|---|---|---|---|
| Chen 2019 | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Multiple Imputation | Good |
| Besarab 2015 | Yes | Unclear | No | Yes | Yes | No | Yes | No | LOCF | Poor |
| Chen 2017 | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Unclear | Good |
| Akizawa 2019 | Yes | Unclear | Yes | Yes | Yes | No | Yes | No | Unclear | Poor |
| Chen 2019 | Yes | Unclear | No | Yes | Yes | No | Yes | Yes | Markov Chain Monte Carlo | Fair |
| Akizawa 2020 | Yes | Unclear | Yes | Yes | Yes | No | Yes | No | Unclear | Poor |
| Provenzano 2016 | Yes | Yes | No | Yes | Yes | No | Yes | No | Unclear | Poor |
| Chen 2017 | Yes | Unclear | No | Yes | Yes | No | Yes | ITT | LOCF | Poor |

Comp.: comparable, Def: definition, ITT: intention-to-treat, LOCF: last observation carried forward, USPSTF: United States Preventive Services Task Force

## Trials of Roxadustat

### *DI-CKD*

### *Key Trials of Roxadustat in the DI-CKD Population*

We identified four Phase III, multicenter RCTs of roxadustat in DI-CKD.[20,22-24] The trials are described in detail below (Table D5 provides an overview of each trial, and additional trial details can be found in Evidence Table 1). All RCTs are currently unpublished, and data for these trials was obtained from a clinical trial report, conference presentation, investor presentation, a pre-approval AMCP dossier, and the clinicaltrials.gov database (OLYMPUS only).

*DOLOMITES*

The DOLOMITES trial was a multicenter, Phase III, open-label RCT conducted primarily in Europe that compared the safety and efficacy of roxadustat and darbepoetin alfa in 616 adults with DI-CKD III, IV, and V.[20] DOLOMITES included patients with Hb ≤10.50 g/dL. Patients with known New York Heart Association (NYHA) Class III or IV congestive heart failure, MI, acute coronary syndrome, stroke, seizure or a thrombotic/thromboembolic event within 12 weeks, and uncontrolled hypertension were excluded from the trial. Patients were randomized to a weight-based starting dose of roxadustat three times weekly (n=323) or darbepoetin alfa (n=293) and treated for 104 weeks before a four-week follow-up period. Doses were titrated to correct and maintain Hb within 10.00 to 12.00 g/dL. Rescue therapy (blood transfusion, IV iron supplementation, and ESA treatment) was permitted. The patients had a mean age of 66 years, 45% were male, 14% were white, and mean Hb was 9.55 g/dL. Additional baseline characteristics can be found in Evidence Table 2.

The primary endpoint was Hb response, defined as Hb ≥11.00 g/dL and a Hb increase from baseline of 1.00 g/dL in patients with baseline Hb >8.00 g/dL, or an increase of ≥2.00 g/dL in patients with baseline Hb ≤8.00 g/dL, during the first 24 weeks of treatment without rescue therapy. Secondary endpoints included IV iron supplementation, HRQoL, change from baseline (CFB) in Hb, and low-density lipoprotein (LDL)-cholesterol.

*ALPS, ANDES, and OLYMPUS*

The ALPS, ANDES, and OLYMPUS trials were global, multicenter, Phase III, double-blind RCTs that compared the safety and efficacy of roxadustat and placebo in adults with DI-CKD III, IV, and V[22-24] ALPS and ANDES had similar inclusion criteria: Hb ≤10 g/dL, ferritin ≥30 ng/mL, and transferrin saturation (TSAT) ≥5%. OLYMPUS included patients with Hb <10.00g/dL, ferritin ≥50 ng/mL, and TSAT ≥15%. Patients who received ESA treatment within 12 weeks were excluded from ALPS and ANDES, while patients who received ESA treatment within six weeks were excluded from OLYMPUS. Patients with known NYHA Class III or IV congestive heart failure, MI, acute coronary syndrome,

stroke, seizure or a thrombotic/thromboembolic event with 12 weeks, and uncontrolled hypertension were excluded from the trials. Patients in ALPS and ANDES were randomized to a weight-based starting dose of roxadustat three times weekly (ALPS: n=394 and ANDES: n=616) or placebo (ALPS: 203 and ANDES: 306) and treated for 52 to 104 weeks in ALPS or up to four and a half years in ANDES (see Evidence Table 2). In OLYMPUS, patients were randomized to a starting dose of roxadustat 70 mg three times weekly (n=1,393) or placebo (n=1,388) and treated for up to four years. In all trials, the follow-up periods were four weeks, and doses were titrated to correct and maintain Hb within 10.00 to 12.00 g/dL. Rescue therapy was permitted. Baseline characteristics were similar across the trials (see Table D5 on the following page and Evidence Table 2).

The trials' primary endpoint was mean CFB in Hb averaged over weeks 28 to 52. Secondary endpoints included rescue therapy, blood transfusion, IV iron supplementation, hepcidin, ferritin, TSAT, and LDL-cholesterol.

**Table D5. Key Trials of Roxadustat in DI-CKD**

| Trial (Number of Patients) | Treatment Arms | Key Baseline Characteristics* |
|---|---|---|
| **DOLOMITES (616)** | Roxadustat TIW†<br>Darbepoetin alfa | Mean age: 66<br>Mean Hb: 9.55 g/dL<br>Mean TSAT: NR<br>Mean ferritin: NR<br>Iron replete: 54%<br>CRP >ULN: 37% |
| **ALPS (594)** | Roxadustat 70 or 100 mg TIW‡<br>Placebo | Mean age: 61<br>Mean Hb: 9.09 g/dL<br>Mean TSAT: NR<br>Mean ferritin: NR<br>Iron replete: 53%<br>CRP >ULN: 36% |
| **ANDES (922)** | Roxadustat 70 or 100 mg TIW‡<br>Placebo | Mean age: 65<br>Mean Hb: 9.10 g/dL<br>Mean TSAT: 26.30%<br>Mean ferritin: 308.50 ng/mL<br>Iron replete: 59%<br>CRP >ULN: 26% |
| **OLYMPUS (2781)** | Roxadustat 70 mg TIW<br>Placebo | Mean age: 62<br>Mean Hb: 9.10 g/dL<br>Mean TSAT: NR<br>Mean ferritin: NR<br>Iron replete: 58%<br>CRP >ULN: 16% |

CRP: C-reactive protein, g/dL: grams per deciliter, Hb: hemoglobin, mg: milligram, NR: not reported, TIW: three times weekly, TSAT: transferrin saturation, ULN: upper limit of normal

*No key trials reported baseline hepcidin or CRP levels.

†Weight-based starting dose not reported.

‡Weight-based starting dose.

*Other Trials of Roxadustat in the DI-CKD Population*

**Phase III RCTs**

The 1517-CL-0310 trial was a 52-week, multicenter, phase III, open-label RCT that compared the efficacy and safety of roxadustat to darbepoetin alfa (comparative group) in 262 Japanese adults with DI-CKD III, IV, and V.[21] Patients who had received treatment with darbepoetin alfa or recombinant human erythropoietin were randomized to receive roxadustat for 52 weeks or darbepoetin alfa for 24 weeks. Additionally, patients who had received treatment with epoetin beta pegol were allocated to receive roxadustat (referential group) for 24 weeks. The trial included patients with Hb ≥10.0 g/dL and ≤12.0 g/dL and either TSAT ≥20% or ferritin ≥100 ng/mL who had been receiving ESA treatment by subcutaneous injection. Patients with NYHA Class III or IV

congestive heart failure, history of hospitalization for treatment of stroke, MI, or pulmonary embolism within 12 weeks, or uncontrolled hypertension were excluded from the trial. At the time of this report, information regarding dosing and rescue therapy was not reported. The primary endpoint of the trial was mean CFB in Hb averaged over weeks 18 to 24. Secondary endpoints included the number of patients who achieved target Hb level and HRQoL. Baseline characteristics are unavailable at the time of this report.

Chen 2019 was a 26-week, multicenter, Phase III, double-blind RCT that compared the efficacy and safety of roxadustat and placebo in 154 Chinese adults with DI-CKD III, IV, and V.[25] The trial included patients with Hb ≥7 to <10 g/dL. Patients with ESA treatment within five weeks, NYHA Class III or IV congestive heart failure, or MI, acute coronary syndrome, stroke, seizure, or a thromboembolic event within 52 weeks, or uncontrolled hypertension were excluded from the trial. However, patients could be rescreened once hypertension was controlled. The trial consisted of two parts; in part one, patients were randomized to a weight-based starting dose of roxadustat 70 or 100 mg three times weekly or placebo for eight weeks; in part two, all patients received roxadustat for 18 weeks. Doses were increased every four weeks to maintain Hb ≥10.00 to ≤12.00 g/dL. Rescue therapy was permitted. The primary endpoint of the trial was mean CFB in Hb averaged over weeks seven to nine. Secondary endpoints included hepcidin, ferritin, TSAT, and LDL-cholesterol. The patients had a mean age of 54 years, 37% were male, and mean Hb was 8.90 g/dL. Additional baseline characteristics can be found in Evidence Table 3.

**Phase II RCTs**

Besarab 2015 was a four-week, Phase IIa, single-blind (patients), randomized, dose-ranging trial with a follow-period of up to 12 weeks that compared the efficacy and safety of roxadustat and placebo in 116 American adults with DI-CKD III and IV.[26] The trial included patients with Hb ≤11.0 g/dL. Patients with ESA treatment within 60 days, NYHA Class III or IV congestive heart failure, MI, or acute coronary syndrome within three months, thrombolytic events within four weeks, and uncontrolled hypertension were excluded from the trial. The trial consisted of a four-week treatment period (day one to day 29 in patients treated with roxadustat two times weekly and day one to day 26 in patients treated with roxadustat three times weekly) and up to a 12-week follow-up period. Patients were sequentially enrolled to one of four roxadustat dose cohorts with administration two or three times weekly or placebo. Additional information on the roxadustat cohorts can be found in Evidence Table 1. A 50% dose reduction occurred when Hb increased ≥2.00 g/dL within any two-week period, while dosing was discontinued when the change in Hb was ≥3.00 g/dL at any assessment during the treatment period. Rescue therapy was prohibited during the treatment period and for the first four weeks of follow-up. However, it was permitted during the remainder of the follow-up period. Endpoints evaluated included Hb, hepcidin, and TSAT. The patients had a mean age of 66 years, 42% were male, and mean Hb was 10.30 g/dL. Additional baseline characteristics can be found in Evidence Table 4.

Chen 2017 was an eight-week, Phase II, parallel-arm, double-blind, dose-ranging RCT that compared the efficacy and safety of roxadustat and placebo in 91 Chinese adults with DI-CKD III, IV, and V.[27] The trial included patients with Hb <10.00 g/dL. Patients with ESA treatment within 12 weeks, NYHA Class III or IV congestive heart failure, or a thromboembolic event within 12 weeks were excluded from the trial. Patients were randomized to roxadustat or placebo three times weekly and then sequentially into roxadustat low-dose (1.1 to 1.75 mg/kg) or high-doses (1.50 to 2.3 mg/kg) using weight-based dosing. A dose-escalation could occur at week five, while dose reductions for excessive erythropoiesis could occur at any time. Rescue therapy with IV iron supplementation or ESA treatment was permitted if Hb <8.0 g/dL, and the investigator felt it was in the patient's medical interest. The primary endpoint was maximum CFB in Hb at any time from baseline to week eight. Secondary endpoints included hepcidin, transferrin, and TSAT. The patients had a mean age of 50 years, 59% were male, and mean Hb was 8.80 g/dL. Additional baseline characteristics can be found in Evidence Table 4.

Akizawa 2019 was a 24-week, multicenter, Phase II, parallel-arm, double-blind RCT that compared the efficacy and safety of roxadustat and placebo in 107 Japanese adults with CKD not on dialysis for three months since trial completion.[28] The trial included patients with Hb <10.00g g/dL and ferritin ≥30 ng/mL and TSAT ≥5%. Patients with ESA treatment within six weeks, NYHA Class III or IV congestive heart failure, history of hospitalization for stroke, MI, or lung infarction within 24 weeks, or uncontrolled hypertension were excluded from the trial. Patients were randomized to three active treatment arms of either roxadustat 50, 70, or 100 mg three times weekly or placebo for six weeks (fixed-dose period), followed by dose adjustments to maintain Hb 10.00 to 12.00 g/dL for 18 weeks (titration period). Patients meeting pre-defined criteria were re-randomized to three times weekly or one-time, weekly dosing. IV iron supplementation was permitted if serum ferritin was <30 ng/mL and TSAT was <5%. The primary endpoint was the mean rate of rise in Hb up to week six. Secondary endpoints included hepcidin, transferrin, and TSAT. The patients had a mean age of 64 years, 83% were male, and mean Hb was 9.38 g/dL. Additional baseline characteristics can be found in Evidence Table 4.

***DD-CKD***

**Key Trials of Roxadustat in the DD-CKD Population**

*HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS*

We identified four Phase III, multicenter RCTs of roxadustat in DD-CKD.[23,24,29,34] The trials are described in detail below (Table D7 provides an overview of each trial, and additional trial details can be found in Evidence Table 16). All RCTs are currently unpublished, and data for these studies was obtained from a clinical trial report, conference presentation, investor presentation, a pre-approval AMCP dossier, and the clinicaltrials.gov database (PYRENEES and ROCKIES only).

The HIMALAYAS, ROCKIES, and SIERRAS trials were multicenter, Phase III, open-label RCTs that compared the efficacy and safety of roxadustat to epoetin alfa in adults with incident DD-CKD (HIMALAYAS) or ID- and stable DD-CKD (ROCKIES and SIERRAS).[23,24,34] While HIMALAYAS and ROCKIES were global trials, SIERRAS was conducted in the US and Latin America. The PYRENEES trial was a multicenter, Phase III, open-label RCT conducted in Europe that compared the safety and efficacy of roxadustat to darbepoetin alfa and epoetin alfa, where most results for the comparators were presented in a pooled ESA treatment arm.[24,29]

HIMALAYAS included patients receiving hemodialysis (HD) or peritoneal dialysis (PD) ≥2 weeks to ≤4 months, Hb ≤10.00 g/dL, and ferritin ≥100 ng/mL and TSAT ≥20%. PYRENEES included patients receiving hemodiafiltration, HD, or PD for ≥4 months, Hb 9.50 to 12.00 g/dL, and receiving ESA treatment ≥8 weeks. ROCKIES included patients receiving HD or PD ≥2 weeks, Hb <12.00 g/dL (if receiving ESA treatment), and Hb <10.00 g/dL (if not receiving ESA treatment), ferritin ≥100 ng/mL, and TSAT ≥20%. SIERRAS included patients receiving HD or PD. Further, stable DD-CKD patients were eligible if their Hb was ≥9.00 to ≤12.00 g/dL, and they had been receiving ESA treatment ≥8 weeks, while incident DD-CKD patients were eligible if their Hb was ≥8.5 to ≤12.0 g/dL and they had been receiving ESA treatment ≥4 weeks. Additional eligibility criteria for SIERRAS included ferritin ≥100 ng/mL and TSAT ≥20%. Patients receiving ESA treatment ≤3 weeks in the previous three months, congestive heart failure, MI, stroke, or blood clots within a major vessel, or uncontrolled hypertension were excluded from HIMALAYAS. PYRENEES, ROCKIES, and SIERRAS excluded patients with known NYHA Class III or IV congestive heart failure, MI, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event with 12 weeks. Patients were randomized to a weight-based starting dose of roxadustat or epoetin alfa or ESA (PYRENEES only) and treated for up to four years (Evidence Table 16). Doses were titrated to maintain Hb, and rescue therapy (blood transfusion and ESA treatment) was permitted. IV iron supplementation was administered per usual care with ESAs and was limited to rescue therapy with roxadustat. Key baseline characteristics are shown in Table D6. Mean Hb at baseline was highest in PYRENEES, followed by SIERRAS, ROCKIES, HIMALAYAS (see Table D6). Additionally, 100% of patients in HIMALAYAS had incident DD-CKD, while in ROCKIES, 20% of patients had incident DD-CKD and in SIERRAS, 10% of patients had incident DD-CKD (see Table D6).

The primary endpoint of all the trials was mean CFB in Hb averaged over weeks 28 to 52. Secondary endpoints included rescue therapy, blood transfusion, IV iron supplementation, hepcidin, ferritin, and LDL-cholesterol.

**Table D6. Key Trials of Roxadustat in DD-CKD**

| Trial (Number of Patients) | Population | Treatment Arms | Key Baseline Characteristics* |
|---|---|---|---|
| **HIMALAYAS (1043)** | Incident DD-CKD | Roxadustat 70 or 100 mg TIW†<br>Epoetin alfa | Mean age: 54<br>Incident DD-CKD: 100%<br>Mean Hb: 8.45 g/dL<br>Mean TSAT: 27.29%<br>Ferritin: 430.00 ng/mL<br>CRP >ULN: 52% |
| **PYRENEES (836)** | Stable DD-CKD | Roxadustat 70 or 100 mg TIW‡<br>ESAs | Mean age: 61<br>Incident DD-CKD: 0%<br>Mean Hb: 10.77 g/dL<br>Mean TSAT: NR<br>Mean ferritin: NR<br>CRP >ULN: NR |
| **ROCKIES (2133)** | Incident and stable DD-CKD | Roxadustat 70, 100, 150, or 200 mg TIW‡<br>Epoetin alfa | Mean Age: 54<br>Incident DD-CKD: 20%<br>Mean Hb: 9.10 g/dL<br>Mean TSAT: NR<br>Mean ferritin: NR<br>CRP >ULN: NR |
| **SIERRAS (741)** | Incident and stable DD-CKD | Roxadustat 70, 100, 150, or 200 mg TIW‡<br>Epoetin alfa | Mean age: NR<br>Incident DD-CKD: 10%<br>Mean Hb: 10.25 g/dL<br>Mean TSAT: NR<br>Mean ferritin: NR<br>CRP >ULN: 49% |

CKD: chronic kidney disease, CRP: C-reactive protein, DD: dialysis-dependent, ESA: erythropoiesis-stimulating agents, g/dL: grams per deciliter, Hb: hemoglobin, mg: milligram, NR: not reported, TIW: three times weekly, TSAT: transferrin saturation, ULN: upper limit of normal

*No key trials reported baseline hepcidin or CRP levels or iron-repletion status.

†Weight-based starting dose.

‡Starting dose varied based on weight and prior ESA use.

*Other Trials of Roxadustat in the DD-CKD Population*

**Phase III RCTs**

Chen 2019 was a 26-week, multicenter, Phase III, open-label RCT that compared roxadustat to epoetin alfa in 305 Chinese adults with stable DD-CKD.[30] The trial included patients with Hb 9.00 to 12.00 g/dL receiving HD or PD ≥16 weeks and stable doses of epoetin alfa ≥6 weeks. Patients with NYHA Class III or IV congestive heart failure, or MI, acute coronary syndrome, stroke, seizure, or thromboembolic event within 52 weeks were excluded from the trial. Patients were randomized to either a weight-based starting dose of roxadustat (100 or 120 mg three times weekly) (n=204) or

epoetin alfa (n=101) for 26 weeks. Doses were adjusted to maintain Hb 10.00 to 12.00 g/dL. Rescue therapy was permitted in patients with Hb <8.00 g/dL or in patients with Hb <9.00 g/dL who had a confirmed decrease from baseline of >1.00 g/dL. The patients had a mean age of 54 years, 59% were male, and mean Hb was 8.45 g/dL. Additional baseline characteristics can be found in Evidence Table 18. The primary endpoint of the trial was mean CFB in Hb averaged over weeks 23 to 27. Secondary endpoints included hepcidin, transferrin, and TSAT.

Akizawa 2020 was a 24-week, multicenter, Phase III, double-blind, double-dummy, parallel-arm RCT that compared roxadustat to darbepoetin alfa in 303 adults with stable DD-CKD.[31] The trial included patients with Hb ≥10.00 to ≤12.0 g/dL receiving HD >12 weeks and recombinant human erythropoietin or darbepoetin alfa >8 weeks with either ferritin ≥100 ng/mL or TSAT ≥20%. Patients with NYHA Class III or IV congestive heart failure, history of hospitalization for treatment of stroke, MI, or pulmonary embolism within 12 weeks were excluded from the trial. Patients were randomized to either roxadustat three times weekly (n=151) or darbepoetin alfa one time weekly (n=152) based on the average pre-randomization weekly dose of recombinant human erythropoietin or darbepoetin alfa for up to 24 weeks. While there was no formal washout period, the treatment period began on the day of dialysis after the longest dialysis interval in the week when ESA had been administered (i.e., within one to two weeks). Doses were titrated to maintain Hb 10.00 to 12.00 g/dL. IV iron was permitted at the discretion of the investigator only to maintain ferritin ng/mL ≥100 and/or TSAT ≥20% when ferritin was <100 ng/ml or TSAT was <20%. The patients had a mean age of 65 years, 69% were male, and mean Hb was 11.02 g/dL. Additional baseline characteristics can be found in Evidence Table 18. The primary endpoint was mean CFB in Hb averaged over weeks 18 to 24. Secondary endpoints included hepcidin, transferrin, and TSAT.

**Phase II RCTs**

Provenzano 2016 was a six to 19 week, multicenter, Phase II, open-label, randomized, dose-ranging trial that compared roxadustat to epoetin alfa in 144 American adults with stable DD-CKD.[32] The trial included patients with Hb 9.00 to 13.50 g/dL receiving HD ≥4 months and epoetin alfa for four weeks. Patients who received any ESA other than epoetin alfa within 12 weeks, NYHA Class III or IV congestive heart failure, MI within three months, or a thromboembolic event within 12 weeks were excluded from the trial. The trial consisted of two parts: in part one, patients were randomized to four cohorts of roxadustat (n=41) 1.0, 1.5, 1.8, or 2.0 mg/kg three times weekly or epoetin alfa (n=13) for six weeks with an eight-week follow-up period. Results from part one were used to inform optimal starting doses of roxadustat in part two. In part two, patients were randomized to 6.5 cohorts of roxadustat with various starting doses (n=67) or continuation of epoetin alfa (n=23) for 19 weeks with a four-week follow-up period. During the follow-up periods, patients randomized to roxadustat were switched back to epoetin alfa. Rescue therapy was permitted. The patients had a mean age of 58 years, 67% were male, 59% were white, and mean Hb was 11.40 g/dL. Additional baseline characteristics can be found in Evidence Table 19. The primary endpoint in part one was

the proportion of patients whose Hb did not decrease ≥0.5 g/dL from baseline, while the primary endpoint in part two was the proportion of patients whose mean Hb was ≥11.0 g/dL over the last four weeks of treatment. Secondary endpoints included hepcidin and TSAT.

Chen 2017 was a seven-week, multicenter, Phase II, parallel-arm, open-label, randomized, dose-ranging trial that compared roxadustat to epoetin alfa in 87 Chinese adults with stable DD-CKD.[27] Patients were stratified by baseline epoetin alfa dose and randomized to roxadustat three times weekly or epoetin alfa (n=22). Patients randomized to roxadustat were sequentially enrolled to low (1.10 to 1.80 mg/kg; n=22), medium (1.50 to 2.30 mg/kg; n=21), or high (1.70 to 2.30 mg/kg; n=22) doses of roxadustat. Dose titration was permitted to maintain Hb, where doses could be increased at week five, and dose decreases were permitted at any time during the dosing period for protocol-defined excessive erythropoiesis. Rescue therapy was permitted if Hb was <8.00 g/dL or <9.00 g/dL with a ≥1.50 g/dL decrease from baseline. The patients had a mean age of 51 years, 60% were male, and mean Hb was 10.70 g/dL. Additional baseline characteristics can be found in Evidence Table 19. The primary endpoint was the percentage of subjects with successful dose conversion, defined as a Hb level maintained at no <0.5g/dL below mean baseline value during the last two weeks of the six-week dosing period in the efficacy evaluable population. Secondary endpoints included hepcidin, transferrin, and TSAT.

The 1517-CL-0304 trial was a multicenter, Phase II, parallel-arm, double-blind (arms one to three), open-label (arm four) RCT that compared roxadustat to darbepoetin alfa in 130 Japanese adults with stable DD-CKD.[33] The trial consisted of three parts: part one was a fixed-dose period from the start of treatment to week six; part two was a titration period from week six to week 24, and part three was a four-week follow-up period. Patients were randomized to one of four arms: roxadustat 50 mg three times weekly (n=33), roxadustat 70 mg three times weekly (n=32), roxadustat 100 mg three times weekly (n=33), or darbepoetin alfa (n=32). Though IV iron supplementation was reported, additional information regarding the administration of rescue therapy is unavailable at the time of this report. The patients had a mean age of 62 years, 73% were male, and mean Hb was 8.83 g/dL. Additional baseline characteristics can be found in Evidence Table 19. The primary endpoint was CFB in the rate of rise in Hb to the final assessment of the fixed-dose period. Secondary endpoints included Hb.

# Clinical Benefits of Roxadustat

The clinical benefits and harms of roxadustat are first detailed in the DI-CKD population, followed by the DD-CKD population.

## DI-CKD

### *Cardiovascular Safety*

As described above, the key RCTs were designed with Hb as the primary endpoint; thus, the number of cardiovascular events was low (see Evidence Table 10).

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): At the time of this report, only DOLOMITES reported adjudicated cardiovascular events (see Table D7).[20] Due to the small sample size, the results were a non-confirmatory analysis. There were no significant differences in the risk of major adverse cardiovascular events (MACE: all-cause mortality, MI, or stroke), MACE+ (MACE, unstable angina requiring hospitalization, or congestive heart failure requiring hospitalization), or all-cause mortality with roxadustat compared to darbepoetin alfa during the safety emergent period (see Table D7). Additionally, there were no significant differences in the risk of first MI, stroke, unstable angina requiring hospitalization, or congestive heart failure requiring hospitalization (see Table D7).

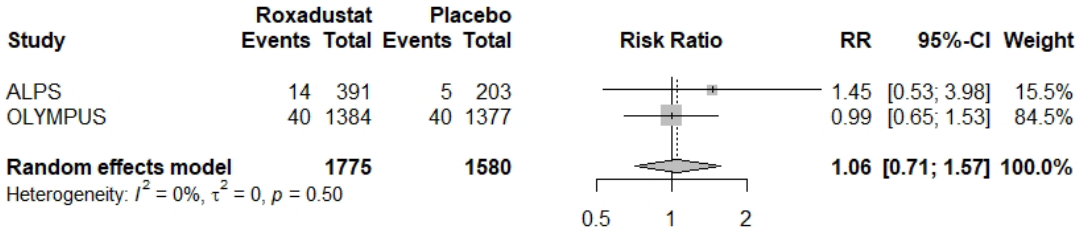
**Table D7. Adjudicated Cardiovascular Events in DOLOMITES**

| Outcomes | Arms | | Between Group Differences |
|---|---|---|---|
| | Roxadustat (N=323) | Darbepoetin Alfa (N=293) | HR (95% CI) |
| MACE, n (%) | 38 (11.8) | 41 (14.0) | 0.81 (0.52, 1.25) |
| MACE+, n (%) | 54 (16.7) | 53 (18.1) | 0.90 (0.61, 1.32) |
| All-Cause Mortality, n (%) | 29 (9.0) | 31 (10.6) | 0.83 (0.50, 1.38) |
| MI, n (%) | 11 (3.4) | 10 (3.4) | 0.96 (0.41, 2.27) |
| Stroke, n (%) | 4 (1.2) | 7 (2.4) | 0.48 (0.14, 1.67) |
| Unstable Angina Requiring Hospitalization, n (%) | 0 (0.0) | 1 (0.3) | -- |
| Congestive Heart Failure Requiring Hospitalization | 25 (7.7) | 21 (7.2) | 1.08 (0.60, 1.95) |

95% CI: 95% confidence interval, HR: hazard ratio, MI: myocardial infarction, N: total number, MACE: major adverse cardiovascular event (all-cause mortality, MI, or stroke), MACE+: MACE, unstable angina requiring hospitalization, or congestive heart failure requiring hospitalization

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): While adjudicated cardiovascular events were not reported for ALPS, ANDES, and OLYMPUS, ALPS and OLYMPUS reported the incidence of several cardiovascular safety events. We performed a MA of MI reported for ALPS and OLYMPUS.[22-24,35] As seen in Figure D2, the MA results suggest that the risk of MI is not significantly different with roxadustat compared to placebo (RR: 1.06; 95% CI: 0.71 to 1.57; $I^2$=0%).

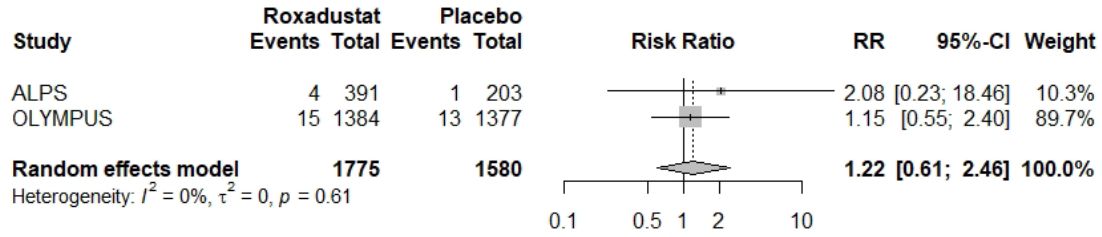
**Figure D2. MA of MI in ALPS and OLYMPUS**




95% CI: 95% confidence interval, $I^2$: I-squared, RR: risk ratio, $\tau^2$: between-study-variance estimator

We also performed a MA of stroke reported for ALPS and OLYMPUS.[22-24,35] As seen in Figure D3, the MA results suggest that the risk of stroke is not significantly different with roxadustat compared to placebo (RR: 1.22; 95% CI: 0.61 to 2.46; $I^2$=0%).

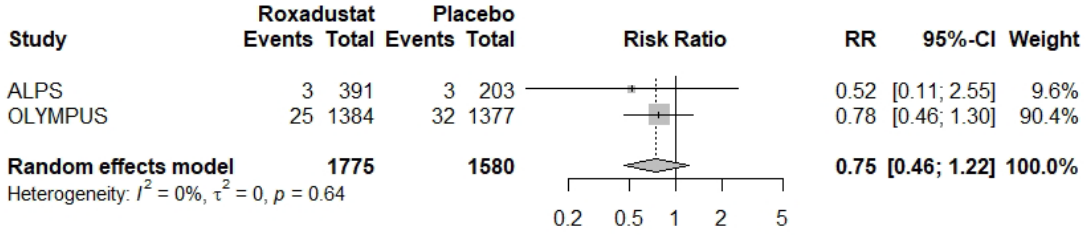
**Figure D3. MA of Stroke in ALPS and OLYMPUS**




95% CI: 95% confidence interval, $I^2$: I-squared, RR: risk ratio, $\tau^2$: between-study-variance estimator

Finally, we performed a MA of heart failure reported for ALPS and OLYMPUS.[22-24,35] As seen in Figure D4, the MA results suggest that the risk of heart failure is not significantly different with roxadustat compared to placebo (RR: 0.75; 95% CI: 0.46 to 1.22; $I^2$=0%).

**Figure D4. MA of Heart Failure in ALPS and OLYMPUS**

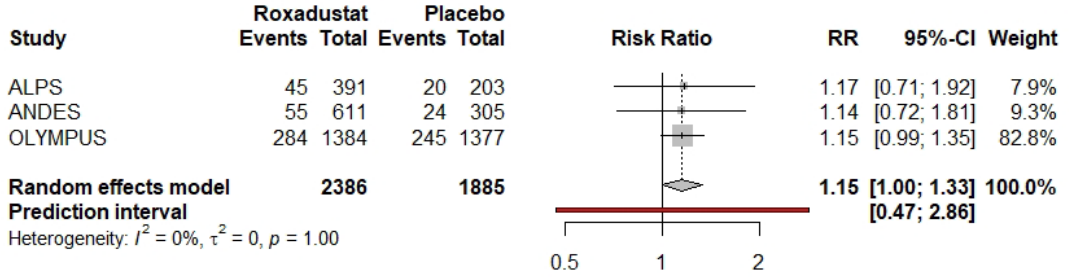



95% CI: 95% confidence interval, $I^2$: I-squared, RR: risk ratio, $\tau^2$: between-study-variance estimator

Only OLYMPUS reported the incidence of unstable angina, and there was no difference in the incidence with roxadustat compared to placebo (0.7% vs. 0.7%, respectively).[23,24]

Further, a pooled analysis of the intention-to-treat populations of ALPS, ANDES, and OLYMPUS reported that roxadustat was not significantly different from placebo in the risk of MACE (HR: 1.08; 95% CI: 0.94 to 1.24), MACE+ (HR: 1.04; 95% CI: 0.91 to 1.18), or all-cause mortality (HR: 1.06; 95% CI: 0.91 to 1.23) in the first 52 weeks.[36] Moreover, there was no significant difference in the risk of hospitalization for congestive heart failure (HR: 0.89; 95% CI: 0.72 to 1.12).[37] However, the number of deaths in the individual RCTs exceeds that of the pooled analyses. As such, we performed a MA of all-cause mortality reported for ALPS, ANDES, and OLYMPUS.[24] As seen in Figure D5, the MA found an increased risk of all-cause mortality with roxadustat of borderline statistical significance (risk ratio [RR]: 1.15; 95% CI: 1.00 to 1.33; $I^2$=0%). However, the summary estimate is higher than was reported in the pooled analysis, likely due to the addition of deaths not included in the pooled analysis.

**Figure D5. MA of All-Cause Mortality for ALPS, ANDES, and OLYMPUS**




95% CI: 95% confidence interval, $I^2$: I-squared, RR: risk ratio, $\tau^2$: between-study-variance estimator

Importantly, these results should be interpreted with caution as the time points in which cardiovascular safety events were reported in the key RCTs are unclear at the time of this report.

Other RCTs had shorter durations and were not powered to detect significant differences in cardiovascular events and reported low event rates (see Evidence Table 11 and Evidence Table 12).

***HRQoL***

The RCTs assessed HRQoL with the SF-36 Health Survey,[38] European Quality of Life Questionnaire-5 Dimensions-5 Levels (EQ-5D-5L) Visual Analogue Scale (VAS),[39] Functional Assessment of Cancer Therapy-Anemia (Fact-An),[40] and Patients' Global Impression of Change (PGIC).[41]

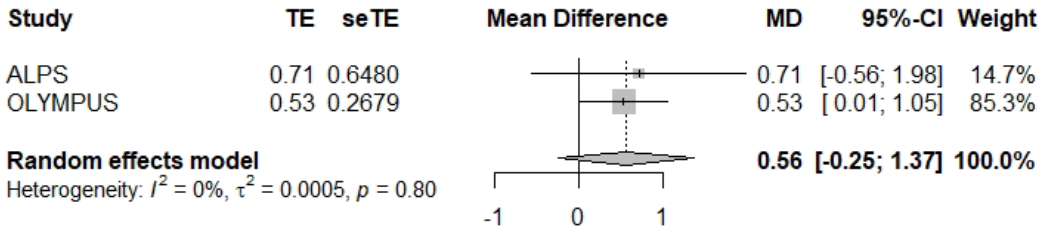
Higher scores on SF-36, EQ-5D-5L, and Fact-An indicate better quality of life. In the PGIC, patients rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse."

*SF-36*

DOLOMITES RCT (roxadustat vs. placebo): Patients receiving roxadustat had a significant decline in SF-36 Physical Functioning (PF) sub-score averaged over weeks 12 to 28 (least squares means [LSM] difference: -1.28; 95% CI: -2.42 to -0.15) compared with those on darbepoetin alfa.[20] However, this difference did not exceed the minimum clinically important difference (MCID) of 3 to 5 points.[42] There was no significant difference between roxadustat and darbepoetin alfa in mean CFB in SF-36 Vitality (VT) sub-score averaged over weeks 12 to 28 (LSM difference: -0.46; 95% CI: -1.66 to 0.74).[20]

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): A pooled analysis of ANDES, ALPS, and OLYMPUS reported a significant increase in mean CFB in SF-36 PF sub-score at week 12 with roxadustat compared to placebo (LSM difference: 0.53; 95% CI: 0.05 to 1.01).[43] However, we performed a MA of this outcome averaged over weeks 12 to 28 for ALPS and OLYMPUS.[22,23,35] As seen in Figure D6, the MA results demonstrate no significant difference with roxadustat compared to placebo (MD: 0.56; 95% CI: -0.25 to 1.37; $I^2$=0%).

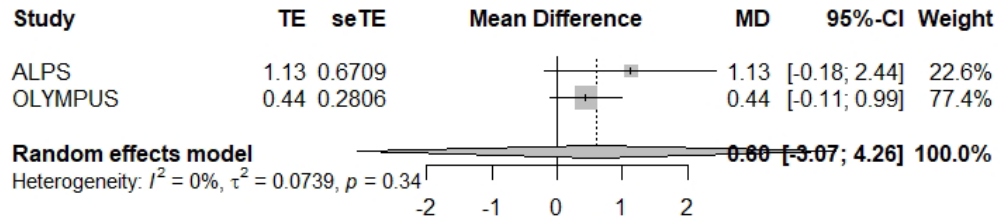
**Figure D6. MA of SF-36 Health Survey PF for ALPS and OLYMPUS**




95% CI: 95% confidence interval, $I^2$: I-squared, MD: mean difference, seTE: standard error, $\tau^2$: between-study-variance estimator, TE: effect size

Further, the pooled analysis also reported a significant increase in mean CFB in SF-36 VT sub-score at 12 weeks with roxadustat compared to placebo (LSM difference: 0.96; 95% CI: 0.44 to 1.47).[43] However, we performed a MA of this outcome averaged over weeks 12 to 18 for ALPS and OLYMPUS.[22,23,35] As seen in Figure D7, the MA results demonstrate no significant difference with roxadustat compared to placebo (MD: 0.60; 95% CI: -3.07 to 4.26; $I^2$=15%).

**Figure D7. MA of SF-36 Health Survey VT for ALPS and OLYMPUS**




95% CI: 95% confidence interval, $I^2$: I-squared, MD: mean difference, seTE: standard error, $\tau^2$: between-study-variance estimator, TE: effect size

Further, a MCID of 3 to 5 points was not reached in SF-36 PF or VT sub-scores.[42] Because there were no significant differences in these endpoints averaged over weeks 12 to 28 in individual RCTs, it unclear if the differences reported for the pooled analysis would also lack statistical significance at later time points.

*EQ-5D-5L VAS*

In the pooled analysis, mean CFB in the EQ-5D-5L VAS score was significantly greater at week 12 with roxadustat compared to placebo (LSM difference: 1.68; 95% CI: 0.76 to 2.59).[43] While a MCID for EQ-5D-5L VAS score has not been established in patients with CKD, in stroke patients undergoing rehabilitation,[44] oncology patients,[45] and patients with chronic obstructive pulmonary disease (COPD),[46] a MCID ranged from 8 to 12 points.

*FACT-An*

In the pooled analysis, mean CFB in Total FACT-An score was significantly greater at week 12 with roxadustat compared to placebo (LSM difference: 1.81; 95% CI: 0.52 to 3.08).[43] Further, mean CFB in FACT-An Anemia Subscale (AnS) sub-score was significantly greater at week 12 with roxadustat compared to placebo (LSM difference: 1.10; 95% CI: 0.45 to 1.74).[43] Importantly, MCIDs of 6 points and 4 points for Total FACT-An and FACT-An AnS, respectively, were not reached.[47]

*PGIC*

The proportion of patients who rated their status as "very much improved" or "much improved" was significantly greater at week 12 with roxadustat compared to placebo (odds ratio difference: 2.03; 95% CI: 1.74 to 2.36).[43]

***Rescue Therapy***

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): Data regarding the composite rescue therapy endpoint and blood transfusion is unavailable at the time of completing this report. However, the risk of IV iron supplementation was significantly reduced with roxadustat compared to darbepoetin alfa in the first 36 weeks (HR: 0.45; 95%: CI: 0.26 to 0.78).[20]

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): In the individual RCTs, the risk of rescue therapy in the first 52 weeks was significantly reduced with roxadustat compared to placebo (see Table D8), and this was demonstrated in a pooled analysis (HR: 0.19; 95% CI: 0.16 to 0.23).[36]

Similarly, the risk of blood transfusion in the first 52 weeks was significantly reduced with roxadustat compared to placebo in these RCTs (see Table D8), and this was also demonstrated in a pooled analysis of these RCTs (HR: 0.26; 95% CI: 0.21 to 0.32).[24,36,48]

In OLYMPUS, the risk of IV iron supplementation was significantly reduced with roxadustat compared to placebo on treatment plus 28 days (HR: 0.41; 95% CI: 0.29 to 0.56).[23]

The risk of ESA treatment on treatment plus 28 days was significantly reduced with roxadustat compared to placebo in OLYMPUS (HR: 0.13; 95% CI: 0.10 to 0.18).[23]

**Table D8. Rescue Therapy in DOLOMITES, ALPS, ANDES, and OLYMPUS**

| Trial | DOLOMITES | | ALPS | | ANDES | | OLYMPUS | |
|---|---|---|---|---|---|---|---|---|
| | Roxadustat (N=323) | Darbepoetin Alfa (N=293) | Roxadustat (N=323) | PBO (N=203) | Roxadustat (N=616) | PBO (N=306) | Roxadustat (N=1384) | PBO (N=1376) |
| Risk of Rescue Therapy,* HR (95% CI) | NR | | 0.24 (0.17, 0.33) | | 0.19 (0.14, 0.28) | | 0.26 (0.23, 0.31) | |
| Risk of Blood Transfusion,* HR (95% CI) | NR | | 0.34 (0.21, 0.55) | | 0.26 (0.17, 0.41) | | 0.37 (0.30, 0.44) | |
| Risk of IV Iron Supplementation, HR (95% CI) | 0.45 (0.26, 0.78)† | | NR | | NR | | 0.41 (0.29, 0.56)‡ | |
| Risk of ESA Treatment, HR (95% CI) | NR | | NR | | NR | | 0.13 (0.10, 0.18)‡ | |

95% CI: 95% confidence interval, ESA: erythropoiesis-stimulating agent, IV: intravenous, HR: hazard ratio, N: total number, NR: not reported, PBO: placebo

*At 52 weeks.

†At 36 weeks.

‡On treatment plus 28 days.

In general, a reduction in the use of rescue therapy was observed with roxadustat compared to placebo in the other RCTs. In Chen 2019, there was a significant reduction in the use of rescue therapy with roxadustat compared to placebo (HR: 0.11; 95% CI: 0.02 to 0.51).[25] Chen 2017 reported a numerical reduction in the use of rescue therapy with roxadustat compared to placebo (pooled roxadustat: 1.6% vs. placebo: 3.3%); however, statistical values were not reported.[27] In Akizawa 2019, no patients required IV iron supplementation.[28] Further, Besarab 2015 reported a numerical reduction in the use of ESA treatment with roxadustat compared with placebo (pooled roxadustat: 9.1% vs. placebo: 17.9%), though statistical values were not reported.[26]

***Hospitalization***

We did not identify any RCTs that assessed the impact of roxadustat on hospitalization.

***Kidney Failure (ESKD)***

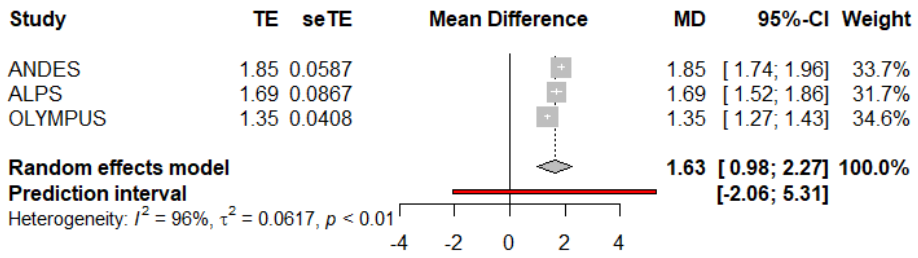
The key RCTs did not report the impact of roxadustat on progression to kidney failure as assessed by the composite of ESKD, defined by the need for chronic dialysis or renal transplantation, doubling of serum creatinine, or death. In OLYMPUS, the annual rate of mean CFB in eGFR prior to the initiation of dialysis or kidney transplant was significantly worse with roxadustat compared to placebo (LSM difference -0.51 mL/min/1.73 $m^2$; 95% CI: -1.00 to -0.01).[35] In contrast, in a post hoc subgroup analysis of ALPS, ANDES, and OLYMPUS, the one-year decline in eGFR was significantly better with roxadustat compared to placebo in patients who had a baseline eGFR of ≥15 mL/min/1.73 $m^2$ (LSM difference: 1.62 mL/min/1.73 $m^2$; p<0.0001).[36] This reduction is not likely to be clinically meaningful. The FDA accepts a doubling of serum creatinine level (corresponding to a change in eGFR of -57% or greater) as a surrogate outcome for ESKD risk because it reflects a substantial decrease in kidney function and predicts the development of ESKD.[49]

***Anemia***

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): Mean CFB in Hb averaged over weeks 28 to 36 was not significantly different with roxadustat compared to darbepoetin alfa (LSM difference: 0.02 g/dL; 95% CI: -0.13 to 0.16).[20]

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): Figure D8 shows the MA results on the primary outcome of mean CFB in Hb averaged over weeks 28 to 52 in ALPS, ANDES, and OLYMPUS.[24] The summary estimate is 1.63 g/dL (95% CI: 0.98 to 2.27) and suggests that roxadustat significantly increased Hb compared to placebo. However, statistical heterogeneity was significant ($I^2$=96%; p<0.01). A source of heterogeneity may be the small number of RCTs included in the MA.

**Figure D8. MA of Hb in ALPS, ANDES, and OLYMPUS**




95% CI: 95% confidence interval, $I^2$: I-squared, MD: mean difference, seTE: standard error, $\tau^2$: between-study-variance estimator, TE: effect size

The 1517-CL-0310 RCT reported no significant difference in mean CFB in Hb averaged over weeks 18 to 24 with roxadustat compared to darbepoetin alfa (difference: -0.07 g/dL; 95% CI: -0.23 to 0.10).[21] Chen 2019, Besarab 2015, Chen 2017, and Akizawa 2019 also demonstrated that roxadustat significantly increased Hb compared to placebo at earlier time points (see Evidence Table 7 and Evidence Table 8).[25-28]

### *Measures of Inflammation and Iron Storage and Availability*

The results for hepcidin and TSAT are described below, while the results for transferrin, soluble transferrin receptor, iron, total iron-binding capacity, and ferritin are presented in Evidence Table 5, Evidence Table 7, and Evidence Table 8.

#### Hepcidin

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): At the time of this report, data regarding hepcidin for DOLOMITES are unavailable.

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): In ANDES, mean CFB in hepcidin at week 44 was significantly reduced with roxadustat compared to placebo (LSM difference: -25.71 ng/mL ± 6.53; 95% CI: -38.52 to -12.90).[24] In a pooled analysis of ANDES, ALPS, and OLYMPUS, there was a significant reduction in mean CFB in hepcidin at week 24 with roxadustat compared to placebo (-23.05 ng/mL ± 86.03 vs. 12.33 ng/mL ± 87.77, respectively; p<0.0001).[50]

Results from other RCTs followed a similar trend. Chen 2019, Besarab 2015, Chen 2017, and Akizawa 2019 also demonstrated significantly reduced hepcidin with roxadustat compared to placebo at earlier time points (see Evidence Table 7 and Evidence Table 8).[25-28]

The clinical significance of the reductions in hepcidin is uncertain.

**TSAT**

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): At the time of this report, data regarding TSAT for DOLOMITES are unavailable.

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): ANDES reported numerically increased TSAT with roxadustat compared to placebo at 52 weeks (1.09% vs. 0.38%, respectively); however, these results should be interpreted with caution as they were obtained through digitization and statistical values were not reported.[24] In a pooled analysis of ANDES, ALPS, and OLYMPUS, TSAT was numerically reduced with roxadustat compared to epoetin alfa at week 20 (-1.15% ± 11.82 vs. 0.38% ± 10.69, respectively); however, statistical values were not reported.[50]

Results from other RCTs are conflicting. Chen 2019 reported a significant reduction in TSAT with roxadustat compared to placebo at week nine (LSM difference: -4.3%; 95% CI: -7.4 to -1.1); however, during the open-label phase, TSAT increased to 22.1% at week 27.[25] Besarab 2015[26] and Chen 2017[27] demonstrated significant reductions in TSAT with roxadustat compared to placebo at end of treatment (26 or 29 days) and eight weeks, respectively (see Evidence Table 7 and Evidence Table 8), while Akizawa 2019[28] reported no significant difference with a pooled roxadustat estimate compared to placebo at the end of treatment (up to 24 weeks). However, low dose roxadustat reached statistical significance compared to placebo (see Evidence Table 8).

**Lipids**

*LDL-Cholesterol*

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): Mean CFB in LDL-cholesterol averaged over weeks 28 to 36 was significantly reduced with roxadustat compared to darbepoetin alfa (LSM difference: -15.58 mg/dL; 95% CI: -19.72 to -11.45).[20]

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): ALPS and ANDES reported significant reductions in mean CFB in LDL-cholesterol averaged over weeks 12 to 28 with roxadustat compared to placebo, while OLYMPUS reported a significant reduction in mean CFB in LDL-cholesterol at 24 weeks with roxadustat compared to placebo (see Evidence Table 5).[23,24] In a pooled analysis of ALPS, ANDES, and OLYMPUS, mean CFB in LDL-cholesterol averaged over weeks 12 to 28 was significantly reduced with roxadustat compared to placebo (LSM difference: -19.83 mg/dL; 95% CI: -22.16 to -17.51).[51]

Similarly, Chen 2019, Chen 2017, and Akizawa 2019 reported significantly reduced LDL-cholesterol with roxadustat compared to placebo at earlier time points (see Evidence Table 7 and Evidence Table 8).[25,27,28]

However, the clinical significance of these reductions in LDL-cholesterol is uncertain.

*HDL-Cholesterol*

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): At the time of this report, data regarding high-density lipoprotein (HDL)-cholesterol for DOLOMITES are unavailable.

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): In a pooled analysis of ALPS, ANDES, and OLYMPUS, mean CFB in HDL-cholesterol averaged over weeks 12 to 28 was significantly reduced with roxadustat compared to placebo (LSM difference: -4.14 mg/dL ± 0.41).[51]

Chen 2017 reported a significant reduction in HDL-cholesterol at an earlier time point with roxadustat compared to placebo (see Evidence Table 8).[27]

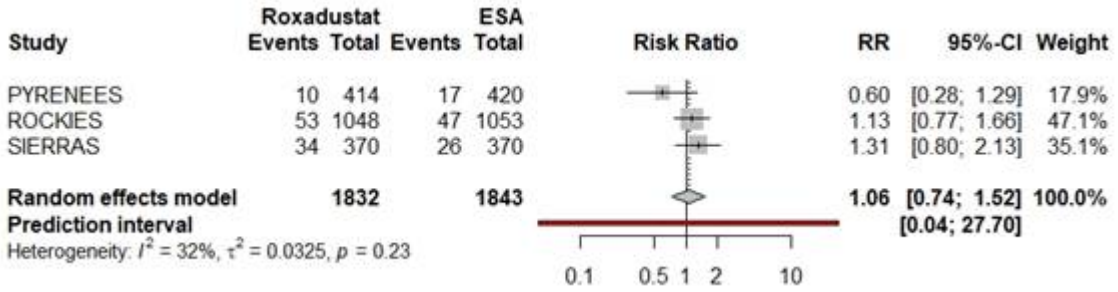
However, the clinical significance of these reductions in HDL-cholesterol is uncertain.

## DD-CKD

### *Cardiovascular Safety*

As described previously, the key RCTs (HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS) were designed with Hb as the primary endpoint; thus, the number of cardiovascular events was low (see Evidence Table 25). Further, at the time of this report, no key RCTs reported adjudicated cardiovascular events. While MI was not reported for HIMALAYAS, we performed a MA of MI reported for PYRENEES, ROCKIES, and SIERRAS.[23,24,29,52,53] As seen in Figure D9, the MA results suggest that the risk of MI is not significantly different with roxadustat compared to ESAs (RR: 1.06; 95% CI: 0.74 to 1.52; I2=32%).

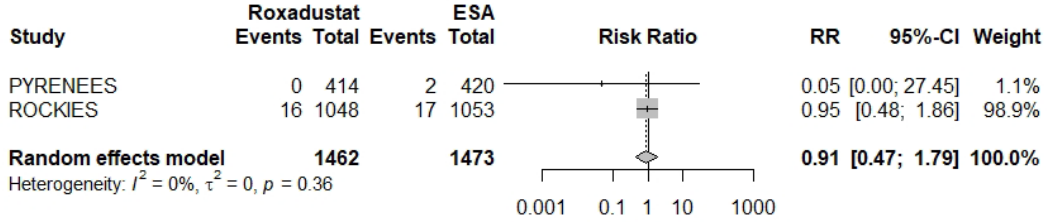
**Figure D9. MAs of MI in PYRENEES, ROCKIES, and SIERRAS**




95% CI: 95% confidence interval, ESA: erythropoiesis-stimulating agent, $I^2$: I-squared, RR: risk ratio, $\tau^2$: between-study-variance estimator

We also performed a MA of stroke reported for PYRENEES and ROCKIES.[23,24,29,52,53] As seen in Figure D10, the MA results suggest that the risk of stroke is not significantly different with roxadustat compared to ESAs (RR: 0.91; 95% CI: 0.47 to 1.79; $I^2$=0%).

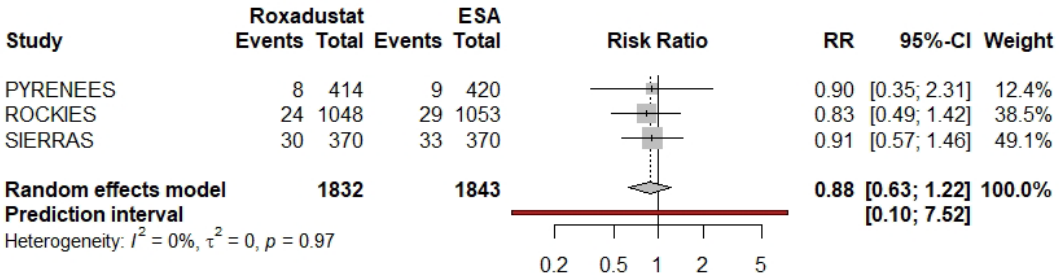
**Figure D10. MA of Stroke in PYRENEES and ROCKIES**




95% CI: 95% confidence interval, ESA: erythropoiesis-stimulating agent, $I^2$: I-squared, RR: risk ratio, $\tau^2$: between-study-variance estimator

We performed a MA of heart failure reported for PYRENEES, ROCKIES, and SIERRAS.[23,24,29,52,53] As seen in Figure D11, the MA results suggest that the risk of heart failure is not significantly different with roxadustat compared to ESAs (RR: 0.88; 95% CI: 0.63 to 1.22; $I^2$=0%).

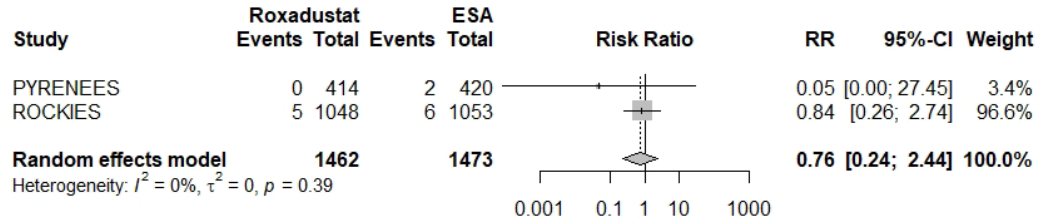
**Figure D11. MA of Heart Failure in PYRENEES, ROCKIES, and SIERRAS**




95% CI: 95% confidence interval, ESA: erythropoiesis-stimulating agent, $I^2$: I-squared, RR: risk ratio, $\tau^2$: between-study-variance estimator

Finally, we performed a MA of unstable angina reported for PYRENEES and ROCKIES.[23,24,29,52,53] As seen in Figure D12, the MA results suggest that the risk of unstable angina is not significantly different with roxadustat compared to ESAs (RR: 0.76; 95% CI: 0.24 to 2.44; $I^2$=0%).

**Figure D12. MAs of Unstable Angina in PYRENEES, ROCKIES, and SIERRAS**




95% CI: 95% confidence interval, ESA: erythropoiesis-stimulating agent, $I^2$: I-squared, RR: risk ratio, $\tau^2$: between-study-variance estimator

A pooled on-treatment analysis of HIMALAYAS, ROCKIES, and SIERRAS reported that roxadustat was not significantly different from epoetin alfa in the risk of MACE (HR: 0.96; 95% CI: 0.82 to 1.13) and all-cause mortality (HR: 0.96; 95% CI: 0.79 to 1.17) in the first 52 weeks.[36] However, the risk of MACE+ was significantly reduced with roxadustat compared to epoetin alfa (HR: 0.85; 95% CI: 0.74 to 0.98).[36] The incidence of the MACE+ components is shown in Table D9. As seen in Table D9, the difference reported between the MACE and MACE+ results is due to the inclusion of reductions in unstable angina requiring hospitalization and congestive heart failure requiring hospitalization.

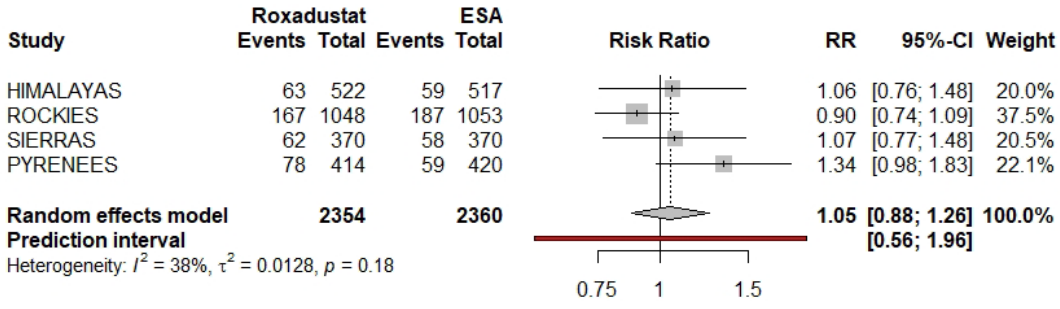
**Table D9. Incidence of MACE+ Components in Pooled Analysis of HIMALAYAS, ROCKIES, and SIERRAS**

| Outcome | Number of Events (%) | | RR (95% CI) |
|---|---|---|---|
| | Roxadustat (N=1940) | Epoetin Alfa (N=1940) | |
| All-Cause Mortality | 207 (10.7) | 232 (12.0) | 0.89 (0.75. 1.06) |
| MI | 103 (5.3) | 109 (5.6) | 0.95 (0.73, 1.23) |
| Stroke | 45 (2.3) | 50 (2.6) | 0.90 (0.60, 1.34) |
| Unstable Angina Requiring Hospitalization | 18 (0.9) | 22 (1.1) | 0.82 (0.44, 1.52) |
| Congestive Heart Failure Requiring Hospitalization | 120 (6.2) | 166 (8.6) | 0.72 (0.58, 0.91) |

95 CI: 95% confidence interval, MI: myocardial infarction, N: total number, RR: risk ratio

Importantly, the number of deaths reported in the individual RCTs exceeds that of the pooled analysis, and the pooled analysis did not include the fourth key RCT (PYRENEES). Thus, we performed a MA of all-cause mortality reported for HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS.[24] As seen in Figure D13, the MA results demonstrate that the risk of all-cause mortality is not significantly different with roxadustat compared to ESAs (RR: 1.05; 95% CI: 0.88 to 1.26; $I^2$=38%). However, the summary estimate is higher than was reported in the pooled analysis, likely due to PYRENEES's inclusion.

**Figure D13. MAs of All-Cause Mortality in HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS**




95% CI: 95% confidence interval, ESA: erythropoiesis-stimulating agent, $I^2$: I-squared, N: total number, No: number, RR: risk ratio

Importantly, these results should be interpreted with caution as the time points in which cardiovascular safety events were reported in the key RCTs are unclear at the time of this report.

Other RCTs with shorter durations were not powered to detect significant differences in cardiovascular safety events and reported low event rates (see Evidence Table 26 and Evidence Table 27).

***HRQoL***

PYRENEES assessed HRQoL with SF-36, EQ-5D-5L, Fact-An, and PGIC.[29,52] Higher scores on SF-36, EQ-5D-5L, and Fact-An indicate better quality of life. In the PGIC, patients rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse."

*SF-36*

There was no significant difference in mean CFB in SF-36 PF sub-score averaged over weeks 12 to 28 with roxadustat compared to ESAs (LSM difference: 0.21; 95% CI: -0.65 to 1.06). There was also no significant difference in mean CFB in SF-36 VT sub-score averaged over weeks 12 to 28 with roxadustat compared to ESAs (LSM difference: 0.86; 95% CI: -0.12 to 1.83). Further, mean CFB in SF-36 Physical Component score was not significantly different between the groups (LSM difference: 0.52; 95% CI: -0.21 to 1.25). Importantly, a MCID of 3 to 5 points was not reached in these assessments.[42]

*EQ-5D-5L VAS*

Mean CFB in EQ-5D-5L VAS score averaged over weeks 12 to 28 was numerically greater with roxadustat compared to ESAs (3.04 ± 14.91 vs. 2.74 ± 14.78, respectively), though statistical values were not reported. While a MCID for EQ-5D-5L VAS score has not been established in patients with CKD, in stroke patients undergoing rehabilitation,[44] oncology patients,[45] and patients with chronic obstructive pulmonary disease,[46] a MCID ranged from 8 to 12 points.

*FACT-An*

There was no significant difference in mean CFB in Total FACT-An score averaged over weeks 12 to 28 with roxadustat compared to ESAs (LSM difference: -0.11; 95% CI: -2.67 to 2.46). There was also no significant difference in mean CFB in FACT-An AnS averaged over weeks 12 to 28 with roxadustat compared to ESAs (LSM difference: 0.17; 95% CI: -1.08 to 1.43). Importantly, MCIDs of 6 points and 4 points for Total FACT-An and FACT-An AnS, respectively, were not reached.[47]

*PGIC*

The proportion of patients who rated their status as "very much improved," "much improved," and "minimally improved" was numerically greater with roxadustat compared to ESAs at week 104 (61.6% vs. 51.3%, respectively), though statistical values were not reported.

***Rescue Therapy***

There was no significant difference in the risk of rescue therapy to end of treatment (up to week 104) with roxadustat compared to ESAs (see Table D10) in PYRENEES.[24,29,52] Similarly, in ROCKIES, there was no significant difference in the risk of rescue therapy in the first 52 weeks with roxadustat compared to epoetin alfa (see Table D10).[23,24,53]

The risk of blood transfusion was significantly reduced with roxadustat compared to epoetin alfa for ROCKIES at the end of study and SIERRAS in the first 52 weeks (see Table D10).[23,24,52] In PYRENEES and HIMALAYAS, there were no significant differences in this endpoint with roxadustat compared to ESAs and epoetin alfa, respectively (see Table D10).[29,48] However, a pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS reported a significant reduction in this endpoint with roxadustat compared to epoetin alfa during treatment (HR: 0.82; 95% CI: 0.679 to 0.997).[48]

**Table D10. Rescue Therapy in HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS**

| | | HIMALAYAS | | PYRENEES | | ROCKIES | | SIERRAS | |
|---|---|---|---|---|---|---|---|---|---|
| | | Roxadustat (N=522) | Epoetin Alfa (N=513) | Roxadustat (N=413) | ESAs (N=420) | Roxadustat (N=1048) | Epoetin Alfa (N=1053) | Roxadustat (N=370) | Epoetin Alfa (N=371) |
| Risk of Rescue Therapy, HR (95% CI) | | NR | | 0.98 (0.66, 1.46)* | | 0.83 (0.64, 1.07)† | | NR | |
| Risk of Blood Transfusion, HR (95% CI) | | 1.26 (0.64, 1.07)‡ | | 0.87 (0.57, 1.31)* | | 0.26 (0.17, 0.41)† | | 0.67 (0.47, 0.97)† | |
| Monthly IV Iron Suppl., mg | Mean (SD) | 46.90 (8.10)¶ | 71.50 (7.50)¶ | 12.00 (47.60)# | 44.80 (88.60)# | 58.70 (236.1)§§ | 91.40 (225.6)§§ | 17.10 (53.40)¶¶ | 37.00 ± 106.80¶¶ |
| | LSM Diff. (95% CI); p-value | NR; p=0.0002 | | -48.70 (-70.30, -27.00); p<0.001 | | NR; p<0.001 | | NR; p=0.00091 | |

95% CI: 95% confidence interval, ESAs: erythropoiesis-stimulating agents, HR: hazard ratio, IV: intravenous, LSM: least squares mean, mg: milligram, N: total number, NR: not reported

*At end of treatment (up to week 104).

†In the first 52 weeks.

‡During treatment.

§At end of study.

¶At week 45 to 52.

#At week 53 to 104.

§§At week 35 to end of study.

¶¶Time period unclear.

HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS reported a significant reduction in mean monthly IV iron use at week 45 to 52, week 53 to 104, and week 36 to end of study, respectively, though the time period for SIERRAS is unclear at the time of this report (see Table D10).[23,24,29,34,52,53] Further, in PYRENEES, the risk of IV iron to end of treatment (up to 104 weeks) was significantly reduced with roxadustat compared to ESAs (HR: 0.37; 95% CI: 0.29 to 0.47).[24,29]

Chen 2019 reported no significant difference in the use of rescue therapy with roxadustat compared to epoetin alfa (HR: 1.68; 95% CI: 0.18 to 16.19).[30] In Chen 2017, no patients required rescue therapy (see Evidence Table 21).[27] Provenzano 2016 reported a numerical reduction in the use of IV iron with roxadustat compared to epoetin alfa, though statistical values were not reported (see Evidence Table 22).[32]

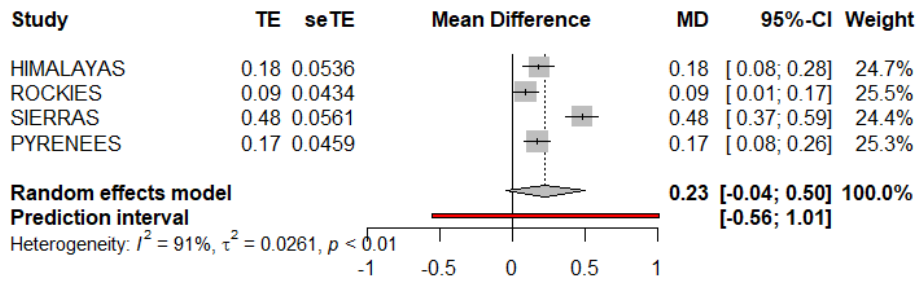
***Hospitalization***

In PYRENEES, the mean number of hospitalizations (included all non-HD hospitalizations) at end of treatment (up to week 104) was comparable with roxadustat compared to ESAs (0.9 ± 1.3 vs. 0.9 ± 1.5, respectively); however, statistical values were not reported[52] However, the mean number of days of hospitalization at end of treatment (up to week 104) was numerically greater with roxadustat compared to ESAs (12.19 days ± 34.12 vs. 7.87 days ± 22.95, respectively), though statistical values were not reported.[52] Further, the risk of hospitalization at end of treatment (up to week 104) was not significantly different with roxadustat compared to ESAs (HR: 1.55; 95% CI: 0.94 to 1.41).[52]

***Anemia***

Figure D9 shows the MA results on the primary outcome of mean CFB in Hb averaged over weeks 28 to 52 in HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS.[23,24,29,34] Though the individual key RCTs each reported a significant increase in Hb with roxadustat compared to ESAs, as seen in Figure D14, the summary estimate of our MA was 0.23 g/dL (95% CI: -0.04 to 0.50) with a wide confidence interval and high heterogeneity ($I^2$=91%; p<0.01). Sources of heterogeneity may be differences in baseline Hb and the small number of RCTs included in the MA.

**Figure D14. MA of Hb in HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS**




95% CI: 95% confidence interval, $I^2$: I-squared, MD: mean difference, seTE: standard error, $\tau^2$: between-study-variance estimator, TE: effect size

Chen 2019, Akizawa 2020, Provenzano 2016, Chen 2017, and the 1517-CL-0304 RCT also demonstrated that roxadustat does not significantly increase Hb compared to darbepoetin alfa and epoetin alfa at earlier time points (see Evidence Table 21 and Evidence Table 22).[27,30-33]

### *Measures of Inflammation and Iron Storage and Availability*

The results for hepcidin and TSAT are presented below, while the results for transferrin, soluble transferrin receptor, iron, total iron-binding capacity, and ferritin are presented in Evidence Table 20, Evidence Table 21, and Evidence Table 22.

*Hepcidin*

In PYRENEES, hepcidin was numerically reduced at the end of study (up to 108 weeks) with roxadustat compared to ESAs (-27.19 ng/mL ± 52.17 vs. -17.67 ng/mL ± 51.69, respectively), though statistical values were not reported.[24,29,52] In ROCKIES, mean CFB in hepcidin at week 24 was significantly reduced with roxadustat compared to epoetin alfa (-44.99 ng/mL vs. -16.77 ng/mL, respectively; p<0.001).[23] In contrast, in SIERRAS, there was no significant difference in mean CFB in hepcidin with roxadustat compared to epoetin alfa at 52 weeks (-95.53 ng/mL ± 148.27 vs. -66.66 ng/mL ± 141.61, respectively; p=0.06).[23] In a pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS, hepcidin was significantly reduced with roxadustat compared to epoetin alfa at 24 weeks (-60.35 ng/mL ± 134.55 vs. -34.08 ng/mL ± 137.37, respectively; p<0.0001).[54]

Results from other RCTs demonstrate a trend towards reduced hepcidin with roxadustat compared to ESAs. Chen 2019 and Akizawa 2020 reported numerically reduced hepcidin with roxadustat compared to epoetin alfa and darbepoetin alfa, respectively, at 27 weeks and end of treatment (up to 24 weeks), though statistical analyses were not reported.[30,31] Provenzano 2016 reported significantly reduced hepcidin with roxadustat compared to epoetin alfa at 19 weeks but not six weeks (see Evidence Table 21 and Evidence Table 22).[32] Further, Chen 2017 reported significantly

reduced hepcidin with a high-starting dose of roxadustat compared to epoetin alfa but not low, medium, or pooled roxadustat (see Evidence Table 22).[27]

Importantly, the clinical significance of the reported changes in hepcidin is uncertain.

*TSAT*

In PYRENEES, TSAT was numerically reduced at end of study (up to week 108) with roxadustat compared to ESAs (-5.47% ± 16.63 vs. -3.76% ± 17.81%, respectively), though statistical values were not reported.[24,29,52] In SIERRAS, the reduction in TSAT at week 52 was significantly smaller with roxadustat compared to epoetin alfa (-7.96% ± 13.70 vs. -9.78% ± 13.07, respectively; p=0.0341).[24] ROCKIES reported no significant difference in TSAT between week 24 and end of treatment with roxadustat compared to epoetin alfa (-1.92% vs. -2.44%, respectively; p=0.287).[23,24] HIMALAYAS reported numerically similar mean CFB in TSAT with roxadustat compared to epoetin alfa at 52 weeks (-2.10% ± 0.7 vs. -2.90% ± 0.5, respectively); however, these results should be interpreted with caution as they were obtained through digitization and statistical values were not reported.[24,34] In a pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS, mean CFB in TSAT was numerically greater with roxadustat compared to epoetin alfa at week 20 (-1.70% ± 13.70 vs. -2.70% ± 12.43, respectively); however, statistical values were not reported.[54]

Results from other RCTs suggest that roxadustat does not consistently lead to increased TSAT compared to ESAs, particularly at earlier time points. Chen 2019 reported a significantly smaller decrease in TSAT with roxadustat compared to epoetin alfa at 27 weeks (LSM difference: 4.2% ± 1.4; 95% CI: 1.5 to 6.9).[30] Akizawa 2020 also reported numerically similar findings, though statistical values were not reported (see Evidence Table 21).[31] In contrast, Provenzano 2016 reported no significant differences in TSAT with roxadustat compared epoetin alfa at six and 19 weeks, while Chen 2017 reported no significant differences in this outcome at six weeks (see Evidence Table 22).[27,32]

***Lipids***

*LDL-Cholesterol*

PYRENEES reported a significant reduction in mean CFB in LDL-cholesterol averaged over weeks 12 to 28 with roxadustat compared to ESAs (LSM difference: -14.70 mg/dL; 95% CI: -0.45 to -0.31).[24,29] Further, SIERRAS also reported a significant reduction in mean CFB in LDL-cholesterol averaged over weeks 12 to 28 with roxadustat compared to epoetin alfa (LSM difference: -14.67 mg/dL; 95% CI: -17.62 to -11.70).[24] ROCKIES reported a significant reduction in mean CFB in LDL-cholesterol at week 24 (LSM difference: -12.76 mg/dL; 95% CI: -0.39 to -0.27).[23,24] Further, a pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS reported a significant reduction in LDL-cholesterol averaged

over weeks 12 to 28 with roxadustat compared to epoetin alfa (LSM difference: -15.80 mg/dL; 95% CI: -17.54 to -14.06).[51]

Chen 2019 and Chen 2017 also reported significant reductions in LDL-cholesterol at earlier time points (see Evidence Table 21 and Evidence Table 22).[27,30]

However, the clinical significance of these reductions in LDL-cholesterol is uncertain.

*HDL-Cholesterol*

A pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS reported a significant reduction in HDL-cholesterol averaged over weeks 12 to 28 with roxadustat compared to epoetin alfa (LSM difference: -8.99 mg/dL ± 2.82; p<0.0001).[51]

Chen 2019 and Chen 2017 reported significant reductions in HDL-cholesterol at earlier time points with roxadustat compared to epoetin alfa (see Evidence Table 21 and Evidence Table 22).[27,30]

However, the clinical significance of these reductions in HDL-cholesterol is uncertain.

## Harms

Importantly, the current package insert for roxadustat in Japan warns that roxadustat may cause serious thromboembolism, including cerebral infarction, MI, and pulmonary embolism, with a possible fatal outcome.[55] Cardiovascular safety events in the key RCTs are discussed above for DI- and DD-CKD populations.

***DI-CKD***

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): Most TEAEs were of mild-to-moderate severity (see Evidence Table 13).[20] The most commonly reported TEAEs included ESKD, hypertension, decrease in eGFR, and peripheral edema. As seen in Table D11, the incidence of any TEAE was marginally lower with roxadustat compared to darbepoetin alfa (91.6% vs. 92.5%, respectively), while the incidence of serious TEAEs was higher with roxadustat (64.7% vs. 61.8%, respectively). Further, the incidence of discontinuation due to TEAEs was higher with roxadustat compared to placebo (7.7% vs. 3.8%, respectively). Serious adverse events reported included all-cause mortality and cardiovascular events, which are presented above.

**Table D11. Adverse Events in DOLOMITES, ALPS, ANDES, and OLYMPUS**

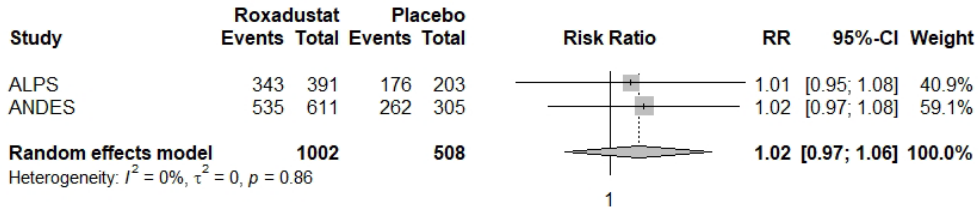
| | DOLOMITES | | ALPS | | ANDES | | OLYMPUS | |
|---|---|---|---|---|---|---|---|---|
| | Roxadustat (N=323) | Darbepoetin alfa (N=293) | Roxadustat (N=391) | Placebo (N=203) | Roxadustat N=611) | Placebo (N=305) | Roxadustat (N=1384) | Placebo (N=1377) |
| Any TEAEs, n (%) | 296 (91.6) | 271 (92.5) | 343 (87.7) | 176 (86.7) | 535 (87.6) | 176 (85.9) | NR | NR |
| Serious TEAEs, n (%) | 209 (64.7) | 181 (61.8) | 241 (61.6) | 115 (56.7) | 203 (33.2) | 91 (29.8) | NR | NR |
| D/C due to TEAEs, n (%) | 25 (7.7)* | 11 (3.8)* | 23 (5.9)* | 8 (3.9)* | NR | NR | 78 (5.6)* | 57 (4.1)* |

D/C: discontinuation, N: total number, NR: not reported, TEAE: treatment-emergent adverse event
*Due to adverse events

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): Most TEAEs in the key RCTs were of mild-to-moderate severity (see Evidence Table 13).[20,22,24,34] The most commonly reported TEAEs included ESKD, decrease in eGFR, nausea, hyperkalemia, and hypertension. The time to first exacerbation of hypertension (systolic blood pressure [SBP] ≥170 mmHg or diastolic blood pressure [DBP] ≥110 mmHg and an increase from baseline ≥20 mmHg [SBP] or ≥15 mmHg [DBP]) was not significantly different with roxadustat compared to placebo (HR: 1.12; 95% CI: 0.95 to 1.32).

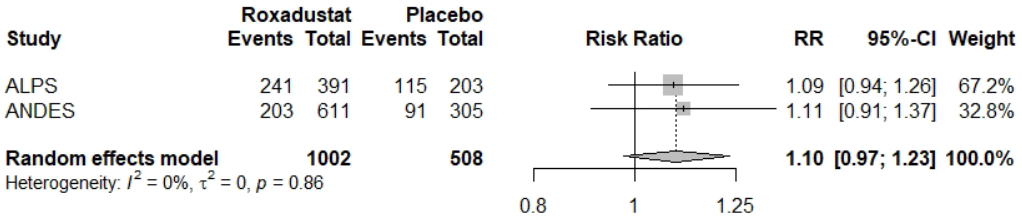
We conducted MAs of any TEAE and serious TEAEs for ALPS and ANDES and a MA of discontinuation due to adverse events for ALPS and OLYMPUS.[23,24,29,34] As seen in Figures D15 and D16, there were no significant differences in the risk of any TEAE (RR: 1.02 95% CI: 0.97 to 1.06; $I^2$=0%) or serious TEAE (RR: 1.10; 95% CI: 0.97 to 1.23; $I^2$=0%) with roxadustat compared to placebo.

**Figure D15. MA of Any TEAE in ALPS and ANDES**




95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, $I^2$: I-squared, N: total number, RR: risk ratio

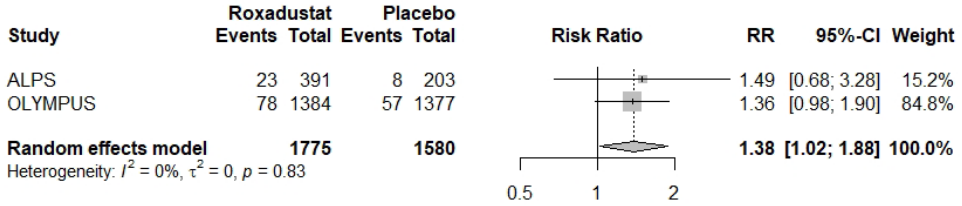
**Figure D16. MA of Serious TEAEs in ALPS and ANDES**




95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, $I^2$: I-squared, N: number: No.: number, RR: risk ratio, $\tau^2$: between-study-variance estimator

However, as seen in Figure D17, the risk of discontinuation due to adverse events was significantly greater with roxadustat compared to placebo (RR: 1.38; 95% CI: 1.02 to 1.88; $I^2$=0%).

**Figure D17. MA of Discontinuation Due to Adverse Events in ALPS and OLYMPUS**




95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, $I^2$: I-squared, N: number: No.: number, RR: risk ratio, $\tau^2$: between-study-variance estimator

Serious adverse events reported included all-cause mortality and cardiovascular events, which are presented above. Importantly, results for adverse events reported in the key RCTs should be interpreted with caution as the timepoints in which they were reported are unclear at the time of this report.

Other RCTs reported similar findings (see Evidence Table 14 and Evidence Table 15).[25-28]

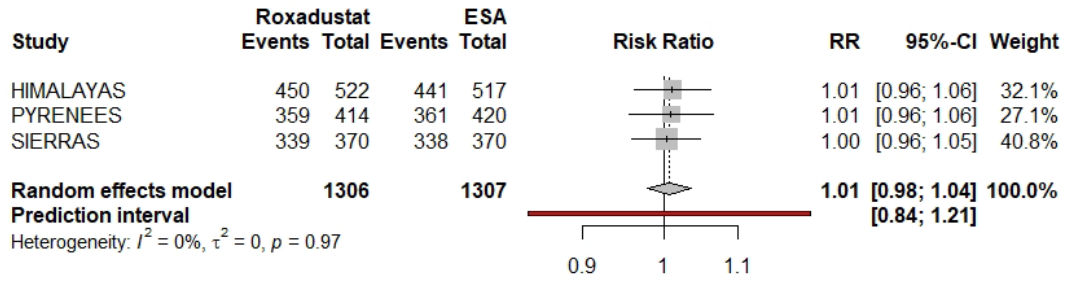
***DD-CKD***

Most TEAEs in the key RCTs of roxadustat were of mild-to-moderate severity (see Evidence Table 28).[23,24,29,34] The most commonly reported TEAEs included nausea, diarrhea, hyperkalemia, and hypertension. In a pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS, the time to first exacerbation of hypertension (SBP ≥170 mmHg or DBP ≥110 mmHg and an increase from baseline ≥20 mmHg [SBP] or ≥15 mmHg [DBP]) was not significantly different with roxadustat compared to epoetin alfa (HR: 1.06; 95% CI: 0.93 to 1.21).

We conducted MAs of any TEAE and serious TEAEs for HIMALAYAS, PYRENEES, and SIERRAS and a MA of discontinuation due to adverse events for HIMALAYAS, PYRENEES, and ROCKIES.[23,24,29,34] As

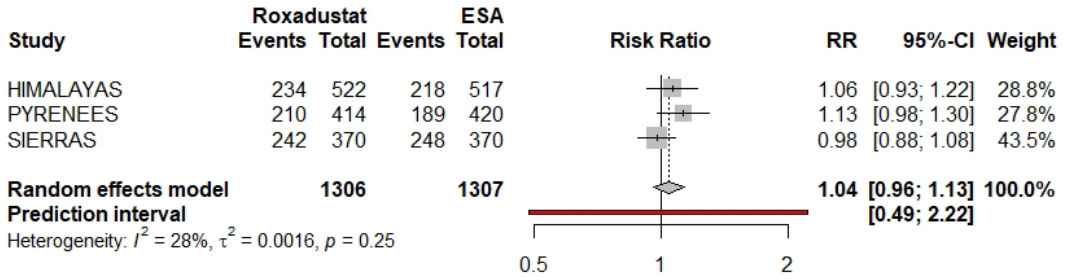
seen in Figures D18 and D19, there were no significant differences in the risk of any TEAE (RR: 1.01; 95% CI: 0.98 to 1.04; $I^2$=0%) or serious TEAE (RR: 1.04; 95% CI: 0.96 to 1.13; $I^2$=28%) with roxadustat compared to ESAs.

**Figure D18. MA of Any TEAE in HIMALAYAS, PYRENEES, and SIERRAS**




95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, $I^2$: I-squared, N: number: No.: number, RR: risk ratio, $\tau^2$: between-study-variance estimator

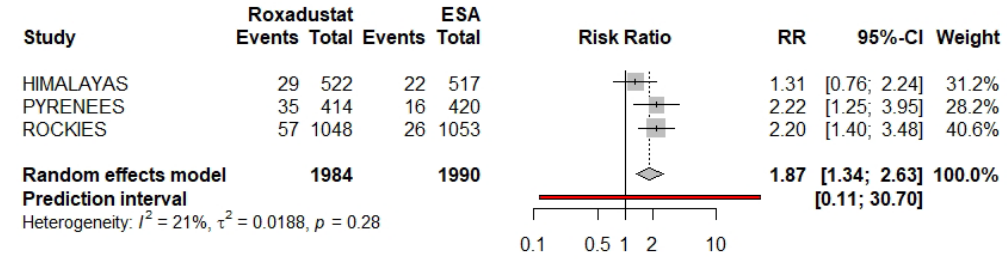
**Figure D19. MA of Serious TEAEs in HIMALAYAS, PYRENEES, and SIERRAS**




95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, $I^2$: I-squared, N: number: No.: number, RR: risk ratio, $\tau^2$: between-study-variance estimator

However, as seen in Figure D20, the risk of discontinuation due to adverse events was significantly greater with roxadustat compared to ESAs (RR: 1.87; 95% CI: 1.34 to 2.63; $I^2$=21%).

**Figure D20. MA of Discontinuation Due to Adverse Events in HIMALAYAS, PYRENEES, and ROCKIES**




95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, $I^2$: I-squared, N: number: No.: number, RR: risk ratio, $\tau^2$: between-study-variance estimator

Serious adverse events reported included all-cause mortality and cardiovascular events, which are presented above. Importantly, results for adverse events reported in the key RCTs should be interpreted with caution as the timepoints in which they were reported are unclear at the time of this report.

Other RCTs reported similar findings (see Evidence Table 29 and Evidence Table 30).[27,30-33]

## D3. Evidence Tables

Evidence Tables 1-39 begin on the following page.

**Evidence Table 1. Study Design**

| Trial Name (NCT), Author | Study Design & Follow-Up Duration | Location | N | Arms | Key Inclusion Criteria | Key Exclusion Criteria | Definitions |
|---|---|---|---|---|---|---|---|
| **ALPS**<br><br>**NCT01887600**[1] | Phase III, multicenter, double-blind, placebo-controlled, randomized trial<br><br>Follow-Up:<br>– Treatment period: 52 to 104 weeks<br>– Post-treatment Follow-up period: 4 weeks | Global | 597 | **Roxadustat (N=394)**<br>Weight-based starting doses:<br>– ≥45 to ≤70 kg: 70 mg TIW<br>– >70 to ≤160 kg: 100mg TIW<br><br>**Placebo (N=203)** | – ≥18 years of age<br>– CKD diagnosis (stage 3-5) not on dialysis<br>– eGFR <60 mL/min/1.73 $m^2$<br>– Hb ≤10.0 g/dL<br>– Ferritin ≥30 ng/mL<br>– TSAT ≥5% | – ESA treatment within 12 weeks<br>– >1 dose of IV iron within 12 weeks<br>– Treatment with iron-chelating agents within 4 weeks<br>– Blood transfusion within 8 weeks<br>– NYHA Class III or IV congestive heart failure<br>– Myocardial infarction, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event within 12 weeks<br>– Uncontrolled hypertension | **Hb Response:**<br>Hb ≥11.0 g/dL and change ≥1.0 g/dL if baseline Hb >8.0 g/dL; or change ≥2.0 g/dL if baseline Hb ≤8.0 g/dL at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy |
| **ANDES**<br><br>**NCT01750190**[2] | Phase III, multicenter, double-blind, placebo-controlled, randomized trial<br><br>Follow-Up:<br>– Treatment period: 52 to 156 weeks<br>– Post-treatment Follow-up period: 4 weeks | Global | 922 | **Roxadustat (N=616)**<br>Weight-based starting doses:<br>– ≥45 to ≤70 kg: 70 mg TIW<br>– >70 to ≤160 kg: 100mg TIW<br><br>**Placebo (N=306)** | – ≥ 18 years of age<br>– CKD diagnosis (stage 3-5) not on dialysis<br>– eGFR <60 mL/min/1.73 $m^2$<br>– Hb ≤10.0 g/dL<br>– Ferritin ≥30 ng/mL<br>– TSAT ≥5% | – ESA treatment within 12 weeks<br>– >1 dose of IV iron within 12 weeks<br>– Blood transfusion within 8 weeks<br>– Severe congestive heart failure, recent heart attack, stroke, seizure, or blood clot<br>– Uncontrolled blood pressure<br>– Renal cell carcinoma<br>– History of malignancy | **Hb Response:**<br>Hb ≥11.0 g/dL and change ≥1.0 g/dL if baseline Hb >8.0 g/dL; or change ≥2.0 g/dL if baseline Hb ≤8.0 g/dL at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy |
| **DOLOMITES**<br><br>**NCT02021318**[3] | Phase III, multicenter, open-label, active-controlled, randomized trial<br><br>Follow-Up:<br>– Treatment period: 104 weeks | Europe | 616 | **Roxadustat (N=323)**<br>Weight-based starting dose<br><br>**Darbepoetin alfa (N=293)**<br>Dosed according to European Summary of | – ≥ 18 years of age<br>– CKD (stage 3-5) not on dialysis<br>– eGFR <60 ml/min/1.73 $m^2$<br>– Hb ≤10.5 g/dL<br>– Suitable for ESA treatment | – ESA treatment within 12 weeks prior to randomization<br>– Received any IV iron within 6 weeks prior to randomization<br>– Treatment with iron-chelating agents within 4 weeks prior to randomization<br>– Blood transfusion within 8 weeks prior to randomization | **Hb Response:**<br>Hb ≥11.0 g/dL and change ≥1.0 g/dL if baseline Hb >8.0 g/dL; or change ≥2.0 g/dL if baseline Hb ≤8.0 g/dL at 2 consecutive visits separated by at least 5 days during the |

| Trial Name (NCT), Author | Study Design & Follow-Up Duration | Location | N | Arms | Key Inclusion Criteria | Key Exclusion Criteria | Definitions |
|---|---|---|---|---|---|---|---|
| | – Post-treatment Follow-up period: 4 weeks | | | Product Characteristics | | – NYHA Class III or IV congestive heart failure<br>– Myocardial infarction, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event within 12 weeks prior to randomization<br>– History of malignancy | first 24 weeks of treatment without rescue therapy |
| **OLYMPUS**<br><br>**NCT02174627**[4] | Phase III, double-blind, placebo controlled, randomized trial<br><br>Follow-Up:<br>– Treatment period: up to 4 years<br>– Post-treatment Follow-up: 4 weeks | Global | 2781 | **Roxadustat (N=1,393)**<br>– 70 mg TIW<br><br>**Placebo (N=1,388)** | – ≥ 18 years of age<br>– CKD (stage 3-5) not on dialysis<br>– eGFR <60 mL/min/1.73 $m^2$<br>– Hb <10.0 g/dL<br>– Ferritin ≥50 ng/mL<br>– TSAT ≥15 % | – ESA treatment within 6 weeks prior to randomization<br>– Blood transfusion during screening period<br>– NYHA Class III or IV congestive heart failure<br>– Myocardial infarction, acute coronary syndrome, stroke, seizure or a thrombotic/thromboembolic event within 12 weeks<br>– History of prostate cancer, breast cancer or any other malignancy | **Hb Response:** Hb ≥11.0 g/dL and change ≥1.0 g/dL if baseline Hb >8.0 g/dL; or change ≥2.0 g/dL if baseline Hb ≤8.0 g/dL at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy |
| **FGCL-4592-808**<br><br>**NCT02174627**<br><br>**Chen 2019**[5] | Phase III, multicenter, double-blind, placebo controlled, randomized and open-label trial<br><br>Follow-Up:<br>– Randomized phase: 8 weeks<br>– Open-label phase: 18 weeks | China | 154 | **Roxadustat (n=102)**<br>Weight-based starting doses:<br>– ≥40-<60 kg: 70 mg TIW<br>– ≥60 kg: 100 mg TIW<br><br>**Placebo (n=52)** | – 18 – 75 years of age<br>– CKD (stage 3-5) not on dialysis<br>– eGFR <60 mL/min/1.73 $m^2$<br>– Hb ≥7.0 g/dL and <10.0 g/dL<br>– ALT and AST < 1.5x ULN<br>– No ESA treatment ≥5 weeks prior to randomization | – IV iron supplementation during the screening period<br>– Blood transfusion within 12 weeks prior to day 1 or anticipated need for transfusion<br>– NYHA Class III or IV congestive heart failure<br>– Myocardial infarction, acute coronary syndrome, stroke, seizure, or a thromboembolic event within 52 weeks<br>– Systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg within 2 weeks prior to randomization<br>– History of malignancy | |

| Trial Name (NCT), Author | Study Design & Follow-Up Duration | Location | N | Arms | Key Inclusion Criteria | Key Exclusion Criteria | Definitions |
|---|---|---|---|---|---|---|---|
| **1517-CL-0310**<br><br>**NCT02988973**[6] | Phase III, randomized, open label, active-controlled trial<br><br>Follow-Up:<br>– Cohorts 1 and 3: 52 weeks<br>– Cohort 2: 24 weeks | Japan | 334 | **Roxadustat (N=NR)**<br>– Converted from rHuEPO or darbepoetin alfa (Cohort 1)<br>– Converted from epoetin beta pegol (Cohort 3)<br><br>**Darbepoetin alfa, (N=NR)**<br>– Converted from rHuEPO or darbepoetin alfa (Cohort 2) | – CKD not on dialysis<br>– Hb ≥10.0 g/dL and ≤12.0 g/dL<br>– TSAT ≥20% or ferritin ≥100 ng/mL<br>– Receiving ESA by SC injection and whose Hb values are considered stable | – Blood transfusion and/or a surgical procedure considered to promote anemia and/or ophthalmological surgery within 4 weeks<br>– Concurrent congestive heart failure (NYHA Class III or higher)<br>– History of hospitalization for treatment of stroke, myocardial infarction, or pulmonary embolism within 12 weeks<br>– Uncontrolled hypertension<br>– Previous or current malignant tumor (no recurrence for at least 5 years is eligible)<br>– Concurrent untreated retinal neovascular lesion or macular edema | |
| **FGCL-SM4592-017**<br><br>**NCT00761657**<br><br>**Besarab 2015**[7] | Phase IIa, single-blind, placebo-controlled, multicenter, dose-ranging trial<br><br>Follow-Up:<br>– Treatment period: 4 weeks<br>– Post-Treatment Follow-up: 8 weeks | US | 116 | **Roxadustat (N=88)**<br>– 0.7 mg/kg BIW<br>– 0.7 mg/kg TIW<br>– 1.0 mg/kg BIW<br>– 1.0 mg/kg TIW<br>– 1.5 mg/kg BIW<br>– 1.5 mg/kg TIW<br>– 2.0 mg/kg BIW<br>– 2.0 mg/kg TIW<br><br>**Placebo (N=28)** | – 18 – 80 years of age<br>– CKD (stage 3 or 4) not on dialysis<br>– eGFR ≥15-≤59 ml/min/1.73 $m^2$<br>– Hb < 11.0 g/dL | – History of chronic liver disease<br>– ESA treatment within 60 days<br>– IV iron supplementation within 60 days<br>– Red blood cell transfusion within 12 weeks<br>– NYHA Class III or IV congestive heart failure<br>– Myocardial infarction or acute coronary syndrome within 3 months<br>– Thrombolytic events within 4 weeks<br>– Uncontrolled hypertension<br>– Any history of malignancy or genetic predisposition for developing cancer | **Hb Response:**<br>Change from BL Hb of ≥1 g/dL at any time from day 1 of treatment through 2 weeks of follow-up |
| **FGCL-4592-047**<br><br>**NCT01599507**<br><br>**Chen 2017**[8] | Phase IIb, double-blind, placebo controlled, parallel-arm trial<br><br>Follow-Up: | China | 91 | **Roxadustat, low dose (N=30)**<br>– ≥40-<60 kg: 1.1-1.75 mg/kg TIW | – 18 – 80 years of age<br>– CKD (stage 3 or 4) not on dialysis<br>– eGFR ≥10 - <60 ml/min/1.73$m^2$<br>– Hb <10.0 g/dL | – ESA treatment within 12 weeks<br>– IV iron supplementation within 4 weeks<br>– RBC transfusion within 12 weeks or anticipated need<br>– NYHA II or IV congestive heart failure | **Hb Response:**<br>Hb rise of _1.0 g/dL from baseline at any time |

| Trial Name (NCT), Author | Study Design & Follow-Up Duration | Location | N | Arms | Key Inclusion Criteria | Key Exclusion Criteria | Definitions |
|---|---|---|---|---|---|---|---|
| | – Treatment period: 8 weeks<br>– Post-treatment follow-up: NR | | | **Roxadustat, high dose (N=31)**<br>– >60-≤80 kg: 1.50-2.25 mg/kg TIW<br>– >80-≤100 kg: 1.50-2.25 mg/kg TIW<br><br>**Placebo (n=30)** | | – Thromboembolic event within 12 weeks<br>– History of malignancy | |
| **1517-CL-0303**<br><br>**NCT01964196**<br><br>**Akizawa 2019[9]** | Phase II, double-blind, placebo-controlled, parallel-arm trial<br><br>Follow-Up:<br>– Fixed-dose period: 6 weeks<br>– Titration period: 18 weeks | Japan | 107 | Fixed-dose period<br>**Roxadustat (N=80)**<br>– 50 mg TIW<br>– 70 mg TIW<br>– 100 mg TIW<br><br>**Placebo (n=27)**<br><br>Titration period<br>**Roxadustat (N=55)**<br>– 50 mg QW<br>– 70 mg QW<br>– 100 mg QW<br>– 50 mg TIW<br>– 70 mg TIW<br>– 100 mg TIW<br><br>**Placebo (N=1)** | – 20 – 74 years of age<br>– CKD not on dialysis<br>– eGFR ≤89 ml/min/1.73 $m^2$<br>– Hb <10.0 g/dL<br>– TSAT ≥5%<br>– Ferritin ≥30 ng/mL | – ESA treatment within 6 weeks<br>– NYHA Class III or higher congestive heart failure<br>– History of hospitalization for stroke, myocardial infarction or lung infarction within 24 weeks<br>– Uncontrolled hypertension<br>– History of malignancies | **Hb response:**<br>Hb ≥10.0 g/dL and increase in Hb from baseline ≥1 g/dL |

BIW: twice weekly, CKD: chronic kidney disease, dL: deciliter, eGFR: estimated glomerular filtration rate, ESA: erythropoiesis-stimulating agent, g: gram, Hb: hemoglobin, IV: intravenous, kg: kilogram, $m^2$: square meter, mg: milligram, min: minute, ml: milliliter, N: total number, NYHA: New York Heart Association, QW: weekly, TIW: thrice weekly, TSAT: transferrin saturation, ULN: upper limit of normal.

**Evidence Table 2. Baseline Characteristics – Key Trials**

| Trial | | ALPS[1,2] | | ANDES[2] | | DOLOMITES[3] | | OLYMPUS[2,4] | |
|---|---|---|---|---|---|---|---|---|---|
| Arm | | ROX (N=391) | PBO (N=203) | ROX (N=616) | PBO (N=306) | ROX (N=323) | DAR (N=293) | ROX (N=1384) | PBO (N=1377) |
| Age, Mean Years (SD) | | 60.6 (13.5) | 61.7 (13.8) | 64.9 (NR) | 64.8 (NR) | 66.8 (13.6) | 65.7 (14.4) | 60.9 (14.7) | 62.4 (14.1) |
| Male, n (%) | | 169 (43.2) | 99 (48.8) | (39.1) | (42.5) | 145 (44.9) | 129 (44.0) | 564 (40.8) | 603 (43.8) |
| White, n (%) | | 335 (85.7) | 182 (89.7) | NR | NR | 306 (94.7) | 281 (95.9) | 623 (45.0) | 611 (44.4) |
| eGFR, mL/min/1.73 $m^2$, Mean (SD) | | 16.5 (10.2) | 17.2 (11.7) | 21.9 (11.5) | 22.4 (11.4) | 20.3 (11.5) | 20.3 (10.7) | 19.7 (11.7) | 20 (11.7) |
| Hb, Mean g/dL (SD) | | 9.08 (0.8) | 9.10 (0.7) | 9.1 (0.75) | 9.09 (0.69) | 9.55 (0.80) | 9.55 (0.7) | 9.1 (0.7) | 9.1 (0.7) |
| Transferrin Saturation, Mean % (SD) | | NR | | 26.4 (10.9) | 26.2 (11.3) | NR | | NR | |
| Ferritin, Mean ng/mL (SD) | | NR | | 308.6 (388.3) | 308.4 (352.5) | NR | | NR | |
| Iron Status - Replete*, n (%) | | NR | | 373 (60.6) | 170 (55.6) | 182 (56.3) | 152 (51.9) | 815 (58.5) | 805 (58.0) |
| CRP | Mean mg/L (SD) | NR | | NR | | NR | | NR | |
| | >ULN†, n (%) | NR | | 156 (25.3) | 81 (26.5) | 111 (34.7) | 116 (39.6) | NR | |
| LDL-C, Mean mg/dL (SD) | | 115.62 (49.88) | 111.37 (44.08) | NR | | 100.6 (40.0) | 102.80 (39.80) | NR | |
| No data reported for the following baseline characteristics: Hepcidin, transferrin, soluble transferrin receptor, serum iron, total iron binding capacity, HDL-cholesterol, total cholesterol. | | | | | | | | | |

DAR: darbepoetin alfa, CRP: c-reactive protein, dL: deciliter, eGFR: estimated glomerular filtration rate, g: gram, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, mg: milligram, min: minute, mL: milliliter, n: number, N: total number, ng: nanogram, NR: not reported, NYHA: New York Heart Association, PBO: placebo, ROX: roxadustat, SD: standard deviation

*: Ferritin ≥100 ng/mL and TSAT ≥20%

†: ULN defined as 4.9 mg/L

**Evidence Table 3. Baseline Characteristics – Other Phase 3 Trials**

| Trial | | FGCL-4592-808[5] | | 1517-CL-0310[6] | |
|---|---|---|---|---|---|
| Arm | | ROX (N=101) | PBO (N=51) | ROX (N=NR) | DAR (N=NR) |
| **Age, Mean Years (SD)** | | 54.7 (13.3) | 53.2 (13.1) | NR | |
| **Male, n (%)** | | 36 (36.0) | 20 (39.0) | NR | |
| **White, n (%)** | | 0 (0)† | 0 (0)† | 0 (0)† | 0 (0)† |
| **eGFR, ml/min/1.73 $m^2$, mean (SD)** | | 16.5 (8.0) | 14.5 (7.6) | NR | |
| **Hb, Mean g/dL (SD)** | | 8.9 (0.8) | 8.9 (0.7) | NR | |
| **Hepcidin, Mean ng/mL (SD)** | | 95.9 (72.4) | 114.7 (85.7) | NR | |
| **Transferrin Saturation, Mean % (SD)** | | 20.6 (9.2) | 23.0 (11.1) | NR | |
| **Ferritin, Mean ng/mL (SD)** | | 191.4 (200.5) | 266.2 (236.7) | NR | |
| **C-Reactive Protein** | **Mean mg/L (SD)** | NR | | NR | |
| | **>ULN*, n (%)** | 12 (12.0) | 5 (10.0) | NR | |
| **Total Cholesterol, Mean mg/dL (SD)** | | 172.8 (45.80) | 181.40 (49.0) | NR | |
| **LDL-C, Mean mg/dL (SD)** | | 97.8 (34.0) | 105.2 (42.2) | NR | |
| **HDL-C, Mean mg/dL (SD)** | | 49.9 (14.6) | 48.6 (16.3) | NR | |
| No data reported for the following baseline characteristics: transferrin, soluble transferrin receptor, serum iron, iron status – replete | | | | | |

DAR: darbepoetin alfa, dL: deciliter, eGFR: estimated glomerular filtration rate, g: gram, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, $m^2$: square meter, mg: milligram, min: minute, mL: milliliter, n: number, N: total number, ng: nanogram, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation.

*: ULN defined as of 4.9 mg/L

†: All patients were Asian

**Evidence Table 4. Baseline Characteristics – Phase II Trials**

| Trial | FGCL-SM4592-017[7] | | | | | | | FGCL-4592-047[8] | | | 1517-CL-0303[9] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm | ROX, 1.0 mg/kg BIW (N=12) | ROX, 1.0 mg/kg TIW (N=9) | ROX, 1.5 mg/kg BIW (N=10) | ROX, 1.5 mg/kg TIW (N=11) | ROX, 2.0 mg/kg BIW (N=11) | ROX, 2.0 mg/kg TIW (N=12) | PBO (N=28) | ROX, Low-Dose (N=30) | ROX, High-Dose (N=31) | PBO (N=30) | ROX, 50 mg (N=27) | ROX, 70 mg (N=26) | ROX, 100 mg (N=27) | PBO (N=27) |
| Age, Mean Years (SD) | 69.5 (Range: 52 - 80) | 67 (Range: 54 - 79) | 63.8 (Range: 52 - 77) | 63.5 (Range: 49 - 72) | 64.3 (Range: 53 - 82) | 66.8 (Range: 49 - 76) | 68.6 (Range: 56 - 79) | 48.1 (13.0) | 49.6 (14.8) | 51.4 (11.9) | 67.3 (7.7) | 60.8 (8.8) | 65.0 (8.5) | 61.9 (10.6) |
| Male, n (%) | 4 (33.3) | 6 (66.7) | 4 (40.0) | 1 (9.1) | 3 (27.3) | 3 (25.0) | 16 (57.1) | 8 (26.7) | 10 (32.3) | 8 (26.7) | 14 (51.9) | 14 (53.8) | 11 (40.7) | 11 (40.7) |
| White, n (%) | 6 (50.0) | 5 (55.6) | 7 (70.0) | 4 (36.4) | 8 (72.7) | 6 (50.0) | 15 (53.6) | 0 (0)‡ | 0 (0)‡ | 0 (0)‡ | 0 (0)‡ | 0 (0)‡ | 0 (0)‡ | 0 (0)‡ |
| eGFR, ml/min/1.73 $m^2$, Mean (SD) | 38.0 (15.5) | 35.2 (9.7) | 27.9 (8.2) | 40.1 (15.3) | 34.7 (15.1) | 32.7 (9.9) | 31.4 (12.4) | 21.1 (10.2) | 17.7 (8.6) | 23.0 (13.4) | 15.8 (6.3) | 17.3 (9.5) | 15.9 (7.5) | 16.3 (8.5) |
| Hb, Mean g/dL (SD) | 10.4 (1.5) | 10.6 (0.9) | 10.3 (0.6) | 10.1 (0.7) | 10.3 (1.0) | 10.1 (1.1) | 10.3 (0.9) | 8.8 (0.9) | 8.8 (0.9) | 8.9 (0.8) | 9.4 (0.6) | 9.4 (0.6) | 9.4 (0.5) | 9.3 (0.7) |
| Hepcidin, Mean ng/mL (SD) | NR | | | | | | | 69.0 (13.1) | 73.9 (12.1) | 69.9 (8.7) | 37.8 (21.3) | 45.9 (25.8) | 36.3 (25.3) | 40.9 (26.2) |
| Transferrin, Mean mg/L (SD) | NR | | | | | | | 2.33 (0.49) | 2.19 (0.35) | 2.16 (0.45) | NR | | | |
| Transferrin Saturation, Mean % (SD) | 24.0 (9.4) | 23.5 (5.2) | 31.1 (8.1) | 25.8 (6.5) | 30.0 (9.3) | 31.6 (11.0) | 28.3 (6.8) | 22.1 (11.4) | 24.2 (8.8) | 21.9 (6.3) | 28.3 (8.2) | 29.7 (10.0) | 31.1 (11.8) | 26.8 (10.6) |
| Soluble Transferrin Receptor, Mean mg/L (SD) | NR | | | | | | | 3.7 (1.9) | 3.5 (1.4) | 3.5 (1.2) | NR | | | |
| Serum Iron, Mean µg/dL (SD) | 69.1 (17.5) | | | | | | 71.1 (19.7) | 61.0 (24.3) | 64.9 (20.7) | 58.1 (14.8) | NR | | | |
| Total Iron Binding Capacity, Mean µg/dL (SD) | 246.3 (43.5) | | | | | | 248.5 (51.6) | 263.0 (52.0) | 242.0 (37.0) | 240.0 (49.0) | 265.92 (54.75)# | 254.19 (43.58)# | 265.92 (50.28)# | 253.63 (26.82)# |
| Ferritin, Mean ng/mL (SD) | 174.0 (181.0) | 167.0 (178.0) | 228.0 (184.0) | 184.0 (101.0) | 242.0 (218.0) | 190.0 (89.4) | 228.0 (193.0) | 201.0 (252.0) | 184.0 (194.0) | 221.0 (181.0) | 119.7 (61.0) | 144.4 (99.7) | 129.8 (89.3) | 125.4 (74.1) |
| CRP Mean mg/L (SD) | NR | | | | | | | 4.0 (12.8) | 1.9 (3.8) | 1.5 (2.2) | NR | | | |

| Trial | | FGCL-SM4592-017[7] | FGCL-4592-047[8] | | | 1517-CL-0303[9] |
|---|---|---|---|---|---|---|
| | **>ULN†, n (%)** | | NR | | | |
| **Total Cholesterol, Mean mg/dL (SD)** | | NR | 164.0 (33.0) | 169.0 (45.0) | 183.0 (52.0) | NR |
| **LDL-C, Mean mg/ dL (SD)** | | NR | 96.0 (24.0) | 110.0 (36.0) | 115.0 (40.0) | NR |
| **HDL-C, Mean mg/ dL (SD)** | | NR | 54.0 (20.0) | 44.0 (17.0) | 48.0 (19.0) | NR |
| No data reported on the following baseline characteristics: number of patients who are iron replete, non-HDL-cholesterol | | | | | | |

CRP: C-reactive protein, DAR: darbepoetin alfa, dL: deciliter, eGFR: estimated glomerular filtration rate, g: gram, HDL-C: high-density lipoprotein cholesterol, L: liter, LDL-C: low-density lipoprotein cholesterol, µg: microgram, mg: milligram, min: minute, mL: milliliter, n: number, N: total number, ng: nanogram, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation

***:** Data for ROX, 0.7 mg/kg BIW and ROX, 0.7 mg/kg TIW not abstracted

†: ULN defined as 4.9 mg/L

‡: All patients were Asian

#: Converted from µmol/L to µg/dL

**Evidence Table 5. Efficacy Outcomes – Key Trials**

| Trial | | | ALPS[1,2] | | ANDES[2] | | DOLOMITES[3] | | OLYMPUS[2,4,10] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | ROX | PBO | ROX | PBO | ROX | DAR | ROX | PBO |
| Change in Hb, g/dL | Timepoint | | Average of 28 - 52 Weeks | | Average of 28 - 52 Weeks | | Average of 28 - 36 Weeks | | Average of 28 - 52 Weeks | |
| | N | | 312 | 146 | 608 | 306 | 323 | 293 | 1334 | 1330 |
| | Mean (SD) | | 2.00 (0.95) | 0.30 (0.98) | 2.00 (0.95) | 0.16 (0.90) | LSM: 1.85 (NR) | LSM: 1.84 (NR) | LSM: 1.75 (0.03) | LSM: 0.40 (0.03) |
| | Between Group Diff. | LSM (95% CI), p-value | 1.69 (1.52, 1.86), <0.001 | | 1.85 (1.74, 1.97), <0.001 | | 0.02 (-0.13, 0.16), NR | | 1.35 (1.27, 1.43), <0.001 | |
| Hb Response | Timepoint | | 24 Weeks | | | | | | | |
| | N | | 389 | 203 | 616 | 306 | 286 | 273 | 1371 | 1357 |
| | n (%) | | 308 (79.2) | 20 (9.9) | 530 (86.0) | 20 (6.60) | 256 (89.5) | 213 (78) | 1056 (77.0) | 115 (8.5) |
| | Between Group Diff. | % (95% CI), p-value | 69.3 (NR), <0.001 | | 79.4 (NR), <0.0001 | | 11.51 (5.66, 17.36), <0.05 | | 68.5 (NR), <0.001 | |
| Change in eGFR, mL/min/1.73 $m^2$ | Timepoint | | NR | | NR | | NR | | On treatment* + 28 days | |
| | N | | | | | | | | 1326 | 1314 |
| | Mean (SD) | | | | | | | | -3.70 (NR) | -3.19 (NR) |
| | Between Group Diff. | Mean (95% CI), p-value | | | | | | | -0.51 (-1.00, -0.01), 0.046 | |
| Use of Rescue Therapy | Timepoint | | 52 Weeks | | | | NR | | On treatment* + 28 days | |
| | N | | 323 | 203 | 608 | 305 | | | 1384 | 1376 |
| | n (%) | | 53 (16.5) | 93 (45.8) | 54 (8.9) | 88 (28.9) | | | Ep100PY: 11.90 | Ep100PY : 39.76 |
| | Between Group Diff. | HR (95% CI), p-value | 0.24 (0.17, 0.33), <0.001 | | 0.19 (0.14, 0.28), <0.0001 | | | | 0.26 (0.23, 0.31), <0.001 | |
| Use of Blood Transfusion | Timepoint | | 52 Weeks | | | | NR | | On treatment* + 28 days | |
| | N | | 389 | 203 | 616 | 305 | | | 1384 | 1376 |
| | n (%) | | 160 (41.2) | 126 (62.1) | 55 (8.9) | 88 (28.9) | | | NR | NR |

| Trial | | | ALPS[1,2] | | ANDES[2] | | DOLOMITES[3] | | OLYMPUS[2,4,10] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | ROX | PBO | ROX | PBO | ROX | DAR | ROX | PBO |
| | Time to Event | HR (95% CI), p-value | 0.34 (0.21, 0.55), <0.001 | | 0.26 (0.165, 0.406), <0.0001 | | | | 0.37 (0.30, 0.44), <0.001 | |
| Use of IV Iron | Timepoint | | On treatment† | | On treatment‡ | | 36 weeks | | On treatment* + 28 days | |
| | N | | 389 | 203 | 608 | 305 | 323 | 293 | 1384 | 1376 |
| | n (%) | | IR per 100PY at risk: 5.4 | IR per 100PY at risk: 9.9 | IR per 100PY at risk: 4.1 | IR per 100PY at risk: 5.3 | 32 (9.9) | 62 (21.2) | IR per 100PY at risk: 2.6 | IR per 100PY at risk: 6.2 |
| | Time to Event | HR (95% CI), p-value | NR, 0.045 | | NR, 0.136 | | 0.45 (0.26, 0.78), 0.004 | | 0.41 (0.29, 0.56), <0.001 | |
| Use of ESA Treatment | Timepoint | | NR | | NR | | NR | | On treatment* + 28 days | |
| | N | | | | | | | | 1384 | 1376 |
| | n (%) | | | | | | | | NR | NR |
| | Time to Event | HR (95% CI), p-value | | | | | | | 0.13 (0.10, 0.18), <0.001 | |
| Change in Hepcidin | Timepoint | | 44 Weeks | | | | | | | |
| | N | | NR | | 616 | 306 | NR | | NR | |
| | Mean ng/mL (SD) | | | | -22.11 (80.90) | 3.88 (80.93) | | | | |
| | Between Group Diff. | LSM (95% CI), p-value | | | -25.71 (-38.52, -12.90), <0.05 | | | | | |
| Change in Transferrin Saturation | Timepoint | | 52 Weeks | | | | | | | |
| | N | | NR | | 608 | 305 | NR | | NR | |
| | Mean % (SD) | | | | 1.09** (NR) | 0.38** (NR) | | | | |
| | Between Group Diff. | LSM (95% CI), p-value | | | NR | | | | | |
| Change in Serum Iron, µg/dL | Timepoint | | 20 Weeks | | | | | | | |
| | N | | NR | | NR | NR | NR | | NR | |
| | Mean (SD) | | | | NR | NR | | | | |
| | Between Group Diff. | LSM (95% CI), p-value | | | 13.6, NR | | | | | |
| Change in Total Iron | Timepoint | | 8 Weeks | | | | | | | |
| | N | | NR | | NR | NR | NR | | NR | |

| Trial | | | ALPS[1,2] | | ANDES[2] | | DOLOMITES[3] | | OLYMPUS[2,4,10] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | ROX | PBO | ROX | PBO | ROX | DAR | ROX | PBO |
| **Binding Capacity, µg/dL** | **Mean (SD)** | | | | NR | NR | | | | |
| | **Between Group Diff.** | **LSM (95% CI), p-value** | | | 63.1, NR | | | | | |
| **Change in Ferritin, ng/mL** | **Timepoint** | | 52 Weeks | | | | | | | |
| | **N** | | NR | | 608 | 305 | NR | | NR | |
| | **Mean (SD)** | | | | 58.02 (38.27, 75.31) | -34.57 (-45.68, -24.69) | | | | |
| | **Between Group Diff.** | **LSM (95% CI), p-value** | | | NR | | | | | |
| **Change in Total Cholesterol, mg/dL** | **Timepoint** | | 52 Weeks | | | | | | | |
| | **N** | | NR | | 616 | 306 | NR | | NR | |
| | **Mean (SD)** | | | | -27.2 (45.79) | -3.21 (49.78) | | | | |
| | **Between Group Diff.** | **LSM (95% CI), p-value** | | | NR | | | | | |
| **Change in LDL-C, mg/dL** | **Timepoint** | | Average of 12 - 28 weeks | | | | | | 24 weeks | |
| | **N** | | 391 | 203 | 564 | 269 | 323 | 293 | 1147 | 1133 |
| | **Mean (SD)** | | NR | | -18.48 (29.6) | 0.22 (29.37) | LSM: -13.77# (NR) | LSM: 1.82# (NR) | LSM: -14.58 (SE: 1.08) | LSM: -0.70 (SE: 1.04) |
| | **Between Group Diff.** | **LSM (95% CI), p-value** | -27.11 (-32.10, -22.04), <0.001 | | -17.26 (-20.65, -13.87) <0.0001 | | -15.584 (-19.72, -11.45), <0.001 | | -13.90 (-16.22, -11.20), <0.001 | |
| Data not reported for the following outcomes: Change in transferrin, change in soluble transferrin receptor, change in HDL-cholesterol | | | | | | | | | | |

100PY: 100 person-years, 95% CI: 95% confidence interval, DAR: darbepoetin alfa, diff.: difference, dL: deciliter, eGFR: estimated glomerular filtration rate, Ep100PY: events per 100 person years, g: gram, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, IR: incidence rate, IV: intravenous, LDL-C: low-density lipoprotein cholesterol, LS: least squares, µg: microgram, mg: milligram, min: minute, mL: milliliter, n: number, N: total number, ng: nanogram, NR: not reported, ns: not significant, PBO: placebo, ROX: roxadustat, SD: standard deviation

*: Up to 4 years

†: Up to 2 years

‡: Up to 3 years

#: Converted to mg/dL

**: Data are digitized and should be interpreted with caution

**Evidence Table 6. Change in Hb – Subgroups**

| Trial | | | ALPS[1,2] | | | | ANDES[2] | | | | OLYMPUS[2,4,10] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subgroups | | | Iron Replete* | | Iron Deplete† | | Iron Deplete† | | Iron Replete* | | Iron Deplete† | | Iron Replete* | | CRP >ULN‡ | |
| Arm | | | ROX (N= 204) | PBO (NR) | ROX (N= 187) | PBO (NR) | ROX (N= 241) | PBO (N= 134) | ROX (N= 366) | PBO (N= 170) | ROX (N= 552) | PBO (N= 560) | ROX (N= 782) | PBO (N= 770) | ROX (N=213) | PBO (N=198) |
| Timepoint | | | Average of Weeks 28 to 52 | | | | Average of Weeks 28 to 36 | | | | | | Average of Weeks 28 to 52 | | | |
| Δ in Hb, g/dL | Mean (SD) | | NR | | NR | | 2.07 (1.03) | 0.37 (1.05) | 1.99 (1.04) | -0.02 (0.88) | 1.76 (NR) | 0.43 (NR) | 1.71 (NR) | 0.39 (NR) | LSM: 1.73 (SE: 0.09) | LSM: 0.62 (SE: 0.09) |
| | Btw. Group Diff. | LSM (95% CI), p-value | 1.97 (1.74, 2.20), NR | | 1.99 (1.69, 2.29), NR | | 1.71 (SE: 0.11), <0.0001 | | 2.03 (SE: 0.09), <0.0001 | | NR, <0.001 | | NR, <0.001 | | 1.13 (0.91, 1.35), <0.001 | |

95% CI: 95% confidence interval, btw.: between, diff.: difference, dL: deciliter, g: gram, Hb: hemoglobin, N: total number, NR: not reported, ns: not significant, PBO: placebo, ROX: roxadustat, SD: standard deviation

*: Ferritin ≥100 ng/mL or TSAT ≥20%

†: Ferritin <100 ng/mL or TSAT <20%

‡: ULN defined as 4.9 mg/L

**Evidence Table 7. Efficacy Outcomes – Other Phase III Trials**

| Trial | | | FGCL-4592-808[5] | | 1517-CL-0310[6] | |
|---|---|---|---|---|---|---|
| Arm | | | ROX | PBO | ROX | DAR |
| Change in Hb, g/dL | Timepoint | | Average of Weeks 7 to 9 | | Average of Weeks 18 to 24 | |
| | N | | 93 | 46 | NR | NR |
| | LSM (SE) | | 1.80 (0.1) | -0.50 (0.20) | NR | NR |
| | Between Group Difference | LSM (95% CI), p-value | 2.30 (1.9, 2.6), <0.0001 | | Mean: -0.07 (-0.23, 0.10), NR | |
| Hb Response | Timepoint | | 9 Weeks | | NR | |
| | N | | 101 | 50 | | |
| | n (%) | | 85 (84) | 0 (0) | | |
| | Between Group Difference | Mean % (95% CI), p-value | 84 (75.00, 91.00), NR | | | |
| Use of Rescue Therapy | Timepoint | | 27 Weeks | | NR | |
| | N | | NR | NR | | |
| | n (%) | | 3 (3.0) | 6 (12.0) | | |
| | Between Group Difference | HR (95% CI), p-value | 0.11 (0.02, 0.51), NR | | | |
| Change in Hepcidin, ng/mL | Timepoint | | 9 Weeks | | NR | |
| | N | | 86 | 44 | | |
| | Mean (SD) | | -56.14 (63.4) | -15.1 (48.06) | | |
| | Between Group Difference | LSM (95% CI), p-value | -49.77 (-66.75, -32.79), NR | | | |
| Change in Transferrin, mg/L | Timepoint | | 9 Weeks | | NR | |
| | N | | 85 | 43 | | |
| | Mean (SD) | | 0.73 (0.48) | -0.01 (0.39) | | |
| | Between Group Difference | LSM (95% CI), p-value | 0.75 (0.59, 0.92), NR | | | |
| Change in Transferrin Saturation, % | Timepoint | | 9 Weeks | | NR | |
| | N | | 85 | 43 | | |
| | Mean (SD) | | -5.2 (10.4) | -1.7 (9.2) | | |
| | Between Group Difference | LSM (95% CI), p-value | -4.3 (-7.4, -1.1), NR | | | |
| | Timepoint | | 9 Weeks | | NR | |

| Trial | | | FGCL-4592-808[5] | | 1517-CL-0310[6] | |
|---|---|---|---|---|---|---|
| Arm | | | ROX | PBO | ROX | DAR |
| Change in Serum Iron, µg/dL | N | | 85 | 43 | | |
| | Mean (SD) | | -1.34 (35.25)* | -3.58 (24.36)* | | |
| | Between Group Difference | LSM (95% CI), p-value | 1.34 (-9.33, 12.01)*, NR | | | |
| Change in Total Iron Binding Capacity, µg/dL | Timepoint | | 9 Weeks | | NR | |
| | N | | 85 | 43 | | |
| | Mean (SD) | | 101.68 (66.82)* | -1.84 (54.3)* | | |
| | Between Group Difference | LSM (95% CI), p-value | 105.53 (82.63, 128.38)*, NR | | | |
| Change in Ferritin, ng/mL | Timepoint | | 9 Weeks | | NR | |
| | N | | 85 | 43 | | |
| | Mean (SD) | | -93.3 (146.3) | -21.9 (115.5) | | |
| | Between Group Difference | LSM (95% CI), p-value | -102.2 (-142.6, -61.7), NR | | | |
| Change in Total Cholesterol, mg/dL | Timepoint | | 9 Weeks | | NR | |
| | N | | 101 | 50 | | |
| | Mean (SD) | | -40.6 (NR) | -7.7 (NR) | | |
| | Between Group Difference | Mean (95% CI), p-value | -32.9 (-1.1, -0.6), NR | | | |
| Change in LDL-C, mg/dL | Timepoint | | 9 Weeks | | NR | |
| | N | | 101 | 50 | | |
| | Mean (SD) | | -25.3 (NR) | -5.8 (NR) | | |
| | Between Group Difference | Mean (95% CI), p-value | -21.2 (-0.8, -0.3), NR | | | |
| Data not reported for the following outcomes: Change in eGFR, use of RBC transfusion, use of ESA treatment, use of IV iron, change in soluble transferrin receptor, change in HDL-cholesterol | | | | | | |

95% CI: 95% confidence interval, DAR: darbepoetin alfa, dL: deciliter, eGFR: estimated glomerular filtration rate, Ep100PY: events per 100 person years, g: gram, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, IV: intravenous, LDL-C: low-density lipoprotein cholesterol, LS: least squares, µg: microgram, mg: milligram, min: minute, mL: milliliter, n: number, N: total number, ng: nanogram, NR: not reported, ns: not significant, PBO: placebo, ROX: roxadustat, SD: standard deviation

*: Converted from µmol/L to µg/mL

**Evidence Table 8. Efficacy Outcomes -Phase II Trials**

| Trial | | | FGCL-SM4592-017‡[7] | | | | | | | FGCL-4592-047[8] | | | 1517-CL-0303[9] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | ROX, 1.0 mg/kg BIW | ROX, 1.0 mg/kg TIW | ROX, 1.5 mg/kg BIW | ROX, 1.5 mg/kg TIW | ROX, 2.0 mg/kg BIW | ROX, 2.0 mg/kg TIW | PBO | ROX, Low-Dose | ROX, High-Dose | PBO | ROX, 50 mg | ROX, 70 mg | ROX, 100 mg | PBO |
| Change in Hb, g/dL | Timepoint | | 6 Weeks | | | | | | | 8 Weeks | | | Average of 18-24 Weeks | | | |
| | N | | 12 | 9 | 10 | 11 | 11 | 12 | 28 | 30 | 31 | 30 | 27 | 26 | 27 | 27 |
| | Mean (SD) | | NR | 0.41 (SE: 0.59)*, ns | NR | 1.20 (SE: 0.22)*, <0.01 | NR | 1.80 (SE: 0.30)*, <0.01 | -0.10 (SE: 0.13)* | 1.55 (1.23) | 2.38 (1.46) | 0.37 (0.87) | 1.10 (0.71) | 1.33 (0.82) | 1.55 (0.88) | -0.17 (0.61) |
| | Between Group Diff. | LSM (95% CI), p-value | NR | | | | | | --- | NR, <0.0001 | NR, <0.0001 | -- | NR, <0.001 | NR, <0.001 | NR, <0.001 | -- |
| Hb Response | Timepoint | | 6 Weeks | | | | | | | 8 Weeks | | | 24 Weeks | | | |
| | N | | 5 | 5 | 10 | 11 | 9 | 11 | 23 | 30 | 31 | 30 | 27 | 26 | 27 | 27 |
| | n (%) | | 3 (60.0) | 2 (40.0) | 8 (80.0) | 10 (91.0) | 9 (100) | 11 (100) | 3 (13.0) | 24 (80.0) | 27 (87.1) | 7 (23.3) | 22 (81.5) | 26 (100) | 27 (100) | 4 (14.8) |
| | Between Group Diff. | Mean % (95% CI), p-value | NR, 0.018 | NR, ns | NR, <0.001 | NR, <0.001 | NR, <0.001 | NR, <0.001 | -- | NR, 0.0004 | NR, <0.0001 | -- | NR, <0.001 | NR, <0.001 | NR, <0.001 | -- |
| Use of Rescue Therapy | Timepoint | | 12 Weeks | | | | | | | 8 weeks | | | NR | | | |
| | N | | Rescue Therapy not permitted during 4 week treatment period and 4 weeks post-treatment | | | | | | | NR | NR | NR | | | | |
| | n (%) | | | | | | | | | 1 (3.3) | 0 (0) | 1 (3.3) | | | | |
| | Time to Event | HR (95% CI) p-value | | | | | | | | NR | NR | --- | | | | |
| Use of ESA Treatment | Timepoint | | 8 to 12 Weeks | | | | | | | NR | | | NR | | | |
| | N | | NR | | | | | | NR | | | | | | | |
| | n (%) | | 8 (9.1) | | | | | | 5 (17.9) | | | | | | | |

| Trial | | | FGCL-SM4592-017‡[7] | | | | | | | FGCL-4592-047[8] | | | 1517-CL-0303[9] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | ROX, 1.0 mg/kg BIW | ROX, 1.0 mg/kg TIW | ROX, 1.5 mg/kg BIW | ROX, 1.5 mg/kg TIW | ROX, 2.0 mg/kg BIW | ROX, 2.0 mg/kg TIW | PBO | ROX, Low-Dose | ROX, High-Dose | PBO | ROX, 50 mg | ROX, 70 mg | ROX, 100 mg | PBO |
| | Time to Event | HR (95% CI), p-value | NR | | | | | | | | | | | | | |
| Change in Hepcidin, ng/mL | Timepoint | | 4 weeks | | | | | | | 8 weeks | | | 24 weeks | | | |
| | N | | NR | | NR | | NR | | 23 | 30 | 31 | 30 | 27 | 26 | 27 | 27 |
| | Mean (SD) | | NR | | -150 (89.5) | | -225 (192) | | -17.8 (114) | -37.8 (9.9) | -37.2 (9.3) | -4.8 (8.2) | -12.5 (24.3) | -3.3 (31.9) | -13 (23.3) | 2.4 (39.6) |
| | Between Group Diff. | LSM (95% CI), p-value | NR | | NR, p=0.048 | | NR, 0.0013 | | -- | NR, 0.0004 | NR, 0.0003 | -- | NR, ns | NR, ns | NR, ns | --- |
| Change in Transferrin, mg/L | Timepoint | | NR | | | | | | | 8 weeks | | | 24 weeks | | | |
| | N | | | | | | | | | 30 | 31 | 30 | 27 | 26 | 27 | 27 |
| | Mean (SD) | | | | | | | | | 0.67 (0.49) | 0.96 (0.54) | 0.02 (0.22) | 0.4 (0.4) | 0.2 (0.4) | 0.3 (0.3) | 0.03 (0.2) |
| | Between Group Diff. | LSM (95% CI), p-value | | | | | | | | NR, <0.0001 | NR, <0.0001 | -- | NR, <0.001 | NR, ns | NR, <0.001 | --- |
| Change in Transferrin Saturation, % | Timepoint | | 4 weeks | | | | | | | 8 weeks | | | 24 weeks | | | |
| | N | | 67 | | | | | | 18 | 30 | 31 | 61 | 27 | 26 | 27 | 27 |
| | Mean (SD) | | −8.1 (9.3) | | | | | | -3.1 (7.8) | -3.9 (9.7) | -8.7 (9.5) | 0.2 (7.9) | -4.2 (6.8) | 1 (14.9) | -0.2 (13.3) | 0.2 (10.2) |
| | Between Group Diff. | LSM (95% CI), p-value | NR, p=0.036 | | | | | | -- | NR, 0.11 | NR, <0.0001 | -- -- | NR, 0.004 | NR, 0.73 | NR, 0.93 | --- |
| Change in Soluble Transferrin | Timepoint | | NR | | | | | | | 8 weeks | | | NR | | | |
| | N | | | | | | | | | 30 | 31 | 61 | | | | |
| | Mean (SD) | | | | | | | | | 2.7 (2.2) | 3.7 (3.0) | 0.05 (0.6) | | | | |

| Trial | | | FGCL-SM4592-017‡[7] | | | | | | | FGCL-4592-047[8] | | | 1517-CL-0303[9] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | ROX, 1.0 mg/kg BIW | ROX, 1.0 mg/kg TIW | ROX, 1.5 mg/kg BIW | ROX, 1.5 mg/kg TIW | ROX, 2.0 mg/kg BIW | ROX, 2.0 mg/kg TIW | PBO | ROX, Low-Dose | ROX, High-Dose | PBO | ROX, 50 mg | ROX, 70 mg | ROX, 100 mg | PBO |
| **Receptor, mg/L** | **Between Group Diff.** | **LSM (95% CI), p-value** | | | | | | | | NR, <0.0001 | NR, <0.0001 | -- | | | | |
| **Change in Serum Iron, µg/dL** | **Timepoint** | | 4 weeks | | | | | | | 8 weeks | | | | | | |
| | **N** | | 67 | | | | | | 18 | 30 | 31 | 30 | | | | |
| | **Mean (SD)** | | 64.1 (19.4) | | | | | | -9.5 (19.3) | 0.2 (23.9) | -8.1 (28.7) | 2.7 (23.7) | | | | |
| | **Between Group Diff.** | **LSM (95% CI), p-value** | NR | | | | | | -- | NR | | | | | | |
| **Change in Total Iron Binding Capacity, µg/dL** | **Timepoint** | | 4 weeks | | | | | | | 8 weeks | | | 24 weeks | | | |
| | **N** | | 67 | | | | | | 18 | 30 | 31 | 30 | 27 | 26 | 27 | 27 |
| | **Mean (SD)** | | 41.8 (45.4) | | | | | | -7.6 (26.6) | 65.1 (47.9) | 102 (56.2) | 1.2 (22.1) | 51.4 (46.93)† | 25.7 (49.72)† | 34.08 (36.31)† | 5.03 (21.79)† |
| | **Between Group Diff.** | **LSM (95% CI), p-value** | NR, <0.0001 | | | | | | -- | NR, <0.0001 | NR, <0.0001 | -- | NR, <0.001 | NR, 0.01 | NR, <0.001 | --- |
| **Change in Ferritin, ng/mL** | **Timepoint** | | 4 weeks | | | | | | | 8 weeks | | | 24 weeks | | | |
| | **N** | | 67 | | | | | | 18 | 30 | 31 | 30 | 27 | 26 | 27 | 27 |
| | **Mean (SD)** | | −68.8 (70.1) | | | | | | -37.8 (40.3) | -124.0 (171.0) | -98.0 (81.0) | -28.0 (64.0) | -38.5 (44.9) | -23.4 (52.7) | -35.9 (63.4) | -16.5 (32.5) |
| | **Between Group Diff.** | **LSM (95% CI), p-value** | NR | | | | | | -- | NR, <0.0001 | NR, <0.0001 | -- | NR, <0.05 | NR, <0.001 | NR, 0.03 | -- |
| **Change in Total** | **Timepoint** | | NR | | | | | | | 8 weeks | | | NR | | | |
| | **N** | | | | | | | | | 30 | 31 | 61 | | | | |

| Trial | | | FGCL-SM4592-017‡[7] | | | | | | | FGCL-4592-047[8] | | | 1517-CL-0303[9] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | ROX, 1.0 mg/kg BIW | ROX, 1.0 mg/kg TIW | ROX, 1.5 mg/kg BIW | ROX, 1.5 mg/kg TIW | ROX, 2.0 mg/kg BIW | ROX, 2.0 mg/kg TIW | PBO | ROX, Low-Dose | ROX, High-Dose | PBO | ROX, 50 mg | ROX, 70 mg | ROX, 100 mg | PBO |
| Cholesterol, mg/dL | Mean (SD) | | | | | | | | | -31.7 (25.3) | -35.6 (37.5) | 8.0 (30) | | | | |
| | Between Group Diff. | LSM (95% CI), p-value | | | | | | | | NR, <0.0001 | NR, <0.0001 | -- | | | | |
| Change in LDL-C, mg/dL | Timepoint | | NR | | | | | | | 8 weeks | | | NR | | | |
| | N | | | | | | | | | 30 | 31 | 30 | | | | |
| | Mean (SD) | | | | | | | | | -22.4 (19.4)# | -32 (33.5)# | 4.0 (25.5)# | | | | |
| | Between Group Diff. | LSM (95% CI), p-value | | | | | | | | NR, <0.0001 | NR, <0.0001 | -- | | | | |
| Change in HDL-C, mg/dL | Timepoint | | NR | | | | | | | 8 weeks | | | NR | | | |
| | N | | | | | | | | | 30 | 31 | 30 | | | | |
| | Mean (SD) | | | | | | | | | -7.7 (10.5) | -6.9 (7.0) | 1.7 (10.6) | | | | |
| | Between Group Diff. | LSM (95% CI), p-value | | | | | | | | NR, 0.0001 | NR, 0.0002 | -- | | | | |
| Data on the following outcomes not reported: change in eGFR, use of blood transfusion, use of IV iron | | | | | | | | | | | | | | | | |

95% CI: 95% confidence interval, DAR: darbepoetin alfa, diff.: difference, dL: deciliter, eGFR: estimated glomerular filtration rate, Ep100PY: events per 100 person years, g: gram, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, IV: intravenous, LDL-C: low-density lipoprotein cholesterol, LS: least squares, µg: microgram, mg: milligram, min: minute, mL: milliliter, n: number, N: total number, ng: nanogram, NR: not reported, ns: not significant, PBO: placebo, ROX: roxadustat, SD: standard deviation

*: Data are digitized and should be interpreted with caution

†: Converted from µmol/L to µg/dL

‡: Data for ROX, 0.7 mg/kg BIW and ROX, 0.7 mg/kg TIW not abstracted

#: Converted from mmol/L to mg/dL

**Evidence Table 9. Patient Reported Outcomes – Key Trials**

| Trial | | | ALPS[1,2] | | ANDES | | DOLOMITES[3] | | OLYMPUS[2,4,10] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | ROX (N=389) | PBO (N=203) | ROX (N=608) | PBO (N=306) | ROX (N=323) | DAR (N=293) | ROX (N=1279) | PBO (N=1235) |
| Timepoint | | | Average of 12-28 weeks | | | | | | | |
| Change in SF-36 Physical Functioning, Points | LSM (SE) | | NR | | NR | | 1.03 (NR) | 2.31 (NR) | 0.14 (0.22) | -0.39 (0.23) |
| | Between Group Diff. | LS Mean (95% CI), p-value | 0.71 (-0.56, 1.98), 0.27 | | | | -1.28 (-2.42, -0.15), NR | | 0.52 (0.00, 1.05), 0.051 | |
| Change in SF-36 Vitality, Points | LSM (SE) | | NR | | NR | | 3.89 (NR) | 4.35 (NR) | 1.59 (0.23) | 1.15 (0.23) |
| | Between Group Diff. | LS Mean (95% CI), p-value | 1.127 (-0.19, 2.44), 0.093 | | | | -0.457 (-1.66, 0.74), NR | | 0.44 (-0.11, 0.99), 0.12 | |
| Other subscales not reported | | | | | | | | | | |

95% CI: 95% confidence interval, DAR: darbepoetin alfa, diff.: difference, LS: least squares, µg: microgram, N: total number, NR: not reported, nPBO: placebo, ROX: roxadustat, SD: standard deviation

**Evidence Table 10. Cardiovascular Safety – Key Trials**

| Trial | | | ALPS[1,2] | | ANDES[2] | | DOLOMITES[3] | | OLYMPUS[2,4,10] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | ROX (N=391) | PBO (N=203) | ROX (N=611) | PBO (N=305) | ROX (N=323) | DAR (N=293) | ROX (N=1384) | PBO (N=1377) |
| MACE* | n (%) | | NR | | NR | | 38 (11.8) | 41 (14.0) | NR | |
| | Time to Event | HR (95% CI), p-value | | | | | 0.81 (0.52, 1.25), 0.339 | | | |
| MACE+† | n (%) | | NR | | NR | | 54 (16.7) | 53 (18.1) | NR | |
| | Time to Event | HR (95% CI), p-value | | | | | 0.9 (0.61, 1.32), 0.583 | | | |
| Myocardial Infarction | n (%) | | 14 (3.5) | 5 (2.5) | NR | | 11 (3.4) | 10 (3.4) | 40 (2.9) | 40 (2.9) |
| | Time to Event | HR (95% CI), p-value | NR | | | | 0.96 (0.41, 2.27), 0.931 | | NR | |
| Stroke | n (%) | | 4 (1) | 1 (0.5) | NR | | 4 (1.2) | 7 (2.4) | 15 (1.1) | 13 (0.9) |
| | Time to Event | HR (95% CI), p-value | NR | | | | 0.48 (0.14, 1.67), 0.25 | | NR | |
| Heart Failure | n (%) | | 3 (0.8) | 3 (1.5) | NR | | NR | | 25 (1.8) | 32 (2.3) |
| | Time to Event | HR (95% CI), p-value | NR | | | | | | NR | |
| Unstable Angina | n (%) | | NR | | NR | | NR | | 10 (0.7) | 10 (0.7) |
| | Time to Event | HR (95% CI), p-value | | | | | | | NR | |
| Heart Failure Requiring Hospitalization | n (%) | | NR | | NR | | 25 (7.7) | 21 (7.2) | NR | |
| | Time to Event | HR (95% CI), p-value | | | | | 1.08 (0.60, 1.95), 0.789 | | | |
| Unstable Angina Requiring Hospitalization | n (%) | | NR | | NR | | 0 (0) | 1 (0.3) | NR | |
| | Time to Event | HR (95% CI), p-value | | | | | NR | | | |
| Data for cardiovascular mortality not reported | | | | | | | | | | |

95% CI: 95% confidence interval, HR: hazard ratio, MACE: major adverse cardiovascular event, n: number, N: total number, NR: not reported, PBO: placebo, ROX: Roxadustat

*: defined as all-cause mortality (not cardiovascular mortality), myocardial infarction (MI), or stroke

†: MACE+: defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization

**Evidence Table 11. Cardiovascular Safety – Other Phase III Trials**

| Trial | | | FGCL-4592-808[5] | | 1517-CL-0310[6] | |
|---|---|---|---|---|---|---|
| Arm | | | ROX (N=101) | PBO (N=51) | ROX (N=NR) | DAR (N=NR) |
| **Cardiovascular Mortality** | **n (%)** | | 0 (0) | 0 (0) | NR | |
| | **Time to Event** | **HR (95% CI), p-value** | NR | | | |
| No data reported for the following outcomes: MACE*, MACE+†, myocardial infarction, stroke, heart failure, unstable angina, heart failure requiring hospitalization, unstable angina requiring hospitalization | | | | | | |

95% CI: 95% confidence interval, HR: hazard ratio, MACE: major adverse cardiovascular event, N: total number, n: number, NR: not reported, PBO: placebo, ROX: Roxadustat

*: Defined as all-cause mortality (not cardiovascular mortality), myocardial infarction (MI), or stroke

†: MACE+: defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization

**Evidence Table 12. Cardiovascular Safety – Phase II Trials**

| Trial | | | FGCL-SM4592-017[7] | | FGCL-4592-047[8] | | | 1517-CL-0303[9] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | Pooled ROX (N=88)* | PBO (N=28) | ROX, Low-Dose (N=30) | ROX, High-Dose (N=31) | PBO (N=30) | ROX, Low-Dose (N=27) | ROX, Middle-Dose (N=27) | ROX High-Dose (N=26) | PBO (N=27) |
| **CV Mortality** | n (%) | | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | Time to Event | HR (95% CI), p-value | NR | | NR | | --- | NR | | | --- |
| **MACE** | n (%) | | NR | | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | Time to Event | HR (95% CI), p-value | | | NR | | --- | NR | | | --- |
| **Myocardial Infarction** | n (%) | | NR | | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | Time to Event | HR (95% CI), p-value | | | NR | | --- | NR | | | --- |
| **Stroke** | n (%) | | NR | | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | Time to Event | HR (95% CI), p-value | | | NR | | --- | NR | | | --- |
| **Heart Failure** | n (%) | | 1 (1.1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (3.7) | 0 (0) | 0 (0) | 1 (3.7) |
| | Time to Event | HR (95% CI), p-value | NR | | NR | | --- | NR | | | --- |
| **Unstable Angina** | n (%) | | NR | | 0 (0) | 0 (0) | 1 (3.3) | NR | | | --- |
| | Time to Event | HR (95% CI), p-value | | | NR | | --- | | | | |
| Data on the following outcomes not reported: MACE+, heart failure requiring hospitalization, unstable angina requiring hospitalization | | | | | | | | | | | |

95% CI: 95% confidence interval, CV: cardiovascular, Diff.: difference, HR: hazard ratio, MACE: major adverse cardiovascular event , n: number, N: total number, NR: not reported, PBO: placebo, ROX: roxadustat

*: Data for individual arms not reported

†: Defined as all-cause mortality (not cardiovascular mortality), myocardial infarction (MI), or stroke

‡: Mace+: defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization

**Evidence Table 13. Safety – Key Trials**

| Trial | | ALPS[1,2] | | ANDES[2] | | DOLOMITES[3] | | OLYMPUS[2,4,10] | |
|---|---|---|---|---|---|---|---|---|---|
| Arm | | ROX (N=391) | PBO (N=203) | ROX (N=611) | PBO (N=305) | ROX (n=323) | DAR (N=293) | ROX (N=1384) | PBO (N=1377) |
| Timepoint | | On treatment* + 28 days | | On treatment† + 28 days | | 36 weeks | | On treatment‡ + 28 days | |
| Any AEs, n (%) | | ERP100PY: 476.7 | ERP100PY: 514.7 | ERP100PY: 554.4 | ERP100PY: 594.5 | NR | | ERP100PY: 182.9 | ERP100PY: 171.9 |
| Any TEAEs, n (%) | | 343 (87.7) | 176 (86.7) | 535 (87.6) | 262 (85.9) | 296 (91.6) | 271 (92.5) | NR | |
| Drug-Related TEAEs, n (%) | | 81 (20.7) | 27 (13..3) | NR | | NR | | NR | |
| Serious AEs, n (%) | | ERP100PY: 78.9 | ERP100PY: 97.1 | ERP100PY: 74.2 | ERP100PY: 66 | NR | | ERP100PY: 42.1 | ERP100PY: 40 |
| Serious TEAEs, n (%) | | 241 (61.6) | 115 (56.7) | 203 (33.2) | 91 (29.8) | 209 (64.7) | 181 (61.8) | NR | |
| D/C due to AEs, n (%) | | 23 (5.9) | 8 (3.9) | NR | | 25 (7.7)¥ | 11 (3.8)¥ | 78 (5.6) | 57 (4.1) |
| All-Cause Mortality# | n (%) | 45 (11.5) | 20 (9.9) | 58 (9.5) | 24 (7.9) | 29 (9) | 31 (10.6) | 284 (20.5) | 245 (17.8) |
| | HR (95% CI), p-value | NR | | NR | | 0.83 (0.50, 1.38), 0.467 | | NR | |
| Hospitalization, n (%) | | NR | | NR | | NR | | NR | |
| End Stage Renal Disease, n (%) | | 135 (34.5) | 62 (30.5) | NR | | 108 (33.4) | 106 (36.2) | 209 (21) | 282 (20.5) |
| Decline in eGFR, n (%) | | 43 (11) | 23 (11.3) | NR | | 55 (17) | 49 (16.7) | NR | |
| Pulmonary Embolism, n (%) | | NR | | NR | | NR | | NR | |
| Hypertension, n (%) | | 87 (22.3) | 28 (13.8) | NR | | NR | | 159 (11.5) | 125 (9.1) |

95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, DAR: darbepoetin alfa, eGFR: estimated glomerular filtration rate, ERP100Y: event rate per 100 person years, HR: hazard ratio, n: number, N: total number, NR: not reported, PBO: placebo, ROX: roxadustat, SAE: serious adverse event, TEAE: treatment-emergent adverse event

*: Up to 2 years

†: Up to 3 years

‡: Up to 4 years

#: At 52 weeks

¥: Due to TEAE

**Evidence Table 14. Safety – Other Phase III Trials**

| Trial | | FGCL-4592-808[5] | | 1517-CL-0310[6] | |
|---|---|---|---|---|---|
| Arm | | ROX (N=101) | PBO (N=51) | ROX (N=NR) | DAR (N=NR) |
| Timepoint | | 8 weeks | | NR | |
| Any AEs, n (%) | | 69 (68) | 38 (75) | | |
| Any TEAEs, n (%) | | NR | | | |
| Drug-Related TEAEs, n (%) | | NR | | | |
| Serious AEs, n (%) | | 9 (9.0) | 6 (12.0) | | |
| Serious TEAEs, n (%) | | NR | | | |
| D/C due to TEAEs, n (%) | | 6 (5.9) | 5 (9.6) | | |
| All-Cause Mortality | n (%) | 0 (0) | 0 (0) | | |
| | HR (95% CI), p-value | NR | | | |
| Hospitalization, n (%) | | NR | | | |
| End Stage Renal Disease, n (%) | | 1 (1.0) | 0 (0) | | |
| Decline in eGFR, n (%) | | NR | | | |
| Pulmonary Embolism, n (%) | | NR | | | |
| Hypertension, n (%) | | 6 (6.0) | 2 (4.0) | | |

95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, eGFR: estimated glomerular filtration rate, HR: hazard ratio, n: number, N: total number, NR: not reported, PBO: placebo, ROX: roxadustat, SAE: serious adverse event, TEAE: treatment-emergent adverse event

**Evidence Table 15. Safety – Phase II Trials**

| Trial | | FGCL-SM4592-017[7] | | FGCL-4592-047[8] | | | | 1517-CL-0303[9] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | Pooled ROX (N=88)* | PBO (N=28) | ROX, Low-Dose (N=30) | ROX, High-Dose (N=31) | Pooled ROX (N=61) | PBO (N=30) | ROX, Low-Dose (N=27) | ROX, Middle-Dose (N=26) | ROX High Dose (N=27) | PBO (N=27) |
| Timepoint | | 12 weeks | | 8 weeks | | | | 24 weeks | | | |
| Any AEs, n (%) | | NR | | NR | | | | NR | | | |
| Any TEAEs, n (%) | | 52 (59.1) | 13 (46.4) | NR | | 36 (59.0) | 19 (63.0) | 20 (74.1) | 23 (88.5) | 20 (74.1) | 19 (70.4) |
| Drug-Related TEAEs, n (%) | | NR | | 17 (57.0) | 19 (61.0) | 36 (59.0) | 19 (63.0) | 10 (37.0) | 4 (15.4) | 5 (18.5) | 4 (14.8) |
| Serious AEs, n (%) | | 4 (5.0) | 1 (4.0) | NR | | | | NR | | | |
| Serious TEAEs, n (%) | | NR | | NR | | 8 (13.1) | 4 (13.3) | 6 (22.2) | 2 (7.7) | 3 (11.1) | 2 (7.4) |
| D/C due to TEAEs, n (%) | | 2 (2.3) | 1 (3.6) | 2 (6.7) | 0 (0) | 2 (3.3) | 1 (3.3) | 8 (29.6) | 0 (0) | 3 (11.1) | 2 (7.4) |
| All-Cause Mortality | n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | HR (95% CI), p-value | NR | | NR | | | --- | NR | | | --- |
| Hospitalization, n (%) | | NR | | NR | | | | NR | | | |
| End Stage Renal Disease, n (%) | | NR | | NR | | | | NR | | | |
| Decline in eGFR, n (%) | | NR | | 1 (3.3) | 0 (0) | 1 (1.6) | 0 (0) | 4 (14.8) | 0 (0) | 1 (3.7) | 1 (3.7) |
| Pulmonary Embolism, n (%) | | NR | | NR | | | | NR | | | |
| Hypertension, n (%) | | 2 (2.3) | NR | 1 (3.0) | 3 (10.0) | 4 (7.0) | 0 (0) | NR | | | |

95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, DAR: darbepoetin alfa, eGFR: estimated glomerular filtration rate, HR: hazard ratio, n: number, N: total number, NR: not reported, PBO: placebo, ROX: roxadustat, SAE: serious adverse event, TEAE: treatment-emergent adverse event

*: Data for individual arms not reported

**Evidence Table 16. Study Design**

| Trial (NCT) & Author | Design & Follow-Up Duration | Location | N | Arms | Key Inclusion Criteria | Key Exclusion Criteria | Definitions |
|---|---|---|---|---|---|---|---|
| **HIMALAYAS**<br><br>**NCT02052310**[11] | Phase III, open-label, active-controlled, randomized trial<br><br><u>Follow-Up</u>:<br>– Treatment period: 52 weeks to 4 years<br>– Post-treatment follow-up: 4 weeks | Global | 1043 | **Roxadustat (N=522)**<br>Weight-based starting dose<br>– ≤70 kg: 70 mg TIW<br>– 70-160 kg: 100 mg TIW<br><br>**Epoetin alfa (N=521)**<br>– HD: dosed per USPI or SmPC<br>– PD dosed per USPI or SmPC or local SOC | – Receiving HD or PD for 2 weeks to 4 months<br>– Hb ≤10.0 g/dL<br>– Ferritin ≥100 ng/mL and TSAT ≥20% | – ESA treatment within 12 weeks<br>– Total duration of prior effective ESA use must be ≤3 weeks within preceding 12 weeks at the time consent is obtained (US only)<br>– IV iron supplementation within 10 days<br>– Use of iron-binding medications within 4 weeks<br>– Blood transfusion within 8 weeks<br>– Congestive heart failure<br>– Heart attack, stroke, or blood clots within a major vessel within 12 weeks<br>– Uncontrolled hypertension<br>– Active cancer<br>– Known and untreated damage to the retina from diabetes | **Hb Response:**<br>Hb ≥11 g/dL and a Hb increase from baseline of ≥1 g/dL for baseline Hb >8 g/dL or ≥2 g/dL for baseline Hb ≤8 g/dL |
| **ROCKIES**<br><br>**NCT02174731**[4] | Phase III, open-label, active-controlled, randomized trial<br><br><u>Follow-Up</u>:<br>– Treatment period: up to 4 years<br>– Post-treatment follow-up: 4 weeks | Global | 2133 | **Roxadustat (N=1,068)**<br><u>ESA-experienced:</u><br>– Epoetin alfa or beta <5000 IU/week or darbepoetin alfa <25 µg/week or methoxy polyethylene glycol-epoetin beta <80 µg/month: 70 mg TIW<br>– Epoetin alfa or beta 5000-8000 IU/week or darbepoetin alfa 25-40 µg/week or methoxy polyethylene glycol-epoetin beta 80-120 µg/month: 100 mg TIW | – Receiving HD or PD for ≥2 weeks<br>– Hb <12 g/dL if on ESA or Hb <10 g/dL if not on ESA for ≥4 weeks or methoxy polyethylene glycol-epoetin beta for ≥8 weeks before the first visit<br>– Ferritin ≥100 ng/mL<br>– TSAT ≥20% | – Blood transfusion during the screening period<br>– NYHA class III or IV congestive heart failure at enrollment<br>– Myocardial infarction, acute coronary syndrome, stroke, seizure, or a thrombotic/ thromboembolic event within 12 weeks<br>– Uncontrolled hypertension<br>– History malignancy<br>– Known and untreated retinal vein occlusion or known and untreated proliferative diabetic retinopathy (risk for retinal vein thrombosis) | **Hb Response:**<br>Hb ≥ 11.0 g/dL and Hb increase from baseline by ≥ 1.0 g/dL, for subjects with baseline Hb > 8.0 g/dL; or Hb increase from baseline by ≥ 2.0 g/dL, for subjects with baseline Hb ≤ 8.0 g/dL<br>and<br>Proportion of total time of Hb |

| Trial (NCT) & Author | Design & Follow-Up Duration | Location | N | Arms | Key Inclusion Criteria | Key Exclusion Criteria | Definitions |
|---|---|---|---|---|---|---|---|
| | | | | – Epoetin alfa or beta >8000-16000 IU/week or darbepoetin alfa 40-80 µg/week or methoxy polyethylene glycol-epoetin beta 120-200 µg/month: 150 mg TIW<br>– Epoetin alfa or beta >16000 IU/week or darbepoetin alfa >80 µg/week or methoxy polyethylene glycol-epoetin beta >200 µg/month: 200 mg TIW<br><br>ESA-naïve:<br>– 45-70 kg: 70 mg TIW<br>– >70-160 kg: 100 mg TIW<br><br>**Epoetin alfa (N=1,065)**<br>ESA-naïve:<br>– 50 IU/kg TIW<br><br>ESA-experienced:<br>– Dosed at approximately the same average weekly dose prior to randomization | | | within the interval of 10-12 g/dL from week 28 to week 52 |
| **SIERRAS**<br><br>**NCT02273726**[2] | Phase III, open-label, active controlled, randomized trial<br><br>Follow-Up: | US and Latin America | 741 | **Roxadustat (N=370)**<br>ESA-experienced:<br>– Epoetin alfa, beta, theta, zeta, delta or omega <5000 IU/week or darbepoetin alfa <25 µg/week or methoxy polyethylene glycol- | – Receiving HD or PD<br>– Ferritin ≥100 ng/mL<br>– TSAT ≥20%<br><br>Stable DD-CKD:<br>– Receiving ESA treatment ≥8 weeks<br>– Hb 9.0-12.0 g/dL<br>ID-CKD: | – Blood transfusion within 8 weeks prior to randomization<br>– NYHA class III or IV congestive heart failure<br>– Heart attack, stroke, seizure, or a thrombotic/thromboembolic event within 12 weeks prior to study participation | |

| Trial (NCT) & Author | Design & Follow-Up Duration | Location | N | Arms | Key Inclusion Criteria | Key Exclusion Criteria | Definitions |
|---|---|---|---|---|---|---|---|
| | – Treatment period: 52 weeks to 3 years<br>– Post-treatment follow-up period: 4 weeks | | | epoetin beta <80 µg/month: 70 mg TIW<br>– Epoetin alfa, beta, theta, zeta, delta or omega 5000-8000 IU/week or darbepoetin alfa 25-40 µg/week or methoxy polyethylene glycol-epoetin beta 80-120 µg/month: 100 mg TIW<br>– Epoetin alfa, beta, theta, zeta, delta or omega: >8000-16000 IU/week or darbepoetin alfa 40-80 µg/week or methoxy polyethylene glycol-epoetin beta 120-200 µg/month: 150 mg TIW<br>– Epoetin alfa, beta, theta, zeta, delta, or omega: >16000 IU/week or darbepoetin alfa >80 µg/week or methoxy polyethylene glycol-epoetin beta >200 µg/month: 200 mg TIW<br><br>**Epoetin alfa (N=371)** | – Receiving ESA treatment ≥4 weeks<br>– Hb 8.5-12.0 g/dL | – History of malignancy, except for 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 | |
| **PYRENEES**<br><br>**NCT02278341**[12] | Phase III, open-label, active-controlled, randomized trial | Europe | 836 | **Roxadustat (N=415)**<br>Dosed per patient's average weekly dose of EPO or DAR within 4 weeks prior to randomization | – Receiving stable HD, HDF, or PD with the same mode of dialysis ≥4 months<br>– IV or SC epoetin or IV or SC darbepoetin alfa treatment for ≥8 | – Blood transfusion within 8 weeks<br>– Myocardial infarction, acute coronary syndrome, stroke, seizure, or a thrombotic/ thrombo-embolic event within 12 weeks | **Hb Response:** mean Hb during weeks 28 to 36 within the target range of 10.0 to 12.0 g/dL without having received |

| Trial (NCT) & Author | Design & Follow-Up Duration | Location | N | Arms | Key Inclusion Criteria | Key Exclusion Criteria | Definitions |
|---|---|---|---|---|---|---|---|
| | Follow-Up:<br>– Treatment period: 52 weeks to 104 weeks<br>– Post-treatment follow-up period: 4 weeks | | | – EPO <8000 IU/week or darbepoetin alfa <40 µ/week: 100 mg TIW<br>– EPO 8000-16000 IU/week or darbepoetin alfa 40-80 µ/week:150 mg TIW<br>– EPO >16000 IU/week or darbepoetin alfa >80 µ/week: 200 mg TIW<br><br>**ESA (N=421)**<br>Dosed at approximately the same average weekly dose prior to randomization<br>– DAR (n=163)<br>– EPO (n=258) | weeks prior to randomization with stable weekly doses during 4 weeks prior to randomization<br>– Hb 9.5–12 g/dL<br>– Ferritin ≥100 ng/mL<br>– TSAT ≥20% | – History of malignancy | rescue therapy within 6 weeks prior to and during this 8-week evaluation period. |
| **FGCL-4592-806**<br><br>**NCT02652806**<br><br>**Chen 2019[13]** | Phase III, open-label, active controlled, randomized trial<br><br>Follow-Up: 26 weeks | China | 305 | **Roxadustat (N=204)**<br>– 45-60 kg: 100 mg TIW<br>– ≥60 kg: 120 mg TIW<br><br>**Epoetin alfa (N=101)**<br>Dose was based on epoetin alfa dose prior to randomization | – 18-75 years of age<br>– End stage kidney disease<br>– Receiving adequate HD or PD ≥16 weeks<br>– Receiving stable doses of epoetin alfa ≥6 weeks<br>– Hb 9.0-12.0 g/dL | – IV iron supplementation during the screening period<br>– Blood transfusion within 12 weeks<br>– NYHA class III or IV congestive heart failure<br>– Myocardial infarction, acute coronary syndrome, stroke, seizure, or a thromboembolic event within 52 weeks<br>– History of malignancy<br>– Uncontrolled hypertension | **Hb Response:**<br>Hb not <1.0 g/dL below baseline |
| **1517-CL-0307**<br><br>**NCT02952092**<br><br>**Akizawa 2020[14]** | Phase III, parallel-arm, double-blind, active controlled, randomized | Japan | 303 | **Roxadustat (N=151)**<br>– 70 or 100 mg BIW or TIW<br><br>**Darbepoetin alfa (N=152)**<br>Dose was based on rHuEPO or darbepoetin | – ≥ 20 years of age<br>– CKD diagnosis and receiving HD TIW >12 weeks prior to the pre-screening<br>– Receiving IV rHuEPO or darbepoetin alfa | – Blood transfusion or a surgical procedure considered to promote anemia and ophthalmological surgery within 4 weeks<br>– NYHA class III or higher congestive heart failure | |

| Trial (NCT) & Author | Design & Follow-Up Duration | Location | N | Arms | Key Inclusion Criteria | Key Exclusion Criteria | Definitions |
|---|---|---|---|---|---|---|---|
| | trial<br><br>Follow-Up:<br>– 24 weeks | | | alfa dose prior to randomization | >8 weeks prior to pre-screening<br>– Hb 10.0-12.0 g/dL<br>– Either TSAT ≥20% or serum ferritin ≥100 ng/mL | – History of hospitalization for treatment of stroke, myocardial infarction, or pulmonary embolism with 12 weeks<br>– History of malignancies<br>– Untreated retinal neovascular lesion; macular edema<br>– Uncontrolled hypertension<br>– Anemia not related to CKD | |
| **FGCL-4592-040**<br><br>**NCT01147666**<br><br>**Provenzano 2016[15]** | Phase II, open-label, active controlled, randomized, dose-ranging trial<br><br>Follow-Up:<br>– Treatment period (part 1): 6 weeks<br>– Treatment period (part 2): 19 weeks<br>– Post-treatment follow-up period (part 1): 8 weeks<br>– Post-treatment follow-up period (part 2): 4 weeks | US | 144 | **Part 1: Roxadustat (n=41)**<br>– Roxadustat 1.0 mg/kg TIW<br>– Roxadustat 1.5 mg/kg TIW<br>– Roxadustat 1.8 mg/kg TIW<br>– Roxadustat 2.0 mg/kg TIW<br><br>**Part 1: Epoetin alfa (N=13)**<br>Continuation of rerandomization dose<br><br>**Part 2: Roxadustat (N=67)**<br>– Roxadustat 1.8 mg/kg TIW<br>– Roxadustat 1.8 mg/kg TIW<br>– 45-60 kg: Roxadustat 70-100-150 mg TIW<br>– >60-90 kg: Roxadustat 70-120-200 mg TIW<br>– Roxadustat 2.0 mg/kg TIW | – 18 – 75 years of age<br>– End stage renal disease and receiving HD ≥4 months<br>– Hb 9.0 to 13.5 g/dL for 8 weeks<br>– Stable epoetin alfa dose ≤450 U/kg/ week for 4 weeks<br>– ALT and AST ≤2x ULN | – Received any ESA other than IV EPO within 12 weeks; received IV EPO within 3 days<br>– IV iron supplementation within 2 weeks<br>– Red blood cell transfusion within 12 weeks<br>– NYHA Class III or IV congestive heart failure<br>– Myocardial infarction or ACS within 3 months<br>– Thromboembolic event within 12 weeks<br>– History of malignancy | **Hb Response:**<br>– Part 1: Hb change ≥0.5 g/dL<br>– Part 2: Mean Hb level ≥11.0 g/dL during the last 4 weeks of treatment |

| Trial (NCT) & Author | Design & Follow-Up Duration | Location | N | Arms | Key Inclusion Criteria | Key Exclusion Criteria | Definitions |
|---|---|---|---|---|---|---|---|
| | | | | – >90-140 kg: Roxadustat: 70-120-200 mg TIW<br><br>**Part 2: Epoetin alfa (n=23)** | | | |
| **FGCL-4592-048**<br><br>**NCT01596855**<br><br>**Chen 2017** | Phase II, open-label, active-controlled, randomized trial<br><br><u>Follow-Up</u>: 7 weeks | China | 87 | **Roxadustat**<br>– Low dose (40-60 kg): 1.1 to 1.8 mg/kg TIW<br>– Medium dose (>60-80 kg): 1.5 to 2.3 mg/kg TIW<br>– High dose (>80-100 kg): 1.7 to 2.3 mg/kg TIW<br><br>**Epoetin alfa (N=22)**<br>Continuation of pre-randomization dose and schedule | – Ages 18 – 75 years of age<br>– CKD diagnosis and receiving HD three times weekly TIW for ≥4 months<br>– Receiving stable doses of epoetin alfa during 7 weeks prior<br>– Mean Hb between ≥9.0 and ≤12.0 g/dL | – Received any ESA other than epoetin alfa within 12 weeks; received epoetin alfa within 3-7 days<br>– IV iron supplementation during the screening visit<br>– RBC transfusion within 12 weeks<br>– NYHA Class III or IV congestive heart failure<br>– Myocardial infarction or acute coronary syndrome within 3 months<br>– Thromboembolic event within 12 weeks<br>– History of malignancy | **Hb Response:** Hb maintained at no more than 0.5 g/dL below mean baseline value (weeks 4-6) |
| **1517-CL-0304**[16]<br><br>**NCT01888445** | Phase II, 4-arm, multicenter, double-blind (arms 1-3), and open-label (arm 4), active controlled, randomized trial<br><br><u>Follow-Up:</u><br>– Fixed-dose | Japan | 130 | **Roxadustat (N=98)**<br>– 50 mg TIW<br>– 70 mg TIW<br>– 100 mg TIW<br><br>**Darbepoetin alfa (N=32)**<br>– 20µg QW | – Receiving HD ≥12 weeks<br>– Patients who are receiving ESA for ≥8 weeks<br>– Hb ≥10.0 g/dL | – Congestive heart failure (NYHA classification III or higher)<br>– History of hospitalization for stroke, myocardial infarction, or lung infarction within 24 weeks | **Hb response:** patient whose Hb is ≥10.0 g/dL and who achieve an increase in Hb of ≥ 1.0 g/dL |

| Trial (NCT) & Author | Design & Follow-Up Duration | Location | N | Arms | Key Inclusion Criteria | Key Exclusion Criteria | Definitions |
|---|---|---|---|---|---|---|---|
| | period: 6 weeks<br>– Titration period: 18 weeks<br>– Post-treatment follow-up period: 4 weeks | | | | | | |

ACS: acute coronary syndrome, DAR: darbepoetin alfa, dL: deciliter, EPO: epoetin alfa, ESA: erythropoiesis stimulating agent, g: gram, Hb: hemoglobin, HD: hemodialysis, HDF: hemodiafiltration, IU: international unit, IV: intravenous, kg: kilogram, µg: microgram, mg: milligram, MI: myocardial infarction, mL: milliliter, N: total number, ng: nanogram, NYHA: New York Heart Association, PD: peritoneal dialysis, QW: weekly, RBC: red blood cell, rHuEPO: recombinant human erythropoietin, SC: subcutaneous, SOC: standard of care, TIW: thrice weekly, TSAT: transferrin saturation.

**Evidence Table 17. Baseline Characteristics – Key Trials**

| Trial | | HIMALAYAS[2,11] | | ROCKIES[2,4,17] | | SIERRAS[2] | | PYRENEES[2,12,18] | |
|---|---|---|---|---|---|---|---|---|---|
| Arm | | ROX (N=522) | EPO (N=521) | ROX (N=1068) | EPO (N=1065) | ROX (N=370) | EPO (N=371) | ROX (N=414) | ESA* (N=420) |
| Age, Mean Years (SD) | | 53.8 (14.7) | 54.3 (14.6) | 53.5 (15.3) | 54.5 (15.0) | 57.6 (NR) | 58.4 (NR) | 61.0 (13.8) | 61.8 (13.4) |
| Male, n (%) | | 309 (59.2) | 307 (58.9) | 625 (59.3) | 626 (59.3) | NR | | 245 (59.2) | 235 (56.0) |
| White, n (%) | | 478 (91.6) | 471 (90.4) | 607 (56.8) | 580 (56.7) | 165 (44.6) | 184 (49.6) | 405 (97.8) | 407 (96.9) |
| Hemodialysis, n (%) | | 469 (89.8) | 462 (88.7) | 953 (89.2) | 947 (88.9) | NR | | NR | |
| Peritoneal Dialysis, n (%) | | 53 (10.2) | 58 (11.1) | 113 (10.6) | 118 (11.1) | NR | | NR | |
| Dialysis Vintage <4 Months, n (%) | | 522 (100) | 521 (100) | 202 (18.9) | 215 (20.2) | 36 (9.7) | 35 (9.5) | 0 (0) | 0 (0) |
| Hb, Mean g/dL (SD) | | 8.43 (1.04) | 8.46 (0.96) | 9.99 (1.20) | 10.02 (1.20) | 10.25 (NR) | 10.25 (NR) | 10.75 (0.62) | 10.78 (0.62) |
| Transferrin Saturation, Mean % (SD) | | 27.02 (9.30) | 27.56 (8.90) | NR | | 33.60 (10.1) | 33.60 (10.0) | NR | |
| Ferritin, Mean ng/mL (SD) | | 441.00 (337.00) | 437.00 (311.40) | NR | | 1000.2 (459.1) | 960.80 | NR | |
| CRP, mg/L | Mean (SD) | NR | | NR | | NR | | NR | |
| | >ULN†, n (%) | 228 (43.7) | 226 (43.4) | NR | | 189 (51.1) | 177 (47.7) | NR | |
| Data not reported for the following baseline characteristics: History of hypertension, hepcidin, transferrin, soluble transferrin receptor, serum iron, total iron binding capacity, iron status – replete, total cholesterol, LDL-cholesterol, HDL-cholesterol | | | | | | | | | |

CRP: C-reactive protein, dL: deciliter, EPO: epoetin alfa, ESA: erythropoiesis-stimulating agent, g: gram, L: liter, mL: milliliter, N: total number, n: number, ng: nanogram, NR: not reported, PBO: placebo, ROX: Roxadustat, SD: standard deviation, ULN: upper limit of normal

*: Includes both epoetin alfa and darbepoetin alfa

†: Defined as 4.9 mg/L

**Evidence Table 18. Baseline Characteristics – Other Phase III Trials**

| Trial | | FGCL-4592-806[13] | | 1517-CL-0307[14] | |
|---|---|---|---|---|---|
| **Arm** | | **ROX (N=204)** | **EPO (N=100)** | **ROX (N=150)** | **DAR (N=151)** |
| **Age, Mean Years (SD)** | | 47.6 (11.7) | 51.0 (11.8) | 64.6 (11.7) | 64.9 (10.1) |
| **Male, n (%)** | | 126 (61.8) | 58 (58.0) | 101 (67.3) | 107 (70.9) |
| **White, n (%)** | | 0 (0)# | 0 (0)# | 0 (0)# | 0 (0)# |
| **Hemodialysis, n (%)** | | 182 (89.2) | 89 (89.0) | 150 (100) | 151(100) |
| **Peritoneal Dialysis, n(%)** | | 22 (10.8) | 11 (11.0) | 0 (0) | 0 (0) |
| **Dialysis Vintage <4 Months, n (%)** | | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Hb, Mean g/dL (SD)** | | 10.4 (0.7) | 10.5 (0.7) | 11.02 (0.56) | 11.01 (0.60) |
| **Hepcidin, Mean ng/mL (SD)** | | 180.70 (SE: 136.80) | 148.30 (SE: 104.2) | 26.44 (21.50) | 24.45 (21.00) |
| **Transferrin, Mean g/L (SD)** | | 1.89 (0.46) | 1.91 (0.39) | 1.80 (0.33) | 1.81 (0.30) |
| **Transferrin Saturation, Mean % (SD)** | | 33.80 (16.6) | 30.00 (13.80) | 28.28 (11.70) | 29.04 (10.18) |
| **Serum Iron, Mean µg/dL (SD)** | | NR | NR | 67.60 (28.49)† | 70.39 (25.14)† |
| **Total Iron binding Capacity, Mean µg/dL (SD)** | | 264.80 (63.69)† | 269.83 (50.28)† | NR | NR |
| **Ferritin, Mean ng/mL (SD)** | | 498.5 (487.4) | 420.1 (406.8) | 102.31 (83.45) | 96.28 (75.14) |
| **Iron Status - Replete‡, n (%)** | | NR | NR | 44 (29.3) | 48 (31.8) |
| **CRP, mg/L** | **Mean (SD)** | NR | NR | 1.32 (2.41) | 1.46 (2.29) |
| | **>ULN*, n (%)** | 46 (22.5) | 20 (20.0) | NR | NR |
| **Total Cholesterol, Mean mg/dL (SD)** | | 168.2 (42.9) | 165.1 (41.4) | NR | NR |
| **LDL-C, Mean mg/dL (SD)** | | 95.1 (34.8) | 90.1 (29.4) | NR | NR |
| **HDL-C, Mean mg/dL (SD)** | | 43.3 (12.0) | 44.5 (15.1) | NR | NR |
| Data for the following baseline characteristics not reported: History of hypertension, Soluble transferrin receptor | | | | | |

CRP: C-reactive protein, DAR: darbepoetin alfa, dL: deciliter, EPO: epoetin alfa, g: gram, HDL-C: High-density lipoprotein cholesterol, L: liter, LDL-C: low density lipoprotein cholesterol, mg: milligram, mL: milliliter, N: total number, n: number, ng: nanogram, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation, SE: standard error, ULN: upper limit of normal

*: Defined as 4.9 mg/L

†: Converted from µmol/L to µg/dL

‡: Ferritin ≥100 ng/ml and TSAT ≥20%

#: All patients were Asian

**Evidence Table 19. Baseline Characteristics – Phase II Trials**

| Trial | FGCL-4592-040[15] | | | | FGCL-4592-048[8] | | | | 1517-CL-0304[16] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm | Pooled ROX (Pt 1) (N=41) | EPO (Pt 1) (N=13) | Pooled ROX (Pt 2) (N=67) | EPO (Pt 2), (N=23) | ROX, Low (N=25) | ROX, Medium (N=24) | ROX, High (N=25) | EPO (N=22) | ROX 50 mg (N=32) | ROX 70 mg (N=32) | ROX 100 mg (N=31) | DAR (N=32) |
| Age, Mean Years (SD) | 55.8 (13.4) | 59.5 (10.1) | 56.9 (12.1) | 57.0 (11.6) | 49.9 (14.7) | 50.2 (9.3) | 49.8 (13.5) | 53.8 (10.0) | 62.3 (8.7) | 62.4 (9.7) | 61.7 (9.8) | 60.0 (7.9) |
| Male, n (%) | 27 (66.0) | 9 (69.0) | 45 (67.0) | 14 (61.0) | 16 (64.0) | 14 (58.3) | 15 (60.0) | 13 (59.1) | 22 (68.8) | 24 (75.0) | 25 (80.6) | 22 (68.8) |
| White, n (%) | 27 (66.0) | 5 (39.0) | 35 (52.0) | 6 (26.0) | 0 (0)‡ | 0 (0)‡ | 0 (0)‡ | 0 (0)‡ | 0 (0)‡ | 0 (0)‡ | 0 (0)‡ | 0 (0)‡ |
| Hemodialysis, n (%) | 41 (100) | 13 (100) | 67 (100) | 23 (100) | 25 (100) | 24 (100) | 25 (100) | 22 (100) | 32 (100) | 32 (100) | 31 (100) | 32 (100) |
| Peritoneal Dialysis, n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Dialysis Vintage <4 Months, n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Hb, Mean g/dL (SD) | 11.3 (0.6) | 11.5 (0.6) | 11.2 (0.7) | 11.2 (1.0) | 10.9 (0.7) | 10.7 (0.8) | 10.8 (0.6) | 10.6 (1.0) | 8.92 (0.38) | 8.79 (0.42) | 8.80 (0.60)¤ | 8.80 (0.51) |
| Hepcidin, Mean ng/mL (SD) | 236.6 (159.7) | 279.3 (137.6) | 327.1 (178.8) | 298.7 (123.1) | 157.0 (124.0) | 198.4 (113.1) | 174.4 (124.0) | 209.0 (127.1) | NR | | | |
| Transferrin, Mean g/L (SD) | NR | NR | NR | NR | 1.88 (0.39)# | 1.94 (0.36)# | 1.86 (0.58)# | 1.87 (0.35)# | 1.70 (0.27) | 1.77 (0.39) | 1.65 (0.25)¤ | 1.78 (0.28) |
| Transferrin Saturation, Mean % (SD) | 30.10 (8.20) | 31.50 (11.50) | 29.20 (10.20) | 28.60 (14.60) | 29.8 (16.7) | 32.1 (18.2) | 32.8 (15.8) | 34.1 (14.6) | 42.37 (16.78) | 44.76 (15.85) | 43.87 (15.79)¤ | 37.26 (16.06) |
| Soluble Tansferrin Receptor, Mean mg/L (SD) | 2.74 (0.86) | 3.25 (0.76) | 4.03 (1.81) | 3.69 (0.93) | 3.90 (1.80) | 3.40 (1.20) | 3.40 (1.10) | 2.90 (1.20) | 0.78 (0.33)§ | 0.78 (0.36)§ | 0.88 (0.43)§ | 1.02 (0.5)§ |
| Serum Iron, Mean µg/dL (SD) | 70.40 (20.90) | 70.20 (27.20) | 66.40 (20.60) | 63.30 (32.00) | 68.0 (35.6) | 75.5 (39.5) | 71.9 (21) | 79.0 (31.9) | 92.18 (29.61)¥ | 103.35 (42.46)¥ | 94.41 (32.96)¥¤ | 85.47 (35.75)¥ |
| TIBC, Mean µg/dL (SD) | 210.80 (41.30) | 200.80 (30.90) | 199.7 (34.00) | 202.10 (26.70) | 218.0 (46.0) | 221.0 (41.0) | 213.0 (61.0) | 214.0 (38.0) | 225.14 (28.49)¥ | 234.08 (46.37)¥ | 218.99 (26.82)¥¤ | 234.64 (32.96)¥ |
| Ferritin, Mean ng/mL (SD) | 917.30 (458.0) | 929.70 (494.2) | 826.8 (484.5) | 1106.60 (642.1) | 380.0 (345.0) | 488.0 (372.0) | 485.0 (391.0) | 458.0 (361.0) | 191.52 (209.26) | 186.70 (220.10) | 192.52 (119.74)¤ | 156.99 (102.49) |

| Trial | | FGCL-4592-040[15] | | | | FGCL-4592-048[8] | | | | 1517-CL-0304[16] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | Pooled ROX (Pt 1) (N=41) | EPO (Pt 1) (N=13) | Pooled ROX (Pt 2) (N=67) | EPO (Pt 2), (N=23) | ROX, Low (N=25) | ROX, Medium (N=24) | ROX, High (N=25) | EPO (N=22) | ROX 50 mg (N=32) | ROX 70 mg (N=32) | ROX 100 mg (N=31) | DAR (N=32) |
| CRP, mg/L | Mean (SD) | NR | | | | 4.04 (5.30) | 6.65 (9.83) | 1.94 (3.04) | 3.00 (4.70) | NR | | | |
| | >ULN*, n (%) | | | | | NR | | | | | | | |
| Total Cholesterol, Mean mg/dL (SD) | | NR | | | | 172.0 (38.0) | 169.0 (32.0) | 172.0 (36.0) | 158.0 (28.0) | NR | | | |
| LDL-C, Mean mg/dL (SD) | | NR | | | | 103.0 (31.0) | 100.0 (30.0) | 103.0 (24.0) | 91.0 (24.0) | NR | | | |
| HDL-C, Mean mg/dL (SD) | | NR | | | | 39.0 (12.0) | 39.0 (14.0) | 39.0 (15.0) | 41.0 (14.0) | NR | | | |
| Data for the following baseline characteristics not reported: iron status – replete** | | | | | | | | | | | | | |

CRP: C-reactive protein, dL: deciliter, EPO: epoetin alfa, ESA: erythropoiesis stimulating agent, g: gram, L: liter, µg: microgram, mL: milliliter, N: total number, n: number, ng: nanogram, NR: not reported, PBO: placebo, Pt.: part, ROX: Roxadustat, SD: standard deviation, TIBC: Total iron binding capacity, ULN: upper limit of normal

*: Defined as 4.9 mg/L

†: N of patients for whom data was available

‡: Participants were Asian

#: Converted from mg/dL to g/L

¥: Converted from µmol/L to µg/dL

§: Converted from nmol/L to mg/L

¤: n=30

**: defined as ≥100 ng/mL and TSAT ≥20%

**Evidence Table 20. Efficacy Outcomes – Key Trials**

| Trials | | | HIMALAYAS[2,11] | | ROCKIES[2,4,17] | | SIERRAS[2] | | PYRENEES[2,12,18] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | ROX | EPO | ROX | EPO | ROX | EPO | ROX | ESA¥ |
| Change in Hb, g/dL | Timepoint | | Average of 28 to 52 Weeks | | | | | | | |
| | N | | 522 | 521 | 1003 | 1016 | 370 | 371 | 413 | 420 |
| | LSM (SE) | | Mean: 2.57 (NR) | Mean: 2.36 (NR) | 0.77 (0.04) | 0.68 (0.04) | Mean: 0.39 (SD: 0.95) | Mean: -0.09 (SD: 0.90) | 0.36 (95% CI: 0.29, 0.44) | 0.19 (95% CI: 0.21, 0.26) |
| | In Between Group Diff. | LSM (95% CI), p-value | 0.18 (0.079, 0.287), 0.0005 | | 0.09 (0.01, 0.18), 0.036 | | 0.48 (0.37, 0.59), <0.0001 | | 0.171 (0.08, 0.26), <0.001 | |
| Hb Response | Timepoint | | 24 Weeks | | Average of 28 to 52 Weeks | | Average of 28 to 52 Weeks | | Average of 28 to 36 weeks | |
| | N | | 522 | 521 | 896 | 941 | 370 | 371 | 386 | 397 |
| | n (%) | | 460 (88.2) | 440 (84.4) | 708 | 715 | 245 (66.1) | 217 (58.6) | 325 (84.2) | 327 (82.4) |
| | Between Group Diff. | LSM (95% CI), p-value | 3.5 (-0.7, 7.7), NR | | 0.03 (0.00, 0.05), <0.045 | | NR | | 2.3 (-2.9, 7.6), NR | |
| Use of Rescue Therapy | Timepoint | | NR | | NR | | NR | | Up to 104 weeks | |
| | N | | | | | | | | 413 | 420 |
| | n (%) | | | | | | | | 53 (12.8) | 60 (14.4) |
| | Time to Event | HR (95% CI), p-value | | | | | | | 0.98 (0.66, 1.46), NR | |
| Use of Blood Transfusion | Timepoint | | During Treatment# | | During Treatment Period# + 28 days | | During Treatment** | | 104 weeks | |
| | N | | 522 | 521 | 1048 | 1053 | 370 | 371 | 413 | 420 |
| | Time to First Transfusion, Months (95% CI) | | NR | | Ep100PY: 6.0 | Ep100PY: 7.2 | NR | | 11.4 (8.0, 14.9) | 14.4 (10.8, 18.0) |
| | n (%) | | | | NR | NR | 46 (12.5) | 78 (21.0) | NR | |
| | Time to Event | HR (95% CI), p-value | 1.26 (0.79, 2.02), 0.328 | | 0.83 (0.64, 1.07), 0.151 | | 0.67 (NR), <0.0037 | | 0.87 (0.57, 1.31), NR | |
| Use of IV Iron | Timepoint | | Average of 45 to 52 Weeks | | Week 36 to End of Study | | 36 Weeks | | Week 53 to 104 | |
| | N | | 522 | 513 | 885 | 920 | 370 | 371 | 413 | 420 |
| | Mean Monthly Use, mg (SD) | | 46.9 (8.1)* | 71.5 (7.5)* | 58.7 (236.1) | 91.4 (225.6) | 17.1 (53.4) | 37.0 (106.8) | LSM: 49.5 (95% CI: 31.0, 67.9) | LSM: 98.1 (95% CI: 81.1, 115.2) |
| | n (%) | | NR | | NR | | NR | | NR | |

| Trials | | | | | | | SIERRAS[2] | | PYRENEES[2,12,18] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | | | | | X | EPO | ROX | ESA¥ |
| | Time to Event | HR (95% CI), p-value | NR, 000028 | | NR, <0.0001 | | NR, =0.00091 | | LSM: -35.1 (-51.8, -18.4), <0.001† | |
| Change in Hepcidin, ng/mL | Timepoint | | NR | | 24 Weeks | | 52 Weeks | | up to 108 weeks | |
| | N | | | | 608 | 625 | 370 | 371 | 280 | 320 |
| | Mean (SD) | | | | -44.99 (NR) | -16.77 (NR) | –95.53 (148.27) | –66.66 (141.61) | -27.19 (52.17) | -17.66 (51.69) |
| | Between Group Diff. | Mean (95% CI), p-value | | | NR, <0.001 | | NR, 0.0662 | | NR | |
| Change in Transferrin Saturation, % | Timepoint | | 52 Weeks | | Week 24 to End of Treatment | | 52 Weeks | | 108 Weeks | |
| | N | | 522 | 513 | 866 | 939 | 370 | 371 | 283 | 321 |
| | Mean (SD) | | -2.10 (0.70)* | -2.30 (0.50)* | -1.92 (NR) | -2.44 (NR) | –7.96 (13.7) | –9.78 (13.07) | -5.47 (16.63) | -3.76 (17.81) |
| | Between Group Diff. | Mean (95% CI), p-value | NR | | -0.52 (NR), 0.287 | | NR, 0.0341 | | NR | |
| Change in Soluble Transferrin Receptor, mg/L | Timepoint | | NR | | Week 24 to end of treatment | | NR | | NR | |
| | N | | | | 874 | 946 | | | | |
| | Mean (SD) | | | | 0.35 (NR) | –0.02 (NR) | | | | |
| | Between Group Diff. | Mean (95% CI), p-value | | | NR, <0.001 | | | | | |
| Change in Serum iron, µg/dL | Timepoint | | NR | | Week 24 to End of Treatment | | 52 Weeks | | NR | |
| | N | | | | 877 | 946 | 370 | 3 | | |
| | Mean (SD) | | | | 6.58 (NR) | -5.54 (NR) | -2.12 (36.12) | -15.64 (28.3) | | |
| | Between Group Diff. | Mean (95% CI), p-value | | | NR, <0.001 | | NR, <0.0001 | | | |
| Change in Ferritin, ng/mL | Timepoint | | NR | | NR | | 52 Weeks | | 108 Weeks | |
| | N | | | | | | 370 | 371 | 290 | 323 |
| | Mean (SD) | | | | | | –4.26 (3.40) | –3.94 (3.39) | NR | NR |

| Trials | | | HIMALAYAS[2,11] | | ROCKIES[2,4,17] | | SIERRAS[2] | | PYRENEES[2,12,18] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | ROX | EPO | ROX | EPO | ROX | EPO | ROX | ESA¥ |
| | Between Group Diff. | Mean (95% CI), p-value | | | | | NR, 0.1356 | | NR | |
| Change in Total Cholesterol, mg/dL | Timepoint | | NR | | NR | | Weeks 12 to 28 | | 104 Weeks | |
| | N | | | | | | 370 | 371 | 247 | 307 |
| | Mean (SD) | | | | | | -23.9 | -1.7 | -0.90 (1.05) | -0.28 (1.00) |
| | Between Group Diff. | Mean (95% CI), p-value | | | | | NR | | NR | |
| Change in LDL-C, mg/dL | Timepoint | | NR | | 24 Weeks | | Average of Weeks 12 to 28 | | Average of Weeks 12 to 28 | |
| | N | | | | 902 | 937 | 370 | 371 | 394 | 412 |
| | Mean (95% CI) | | | | -14.67 (SD: 1.00)‡ | -1.93 (SD: 1.00)‡ | -13.70 (NR) | 1.23 (NR) | LSM: -17.72 (20.07, -15.44) | LSM: -3.17 (-5.33, -1.00) |
| | Between Group Diff. | LSM (95% CI), p-value | | | -12.74 (-15.05, -10.42)‡, <0.001 | | –14.67 (–17.64, –11.70), <0.0001 | | -14.67 (-17.37, -11.58), <0.001 | |
| Data on the following outcomes not reported: Use of ESA treatment, change in transferrin, change in total iron binding capacity, change in HDL-C | | | | | | | | | | |

95% CI: 95% confidence interval, Diff.: difference, dL: deciliter, EPO: epoetin alfa, Ep100PY: event per 100 person years, ESA: erythropoiesis stimulating agent, g: gram, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, IV: intravenous, L: liter, LDL-C: low-density lipoprotein cholesterol, HR: hazard ratio, LSM: least squares mean, µg: microgram, mg: milligram, mL: milliliter, N: total number, n: number, ng: nanogram, NR: not reported, ns: not significant, PBO: placebo, ROX: Roxadustat, SD: standard deviation, SE: standard error

*: Data are digitized and should be interpreted with caution

†: LSM difference in monthly IV iron use

‡: Converted to mg/dL

¥: Includes both epoetin alfa and darbepoetin alfa

#: Up to 4 years

**: Up to 3 years

**Evidence Table 21. Efficacy Outcomes – Other Phase III Trials**

| Trials | | | FGCL-4592-806[13] | | 1517-CL-0307[14] | |
|---|---|---|---|---|---|---|
| Arm | | | ROX (N=204) | EPO (N=100) | ROX (N=114) | DAR (N=131) |
| Change in Hb, g/dL | Timepoint | | Average of 23 to 27 Weeks | | Average of 18 to 24 Weeks | |
| | LSM (SE) | | Mean: 0.70 (SD: 1.1) | Mean: 0.50 (SD: 1.00) | -0.04 (95% CI: -0.16, 0.08) | -0.03 (95% CI: -0.14, 0.09) |
| | Between Group Difference | LSM (95%C), p-value | 0.20 (-0.02, 0.50), NR | | -0.02 (-0.18, 0.15), NR | |
| Hb Response | Timepoint | | 23 to 27 Weeks | | NR | |
| | n (%) | | 189 (92.5) | 93 (92.5) | | |
| | Between Group Diff. | LSM (95% CI), p-value | 0.2 (-7.1, 7.6), NR | | | |
| Use of Rescue Therapy | Timepoint | | 27 Weeks | | NR | |
| | n (%) | | 3 (1.5) | 1 (1.0) | | |
| | Time to Event | HR (95% CI), p-value | 1.68 (0.18, 16.19), NR | | | |
| Use of ESA Treatment | Timepoint | | Up to and including 2 days after trial-drug discontinuation | | NR | |
| | n (%) | | 2 (1.0) | NR | | |
| | Time to Event | HR (95% CI), p-value | NR | | | |
| Change in Hepcidin, ng/mL | Timepoint | | 27 Weeks | | 24 Weeks | |
| | N | | 155 | 90 | 150 | 151 |
| | Mean (SD) | | -30.20 (SE: 113.30) | -2.30 (SE: 130.70) | 2.31 (27.28) | -0.60 (27.06) |
| | Between Group Diff. | LSM (95% CI), p-value | NR | | NR | |
| Change in Transferrin, g/L | Timepoint | | 27 Weeks | | 24 Weeks | |
| | N | | 160 | 94 | 150 | 151 |
| | Mean (SD) | | LSM: 0.38 (SE: 0.05) | LSM: -0.05 (SE: 0.04) | 0.42 (0.39) | 0.11 (0.29) |
| | Between Group Diff. | LSM (95% CI), p-value | 0.43 (0.32, 0.53), NR | | NR | |
| Change in Transferrin Saturation, % | Timepoint | | 27 Weeks | | 24 Weeks | |
| | N | | 159 | 93 | 150 | 151 |
| | Mean (SD) | | LSM: -4.50 (SE: 1.20) | LSM: -8.70 (SE: 1.00) | -1.09 (13.84) | -2.44 (13.83) |
| | Between Group Diff. | LSM (95% CI), p-value | 4.20 (1.50, 6.90), NR | | NR | |

| Trials | | | FGCL-4592-806[13] | | 1517-CL-0307[14] | |
|---|---|---|---|---|---|---|
| Arm | | | ROX (N=204) | EPO (N=100) | ROX (N=114) | DAR (N=131) |
| Change in Soluble Transferrin Receptor, mg/L | Timepoint | | NR | | 24 weeks | |
| | N | | | | 150 | 151 |
| | Mean (SD) | | | | 0.14 (0.90)† | 0.36 (0.96)† |
| | Between Group Diff. | Mean (95% CI), p-value | | | NR | |
| Change in Serum iron, µg/dL | Timepoint | | 27 Weeks | | 24 Weeks | |
| | N | | 160 | 94 | 150 | 151 |
| | Mean (SD) | | LSM: 3.35 (SE: 3.91)* | LSM: -21.79 (SE: 2.79)* | 6.70 (35.75)* | -5.03 (30.73)* |
| | Between Group Diff. | LSM (95% CI), p-value | 24.58 (16.76, 32.96)*, NR | | NR | |
| Change in Total Iron Binding Capacity, µg/dL | N | | 159 | 93 | 150 | 151 |
| | Timepoint | | 27 weeks | | 24 weeks | |
| | Mean (SD) | | LSM: 53.07 (SE: 6.70)* | LSM: -6.70 (SE: 6.15)* | 43.58 (45.25)* | 8.94 (31.84)* |
| | Between Group Diff. | LSM (95% CI), p-value | 59.78 (45.25, 74.30)*, NR | | NR | |
| Change in Ferritin, ng/mL | Timepoint | | 27 Weeks | | 24 weeks | |
| | N | | 160 | 94 | 150 | 151 |
| | Mean (SD) | | LSM: -99.00 (SE: 19.00) | LSM: -133.00 (SE: 21.00) | -3.98 (78.41) | 18.75 (64.64) |
| | Between Group Diff. | LSM (95% CI), p-value | 35.00 (-12.00, 82.00), NR | | NR | |
| Change in Total Cholesterol, mg/dL | Timepoint | | 27 Weeks | | NR | |
| | N | | 158 | 94 | | |
| | Mean (SD) | | -26.70 (30.60) | 3.99 (NR)‡ | | |
| | Between Group Diff. | Mean (95% CI), p-value | -22.00 (-29.00, 16.00), NR | | | |
| Change in LDL-C, mg/dL | Timepoint | | 27 Weeks | | NR | |
| | N | | 204 | 101 | | |
| | Mean (SD) | | -24.00 (24.70) | 1.53 (NR)‡ | | |
| | Between Group Diff. | LSM (95% CI), p-value | -18.00 (-23.00, -13.00), NR | | | |
| Change in HDL-C, mg/dL | Timepoint | | 27 Weeks | | NR | |

| Trials | | | FGCL-4592-806[13] | | 1517-CL-0307[14] | |
|---|---|---|---|---|---|---|
| Arm | | | ROX (N=204) | EPO (N=100) | ROX (N=114) | DAR (N=131) |
| | N | | 204 | 101 | | |
| | Mean (SD) | | 4.3 (7.7) | 2.67 (NR)‡ | | |
| | Between Group Diff. | Mean (95% CI), p-value | -2.00 (-4.00, -0.10), NR | | | |
| No data reported on the following outcomes: Use of blood transfusion, use of IV iron | | | | | | |

95% CI: 95% confidence interval, DAR: darbepoetin alfa, Diff.: difference, dL: deciliter, EPO: epoetin alfa, Ep100PY: event per 100 person years, ESA: erythropoiesis stimulating agent, g: gram, Hb: hemoglobin, HR: hazard ratio, IV: intravenous, L: liter, LSM: least squares mean, µg: microgram, mL: milliliter, N: total number, n: number, ng: nanogram, NR: not reported, ns: not significant, ROX: Roxadustat, SD: standard deviation, SE: standard error

*: Converted from µmol/L to µg/dL

†: Converted from nmol/L to mg/L

‡: Data are digitized and should be interpreted with caution

**Evidence Table 22. Efficacy Outcomes – Phase II Trials**

| Trials | | | FGCL-4592-040[15] | | | | FGCL-4592-048[8] | | | | | 1517-CL-0304[16] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | Pooled ROX (Pt 1) | EPO (Pt 1) | Pooled ROX (Pt 2) | EPO (Pt 2) | ROX low | ROX medium | ROX high | Pooled ROX | EPO | ROX, 50 mg | ROX, 70 mg | ROX, 100 mg | DAR |
| Change in Hb, g/dL | Timepoint | | 6 Weeks | | 19 Weeks | | 6 Weeks | | | | | Average of 18 to 24 Weeks | | | |
| | N | | 41 | 13 | 61 | 22 | 22 | 18 | 20 | 60 | 22 | 17 | 24 | 22 | 27 |
| | Mean (SD) | | LSM (SE): 0.30 (NR) | LSM (SE): -1.00 (NR) | LSM (SE): -0.50 (0.20) | LSM (SE): -0.50 (0.30) | 0.11 (1.00) | 1.10 (1.00) | 1.42 (1.21) | 0.84 (1.18) | 0.17 (0.96) | 1.33 (0.81) | 1.37 (0.93) | 1.57 (0.98) | 1.42 (1.02) |
| | Between Group Diff. | LSM (95% CI) p-value | NR | | -0.03 (-0.39, 0.33), NR | | NR | | | | | NR | | | |
| Hb Response | Timepoint | | 4 Weeks | | 15 – 19 Weeks | | 6 Weeks | | | | | 24 Weeks | | | |
| | N | | 33 | 9 | 61 | 22 | 22 | 18 | 20 | 60 | 22 | 15 | 22 | 19 | 24 |
| | n (%) | | 23 (67.9) | 3 (33.3) | 31 (51.0) | 8 (36.0) | 13 (59.1) | 16 (88.9) | 20 (100.0) | 49 (81.7) | 11 (50.0) | 9 (60.0) | 15 (68.2) | 14 (73.7) | 15 (62.5) |
| | Between Group Diff. | LSM (95% CI), p-value | NR, 0.063 | | NR | | NR, 0.53 | NR, 0.008 | NR, 0.0003 | NR, 0.004 | -- | NR | NR | NR | --- |
| Use of Rescue Therapy | Timepoint | | NR | | | | 6 Weeks | | | | | NR | | | |
| | N | | | | | | 22 | 18 | 20 | 60 | 22 | | | | |
| | n (%) | | | | | | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | | | |
| | Time to Event | HR (95% CI), p-value | | | | | NR | | | | | | | | |
| Use of Blood Transfusion | Timepoint | | NR | | | | 6 Weeks | | | | | NR | | | |
| | N | | | | | | 22 | 18 | 20 | 60 | 22 | | | | |
| | Time to First Transfusion | | | | | | NR | NR | NR | NR | NR | | | | |
| | n (%) | | | | | | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | | | |

| Trials | | | FGCL-4592-040[15] | | | | FGCL-4592-048[8] | | | | | 1517-CL-0304[16] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | Pooled ROX (Pt 1) | EPO (Pt 1) | Pooled ROX (Pt 2) | EPO (Pt 2) | ROX low | ROX medium | ROX high | Pooled ROX | EPO | ROX, 50 mg | ROX, 70 mg | ROX, 100 mg | DAR |
| | Time to Event | HR (95% CI), p-value | | | | | NR | | | | | | | | |
| Use of IV Iron | Timepoint | | 6 Weeks | | 19 Weeks | | 6 Weeks | | | | | | | | |
| | N | | 41 | 13 | 67 | 23 | 22 | 18 | 20 | 60 | 22 | | | | |
| | Mean monthly use, mg (SD) | | NR | NR | NR | NR | | | | | | | | | |
| | n (%) | | 5 (12.0) | 2 (15.0) | 2 (3.0) | 3 (13.0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | | | |
| | Time to Event | HR (95% CI) p-value | NR | | NR, 0.1 | | NR | | | | | | | | |
| Use of ESA Treatment | N | | NR | | | | 22 | 18 | 20 | 60 | 22 | | | | |
| | Timepoint | | | | | | 6 Weeks | | | | | | | | |
| | n (%) | | | | | | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | | | |
| | Time to Event | HR (95% CI) p-value | | | | | NR | | | | | | | | |
| Change in Hepcidin, ng/mL | Timepoint | | 6 Weeks | | 19 Weeks | | 6 Weeks | | | | | | | | |
| | N | | 33 | 9 | 61 | 22 | 22 | 18 | 20 | 60 | 22 | | | | |
| | Mean (SD) | | -39.2 (226.9) | -6.5 (140.1) | -60.4 (187.8) | 35.6 (123.4) | -25.70 (108.68) | -86.00 (109.41) | -102.70 (80.40) | -70.20 (104.19) | -77.90 (75.18) | | | | |
| | Between Group Diff. | Mean (95% CI), p-value | NR 0.3 | | NR 0.04 | | NR 0.13 | NR 0.65 | NR 0.005 | NR 0.71 | -- | | | | |
| Change in Transferrin, g/L | N | | NR | | | | 22 | 18 | 20 | 60 | 22 | | | | |
| | Timepoint | | | | | | 6 weeks | | | | | | | | |
| | Mean (SD) | | | | | | 0.40 (0.38)* | 0.50 (0.44)* | 0.59 (0.41)* | 0.50 (0.41)* | 0.03 (0.16)* | | | | |

| Trials | | | FGCL-4592-040[15] | | | | FGCL-4592-048[8] | | | | | 1517-CL-0304[16] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | Pooled ROX (Pt 1) | EPO (Pt 1) | Pooled ROX (Pt 2) | EPO (Pt 2) | ROX low | ROX medium | ROX high | Pooled ROX | EPO | ROX, 50 mg | ROX, 70 mg | ROX, 100 mg | DAR |
| | Between Group Diff. | Mean (95% CI) p-value | | | | | NR, 0.0004 | NR, <0.0001 | NR, <0.0001 | NR, <0.0001 | -- | | | | |
| Change in Transferrin Saturation, % | Timepoint | | 6 Weeks | | 19 Weeks | | 6 Weeks | | | | | NR | | | |
| | N | | 33 | 9 | 61 | 22 | 22 | 18 | 20 | 60 | 22 | | | | |
| | Mean (SD) | | -2.50 (13.7) | -7.00 (4.1) | -2.40 (18.9) | -5.30 (12.5) | -3.77 (21.41) | -8.98 (14.73) | -4.87 (17.22) | -5.77 (17.93) | -8.29 (10.46) | | | | |
| | Between Group Diff. | Mean (95% CI) p-value | NR, 0.4 | | NR, 0.4 | | NR, 0.8 | NR, 0.98 | NR, 0.57 | NR, 0.74 | -- | | | | |
| Change in Soluble Transferrin Receptor, mg/L | Timepoint | | 6 Weeks | | 19 Weeks | | 6 Weeks | | | | | NR | | | |
| | N | | 33 | 9 | 61 | 22 | 22 | 18 | 20 | 60 | 22 | | | | |
| | Mean (SD) | | 0.69 (1.54) | 0.20 (0.73) | 0.86 (2.69) | 20.33 (1.52) | 0.51 (2.38) | 0.52 (0.95) | 2.05 (1.81) | 1.05 (1.95) | 0.88 (1.19) | | | | |
| | Between Group Diff. | Mean (95% CI) p-value | NR, 0.6 | | NR, 0.2 | | NR, 0.59 | NR, 0.48 | NR, 0.011 | NR, 0.52 | -- | | | | |
| Change in Serum iron, µg/dL | Timepoint | | 6 Weeks | | 19 Weeks | | 6 Weeks | | | | | NR | | | |
| | N | | 33 | 9 | 61 | 22 | 22 | 18 | 20 | 60 | 22 | | | | |
| | Mean (SD) | | 7.10 (33.9) | -14.00 (11.1) | 5.2 (42.2) | -5.5 (30.2) | 3.20 (55.8) | -3.30 (34.5) | 8.90 (35.9) | 3.10 (43.0) | -18.90 (26.7) | | | | |
| | Between Group Diff. | Mean (95% CI) p-value | NR, 0.07 | | NR, 0.1 | | NR, ns | NR, ns | NR, <0.05 | NR, ns | -- | | | | |
| Change in Total Iron Binding Capacity, µg/dL | Timepoint | | 6 Weeks | | 19 Weeks | | 6 Weeks | | | | | NR | | | |
| | N | | 33 | 9 | 61 | 22 | 22 | 18 | 20 | 60 | 22 | | | | |
| | Mean (SD) | | 51.0 (27.4) | 5.0 (26.4) | 37.6 (41.4) | 25.6 (47.3) | 41.5 (37.5) | 50.6 (46.0) | 59.1 (40.5) | 50.5 (41.3) | 0.5 (17.4) | | | | |
| | Between Group Diff. | Mean (95% CI) p-value | NR, <0.001 | | NR, 0.3 | | NR, 0.0001 | NR, <0.0001 | NR, <0.0001 | NR, <0.0001 | -- | | | | |
| | Timepoint | | 6 Weeks | | 19 Weeks | | 6 Weeks | | | | | NR | | | |

| Trials | | | FGCL-4592-040[15] | | | | FGCL-4592-048[8] | | | | | 1517-CL-0304[16] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | Pooled ROX (Pt 1) | EPO (Pt 1) | Pooled ROX (Pt 2) | EPO (Pt 2) | ROX low | ROX medium | ROX high | Pooled ROX | EPO | ROX, 50 mg | ROX, 70 mg | ROX, 100 mg | DAR |
| Change in Ferritin, ng/mL | N | | 33 | 9 | 61 | 22 | 22 | 18 | 20 | 60 | 22 | | | | |
| | Mean (SD) | | -185.5 (190.5) | -146.5 (180.7) | -201.1 (334.4) | -211.6 (445.2) | 21.0 (186.0) | -149.0 (145.0) | -162.0 (179.0) | -95.0 (189.0) | -70.0 (157.0) | | | | |
| | Between Group Diff. | Mean (95% CI), p-value | NR, 0.5 | | NR, 0.8 | | NR, 0.06 | NR, 0.13 | NR, 0.04 | NR, 0.52 | -- | | | | |
| Change in Total Cholesterol, mg/dL | Timepoint | | 6 Weeks | | 19 Weeks | | 6 Weeks | | | | | | | | |
| | N | | NR | | 67 | 23 | 22 | 18 | 20 | 60 | 22 | | | | |
| | Mean (SD) | | | | 30.93 (NR)† | 0.72 (NR)† | -11.10 (31.31) | -13.10 (31.64) | -15.80 (48.63) | -13.30 (37.55) | 18.30 (24.32) | | | | |
| | Between Group Diff. | Mean (95% CI) p-value | | | NR, ns | | NR, 0.0045 | NR, 0.0045 | NR, 0.0012 | NR, 0.0003 | -- | | | | |
| Change in LDL-C, mg/dL | Timepoint | | NR | | | | 6 Weeks | | | | | | | | |
| | N | | | | | | 22 | 18 | 20 | 60 | 22 | | | | |
| | Mean (SD) | | | | | | -25.0 (20.2) | -23.4 (20.6) | -25.8 (27.6) | -24.8 (22.6) | -5.0 (15.3) | | | | |
| | Between Group Diff. | Mean (95% CI), p-value | | | | | NR 0.008 | NR 0.013 | NR 0.007 | NR 0.001 | -- | | | | |
| Change in HDL-C, mg/dL | Timepoint | | NR | | | | 6 Weeks | | | | | | | | |
| | N | | | | | | 22 | 18 | 20 | 60 | 22 | | | | |
| | Mean (SD) | | | | | | -8.2 (7.8) | -6.6 (8.4) | -6.6 (12.5) | -7.2 (9.6) | -1.9 (7.4) | | | | |
| | Between Group Diff. | Mean (95% CI) p-value | | | | | NR, 0.005 | NR, 0.034 | NR, 0.014 | NR, 0.002 | -- | | | | |

95% CI: 95% confidence interval, DAR: darbepoetin alfa, Diff.: difference, dL: deciliter, EPO: epoetin alfa, Ep100PY: event per 100 person years, ESA: erythropoiesis-stimulating agent, g: gram, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, IV: intravenous, L: liter, LDL-C: low-density lipoprotein cholesterol, LSM: least squares mean, µg: microgram, mg: milligram, mL: milliliter, N: total number, n: number, ng: nanogram, NR: not reported, ns: not significant, PBO: placebo, pt.: part, ROX: roxadustat, SD: standard deviation, SE: standard error, ULN: upper limit of normal

*: Converted from mg/dL to mg/L

†: Data are digitized and should be interpreted with caution

**Evidence Table 23. Changes in Hb - Subgroups**

| Trial | | | HIMALAYAS[2,11] | | | | | | | | ROCKIES[2,4,17] | | SIERRAS[2] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Population | | | Iron Status – Replete* | | Iron Status - Deplete† | | CRP ≤ULN‡ | | CRP >ULN‡ | | CRP >ULN‡ | | CRP >ULN‡ | |
| Arm | | | ROX (N=NR) | EPO (N=NR) | ROX (N=NR) | EPO (N=NR) | ROX (N=NR) | EPO (N=NR) | ROX (N=NR) | EPO (N=NR) | ROX (N=280) | EPO (N=301) | ROX (N=NR) | EPO (N=NR) |
| Timepoint | | | During Treatment# + 28 Days | | | | | | | | Average of Weeks 28 to 52 | | Average of Weeks 18 to 24 | |
| Change in Hb, g/dL | Mean (SD) | | NR | | NR | | NR | | NR | | 0.80 (NR) | 0.59 (NR) | 0.61 (NR) | -0.03 (NR) |
| | Btw. Group Diff. | Mean (95% CI), p-value | 0.15 (0.03, 0.27), NR | | 0.31 (0.08, 0.54), NR | | 0.18 (0.05, 0.31), NR | | 0.19 (0.02, 0.36), NR | | NR, 0.012 | | 0.69 (0.50, 0.87), <0.0001 | |

95% CI: 95% confidence interval, btw.: between, CRP: c-reactive protein, Diff.: difference, dL: deciliter, EPO: epoetin alfa, g: gram, Hb: hemoglobin, N: total number, NR: not reported, ULN: upper limit of normal, ROX: roxadustat, SD: standard deviation

*: Ferritin ≥100 ng/ml and TSAT ≥20%

†: Ferritin <100 ng/mL or TSAT <20%

‡: Defined as 4.9 mg/L

#: Up to 4 years

**Evidence Table 24. Patient Reported Outcomes – Key Trials**

| Trials | | | HIMALAYAS | | ROCKIES | | SIERRAS | | PYRENEES[17] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | ROX | EPO | ROX | EPO | ROX | EPO | ROX (N=415) | ESA* (N=421) |
| Timepoint | | | Weeks 12-28 | | | | | | | |
| Change in SF-36 Physical Functioning, Points | Mean (95% CI) | | NR | | NR | | NR | | 0.05 (-0.64, 0.74) | -0.16 (-0.83, 0.51) |
| | Between Group Diff. | LSM (95% CI), p-value | | | | | | | 0.21 (-0.65, 1.06), NR | |
| Change in SF-36 Vitality, Points | N | | NR | | NR | | NR | | NR | NR |
| | Mean (95% CI) | | | | | | | | 0.46 (-0.33, 1.25) | -0.396 ('-1.17, 0.37) |
| | Between Group Diff. | LSM (95% CI), p-value | | | | | | | 0.86 (-0.12, 1.83), NR | |
| Change in SF-36 Physical Component Summary, Points | N | | NR | | NR | | NR | | 384 | 404 |
| | Mean (95% CI) | | | | | | | | 0.56 (-0.03, 1.15) | 0.04 (-0.53, 0.61) |
| | Between Group Difference | LSM (95% CI), p-value | | | | | | | 0.52 (-0.21, 1.25), NR | |
| Change in FACT-An Anemia, Points | N | | NR | | NR | | NR | | 384 | 403 |
| | LSM (95% CI) | | | | | | | | 0.53 (-0.49, 1.55) | 0.36 (-0.62, 1.34) |
| | Between Group Diff. | LSM (95% CI), p-value | | | | | | | 0.17 (-1.08, 1.43), 0.788 | |
| Change in FACT-An Total Score, Points | N | | NR | | NR | | NR | | 383 | 403 |
| | LSM (95% CI) | | | | | | | | -0.39 (-2.47, 1.68) | -0.29 (-2.28, 1.70) |
| | Between Group Diff. | LSM (95% CI), p-value | | | | | | | -0.11 (-2.667, 2.46), 0.936 | |
| Change in EQ-5D 5L, VAS | N | | NR | | NR | | NR | | 385 | 401 |
| | LSM (SD) | | | | | | | | 3.04 (14.91) | 2.74 (14.78) |
| | Between Group Diff. | LSM (95% CI), p-value | | | | | | | NR | NR |
| Improvement in PGIC, % | Timepoint | | NR | | NR | | NR | | 104 Weeks | |
| | N | | | | | | | | 413 | 420 |
| | n (%) | | | | | | | | 254 (61.6) | 215 (51.3) |
| | Between Group Diff. | LSM (95% CI), p-value | | | | | | | NR | NR |
| Data for other subscales not reported | | | | | | | | | | |

95% CI: 95% confidence interval, Diff.: difference, EQ-5D-5L: European Quality of Life Questionnaire-5 Dimensions-5 Levels, EPO: epoetin alfa, ESA: erythropoiesis-stimulating agent, FACT-An: Functional Assessment of Cancer Therapy – Anemia, LS: least squares, N: total number, n: number, NR: not reported, ns: not significant, PGIC: patients' Global Impression of Change, ROX: roxadustat, SD: standard deviation, SF-36: 36-Item Short Form Survey, VAS: viasual analog scale

*: Includes both epoetin alfa and darbepoetin alfa

**Evidence Table 25. Cardiovascular Safety – Key Trials**

| Trials | | | HIMALAYAS[2,11] | | ROCKIES[2,4,17] | | SIERRAS[2] | | PYRENEES[2,12,18] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | ROX (N=522) | EPO (N=521) | ROX (N=1048) | EPO (N=1053) | ROX (N=370) | EPO (N=370) | ROX (N=414) | ESA* (N=420) |
| Timepoint | | | Treatment + 28 days post treatment | | | | | | | |
| CV Mortality | n (%) | | NR | | NR | | NR | | 1 (0.2) | 1 (0.2) |
| | Time to Event | HR (95% CI), p-value | | | | | | | NR | |
| Myocardial Infarction | n (%) | | NR | | 53 (5.0) | 47 (4.5) | 34 (9.2) | 26 (7.0) | 10 (2.4) | 17 (4.0) |
| | Time to Event | HR (95% CI), p-value | | | NR | | NR | | NR | |
| Stroke | n (%) | | NR | | 16 (1.5) | 17 (1.6) | NR | | 0 (0) | 2 (0.5) |
| | Time to Event | HR (95% CI), p-value | | | NR | | | | NR | |
| Heart Failure | n (%) | | NR | | 24 (2.3) | 29 (2.8) | 30 (8.1) | 33 (8.9) | 8 (1.9) | 9 (2.1) |
| | Time to Event | HR (95% CI), p-value | | | NR | | NR | | NR | |
| Unstable Angina | n (%) | | NR | | 5 (0.5) | 6 (0.6) | NR | | 0 (0) | 2 (0.5) |
| | Time to Event | HR (95% CI) p-value | | | NR | | | | NR | |
| Data for the following outcomes not reported: MACE†, MACE+‡, heart failure requiring hospitalization, unstable angina requiring hospitalization | | | | | | | | | | |

95% CI: 95% confidence interval, CV: cardiovascular, EPO: epoetin alfa, ESA: erythropoiesis-stimulating agent, HR: hazard ratio, MACE: major adverse cardiovascular event, N: total number, n: number, NR: not reported, ROX: roxadustat

*: Includes both epoetin alfa and darbepoetin alfa

†: Defined as all-cause mortality (not cardiovascular mortality), myocardial infarction (MI), or stroke

‡: Defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization

**Evidence Table 26. Cardiovascular Safety – Other Phase III Trials**

| Trials | | | FGCL-4592-806[13] | | 1517-CL-0307[14] | |
|---|---|---|---|---|---|---|
| Arm | | | ROX (N=204) | EPO (N=100) | ROX (N=150) | DAR (N=152) |
| Timepoint | | | 27 Weeks | | 24 Weeks | |
| Cardiovascular Mortality | n (%) | | 0 (0) | 0 (0) | NR | |
| | Time to Event | HR (95% CI), p-value | NR | | | |
| Myocardial Infarction | n (%) | | 1 (0.5)# | 0 (0)# | 1 (0.7)* | 0 (0) |
| | Time to Event | HR (95% CI), p-value | NR | | NR | |
| Stroke | n (%) | | NR | | 1 (0.7)¥ | 0 (0) |
| | Time to Event | HR (95% CI), p-value | | | NR | |
| Heart Failure | n (%) | | 3 (1.5) | 0 (0) | 1 (0.7) | 1 (0.7) |
| | Time to Event | HR (95% CI), p-value | NR | | NR | |
| Data on the following outcomes not reported: MACE, MACE+, unstable angina, Heart Failure Requiring Hospitalization, Unstable Angina Requiring Hospitalization | | | | | | |

95% CI: 95% confidence interval, EPO: epoetin alfa, ESA: erythropoiesis-stimulating agent, HR: hazard ratio, MACE: major adverse cardiovascular event, N: total number, n: number, NR: not reported, ROX: roxadustat

*: Includes both epoetin alfa and darbepoetin alfa

†: Defined as all-cause mortality (not cardiovascular mortality), myocardial infarction (MI), or stroke

‡: Defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization

#: Acute myocardial infarction

¥: Cerebral infarction

**Evidence Table 27. Cardiovascular Safety – Phase II Trials**

| Trials | | | FGCL-4592-040[15] | | FGCL-4592-048[8] | | | | 1517-CL-0304[16] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | All Pooled ROX (N=108) | All Pooled EPO (N=36) | ROX, Low (N=25) | ROX, Medium (N=24) | ROX, High (N=25) | EPO (N=22) | ROX 50 mg (N=33) | ROX 70 mg (N=32) | ROX 100 mg (N=32) | DAR (N=32) |
| Timepoint | | | Weeks 6 and 19 | | Week 6 | | | | 24 weeks | | | |
| CV Mortality | n (%) | | NR | | 0 (0) | 0 (0) | 0 (0) | 0 (0) | NR | | | |
| | Time to Event | HR (95% CI), p-value | | | NR | | | --- | | | | |
| MACE* | n (%) | | NR | | 0 (0) | 0 (0) | 0 (0) | 0 (0) | NR | | | |
| | Time to Event | HR (95% CI), p-value | | | NR | | | --- | | | | |
| MACE+† | n (%) | | NR | | NR | | | | NR | | | |
| | Time to Event | HR (95% CI), p-value | | | | | | | | | | |
| Myocardial Infarction | n (%) | | 0 (0) | 1 (3.0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | NR | | | |
| | Between Group Diff. | HR (95% CI), p-value | NR | | NR | | | | | | | |
| Stroke | n (%) | | NR | | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (3.1)‡ | 0 (0) | 0 (0) |
| | Time to Event | HR (95% CI), p-value | | | NR | | | | NR | | | |
| Heart Failure | n (%) | | 1 (0.9) | 1 (3.0) | NR | | | | 1 (3.0) | 0 (0) | 2 (6.3) | 0 (0) |
| | Time to Event | HR (95% CI), p-value | NR | | | | | | NR | | | |
| Data on the following outcomes not reported: unstable angina, Heart Failure Requiring Hospitalization, Unstable Angina Requiring Hospitalization | | | | | | | | | | | | |

95% CI: 95% confidence interval, DAR: darbepoetin alfa, EPO: epoetin alfa, HR: hazard ratio, MACE: major adverse cardiovascular event, N: total number, n: number, NR: not reported, ROX: roxadustat

*: Defined as all-cause mortality (not cardiovascular mortality), myocardial infarction (MI), or stroke

†: Defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization

‡: Cerebral infarction

**Evidence Table 28. Safety – Key Trials**

| Trials | | | HIMALAYAS[2,11] | | ROCKIES[2,4,17] | | SIERRAS[2] | | PYRENEES[2,12,18] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | ROX (N=522) | EPO (N=517) | ROX (N=1048) | EPO (N=1053) | ROX (N=370) | EPO (N=370) | ROX (N=414) | ESA* (N=420) |
| Timepoint | | | Treatment + 28 days post treatment | | | | | | | |
| Any AE, n (%) | | | NR | | 891 (85.0) | 890 (84.5) | NR | | 77 (86.7) | 361 (86.0) |
| Any TEAE, n (%) | | | 450 (86.2) | 441 (85.3) | NR | | 339 (91.6) | 338 (91.4) | 359 (86.7) | 361 (86.0) |
| TEAEs Related to Study Drug, n (%) | | | NR | | 15 (7.4) | 1 (1.0) | NR | | 33 (8.0) | 10 (2.4) |
| Any Serious AE, n (%) | | | NR | | 604 (57.6) | 605 (57.5) | NR | | NR | |
| Serious TEAEs, n (%) | | | 234 (44.8) | 218 (42.2) | NR | | 242 (65.4) | 248 (67.0) | 210 (50.7) | 189 (45.0) |
| D/C Due to AE, n (%) | | | 29 (5.6) | 22 (4.2) | 57 (5.4) | 26 (2.5) | NR | NR | 35 (8.5) | 16 (3.8) |
| All-Cause Mortality | n (%) | | 63 (12.1) | 59 (11.4) | 167 (15.9) | 187 (17.8) | 62 (16.8) | 58 (15.7) | 78 (18.8) | 59 (14.0) |
| | Time to Event | HR (95% CI), p-value | NR | | NR | | NR | | NR | |
| Hospitalization, n (%) | | | NR | | NR | | NR | | 4 (0.9)† | 4 (0.9) |
| Pulmonary Embolism, n (%) | | | NR | | 6 (0.6) | 8 (0.8) | NR | | 4 (1.0) | 1 (0.2) |
| Hypertension, n (%) | | | 99 (19.0) | 88 (17.0) | 92 (8.8) | 94 (8.9) | 62 (16.8) | 47 (12.7) | 74 (17.9) | 79 (18.8) |
| Pulmonary Hypertension, n (%) | | | NR | | 0 (0) | 2 (0.2) | NR | | 2 (0.5) | 1 (0.2) |

95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, EPO: epoetin alfa, ESA: erythropoiesis-stimulating agent, HR: hazard ratio, N: total number, n: number, NR: not reported, ROX: roxadustat, EAE: treatment-emergent adverse event

*: Includes both epoetin alfa and darbepoetin alfa

†: N=413

**Evidence Table 29. Safety – Other Phase III Trials**

| Trials | | | FGCL-4592-806[13] | | 1517-CL-0307[14] | |
|---|---|---|---|---|---|---|
| Arm | | | ROX (N=204) | EPO (N=100) | ROX (N=150) | DAR (N=152) |
| Timepoint | | | 27 weeks | | 24 weeks | |
| Any AE, n (%) | | | NR | | NR | |
| Any TEAE, n (%) | | | 159 (77.9) | 63 (63.0) | NR | |
| TEAEs Related to Study Drug, n (%) | | | 96 (47.1) | 38 (38.0) | 129 (86.0) | 126 (82.9) |
| Any Serious AE, n (%) | | | NR | | NR | |
| Serious TEAEs, n (%) | | | 29 (14.2) | 10 (10.0) | 31 (20.7) | 22 (14.5) |
| D/C Due to TEAE, n (%) | | | 17 (8.4) | 1 (1.0) | 13 (8.7) | 8 (5.3) |
| All-Cause Mortality | n (%) | | 0 (0) | 0 (0) | 2 (1.3) | 0 (0) |
| | Time to Event | HR (95% CI), p-value | NR | | NR | |
| Hospitalization, n (%) | | | NR | | NR | |
| Pulmonary Embolism, n (%) | | | NR | | NR | |
| Hypertension, n (%) | | | 25 (12.3) | 16 (16.0) | NR | |
| Pulmonary Hypertension, n (%) | | | NR | | NR | |

95% CI: 95% confidence interval, AE: adverse event, DAR: darbepoetin alfa, D/C: discontinuation, EPO: epoetin alfa, ESA: erythropoiesis stimulating agent, HR: hazard ratio, N: total number, n: number, NR: not reported, ROX: roxadustat, TEAE: treatment-emergent adverse event

**Evidence Table 30. Safety – Phase II Trials**

| Trials | | | FGCL-4592-040[15] | | FGCL-4592-048[8] | | | | 1517-CL-0304[16] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm | | | All Pooled ROX (N=108) | All Pooled EPO (N=36) | ROX, Low (N=25) | ROX, Medium (N=24) | ROX, High (N=25) | EPO (N=22) | ROX 50 mg (N=33) | ROX 70 mg (N=32) | ROX 100 mg (N=33) | DAR (N=32) |
| Timepoint | | | 6 and 19 weeks | | 6 weeks | | | | 24 weeks | | | |
| Any AE, n (%) | | | 69 (63.9) | 22 (61.0) | NR | | | | NR | | | |
| Any TEAE, n (%) | | | NR | | 10 (40.0) | 13 (54.0) | 9 (36.0) | 4 (18.0) | 24 (72.7) | 26 (81.3) | 27 (84.4) | 25 (78.1) |
| TEAEs Related to Study Drug, n (%) | | | NR | | NR | | | | 8 (24.2) | 7 (21.9) | 12 (37.5) | 2 (6.3) |
| Any Serious AE, n (%) | | | 26 (24.1) | 6 (17.0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | NR | | | |
| Serious TEAEs, n (%) | | | NR | | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 4 (12.1) | 7 (21.9) | 4 (12.5) | 2 (6.3) |
| D/C Due to TEAE, n (%) | | | 3 (4.5)* | 0 (0) | 0 (0) | 1 (4.8) | 0 (0) | 0 (0) | 2 (6.1) | 2 (6.3) | 3 (9.4) | 0 (0) |
| All-Cause Mortality | n (%) | | 3 (4.5)† | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (3.0) | 0 (0) | 0 (0) | 0 (0) |
| | Time to Event | HR (95% CI), p-value | NR | | NR | | | | NR | | | |
| Hospitalization, n (%) | | | NR | | NR | | | | NR | | | |
| Pulmonary Embolism, n (%) | | | NR | | NR | | | | NR | | | |
| Hypertension, n (%) | | | NR | | 0 (0) | 2 (8.0) | 1 (4.0) | 1 (5.0) | NR | | | |
| Pulmonary Hypertension, n (%) | | | NR | | NR | | | | NR | | | |

95% CI: 95% confidence interval, AE: adverse event, DAR: darbepoetin alfa, D/C: discontinuation, EPO: epoetin alfa, ESA: erythropoiesis stimulating agent, HR: hazard ratio, N: total number, n: number, NR: not reported, ROX: roxadustat, TEAE: treatment-emergent adverse event

*: Occurred during Part 1

†: Occurred during Part 2

**Evidence Table 31. Baseline Characteristics**

| Trials | | DI-CKD *(ALPS, ANDES, OLYMPUS)*[2,19-21] | | DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[2,19-21] | |
|---|---|---|---|---|---|
| **Arm** | | **ROX (N=2391)** | **PBO (N=1886)** | **ROX (N=1943)** | **EPO (N=1947)** |
| **Age, Mean Years (SD)** | | 61.9 (14.1) | 62.7 (14.0) | 54.3 (14.9) | 55.1 (14.6) |
| **Male, n (%)** | | 974 (40.7) | 832 (44.1) | 1121 (57.7) | 1148 (59.0) |
| **White, n (%)** | | 1134 (47.4) | 892 (47.3) | 1177 (60.6) | 1182 (60.7) |
| **History of Cardiac, Cerebrovascular, or Thromboembolic Disease; n (%)** | | 886 (37.1) | 695 (36.9) | 940 (48.7) | 923 (47.9) |
| **Hemodialysis, n (%)** | | N/A | | 1750 (90.7) | 1740 (90.2) |
| **Peritoneal Dialysis, n (%)** | | N/A | | 177 (9.2) | 188 (9.8) |
| **Dialysis Vintage ≤4 Months, n (%)** | | N/A | | 760 (39.4) | 770 (39.9) |
| **Hb, Mean g/dL (SD)** | | 9.10 (0.74) | 9.10 (0.73) | 9.63 (1.30) | 9.67 (1.30) |
| **Hepcidin, Mean ng/mL (SD)** | | 114.79 (NR) | 122.04 (NR) | 240.58 (NR) | 236.90 (NR) |
| **Transferrin, Mean mg/L (SD)** | | 2.40 (NR)† | 2.37 (NR)† | 2.16 (NR)† | 2.15 (NR)† |
| **Transferrin Saturation, Mean % (SD)** | | 28.18 (NR) | 28.98 (NR) | 33.00 (12.74) | 32.70 (12.40) |
| **Ferritin, Mean ng/mL (SD)** | | 262.92 (NR) | 257.88 (NR) | 608.64 (466.50) | 602.15 (469.60) |
| **Iron Status, Replete‡, n (%)** | | 1433 (59.9) | 1127 (59.8) | 1690 (87.0) | 1692 (86.9) |
| **Serum Iron, Mean µg/dL (SD)** | | 65.71 (NR) | 66.74 (NR) | 70.21 (NR) | 69.73 (NR) |
| **C-Reactive Protein, mg/L** | **Mean (SD)** | NR | | NR | |
| | **> ULN#, n (%)** | 526 (22.0) | 357 (18.9) | 723 (37.2) | 722 (37.1) |
| **eGFR, Mean mL/min/1.73 m² (SD)** | | 19.72 (11.6) | 20.04 (11.8) | NR | |
| **HDL-C, Mean mg/dL (SE)** | | 45.45 (0.7)§ | 45.45 (0.7)§ | 43.04 (1.26)§ | 43.67 (1.27)§ |
| **LDL-C, Mean mg/dL (SD)** | | 98.97 (44.15) | 95.53 (42.40) | 93.25 (39.78) | 93.02 (39.36) |
| **Total Cholesterol, Mean mg/dL (SE)** | | 176.22 (1.40)§ | 172.73 (2.1)§ | 168.99 (1.26)§ | 169.62 (1.27) § |

CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, dL: deciliter, EPO: epoetin alfa, eGFR: estimated glomerular filtration rate, g: gram, HDL-C: high-density lipoprotein cholesterol, L: liter, LDL-C: low-density lipoprotein cholesterol, $m^2$: square meter, min: minute, mg: milligram, mL: milliliter, µg: microgram, N/A: not applicable, N: total number, n: number, ng: nanogram, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation, SE: standard error ULN: upper of limit normal

*: Assumption made based on study protocol

†: Converted from µg/dL to mg/L

‡: Ferritin ≥100 ng/mL and TSAT ≥20%

§: Data are digitized and should be interpreted with caution

#: Defined as 4.9 mg/L

**Evidence Table 32. Efficacy Outcomes**

| Trials | | | DI-CKD *(ALPS, ANDES, OLYMPUS)*[2,19-21] | | DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[2,19-21] | |
|---|---|---|---|---|---|---|
| **Arms** | | | **ROX (N=2391)** | **PBO (N=1886)** | **ROX (N=1943)** | **EPO (N=1947)** |
| **Change in Hb, g/dL** | **Timepoint** | | Average of Weeks 28 to 52 | | | |
| | **N** | | 2931 | 1886 | 1612 | 1634 |
| | **Mean (SE)** | | 1.85 (NR) | 0.13 (NR) | 1.22 (NR) | 0.99 (NR) |
| | **Between Group Difference** | **LS Mean (95% CI), p-value** | NR, <0.001 | | NR, <0.001 | |
| **Hb Response** | **Timepoint** | | Week 24 | | | |
| | **N** | | 2391 | 1886 | NR | |
| | **n (%)** | | 1918 (80.2) | 164 (8.7) | | |
| | **Between Group Difference** | **Mean % (95% CI), p-value** | 71.5 (69.4, 73.5), <0.001 | | | |
| **Change in eGFR in Patients with Baseline eGFR ≥15 mL/min/1.73 m²** | **Timepoint** | | Week 52 | | | |
| | **N** | | 990 | 657 | NR | |
| | **Mean (SE)** | | -1.88 (0.27)* | -2.49 (0.32)* | | |
| | **Between Group Difference** | **LS Mean (95% CI), p-value** | 1.60 (NR), <0.0001 | | | |
| **Use of Rescue Therapy** | **Timepoint** | | Week 52 | | | |
| | **N** | | NR | | NR | |
| | **n (%)** | | 213 (8.9) | 587 (31.1) | | |
| | **Time to Event** | **HR (95% CI), p-value** | 0.19 (0.16, 0.23), <0.0001 | | | |
| **Use of Blood Transfusion** | **Timepoint** | | Week 52 | | | |
| | **N** | | NR | | NR | |
| | **n (%)** | | 124 (5.2) | 290 (15.4) | 183 (9.5) | 247 (12.8) |
| | **Time to Event** | **HR (95% CI), p-value** | 0.26 (0.21, 0.32), <0.0001 | | 0.82 (0.679, 0.997), 0.046 | |
| **Monthly IV Iron Use** | **Timepoint** | | Average of Weeks 28 to 52 | | | |
| | **n (%)** | | NR | | NR | |
| | **Mean mg (SD)** | | | | 80.30 (NR) | 108.20 (NR) |
| | **Between Group Difference** | **LSM (95% CI), p-value** | | | NR p<0.0001 | |
| **Change in Hepcidin, ng/mL** | **Timepoint** | | Week 24 | | | |

| Trials | | | DI-CKD *(ALPS, ANDES, OLYMPUS)*[2,19-21] | | DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[2,19-21] | |
|---|---|---|---|---|---|---|
| **Arms** | | | **ROX (N=2391)** | **PBO (N=1886)** | **ROX (N=1943)** | **EPO (N=1947)** |
| | **N** | | 1456 | 913 | 1326 | 1361 |
| | **Mean (SD)** | | -23.05 (86.03) | 12.33 (87.77) | -60.35 (134.55) | -34.08 (137.37) |
| | **Between Group Difference** | **Mean (95% CI), p-value** | NR, <0.0001 | | NR, <0.0001 | |
| **Change in Transferrin, mg/L** | **Timepoint** | | Average of Weeks 12 to 28 | | | |
| | **N** | | 2149 | 1604 | 1735 | 1817 |
| | **Mean (SD)** | | 0.41 (0.58)† | -0.02 (0.42) † | 0.37 (0.58)† | 0.005 (0.55)† |
| | **Between Group Difference** | **Mean (95% CI), p-value** | NR | | NR | |
| **Change in Transferrin Saturation, %** | **Timepoint** | | Average of Weeks 12 to 28 | | | |
| | **N** | | 2148 | 1597 | 750 | 750 |
| | **Mean % (SD)** | | -1.15 (11.82) | 0.38 (10.69) | -1.70 (13.70) | -2.70 (12.43) |
| | **Between Group Difference** | **Mean (95% CI), p-value** | NR | | NR | |
| **Change in Serum iron, µg/dL** | **Timepoint** | | Average of Weeks 12 to 28 | | | |
| | **N** | | 2152 | 1604 | 1737 | 1819 |
| | **Mean (SD)** | | 6.85 (30.58) | 0.80 (27.37) | 4.83 (34.30) | -5.70 (35.33) |
| | **Between Group Difference** | **Mean (95% CI), p-value** | NR | | NR | |
| **Change in Ferritin, ng/mL** | **Timepoint** | | Average of Weeks 12 to 28 | | | |
| | **N** | | 2155 | 1604 | 1736 | 1819 |
| | **Mean (SD)** | | -76.14 (169.41) | -5.88 (149.84) | -142.02 (289.18) | -102.39 (321.83) |
| | **Between Group Difference** | **Mean (95% CI), p-value** | NR | | NR | |
| **Change in HDL-C, mg/dL** | **Timepoint** | | Average of Weeks 12 to 28 | | | |
| | **N** | | NR | | NR | |
| | **Mean (SE)** | | 41.26 (1.4)* | 45.45 (1.4)* | 38.61 (0.63)* | 43.04 (0.63)* |
| | **Between Group Difference** | **LSM (SE), p-value** | -4.14 (0.41), <0.0001 | | -4.15 (0.32), <0.0001 | |
| **Change in LDL-C, mg/dL** | **Timepoint** | | Average of Weeks 12 to 28 | | | |
| | **N** | | 2368 | 1865 | 1929 | 1928 |
| | **Mean (SD)** | | 81.83 (36.19) | 97.55 (43.79) | 76.67 (32.95) | 91.81 (38.54) |

| Trials | | | DI-CKD *(ALPS, ANDES, OLYMPUS)*[2,19-21] | | DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[2,19-21] | |
|---|---|---|---|---|---|---|
| **Arms** | | | **ROX (N=2391)** | **PBO (N=1886)** | **ROX (N=1943)** | **EPO (N=1947)** |
| | **Between Group Difference** | **LSM (95% CI), p-value** | -19.83 (-22.16, -17.51), <0.001 | | -15.80 (-17.54, -14.06), <0.0001 | |
| **Change in Total Cholesterol, mg/dL** | **Timepoint** | | Average of Weeks 12 to 28 | | | |
| | **N** | | NR | | NR | |
| | **Mean (SE)** | | 151.75 (2.1)* | 175.52 (2.1)* | 144.94 (1.26)* | 167.09 (1.9)* |
| | **Between Group Difference** | **LSM (SE), p-value** | -27.54 (1.51), <0.0001 | | -22.69 (1.12), <0.0001 | |
| No data reported for the following outcomes: Use of ESA treatment, soluble transferrin receptor, total iron binding capacity | | | | | | |

95% CI: 95% confidence interval, CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, dL: deciliter, EPO: epoetin alfa, eGFR: estimated glomerular filtration rate, g: gram, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, L: liter, LDL-C: low-density lipoprotein cholesterol, LSM: least squares mean, $m^2$: square meter, min: minute, mg: milligram, mL: milliliter, µg: microgram, N: total number, n: number, ng: nanogram, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation, SE: standard error, SEM: standard error of means

* Data are digitized and should be interpreted with caution

† Converted from µg/dL to mg/L

## Evidence Table 33. Efficacy Outcomes – Subgroups (DI-CKD)

| Trials | | | DI-CKD *(ALPS, ANDES, OLYMPUS)*[2,19,22-24] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Population | | | Iron Replete‡ | | Iron Deplete# | | CRP >ULN† | | CRP ≤ULN† | |
| Arm | | | ROX | PBO | ROX | PBO | ROX | PBO | ROX | PBO |
| Change in Hb, g/dL | Timepoint | | | | | | | | | |
| | N | | 1433 | 1127 | 956 | 755 | 526 | 357 | 1222 | 855 |
| | LSM (SE) | | 1.94 (0.03) | 0.13 (NR) | 1.94 (0.03) | 0.33 (NR) | Mean: 1.95 (SEM: 0.02*) | 0.36 (SEM: 0.04*) | 1.88 (SEM: 0.03*) | 0.1 (SEM: 0.04*) |
| | Between Group Diff. | LSM (95% CI), p-value | 1.81 (1.71, 1.90), <0.0001 | | 1.61 (1.50, 1.72), <0.0001 | | 1.67 (1.53, 1.82), <0.0001 | | 1.74 (1.65, 1.82), <0.0001 | |
| Use of Rescue Therapy | Timepoint | | 52 Weeks | | | | | | | |
| | N | | NR | NR | NR | NR | NR | | NR | |
| | n (%) | | NR | NR | NR | NR | | | | |
| | Incidence Rate Difference | Mean (95% CI), p-value | -24.3 (-27.43, -21.12), NR | | -18.9 (-22.58, -15.29), NR | | | | | |
| Use of Blood Transfusion | Timepoint | | 52 Weeks | | | | | | | |
| | N | | 1420 | 1114 | 947 | 748 | NR | | NR | |
| | n (%) | | 82 (5.8) | 189 (17) | 41 (4.3) | 98 (13.1) | | | | |
| | Time to Event | HR (95% CI), p-value | 0.25 (0.19, 0.33), <0.0001 | | 0.26 (0.18, 0.38), <0.0001 | | | | | |
| Use of IV Iron, no | Timepoint | | 52 Weeks | | | | | | | |
| | N | | 1420 | 1114 | 947 | 748 | NR | | NR | |
| | n (%) | | 33 (2.3) | 47 (4.2) | 29 (3.1) | 65 (8.7) | | | | |
| | Time to Event | HR (95% CI), p-value | 0.44 (0.28, 0.70), 0.0004 | | 0.3 (0.19, 0.47), <0.0001 | | | | | |
| Change in Transferrin Saturation, % | Timepoint | | | | | | | | | |
| | N | | 1111 | 770 | 735 | 511 | NR | | NR | |
| | Mean (SD) | | -2.59 (NR) | -2.34 (NR) | 4.88 (NR) | 4.28 (NR) | | | | |
| | Between Group Diff. | Mean (95% CI), p-value | NR | | NR | | | | | |
| No data reported for the following outcomes: Hb response, eGFR, hepcidin, transferrin, transferrin saturation, serum iron, ferritin, HDL-C, LDL-C, total cholesterol | | | | | | | | | | |

95% CI: 95% Confidence interval, CKD: chronic kidney disease, DI: dialysis-independent, dL: deciliter, g: gram, eGFR: estimated glomerular filtration rate, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, L: liter, LDL-C: low-density lipoprotein cholesterol, LSM: least squares mean, mg: milligram, mL: milliliter, µg: microgram, N: total number, n: number, ng: nanogram, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation, SE: standard error, SEM: standard error of the mean

*: Data are digitized and should be interpreted with caution

†: Defined as 4.9 mg/L

‡: Ferritin ≥100 ng/mL and TSAT ≥20%

#: Ferritin <100 ng/mL and TSAT <20%

## Evidence Table 34. Efficacy Outcomes – Subgroups (DD- and ID-CKD)

| Trials | | | DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[2,25] | | | | ID-CKD *(HIMALAYAS, ROCKIES, SIERRAS)* [2,26] | |
|---|---|---|---|---|---|---|---|---|
| Population | | | CRP >ULN† | | CRP ≤ULN† | | ID-CKD | |
| Arms | | | ROX (N=723) | EPO (N=722) | ROX (N=889) | EPO (N=912) | ROX (N=760) | EPO (N=770) |
| Change in Hb, g/dL | Timepoint | | Average of Weeks 28 to 52 | | | | Average of Weeks 28 to 52 | |
| | N | | 723 | 722 | 889 | 912 | 760 | 770 |
| | Mean (SD) | | 1.30 (NR) | 0.90 (NR) | 1.30 (NR) | 1.10 (NR | 2.12 (1.45) | 1.91 (1.42) |
| | Between Group Difference | LSM (95% CI), p-value | NR, <0.0001 | | NR, p<0.0001 | | 0.22 (0.05, 0.40), 0.013 | |
| Monthly IV Iron Use, mg | Timepoint | | NR | | | | Average of Weeks 28 to 52 | |
| | N | | | | | | NR | NR |
| | n (%) | | | | | | NR | NR |
| | Mean (SD) | | | | | | 53.57 (143.10) | 70.22 (173.33) |
| | Between Group Difference | LSM (95% CI), p-value | | | | | -40.8 (-77.3, -4.3), <0.0001 | |
| Change in HDL-C, mg/dL | Timepoint | | NR | | | | Average of Weeks 12 to 28 | |
| | N | | | | | | NR | NR |
| | Mean (SE) | | | | | | 37.97 (0.64)* | 43.04 (0.63)* |
| | Between Group Difference | LSM (SE), p-value | | | | | -3.85 (0.807), <0.0001 | |
| Change in LDL-C, mg/dL | Timepoint | | NR | | | | Average of Weeks 12 to 28 | |
| | N | | | | | | 756 | 759 |
| | Mean (SD) | | | | | | 82.66 (34.02) | 100.79 (37.63) |
| | Between Group Difference | LSM (95% CI), p-value | | | | | -17.50 (-22.22, -12.78), <0.0001 | |
| Change in Total Cholesterol, mg/dL | Timepoint | | NR | | | | Average of Weeks 12 to 28 | |
| | N | | | | | | NR | NR |
| | Mean (SE) | | | | | | 150.63 (1.9)* | 175.32 (2.53)* |
| | Between Group Difference | LSM (SE), p-value | | | | | -23.31 (3.01), <0.0001 | |
| Data for the following outcomes not reported: Hb response, rescue therapy, blood transfusion, hepcidin, transferrin, transferrin saturation, serum iron, ferritin | | | | | | | | |

95% CI: 95% Confidence interval, CKD: chronic kidney disease, CRP: c-reactive protein, DD: dialysis-dependent, DI: dialysis-independent, dL: deciliter, EPO: epoetin alfa, eGFR: estimated glomerular filtration rate, g: gram, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, IV: intravenous, L: liter, LDL-C: low-density lipoprotein cholesterol, LSM: least squares mean, $m^2$: square meter, min: minute, mg: milligram, mL: milliliter, µg: microgram, N: total number, n: number, ng: nanogram, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation, SE: standard error, SEM: standard error of means, LN: upper limit of normal

* Data are digitized and should be interpreted with caution

†: defined as 4.9 mg/L

**Evidence Table 35. Patient Reported Outcomes**

| Trials | | | DI-CKD *(ALPS, ANDES, OLYMPUS)*[27] | | DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[27] | |
|---|---|---|---|---|---|---|
| Timepoint | | | 12 weeks | | | |
| Arm | | | ROX | PBO | ROX | EPO |
| Change in SF-36 Physical Functioning, Points | N | | 2352 | 1851 | NR | |
| | LSM (SE) | | 1.23 (0.21)* | 0.7 (0.21)* | | |
| | Between Group Difference | LS Mean (95% CI), p-value | 0.53 (0.05, 1.01), 0.0311 | | | |
| Change in SF-36 Vitality, Points | N | | 2351 | 1852 | NR | |
| | LSM (SE) | | 2.58 (0.22)* | 1.63 (0.21)* | | |
| | Between Group Difference | LS Mean (95% CI), p-value | 0.96 (0.44, 1.47) 0.0003 | | | |
| Change in FACT-An Anemia, Points | N | | 2346 | 1854 | NR | |
| | LSM (SE) | | 3.17 (0.26)* | 2.08 (0.31)* | | |
| | Between Group Difference | LS Mean (95% CI), p-value | 1.10 (0.45, 1.74), 0.0008 | | | |
| Change in FACT-An Total Score, Points | N | | 2345 | 1852 | NR | |
| | LSM (SE) | | 4.86 (0.49)* | 3.05 (0.58)* | | |
| | Between Group Difference | LS Mean (95% CI), p-value | 1.81 (0.54, 3.08), 0.0051 | | | |
| Change in EQ-5D-5L VAS Score, Points | N | | 2350 | 1853 | NR | |
| | LSM (SE) | | 2.93 (0.34)* | 1.25 (0.43)* | | |
| | Between Group Difference | LS Mean (95% CI), p-value | 1.68 (0.76, 2.59), 0.0003 | | | |
| PGIC Response | N | | 2368 | 1865 | NR | |
| | n (%) | | 720 (30.4) | 421 (22.6) | | |
| | Between Group Difference | OR (95% CI), p-value | 2.03 (1.74, 2.36), <0.0001 | | | |

95% CI: 95% Confidence interval, CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, EPO: epoetin alfa, EQ-5D-5L: European Quality of Life Questionnaire-5 Dimensions-5 Levels, FACT-An: Functional Assessment of Cancer Therapy – Anemia, LS: least squares, N: total number, n: number, NR: not reported, OR: odds ratio, PBO: placebo, ROX: roxadustat, SE: standard error, SF-36: 36-Item Short Form Survey, VAS: visual analog scale

*: SEs were digitized and should be interpreted with caution

**Evidence Table 36. Patient Reported Outcomes - Subgroups**

| Trials | | | DI-CKD *(ALPS, ANDES, OLYMPUS)*[27] | | | | | | | | DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[27] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Population | | | Iron Replete | | Iron Deplete | | CRP >ULN* | | CRP ≤ULN* | | CRP >ULN* | | CRP ≤ULN* | |
| Timepoint | | | 12 weeks | | | | | | | | | | | |
| Arm | | | ROX | PBO | ROX | PBO | ROX | PBO | ROX | PBO | ROX | EPO | ROX | EPO |
| Change in SF-36 Physical Functioning, Points | N | | NR | | | | 520 | 351 | 1206 | 848 | NR | | | |
| | Mean (SD) | | | | | | 0.96 (8.71) | 0.26 (8.87) | 1.22 (7.94) | 0.85 (7.60) | | | | |
| | Between Group Difference | LSM (95% CI), p-value | | | | | 0.51 (-0.61, 1.64), 0.3711 | | 0.66 (-0.00, 1.31), 0.051 | | | | | |
| Change in SF-36 Vitality, Points | N | | NR | | | | 519 | 351 | 1206 | 849 | NR | | | |
| | Mean (SD) | | | | | | 3.23 (9.62) | 2.45 (9.67) | 2.67 (8.91) | 1.91 (8.75) | | | | |
| | Between Group Difference | LSM (95% CI), p-value | | | | | 0.97 (-0.25, 2.18), 0.1191 | | 1.05 (0.33, 1.78), 0.0043 | | | | | |
| Other subscales not reported | | | | | | | | | | | | | | |

95% CI: 95% Confidence interval, CKD: chronic kidney disease, CRP: C-reactive protein, DD: dialysis-dependent, DI: dialysis-independent, diff.: difference, EPO: epoetin alfa, LSM: least square mean, N: total number, n: number, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation, SF-36: 36-Item Short Form Survey, ULN: upper limit of normal

*: Defined as 4.9 mg/L

**Evidence Table 37. Cardiovascular Safety**

| Trials | | | DI-CKD *(ALPS, ANDES, OLYMPUS)*[2,19] | | DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[2,19] | |
|---|---|---|---|---|---|---|
| Timepoint | | | Week 52 | | | |
| Arm | | | ROX (N=2391) | PBO (N=1886) | ROX (N=1940) | EPO (N=1940) |
| MACE* | n (%) | | NR | | NR | |
| | Time to Event | HR (95% CI), p-value | 1.08 (0.94, 1.24), NR | | 0.96 (0.82, 1.13), NR | |
| MACE+† | n (%) | | NR | | NR | |
| | Time to Event | HR (95% CI), p-value | 1.04 (0.91, 1.18), | | 0.86 (0.74, 0.98), 0.028 | |
| Myocardial Infarction | n (%) | | NR | | 103 (5.3) | 109 (5.6) |
| | Time to Event | HR (95% CI), p-value | | | NR | |
| Stroke | n (%) | | NR | | 45 (2.3) | 50 (2.6) |
| | Time to Event | HR (95% CI), p-value | | | NR | |
| Unstable Angina Requiring Hospitalization | n (%) | | NR | | 18 (0.9) | 22 (1.1) |
| | Time to Event | HR (95% CI), p-value | | | NR | |
| Congestive Heart Failure Requiring Hospitalization | N | | 2386 | 1884 | 1940 | 1940 |
| | n (%) | | NR | | 120 (6.2) | 166 (8.6) |
| | Time to Event | HR (95% CI), p-value | 0.89 (0.72, 1.12), NR | | 0.73 (0.58, 0.94), 0.013 | |

95% CI: 95% confidence interval, CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, diff.: difference, EPO: epoetin alfa, HR: hazard ratio, MACE: major adverse cardiovascular event, N: total number, n: number, NR: not reported, ns: not significant, PBO: placebo, ROX: roxadustat

*: Defined as all-cause mortality (not cardiovascular mortality), myocardial infarction, or stroke

†: Defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization

**Evidence Table 38. Cardiovascular Safety – Subgroup (ID-CKD)**

| Trials | | | DI-CKD *(ALPS, ANDES, OLYMPUS)* | DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)* | ID-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[2,19,26] | |
|---|---|---|---|---|---|---|
| **Timepoint** | | | NR | NR | **Week 52** | |
| **Arm** | | | | | **ROX (N=760)** | **EPO (N=770)** |
| **MACE*** | **n (%)** | | | | NR | |
| | **Time to Event** | **HR (95% CI), p-value** | | | 0.70 (0.51, 0.96), 0.029 | |
| **MACE+†** | **n (%)** | | | | 672 (88.4) | 649 (84.3) |
| | **Time to Event** | **HR (95% CI), p-value** | | | 0.66 (0.50, 0.89), 0.005 | |
| **All-Cause Mortality** | **n (%)** | | | | NR | |
| | **Time to Event** | **HR (95% CI), p-value** | | | 0.76 (0.52, 1.11), 0.154 | |
| **Congestive Heart Failure Requiring Hospitalization** | **N** | | | | 1526 | |
| | **n (%)** | | | | NR | |
| | **Time to Event** | **HR (95% CI), p-value** | | | 0.77 (0.42, 1.40), NR | |
| No data were reported for the following cardiovascular safety events: myocardial infarction, stroke, unstable angina requiring hospitalization | | | | | | |

95% CI: 95% confidence interval, CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, diff.: difference, EPO: epoetin alfa, HR: hazard ratio, ID: incidence-dialysis, MACE: major adverse cardiovascular event, N: total number, n: number, NR: not reported, ns: not significant, ROX: roxadustat

*: Defined as all-cause mortality (not cardiovascular mortality), myocardial infarction, or stroke

†: Defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization

**Evidence Table 39. Safety**

| Trials | | | DI-CKD *(ALPS, ANDES, OLYMPUS)*[2,19,28] | | DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[2,19,28] | |
|---|---|---|---|---|---|---|
| **Arms** | | | **ROX (N=2391)** | **PBO (N=1886)** | **ROX (N=1929)** | **EPO (N=1928)** |
| **Timepoint** | | | Treatment Period + 28 Days | | | |
| **Any AE, n (%)** | | | NR | | NR | |
| **Any TEAE, n (%)** | | | 2138 (89.4) | 1611 (85.4) | NR | |
| **Study Drug-Related AEs, n (%)** | | | NR | | NR | |
| **Serious AEs, n (%)** | | | NR | | NR | |
| **Serious TEAEs, n (%)** | | | NR | | NR | |
| **D/C due to AEs, n (%)** | | | NR | | NR | |
| **All-Cause Mortality*** | **n (%)** | | NR | NR | 207 (10.7) | 232 (12.0) |
| | **Time to Event** | **HR (95% CI), p-value** | 1.06 (0.91, 1.23), NR | | 0.96 (0.79, 1.17), NR | |
| **Hospitalization, n (%)** | | | NR | | NR | |
| **End Stage Renal Disease, n (%)** | | | NR | | NR | |
| **Decline in eGFR, n (%)** | | | NR | | NR | |
| **Pulmonary Embolism, n (%)** | | | NR | | NR | |
| **Hypertensive Emergency, events/100 patient-exposure years†** | | | 1.1 | 1.1 | 2.2 | 2.5 |
| **Pulmonary Hypertension, n (%)** | | | NR | | NR | |
| **Exacerbation of Hypertension†‡** | **n (%)** | | NR | | NR | |
| | **Time to Exacerbation of Hypertension** | **HR (95% CI), p-value** | 1.12 (0.95, 1.32), NR | | 1.06 (0.93, 1.21), NR | |

95% CI: 95% confidence interval, AE: adverse event, CKD: chronic kidney disease, D/C: discontinuation, DD: dialysis-dependent, DI: dialysis-independent, eGFR: estimated glomerular filtration rate, EPO: epoetin alfa, HR: hazard ratio, N: total number, n: number, NR: not reported, ns: not significant, PBO: placebo, ROX: roxadustat, TEAE: treatment-emergent adverse event

*: In the first 52 weeks

†: Time period not reported

‡: Systolic blood pressure (SBP) ≥170 mmHg or diastolic blood pressure (DBP) ≥110 mmHg and an increase from baseline ≥20 mmHg (SBP) or ≥15 mmHg (DBP)

## D4. Heterogeneity and Subgroups

We did not identify any RCTs that assessed the impact of roxadustat on subgroups of patients with cardiovascular disease or cancer. As seen in Evidence Table 1 and Evidence Table 16, these patients were excluded from the RCTs. RCTs that investigated the impact of roxadustat on subgroups of patients defined by iron and inflammation states or patients with incident DD-CKD are described below.

### DI-CKD

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): Data regarding subgroups based on iron or inflammation states for DOLOMITES are unavailable at the time of this report.

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): We identified eight references for subgroup analyses of the key RCTs and pooled analysis.[24,36,43,56-60] The results demonstrated significant improvements with roxadustat compared to placebo (on use of rescue therapy, blood transfusion, IV iron supplementation, change in Hb, and change in TSAT) regardless of iron states (see Evidence Table 6, Evidence Table 33, and Evidence Table 36). Further, the results showed significant improvements in change in Hb with roxadustat compared to placebo regardless of inflammation states, though the differences reported in HRQoL did not meet MCIDs (see Evidence Table 33 and Evidence Table 36). Qualitatively, there were no subgroup effects based on iron or inflammation states.

### DD-CKD

We identified three references for subgroup analyses of HIMALAYAS, ROCKIES, SIERRAS, and a pooled analysis of these RCTs.[24,34,61] The results demonstrated that roxadustat resulted in significant improvements compared to epoetin alfa (on change in Hb) regardless of iron and inflammation states (see Evidence Table 23 and Evidence Table 34). Qualitatively, there were no subgroup effects based on iron or inflammation states. However, comparable data for PYRENEES are unavailable at the time of this report.

Other RCTs demonstrated similar trends regardless of inflammation state, though statistical values were not reported.[30,31]

*Incident Dialysis Subgroup*

We identified one reference for a subgroup analysis of incident DD-CKD patients.[62] As described above, the HIMALAYAS RCT only included incident DD-CKD patients, while in the ROCKIES and the SIERRAS RCTs, 10% and 20% of the enrolled patients, respectively, were incident DD-CKD patients. A pooled analysis of HIMALAYAS and the incident DD-CKD subgroups of ROCKIES and SIERRAS

showed the risk of MACE and MACE+ was significantly reduced with roxadustat compared to placebo; however, there was no significant difference in the risk of all-cause mortality (see Evidence Table 38). Because these endpoints were not available for the stable DD-CKD subgroups of ROCKIES and SIERRAS at the time of this report, we were unable to assess whether these results differ. However, as mentioned previously, in a pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS, only the risk of MACE+ was significantly reduced with roxadustat compared to epoetin alfa.[36]

## D5. Ongoing Studies

**Table D12. Ongoing Studies**

| Trial | Study Design | Study Arms | Patient Population | Key Outcomes | Estimated Completion Date |
|---|---|---|---|---|---|
| **Different Doses of Roxadustat Treatment for Anemia in Peritoneal Dialysis Patients**<br><br>**NCT04454879**<br><br>**Sponsors:**<br>**Peking University First Hospital**<br>**Beijing Haidian Hospital**<br>**Beijing Hospital of Traditional Chinese Medicine** | Phase IV, randomized, open-label study<br><br>Estimated N: 100<br><br>Location: China | Roxadustat (oral)<br>• Standard dosage (weight based)<br>• Lower dosage (weight based) | **Inclusion Criteria:**<br>• CKD Stage V<br>• Maintenance on PD for ≥3 months<br>• Renal anemia, and Hb between 90g/L-120g/L<br>• Stop taking erythropoietin for enough time or free of erythropoietin use<br>**Exclusion Criteria:**<br>• Hematologic malignancy or aplastic anemia<br>• Blood loss or hemolysis<br>• Currently taking roxadustat, or allergy or intolerance to roxadustat<br>• Severe liver injury or active hepatitis<br>• Cancer, receiving radiotherapy and chemotherapy within 6 months<br>• Refractory hypertension | *[Timeframe: 12 weeks]*<br>**Primary Outcome(s):**<br>• The ratio of Hb achieving the target (115g/L)<br>**Secondary Outcome(s):**<br>• Variation ratio of Hb levels<br>• The ratio of Hb over-shooting (> 130g/L) | March 2022 |
| **Post-marketing Surveillance of EVRENZO® Tablets (Roxadustat) in Dialysis-dependent Patients with Renal Anemia**<br><br>**NCT04408820** | Prospective cohort study<br><br>Estimated N: 1000<br><br>Location: Japan | Roxadustat (oral) | **Inclusion Criteria:**<br>• Renal anemia patients on dialysis who are naïve to roxadustat<br>**Exclusion Criteria:**<br>N/A | *[Timeframe: Up to 104 Weeks]*<br>**Primary Outcome(s):**<br>• CFB in Hb levels<br>• Mean value of Hb levels over time<br>• Achievement rate for target Hb level<br>• Mean Hb levels at 4 weeks after switching to roxadustat | November 2023 |

| Trial | Study Design | Study Arms | Patient Population | Key Outcomes | Estimated Completion Date |
|---|---|---|---|---|---|
| **Sponsor:**<br>**Astellas Pharma Inc.** | | | | Proportion of participants with<br>• Adverse drug reactions (ADRs)<br>• Serious ADRs<br>• Thromboembolism<br>• Hypertension<br>• Hepatic function disorder<br>• Malignant tumors<br>• Retinal hemorrhage<br>• Myopathy events<br>• ADR within 4 weeks after switching to roxadustat<br>• ADR with high doses of roxadustat | |
| **A Prospective Cohort Study of Roxadustat for Anemia in Patients With CKD**<br><br>**NCT04502537**<br><br>**Sponsor:**<br>**Shenzhen Second People's Hospital** | Prospective cohort study<br><br>Estimated N: 200<br><br>Location: China | • Roxadustat (oral)<br>• Erythropoietin (IV) | **Inclusion Criteria:**<br>• ≥18 years of age<br>• Hb level of <10 g/dL if patient received ESA treatment<br>• Hb level of ≥7 and ≤ 12 g/dL if patient has received ESA treatment for ≥4 weeks<br>• Expected survival time ≥1 year<br>**Exclusion Criteria:**<br>• History of severe, chronic, end-stage or uncontrolled autoimmune liver disease, Child Pugh score was grade C, or with active hepatitis<br>• Anemia caused by any other disease other than CKD<br>• Malignant tumor<br>• RBC infusion during the screening period | *[Timeframe: Up to 52 weeks]*<br>**Primary Outcome(s):**<br>• Mean value of Hb levels over time<br>• Achievement rate for target Hb level<br>**Secondary Outcome(s):**<br>• Mean Hb levels at 4 and 8 weeks after using roxadustat<br>• Dose of roxadustat used<br>• CFB in Hb levels<br>• Proportion of patients with different Hb levels<br>• Proportion of patients with low response to ESA<br>• Serum iron<br>• Adverse events | September 2023 |

| Trial | Study Design | Study Arms | Patient Population | Key Outcomes | Estimated Completion Date |
|---|---|---|---|---|---|
| **Study of Roxadustat Conversion in Subjects Receiving Stable ESA or as Initial Anemia Treatment in Hemodialysis Patients**<br><br>NCT04484857<br><br>**Sponsor: FibroGen** | Phase III, open label, single group assignment trial<br><br>Estimated N: 300<br><br>Location: US | Roxadustat (oral) | **Inclusion Criteria:**<br>• ≥18 years of age<br>• Receiving chronic dialysis for ESRD<br>• Vascular access must be functioning native arteriovenous fistula or graft with adequate flow, or permanent tunneled catheter<br>• Subjects converting from ESA: between 9.0-12.0 g/dL<br>• Subjects initiating anemia treatment: <10.0 g/dL<br>• Ferritin ≥50 ng/mL, TSAT ≥10%<br>• ALT and AST ≤3 x ULN, and total bilirubin ≤1.5 x ULN<br>• Weight 45-160 kg<br>**Exclusion Criteria:**<br>• RBC transfusion within 4 weeks<br>• History of myelodysplastic syndrome, multiple myeloma, or malignancies<br>• Hereditary hematologic disease or other known causes for anemia other than CKD<br>• Active or chronic GI bleeding<br>• Treated with iron-chelating agents within 4 weeks<br>• NYHA Class III or IV CHF<br>• History of MI, acute coronary syndrome, stroke, seizure<br>• Uncontrolled hypertension<br>• Diagnosis or suspicion of renal cell carcinoma | *[Timeframe: week 16 to 24]*<br>**Primary Outcome(s):**<br>• Proportion of subjects with mean Hb ≥10g/dL<br>• Mean Hb CFB | August 2021 |

| Trial | Study Design | Study Arms | Patient Population | Key Outcomes | Estimated Completion Date |
|---|---|---|---|---|---|
| **Evaluate the Efficacy and Safety of Roxadustat for the Treatment of Anemia and Risks of Cardiovascular and Cerebrovascular Events in ESRD Newly Initiated Dialysis Patients**<br><br>**NCT04134026**<br><br>**Sponsor:**<br>**Second Xiangya Hospital of Central South University** | Phase IV, randomized, open label trial<br><br>Estimated N: 400<br><br>Location: China | • Roxadustat (oral)<br>• Epoetin alfa (IV) | *[Timeframe: 52 weeks]*<br>**Inclusion Criteria:**<br>• ≥18 years of age<br>• Weight: 45-100 kg<br>• Patients with CKD ESRD received hemodialysis treatment ≤4 weeks<br>• No iron, folate, vitamin B12 deficiencies<br>• No abnormal liver tests<br>• Hb level <10.0 g/dL<br>**Exclusion Criteria:**<br>• Clinically significant infection or active potential infection<br>• Active hepatitis or any of following abnormalities: ALT ≥2x ULN, AST ≥2x ULN, direct bilirubin ≥2x ULN<br>• Patients with severe CVD have had MI, coronary artery bypass, or PCI operation within 3 months<br>• Severe cerebrovascular diseases within 3 months<br>• Active GI bleeding occurred within 3 months<br>• Poorly controlled hypertension<br>• Previous or current malignancies<br>• Causes of anemia other than CKD<br>• Known autoimmune diseases<br>• Any previous functional organ transplant or scheduled organ transplant or no kidney<br>• Serum albumin <25 g / L | **Primary Outcome(s):**<br>• Mean Hb CFB to average levels from week 28-52<br>• Proportion of subjects who achieve a Hb response at 24 weeks<br>• The incidence of CV and cerebrovascular events<br>**Secondary Outcome(s):**<br>• All-cause mortality<br>• Proportion of subjects with increased hypertension *[Timeframe: 27 weeks]*<br>• Mean BP CFB to average levels from week 28-52<br>• Change of left ventricular structure; change of systolic function; change of diastolic function at 12, 36, and 52 weeks<br>• Serum lipid parameters *[Timeframe: 25-27 Weeks]*<br>• Mean change level of CRP *[Timeframe: 25-27 Weeks]* | October 2023 |

| Trial | Study Design | Study Arms | Patient Population | Key Outcomes | Estimated Completion Date |
|---|---|---|---|---|---|
| | | | • Treatment with androgen, deferoxamine, deferrone, or deferestron within 8 weeks<br>• RBC within 4 weeks | | |
| **Evaluate the Efficacy and Safety of Multiple Roxadustat Dosing Regimens for the Treatment of Anemia in Dialysis Subjects with Chronic Kidney Disease**<br><br>**NCT04059913**<br><br>**Sponsor: FibroGen** | Phase IV, randomized, open label trial<br><br>Estimated N: 306<br><br>Location: China | Part 1: **Roxadustat**<br>• low dose (oral)<br>• standard weight-based dose (oral)<br>Part 2: **Roxadustat**<br>• Subjects will receive roxadustat at different dose frequencies | **Inclusion Criteria:**<br>• 18-75 years of age<br>• CKD with ESRD on either hemodialysis or peritoneal dialysis<br>**Exclusion Criteria**:<br>• HIV, hepatitis B surface antigen, or anti-hepatitis C virus antibody<br>• CV risks<br>• History of malignancy, myelodysplastic syndrome, and multiple myeloma<br>• Disease conditions that could impact RBC production<br>• Recent blood loss | **Primary Outcome(s):**<br>Part 1 (Weeks 1-20):<br>• ESA-naïve: proportion of subjects who achieve Hb ≥11.0 g/dL in the first 20 weeks<br>• ESA-treated: proportion of subjects who achieve mean Hb ≥10.0 g/dL averaged over week 17 visit to week 21<br>Part 2 (Weeks 33-37)<br>• Mean Hb averaged at weeks 33-37 visits<br>**Secondary Outcome(s):**<br>• Mean change in Hb level from baseline to average over weeks 17-21<br>• ESA-naïve: proportion of subjects with mean Hb (averaged week 17-21 visits) ≥10 g/dL<br>• Proportion of subjects with mean Hb (averaged weeks 33-37 visits) ≥10 g/dL | |

ALT: alanine transferase, AST: aspartate transferase, CKD: chronic kidney disease, CVD: cardiovascular disease, dL: deciliter, ESA: erythropoiesis-stimulating agent, ESRD: end-stage renal disease, g: gram, Hb: hemoglobin, HIV: human immunodeficiency virus, IV: intravenous, kg: kilogram, L: liter, MI: myocardial infarction, N: total number, N/A: not available, NYHA: New York Heart Association, PCI: Percutaneous Coronary Intervention, PD: peritoneal dialysis, RBC: red blood-cell, ULN: upper-limit of normal

Source: www.ClinicalTrials.gov (NOTE: studies listed on-site include both clinical trials and observational studies).

# D6. Previous Systematic Reviews and Technology Assessments

We identified one ongoing health technology assessment (HTA) conducted by NICE and four previously conducted systematic reviews of roxadustat. These reviews are summarized below. It should be noted that none of the previous systematic reviews we identified include the key trials required for FDA review.

## Health Technology Assessments

### *NICE*

**Roxadustat for Treating Anaemia in People with Chronic Kidney Disease [ID1483]**

NICE is currently conducting an appraisal of the clinical and cost effectiveness of roxadustat for the treatment of anemia associated with CKD. The expected publication date is to be confirmed.

## Previous Systematic Reviews

**Jia L, Dong X, Yang J, Jia R, Zhang H. Effectiveness of hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat on renal anemia in non-dialysis-dependent chronic kidney disease: a systematic review and meta-analysis. Ann Transl Med. 2019 Dec;7(23):720. doi: 10.21037/atm.2019.12.18. PMID: 32042736; PMCID: PMC6989965.**

The authors conducted a systematic literature review and MA that included three Phase II RCTs evaluating roxadustat for the treatment of renal anemia in DI-CKD patients. Efficacy was evaluated based on changes in Hb levels from baseline and Hb response. Safety was evaluated based on the occurrence of adverse events and serious adverse events. Roxadustat was found to significantly increase Hb when compared to placebo. While roxadustat was generally found to be safe, the authors stated that significant uncertainties about the safety profile of roxadustat compared to placebo remain. The authors judged the clinical evidence to be of low and very low quality and found that the risk of bias was high because pharmaceutical companies sponsored all RCTs that were included in the network meta-analysis (NMA). The authors concluded that further independent research was needed to provide independent, high-quality evidence of the efficacy and safety of roxadustat.

**Liu J, Zhang A, Hayden JC, Bhagavathula AS, Alshehhi F, Rinaldi G, Kontogiannis V, Rahmani J. Roxadustat (FG-4592) treatment for anemia in dialysis-dependent (DD) and not dialysis-dependent (NDD) chronic kidney disease patients: A systematic review and meta-analysis. Pharmacol Res. 2020 May;155:104747. doi: 10.1016/j.phrs.2020.104747. Epub 2020 Mar 17. PMID: 32171893.**

This systematic review and MA were performed to evaluate the comparative efficacy and safety of roxadustat versus placebo and epoetin alfa for the treatment of anemia in patients with CKD. The MA included six RCTs (two Phase III and four Phase II trials), assessing roxadustat treatment in DI-CKD patients and patients receiving dialysis treatment (DD-CKD). It was found that in patients who were not on dialysis, roxadustat significantly increased Hb levels when compared to placebo. Similar results were found in the DD-CKD population, where roxadustat was shown to significantly increase Hb levels when compared to epoetin alfa. This MA found the safety profile of roxadustat and placebo to be comparable with regards to the occurrence of TEAEs in the DI-CKD population. However, in the DD-CKD population, roxadustat was found to significantly increase the risk of TEAEs when compared to epoetin alfa. The authors concluded that roxadustat is efficacious in increasing Hb levels in both DI- and DD-CKD patients. They also noted that the studies included in this MA were not powered to detect differences in safety or long-term clinical outcomes and that additional studies are needed to fill this gap.

**Zheng Q, Yang H, Fu X, Huang Y, Wei R, Wang Y, Liu YN, Liu WJ. The efficacy and safety of roxadustat for anemia in patients with chronic kidney disease: a meta-analysis. Nephrol Dial Transplant. 2020 Oct 14:gfaa110. doi: 10.1093/ndt/gfaa110. Epub ahead of print. PMID: 33051677.**

This systematic review and MA included six RCTs (two Phase III and four Phase II trials) evaluating the efficacy and safety of roxadustat for the treatment of renal anemia versus placebo in DI-CKD patients and versus epoetin alfa in DD-CKD patients. Roxadustat was found to lead to significantly higher Hb levels when compared to both placebo and epoetin alfa. The safety profile for roxadustat was found to be comparable to placebo in the DI-CKD patient population. When compared to epoetin alfa, however, DD-CKD patients treated with roxadustat experienced significantly more adverse events. The incidence of serious adverse events did not significantly differ with roxadustat compared to placebo and epoetin alfa. The authors noted that the quality of the clinical evidence was of low or very low quality. Nonetheless, the authors concluded that evidence suggests roxadustat is safe and efficacious in the short-term treatment of anemia in patients with CKD.

**Zheng Q, Yang H, Sun L, Wei R, Fu X, Wang Y, Huang Y, Liu YN, Liu WJ. Efficacy and safety of HIF prolyl-hydroxylase inhibitor vs epoetin and darbepoetin for anemia in chronic kidney disease patients not undergoing dialysis: A network meta-analysis. Pharmacol Res. 2020 Sep;159:105020. doi: 10.1016/j.phrs.2020.105020. Epub 2020 Jun 16. PMID: 32561478.**

This systematic review and NMA sought to compare HIF-PHIs versus ESAs for the treatment of anemia in DI-CKD patients. A total of 19 RCTs evaluating eight different anti-anemia treatment agents, including six HIF-PHIs (roxadustat, daprodustat, molidustat, enarodustat, desidustat, and vadadustat) and two ESAs (epoetin alfa and darbepoetin alfa) were included in this analysis. Efficacy was evaluated based on Hb level elevation and safety was assessed based on all-cause mortality. Roxadustat was found to lead to significantly greater change in Hb levels when compared to placebo, but not when compared to the two ESAs. All-cause mortality rates for DI-CKD patients treated with roxadustat, epoetin alfa, and darbepoetin alfa were comparable to those observed in those who received placebo. The authors concluded that while HIF-PHIs, such as roxadustat, are efficacious and well-tolerated, further studies are needed to evaluate their efficacy and safety profiles.

# E. Long-Term Cost-Effectiveness: Supplemental Information

## E1. Detailed Methods

**Table E1. Impact Inventory**

| Sector | Type of Impact (Add Additional Domains, as Relevant) | Included in This Analysis from […] Perspective? | | Notes on Sources (if Quantified), Likely Magnitude & Impact (if Not) |
|---|---|---|---|---|
| | | Health Care Sector | Societal | |
| **Formal Health Care Sector** | | | | |
| **Health Outcomes** | Longevity effects | X | X | |
| | Health-related quality of life effects | X | X | |
| | Adverse events | X | X | |
| **Medical Costs** | Paid by third-party payers | X | X | |
| | Paid by patients out-of-pocket | ☐ | ☐ | |
| | Future related medical costs | X | X | |
| | Future unrelated medical costs | ☐ | ☐ | |
| **Informal Health Care Sector** | | | | |
| **Health-Related Costs** | Patient time costs | NA | X | |
| | Unpaid caregiver-time costs | NA | X | |
| | Transportation costs | NA | ☐ | |
| **Non-Health Care Sector** | | | | |
| **Productivity** | Labor market earnings lost | NA | X | |
| | Cost of unpaid lost productivity due to illness | NA | X | |
| | Cost of uncompensated household production | NA | X | |
| **Consumption** | Future consumption unrelated to health | NA | ☐ | |
| **Social Services** | Cost of social services as part of intervention | NA | ☐ | |
| **Legal/Criminal Justice** | Number of crimes related to intervention | NA | ☐ | |
| | Cost of crimes related to intervention | NA | ☐ | |
| **Education** | Impact of intervention on educational achievement of population | NA | ☐ | |
| **Housing** | Cost of home improvements, remediation | NA | ☐ | |
| **Environment** | Production of toxic waste pollution by intervention | NA | ☐ | |
| **Other** | Other impacts (if relevant) | NA | ☐ | |

NA: not applicable

Adapted from Sanders et al [63]

## Target Population

Two target populations were considered: those with DI-CKD (CKD stages IIIb, IV, and V) and DD-CKD.

The DI-CKD population entered the model as CKD stage IIIb (60.6%), stage IV (23.6%), and stage V (15.8%), based on an analysis of commercial claims data for DI-CKD patients with anemia.[64] The baseline Hb for each population and for incident DD-CKD was presented in Table E2. Although anemia tends to worsen as CKD progresses, our DD-CKD cohort entered the model with a higher baseline Hb than the DI-CKD cohort, which was likely due to use of ESAs in the DD-CKD population prior to study enrollment.

**Table E2. Baseline Population Characteristics**

| CKD Stage | Baseline Hb (g/dL) | Source |
|---|---|---|
| DI-CKD Stage IIIb | 9.55 | [20] |
| DI-CKD Stage IV | 9.55 | [36] |
| DI-CKD Stage V | 9.55 | [36] |
| DD-CKD | 9.7 | [36] |
| Incident DD-CKD | 8.9 | [36] |

CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, ESA: erythropoiesis stimulating agent, g/dL: grams per deciliter, Hb: hemoglobin

We considered subpopulations such as those newly on dialysis (incident dialysis) versus established, hyporesponsive to ESAs versus non-hyporesponsive, by iron repletion status, and those with co-morbid cancer or cardiovascular disease. Because of a potentially more favorable profile for roxadustat in terms of MACE+ versus ESAs in the incident dialysis subpopulation, this was included as a scenario analysis. For the subpopulations of ESA hyporesponsiveness, iron repletion status, or comorbid cancer or cardiovascular disease, limited data were available to inform stratification by subpopulation and/or the relative impact of the data available to us did not meaningfully change the results of the cost-effectiveness analysis.

## Treatment Strategies

The intervention of interest is roxadustat (AstraZeneca).

In both populations, we intend to compare roxadustat to ESAs. The efficacy of ESAs was represented by the comparators within the roxadustat trial, with the assumption of equivalent efficacy across ESAs.

- Darbepoetin alfa (Aranesp, Amgen)
- Epoetin alfa (Epogen, Amgen; Procrit, Janssen)
- Epoetin alfa-epbx (Retacrit, Pfizer)
- Methoxy polyethylene glycol-epoetin beta (Mircera, Roche)

Cost of ESAs were represented by a market basket of ESAs. As data to inform a market basket for each population separately was not available to us, a consistent market basket was applied across the DI-CKD and DD-CKD populations consisting of darbepoetin alpha (28%), epoetin alpha (Epogen) (28%), epoetin alpha (Procrit) 15%, epoetin alpha-epbx (9%), and epoetin beta (20%).

# E2. Model Inputs and Assumptions

## Model Inputs

### *Transition Probabilities*

The underlying transitions between CKD stages and death were based on prior published models of CKD, data from the US Renal Data System (USDRS) Annual Report, or for death in DD-CKD, the pooled roxadustat Phase III trials. The annual probability of death from the post-transplant health state was estimated based on a weighted averaged five-year survival of 84.7% from deceased donor recipients and 91.9% among living donor recipients, with 28% of patients receiving a kidney from a living donor.[65]

**Table E3. Annual Transition Probabilities**

| | Ending State | | | | | |
|---|---|---|---|---|---|---|
| **Initial State** | **DI-CKD Stage IIIb** | **DI-CKD Stage IV** | **DI-CKD Stage V** | **DD-CKD** | **Transplant** | **Death†** |
| **DI-CKD Stage IIIb** | 0.822* | 0.137[66] | -- | -- | -- | 0.041[67] |
| **DI-CKD Stage IV** | -- | 0.839* | 0.081[66] | -- | -- | 0.080[67] |
| **DI-CKD Stage V** | -- | -- | 0.257* | 0.626[66] | 0.009[66] | 0.108[66] |
| **DD-CKD** | -- | -- | -- | 0.811* | 0.035[65] | 0.154† |
| **Transplant** | -- | -- | -- | 0.046[66] | 0.926* | 0.028[65, 66] |

CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent

*Calculated by subtracting probabilities of all other transitions from 1.

†Based on the pooled analysis of the ESA arms of HIMALAYAS, SIERRAS, ROCKIES, and PYRENEES.

"--" represents no probability of transitioning to that state.

### *Clinical Inputs*

*Clinical Probabilities/Response to Treatment*

Treatment effectiveness was estimated using the mean CFB in Hb level for roxadustat and ESAs from the roxadustat Phase III trials (Table E4). We estimated the treatment benefit of roxadustat over ESAs in the DD-CKD population based on a MA all four Phase III trials of HIMALAYAS, ROCKIES, PYRENEES, and SIERRAS. We also considered the proportion of patients who achieve Hb ≥10 g/dL.

**Table E4. Treatment-Related Efficacy**

| Mean CFB in Hb | Roxadustat | ESA | Absolute Difference | Source |
|---|---|---|---|---|
| DI-CKD | 1.85 g/dL | 1.84 g/dL | 0.015 (-0.13, 0.16) | [20] |
| DD-CKD | Based on MA | Based on MA | 0.23 (-0.04, 0.50) | ICER-conducted MA |
| Hb Level, DI-CKD | | | | |
| <10 g/dL | 18% | 18%* | None* | [20] |
| ≥10 g/dL | 82% | 82% | None* | |
| Hb Level, DD-CKD | | | | |
| <10 g/dL | 33.9% | 41.4% | -7.5% | [68] |
| ≥10 g/dL | 66.1% | 58.6% | +7.5% | |

CFB: change from baseline, CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-dependent, ESA: erythropoiesis stimulating agent, g/dL: grams per deciliter, Hb: hemoglobin, ICER: Institute for Clinical and Economic Review, MA: meta-analysis

*Assumed equal to roxadustat based on findings of a Phase III head-to-head, non-inferiority study.

*Discontinuation*

Patients continued treatment with roxadustat or ESAs with no discontinuation of treatment except for those in the post-transplant state. For the DI-CKD population all patients were assumed to switch to ESAs upon progression to DD-CKD in the base case.

*Mortality*

Patients with CKD are known to have increased risk of mortality, with increasing risk as the disease progresses. Overall mortality for CKD by health state was captured using published transition probabilities (see Table E3). Although not powered to detect a statistically significant difference, the Phase III trials of roxadustat showed a numeric reduction in mortality among patients treated with roxadustat compared with ESAs with a high degree of uncertainty. We considered a scenario where a potential reduction in all-cause mortality was considered based on point estimates, with 95% confidence intervals for those point estimates varied in one-way and probabilistic sensitivity analyses. Treatment-related impact on mortality were applied based on the relative reduction in risk of all-cause mortality from DOLOMITES in the DI-CKD population (0.83 [95% CI 0.50, 1.38]) *(scenario analysis only)*.[20] For the scenario which considered MACE+ events in the DI-CKD population, a relative increase in mortality for DI-CKD patients after experiencing a MACE+ event was applied based on observational real-world data (HR 4.15 [95% CI 3.30, 5.23]).[69] For the DD-CKD population a relative reduction in risk of mortality for roxadustat compared with ESAs derived from a MA of all four Phase III trials of HIMALAYAS, ROCKIES, PYRENEES, and SIERRAS (RR 0.89 [95% CI 0.75, 1.06]).

***Economic Inputs***

*Drug Utilization*

For roxadustat and ESAs, dose adjustments are made to achieve and maintain Hb levels within a target range. For the DI-CKD population, average utilization was based on use of pre-filled syringes at a representative dose for each ESA. For DD-CKD, utilization was based on average units per cycle for epoetin alpha.[70] Epoetin alpha units per cycle were converted to darbepoetin alpha units per cycle based on a published conversion table.[71] Average utilization of epoetin beta was based on the median dose administered in a trial of DD-CKD patients.[72]

**Table E5. Treatment Regimen Dosage and Utilization**

| | Darbepoetin Alfa | Epoetin Alfa | Methoxy Polyethylene Glycol-Epoetin Beta |
|---|---|---|---|
| **Brand Name** | Aranesp | Epogen, Procrit, Retacrit | Mircera |
| **Manufacturer** | Amgen | Amgen, Janssen | Roche |
| **Route of Administration** | IV or SC | IV or SC | SSC |
| **Labeled Dosing in DI-CKD** | Starting dose: 0.45 mcg/kg every 4 weeks | Starting dose: 50 to 100 units/kg 3 times weekly | Starting dose: 0.6 mcg/kg every 2 weeks<br>Maintenance dose: 2x the starting dose every month |
| **Labeled Dosing in DD-CKD** | Starting dose: 0.45 mcg/kg every week or 0.75 mcg/kg every 2 weeks | Starting dose: 50 to 100 units/kg 3 times weekly | Starting dose: 0.6 mcg/kg every 2 weeks<br>Maintenance dose: 1.2 mg per month |
| **DI-CKD Utilization Assumption** | One 40 mcg prefilled syringe administered SC per cycle | One 10,000-unit prefilled syringe administered SC 12 times per cycle | One 100 mcg/0.3 ml syringe administered SC per cycle |
| **DD-CKD Utilization Assumption** | 160 mcg per cycle† | 52,682 units per cycle* | 120 mcg per cycle‡ |

CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, IV: intravenous, kg: kilogram, mcg: microgram, SC: subcutaneous

*Based on weighted average of ESA non-responsive and hyporesponsive groups.[70]

†Based on converting epoetin alpha dose to darbepoetin dose.[71]

‡In the RUBRA (targeting sustained Hb in dialysis with IV and SC CERA. Administration) study, the median dose was 60 mcg once every 2 weeks during the evaluation period.[72]

*Drug Acquisition Costs*

### *Commercial Perspective*

Roxadustat is not yet approved by the FDA and the drug cost is not yet available. At the time of the draft report, we had heard that analysts predict roxadustat to be priced at approximately $13,000 per year with a 50% discount. For ESAs in the base case from the commercial perspective, we used Average Sales Price (ASP, October 2020 pricing) for subcutaneously administered products in the DI-CKD population. Combining the net annual drug cost in Table E6 with the market share in Table E6 yields an average annual cost of $7,943 per year for ESAs in the DI-CKD population. For IV-administered products in the DD-CKD population we assumed ASP plus 9.5% to represent a commercial payer cost, yielding an average cost of $6,934 per year.

### *Medicare Perspective*

For the Medicare perspective for the DD-CKD population, no costs for ESAs are itemized as these are reimbursed as part of a bundled payment. For roxadustat, we assumed incremental cost outside of the bundled payment equal to that of the commercial perspective ($6,500 per year) for three years, after which the roxadustat would be entered into the bundled payment.

**Table E6. DI-CKD Drug Cost Inputs**

| Interventions | Administration | Unit | WAC per Unit/Dose* | Net Price per Units | Annual Drug Cost |
|---|---|---|---|---|---|
| **Roxadustat** | Oral | -- | -- | -- | $6,500 |
| **Darbepoetin alpha** | SC | 40 mcg syringe | $309.60 | $134.06 | $1,747 |
| **Epoetin alpha (Epogen)** | SC | 10,000-unit syringe | $165.80 | $81.41 | $12,732 |
| **Epoetin alpha (Procrit)** | SC | 10,000-unit syringe | $267.25 | $108.77 | $17,012 |
| **Epoetin alpha-epbx** | SC | 10,000-unit syringe | $110.30 | $71.25 | $11,144 |
| **Epoetin beta** | SC | 120 mcg syringe | $288.48 | $128.09 | $1,669 |

SC: subcutaneous, WAC: wholesale acquisition cost
*WAC as of October 20, 2020.

**Table E7. DD-CKD ESA Drug Costs**

| Interventions | Administration | Unit | ASP per Unit/Dose* | ASP + 9.5% | Annual Drug Cost |
|---|---|---|---|---|---|
| Roxadustat | Oral | -- | -- | -- | $6,500 |
| Darbepoetin alpha | IV | mcg | $3.506 | $3.839 | $8,005 |
| Epoetin alpha | IV | 1,000 units | $8.593 | $9.410 | $6,461 |
| Epoetin alpha-epbx | IV | 1,000 units | $8.125 | $8.896‡ | $6,108 |
| Epoetin beta | IV | mcg | $1.45 | $1.595 | $2,495 |

ASP: Average Sales Price, IV: intravenous

*ASP as of October 2020.

‡Calculated as ASP plus 9.5% of the originator product ASP.

*Administration and Monitoring Costs*

In the base case, it is assumed that DI-CKD patients will use self-administered formulations of subcutaneously administered ESAs, resulting in no direct cost for administration. In the DD-CKD population, it is assumed that ESAs will be administered as part of regular dialysis sessions with no incremental cost of administration.

*Direct Cost by CKD Stage*

Direct cost of CKD by stage and transplant status were included in the model based on annual mean per-patient estimates from the USDRS 2018 and 2019 Annual Reports.[10,27] A one-time cost of undergoing transplant were based on CMS diagnosis-related group (DRG) amount (MS-DRG 652).[26] In the post-transplant state, some patients experienced graft failure as an adverse outcome of transplant, which was associated with significant cost. For the purposes of our model, those with graft failure were represented by the transition back to DD-CKD and incurred the cost of DD-CKD.

**E8. Direct Cost of CKD**

| Cost Type | Cost | Source |
|---|---|---|
| Annual Cost of DI-CKD Stage IIIb | $22,000 | [65] |
| Annual Cost of DI-CKD Stage IV and V | $33,000 | [65] |
| Annual Cost of DD-CKD | $89,953 | [73] |
| Transplant Event | $19,636 | DRG 652*[74] |
| Annual Cost Post-Transplant, Functioning Graft | $26,988 | [73] |

CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, DRG: diagnosis-related group, UPDRS: United States Renal Data System

*Sum of labor ($3,962.17) and non-labor ($1,838.96) national adjusted operating standardized amounts for wage index >1 and meaningful electronic health record user then multiplied by DRG weight of 3.3849.

Additionally, the cost of dialysis bundled payment will be considered under the Medicare perspective. For all patients with DD-CKD, a cost of $239.33 per encounter and 12 encounters per

cycle will be applied based on rates from the CMS End Stage Renal Disease (ESRD) Prospective Payment System (PPS).[75]

*Direct Cost of Anemia Management*

In addition to drug cost, anemia management included red blood cell transfusions and IV iron supplementation. The utilization of these were taken directly from the roxadustat Phase III trials (Table E9, Table E10). Where information was unavailable separately for each population (DI-CKD and DD-CKD), we used the best available data applied to both populations.

From the commercial perspective, the cost of a red blood cell transfusion was informed by the Current Procedural Terminology (CPT) code for reimbursement for blood transfusion services (CPT 36430, $35.73), assuming one unit of blood per transfusion at a cost of $550.46 per unit.[76,77] This cost was based on a mean amount charged to the patient ($343.63 ± $135) in 2007 dollars, inflated to 2020 USD using the Personal Health Care Expenditure deflator up to 2017 and then the personal consumption expenditure price index to update to 2020. From the Medicare perspective, red blood cell transfusions are included in the bundle and have no incremental cost.

**Table E9. Red Blood Cell Transfusions over 52 Weeks**

| | ESA (95% CI) | HR for Roxadustat vs. ESAs (95% CI) | Source |
|---|---|---|---|
| DI-CKD | 5.2%* | N/A* | [36,78] |
| DD-CKD | 12.8% (11.3%, 14.3%) | 0.82 (0.679, 0.997) | [36] |

CI: confidence interval, CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent; ESA: erythropoiesis-stimulating agent, HR: hazard ratio, RBC: red blood cell

*Assumed equal to roxadustat based on findings of a Phase III head-to-head, non-inferiority study.

The cost of IV iron included both the cost of the drug and physician administration. From the commercial perspective, drug cost was based on ASP of ferumoxytol ($0.983 per unit) plus 9.5% and direct cost of administration was $72.18 (CPT 96365 National Payment Amount).[76,79] Iron dose in the DI-CKD population each iron infusion was based on the recommended labeled dose of Feraheme® of an initial 510 mg dose followed by a second 510 mg dose three to eight days later.[80] No information was identified to inform the number of infusions for ESAs or roxadustat in the Phase III trials. For the draft model, one administration per cycle was assumed for both treatments. From the Medicare perspective, IV iron infusions are included in the bundle and have no incremental cost.

**Table E10. IV Iron**

| | Roxadustat | ESA | HR (95% CI) | Source |
|---|---|---|---|---|
| **DI-CKD** | Calculated based on HR | 21.2 infusions per 100 person-years | 0.45 (0.26, 0.78) | [20] |
| **DD-CKD** | Calculated based on LSM difference | 44.0 ± 88.6 mg per month | LSM difference: -31.9 mg (95% CI -41.4, -22.4) | [81] |

CI: confidence interval, CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent; ESA: erythropoiesis stimulating agent, HR: hazard ratio, IV: intravenous, LSM: least squared mean, mg: milligram.

*Direct Cost of MACE+*

Cost of MACE+ events included cost of the first cycle when the acute event occurred and cost of care for subsequent cycles attributable to higher health care resource utilization following MACE+ events. The cost of post-MI and post-stroke cycles was based on published three-year cumulative cost estimates, calculated as the total 36-month cost minus the first month divided by 35 months to arrive at a monthly long-term cost and then inflated to 2020 values.[29] Hospitalization for congestive heart failure and hospitalization for unstable angina were considered acute worsening events in patients with existing congestive heart failure and angina, respectively, and incurred costs only in the cycle when the event occurred.

**Table E11. Cost of MACE+ Events**

| Parameter | Value* | Source |
|---|---|---|
| **Death** | $24,669 | [82] |
| **MI Event** | $54,785 | [82] |
| **Unstable Angina Event** | $27,713 | [82] |
| **Hospitalization for CHF** | $7,807 | DRG 291†[74] |
| **Stroke Event** | $16,980 | Ischemic stroke[82] |
| **Post-MI Cycles** | $1,790 | [82] |
| **Post-Stroke Cycles** | $430 | [82] |

CHF: congestive heart failure, CI: confidence interval, DRG: diagnosis-related group, MI: myocardial infarction
*Original 2007 values inflated to 2020 USD using the Personal Health Care Expenditure deflator up to 2017 and then the personal consumption expenditure price index to update to 2020.
†Sum of labor ($3,962.17) and non-labor ($1,838.96) national adjusted operating standardized amounts for wage index >1 and meaningful electronic health record user then multiplied by DRG weight of 1.3458.

**Table E12. Utility Tolls for MACE+ Events**

| Parameter | Value (95% CI) | Source |
|---|---|---|
| Unstable Angina Event (Applied to Cycle) | -0.0412 | [83] |
| Hospitalization for CHF (Applied to Cycle) | -0.089 (-0.132, -0.047) | [84] |
| Acute Stroke Event (Applied to Cycle) | -0.204 (-0.272, -0.136) | [84] |
| Acute MI Event (Applied to Cycle) | -0.042 (-0.074, -0.010) | [84] |
| Post-Stroke Cycles | -0.101 (-0.117, -0.086) | [84] |
| Post-MI Cycles | -0.011 (-0.022, 0.001) | [84] |

CHF: congestive heart failure, CI: confidence interval, MI: myocardial infarction

*Indirect Costs*

A modified societal perspective including indirect costs of presenteeism and absenteeism were included as a scenario analysis. Work Productivity and Activity Impairment Questionnaire (WPAI) estimates from a US patient survey were combined with US Bureau of Labor Statistics average working hours per week (38.6) and average hourly wage ($29.47) to produce an indirect cost for each health state.[85,86]

**Table E13. Overall Work Impairment (% of Time Impaired)**

| | Hb <10 % (SD) | Hb 10-12 % (SD) | Source |
|---|---|---|---|
| DI-CKD | 37.4 (27.0) | 28.9 (24.6) | [87] |
| DD-CKD | 42.7 (29.3) | 39.8 (27.5) | [87] |

CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, Hb: hemoglobin, SD: standard deviation

Indirect cost to patients for each IV iron infusion was calculated as 121 minutes per infusion multiplied by average hourly wage ($29.47) to estimate indirect cost.[88] The patient time for each red blood cell transfusion were approximated at four hours per transfusion.[89]

ESRD is associated with substantial indirect costs for both patients and caregivers. Table E14 outlines indirect cost inputs for ESRD. For DD-CKD patients, we attributed $10,752 per year to lost productivity of the patient and caregivers, an estimate from autosomal dominant polycystic kidney disease that includes unemployment, lost productivity, and caregiver lost productivity. Kidney transplants affected the patient, caregiver, and donor (if a living donor), and caregiver of the donor. Hours were multiplied by the average hourly wage ($29.47) to produce an indirect cost estimate.[85]

Utility Tolls for MACE+

**Table E14. Indirect Cost of ESRD**

| | Value | Source |
|---|---|---|
| **DD-CKD, Including Patient and Caregiver** | $10,752 per year | [90] |
| **Transplant, Patient** | 252 hours of work lost | Assumed same value as donor |
| **Transplant, Patient Caregiver** | 81 hours of work lost | Assumed same value as donor caregiver |
| **Transplant, Donor** | 252 hours of work lost | [91] |
| **Transplant, Donor Caregiver** | 81 hours of work lost | [91] |
| **Transplant, Donor Caregiver** | $1,193 (SD $1,968) in direct costs* | [91] |

CKD: chronic kidney disease, DD: dialysis dependent, SD: standard deviation
*Original values inflated to 2020 USD.

Lastly, stroke and MI events were associated with an indirect cost due to lost productivity. Each stoke and MI event incurred 78.7 (SD 63.5) hours of lost productivity in the first month and 21.3 (SD 16.2) hours in subsequent cycles.[92] These lost productive hours were multiplied by the average hourly wage ($29.47) to produce an indirect cost estimate.[85]

### *Adverse Events*

Serious adverse events other than MACE+ occurring in patients treated with roxadustat or ESAs were considered for inclusion. At present, the rate of non-MACE specific severe adverse events in the DI-CKD population is unclear. In the DD-CKD population, one study (PYRENEES) presented the event rate per 100 person-years for severe adverse events occurring in ≥1% of patients in any treatment group. In the absence of any other data on severe adverse events from other studies, those occurring in ≥5% of patients in either arm of PYRENEES were applied to both the DI-CKD and DD-CKD population as a constant per-cycle probability. Following this rule, only serious pneumonia was included.

**Table E15. Serious Non-MACE Adverse Events Occurring in ≥5% of Patients in any Treatment Group (PYRENEES)**

| | Roxadustat Event Rate per 100 Person-Years | ESA Event Rate per 100 Person-Years | Source |
|---|---|---|---|
| **Pneumonia** | 2.3 | 2.9 | [93] |

ESA: erythropoiesis-stimulating agent

**Table E16. Adverse Event Cost and Utility Inputs**

| Input | Value | Source |
|---|---|---|
| **Cost of Pneumonia** | $10,655 (95% CI $9,737, $11,708) | [94] |
| **Disutility of Pneumonia (1 Cycle)** | -0.0709 ± 0.020 | [95] |

CI: confidence interval
*Value inflated to 2020 USD.

## Planned Subgroup Analyses

### *ESA Normo-Responsive versus Hyporesponsive*

Data regarding subgroups based on ESA-responsiveness for DOLOMITES are unavailable at the time of this report.

In the pooled roxadustat trials of HIMALAYAS, SIERRAS, and ROCKIES in the DD-CKD population, CFB in patients with inflammation and without inflammation (as a marker for responsiveness) were consistent with the overall outcomes.[61] However, patients who are ESA hyporesponsive may require higher doses to achieve correction of Hb levels. Based on real-world evidence, patients receiving dialysis who are ESA hyporesponders may require as much as a 3.8-fold higher ESA doses than normo-responders.[70] A scenario analysis was undertaken assuming higher and lower doses are needed in the DD-CKD population in hyporesponsive and normo-responsive patients, respectively.

**Table E17. ESA Responsiveness Inputs (per Cycle)**

| Input | Base-Case Dose | Normoresponsive Dose | Hyporesponsive Dose | Source |
|---|---|---|---|---|
| **Darbepoetin alfa** | 160 mcg | 100 mcg | 240 mcg | Epoetin dose converted to darbepoetin[71] |
| **Epoetin alfa** | 52,682 units | 24,331 units | 94,831 units | [70] |
| **Epoetin beta** | 120 mcg | No information | No information | N/A |

### *Iron Replete versus Non-Replete*

No data regarding subgroups based on iron status for DOLOMITES or the pooled analysis of DD-CKD trials are unavailable at the time of this report.

### *Incident Dialysis versus Stable Dialysis*

In the pooled analysis of incident dialysis patients, mean CFB in Hb was similar to the overall population (LSM difference vs. ESAs of 0.22 [0.05, 0.40]).[62] The reduction in mean monthly IV iron use was slightly greater in the incident dialysis subpopulation relative to the overall pooled analysis -40.8 (-77.3, -4.3).[62] As described in the Subgroup Analyses and Heterogeneity section of the main report, no information was available at the time of this report for the subgroup with stable (non-incident dialysis), we were unable to complete the analysis stratified by these subgroups.

***Comorbid Cardiovascular Disease***

No data were identified from the roxadustat trials to inform relative impact on outcomes in patients with and without existing comorbid cardiovascular disease.

***Comorbid Malignancy***

No data were identified from the roxadustat trials to inform relative impact on outcomes in patients with and without existing comorbid malignancy.

# E3. Results

## Description of evLYG Calculations

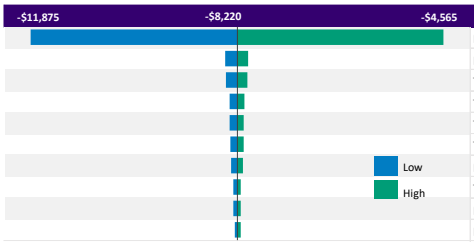
The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[96]
2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional LYs gained (ΔLYG).
3. We sum the product of the LYs and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the evLY (evLY) for that cycle.
4. If no LYs were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.
5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.
6. We use the same calculations in the comparator arm to derive its evLY.
7. Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

# E4. Sensitivity Analyses

One-way sensitivity analyses were conducted for the outcome of total incremental cost in each population. In the DI-CKD population (Figure E1), the cost of roxadustat was by far the most impactful parameter on total incremental cost versus ESAs. In the DD-CKD population (Figure E2), the impact on all-cause mortality, stroke, and MI were the most impactful parameters, followed by cost of roxadustat and ESAs.

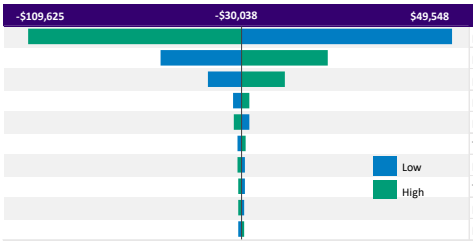
## Figure E1. Tornado Diagram, DI-CKD, Commercial, One-Way Sensitivity Analysis of Incremental Cost




| Parameter | Base Case | Low Value | High Value | Range | Low Result | High Result | Δ |
|---|---|---|---|---|---|---|---|
| Direct cost of roxadustat, DI-CKD | $498.71 | $448.84 | $548.59 | ±10% | -$11,875 | -$4,565 | $7,310 |
| HR for mortality post-stoke & MI, DI-CKD | 4.15 | 3.30 | 5.23 | 95% CI | -$8,426 | -$8,033 | $393 |
| Transition probability Stage IV to death | 0.080 | 0.072 | 0.1 | ±10% | -$8,413 | -$8,045 | $369 |
| Transition probability Stage IIIb to death | 0.041 | 0.037 | 0.0 | ±10% | -$8,359 | -$8,089 | $270 |
| Transition probability Stage IIIb to IV | 0.137 | 0.123 | 0.2 | ±10% | -$8,354 | -$8,100 | $255 |
| Transition probability Stage IV to Stage V | 0.081 | 0.073 | 0.1 | ±10% | -$8,343 | -$8,105 | $237 |
| Discount rate for costs | 0.23% | 0.21% | 0.0 | ±10% | -$8,325 | -$8,118 | $207 |
| Transition probability Stage V to DD-CKD | 0.626 | 0.563 | 0.7 | ±10% | -$8,292 | -$8,156 | $136 |
| Risk of MI, ESAs, DI-CKD | 0.27% | 0.2% | 0.3% | ±10% | -$8,284 | -$8,158 | $126 |
| HR for IV iron roxadustat vs ESAs, DI-CKD | 0.45 | 0.26 | 0.78 | 95% CI | -$8,257 | -$8,156 | $100 |

DD-CKD: dialysis-dependent chronic kidney disease, DI-CKD: dialysis-independent chronic kidney disease, ESA: erythropoiesis-stimulating agent, HR: hazard ratio, MI: myocardial infarction

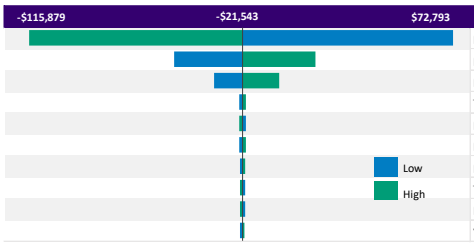
## Figure E2. Tornado Diagram, DD-CKD, Commercial, One-Way Sensitivity Analysis of Incremental Cost




| Parameter | Base Case | Low Value | High Value | Range | Low Result | High Result | Δ |
|---|---|---|---|---|---|---|---|
| RR for all-cause mortality vs ESAs, DD-CKD | 1.05 | 0.88 | 1.26 | 95% CI | $48,658 | -$109,625 | $158,283 |
| RR for MI vs ESAs, DD-CKD | 0.95 | 0.73 | 1.23 | 95% CI | -$60,067 | $2,198 | $62,264 |
| RR for stroke vs ESAs, DD-CKD | 0.90 | 0.60 | 1.34 | 95% CI | -$42,513 | -$13,926 | $28,587 |
| Direct cost of roxadustat, DD-CKD | $498.71 | $448.84 | $548.59 | ±10% | -$33,049 | -$27,028 | $6,022 |
| Direct cost of ESAs, DD-CKD | $465.59 | $419.04 | $512.15 | ±10% | -$27,149 | -$32,927 | $5,778 |
| Transition probability DD-CKD to death | 0.154 | 0.138 | 0.2 | ±10% | -$31,606 | -$28,552 | $3,054 |
| Direct cost of transplant event | $19,636 | $17,672 | $21,600 | ±10% | -$28,594 | -$31,483 | $2,889 |
| Transition probability DD-CKD to transplant | 0.035 | 0.032 | 0.0 | ±10% | -$28,838 | -$31,206 | $2,368 |
| Direct cost of DD-CKD | $6,902 | $6,212 | $7,592 | ±10% | -$28,880 | -$31,196 | $2,316 |
| Discount rate for costs | 0.23% | 0.21% | 0.0 | ±10% | -$31,162 | -$28,979 | $2,184 |

DD-CKD: dialysis-dependent chronic kidney disease, ESA: erythropoiesis-stimulating agent, MIL myocardial infarction, RR: risk ratio.

## Figure E3. Tornado Diagram, DD-CKD, Medicare, One-Way Sensitivity Analysis of Incremental Cost




| Parameter | Base Case | Low Value | High Value | Range | Low Result | High Result | Δ |
|---|---|---|---|---|---|---|---|
| RR for all-cause mortality vs ESAs, DD-CKD | 1.05 | 0.88 | 1.26 | 95% CI | $71,677 | -$115,879 | $187,556 |
| RR for MI vs ESAs, DD-CKD | 0.95 | 0.73 | 1.23 | 95% CI | -$51,744 | $10,891 | $62,636 |
| RR for stroke vs ESAs, DD-CKD | 0.90 | 0.60 | 1.34 | 95% CI | -$34,124 | -$5,286 | $28,837 |
| Transition probability DD-CKD to death | 0.154 | 0.138 | 0.2 | ±10% | -$23,064 | -$20,119 | $2,945 |
| Direct cost of transplant event | $19,636 | $17,672 | $21,600 | ±10% | -$20,099 | -$22,988 | $2,889 |
| Direct cost of roxadustat, DD-CKD | $498.71 | $448.84 | $548.59 | ±10% | -$22,970 | -$20,117 | $2,853 |
| Discount rate for costs | 0.23% | 0.21% | 0.0 | ±10% | -$22,753 | -$20,402 | $2,351 |
| Transition probability DD-CKD to transplant | 0.035 | 0.032 | 0.0 | ±10% | -$20,367 | -$22,689 | $2,322 |
| Direct cost of DD-CKD | $6,902 | $6,212 | $7,592 | ±10% | -$20,385 | -$22,701 | $2,316 |
| Years until included in the bundled payment | 3.0 | 2.7 | 3.3 | ±10% | -$22,605 | -$20,555 | $2,051 |

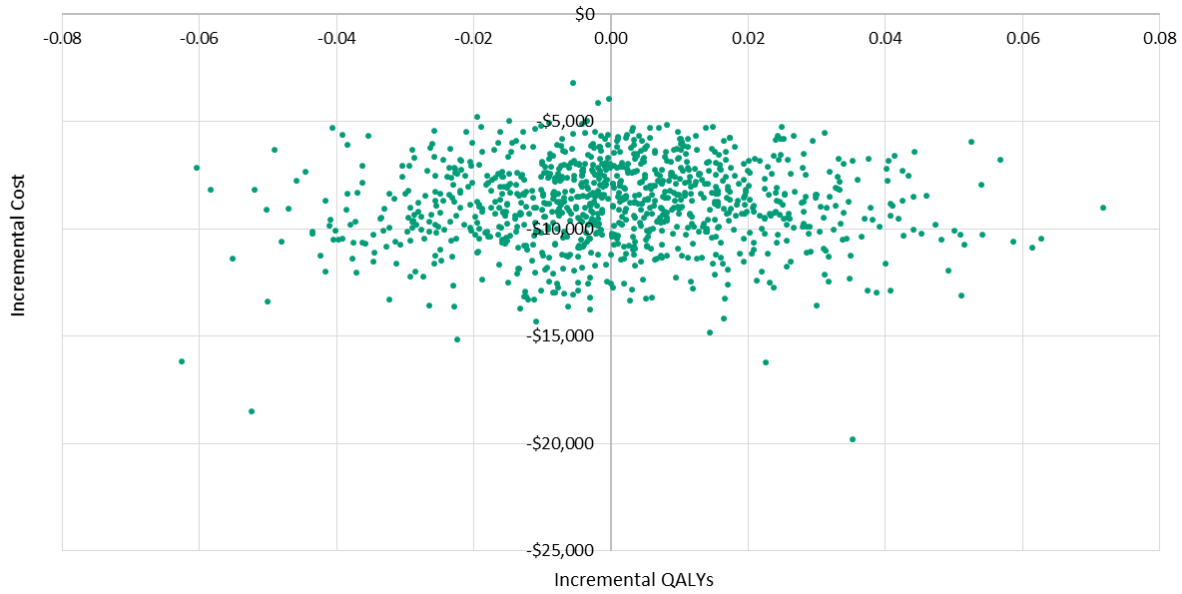
DD-CKD: dialysis-dependent chronic kidney disease, ESA: erythropoiesis-stimulating agent, MI: myocardial infarction, RR: risk ratio.

**Table E18. Results of Probabilistic Sensitivity Analysis for Roxadustat versus ESAs**

| | Roxadustat | | ESAs | | Incremental | |
|---|---|---|---|---|---|---|
| | Mean | Credible Range | Mean | Credible Range | Mean | Credible Range |
| **DI-CKD** | | | | | | |
| **Total Costs** | $453,000 | ($326,000, $630,0001) | $462,000 | ($334,000, $641,000) | -$9,000 | (-$13,000, -$5,000) |
| **Total QALYs** | 5.7 | (4.2, 7.7) | 5.7 | (4.2, 7.7) | 0.00 | (-0.04, 0.04) |
| **DD-CKD, Commercial** | | | | | | |
| **Total Costs** | $887,000 | ($404,000, $1,580,000) | $895,000 | ($487,000, $1,550,000) | -$7,414 | (-$368,000, $329,000) |
| **Total QALYs** | 4.3 | (2.1, 7.4) | 4.1 | (2.4, 6.5) | 0.26 | (-1.33, 1.73) |
| **DD-CKD, Medicare** | | | | | | |
| **Total Costs** | $1,031,000 | ($505,000, $1,712,000) | $1,040,000 | ($598,000, $1,657,000) | -$8,000 | (-$426,000, $382,000) |
| **Total QALYs** | 4.2 | (2.1, 7.1) | 4.0 | (2.4, 6.4) | 0.18 | (-1.35, 1.86) |

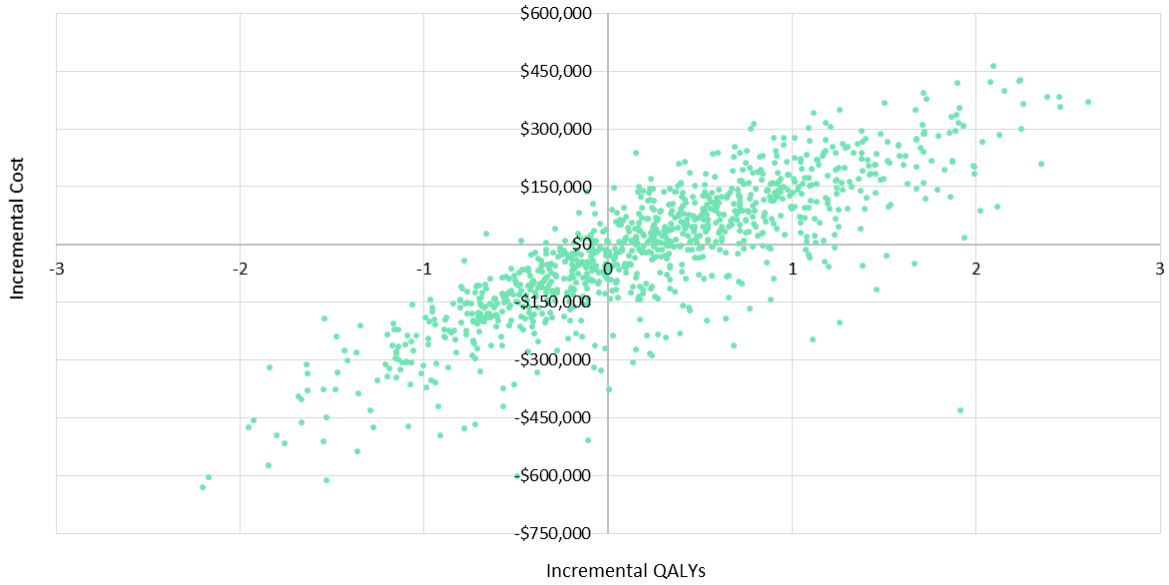
CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, ESA: erythropoiesis-stimulating agent, QALY: quality-adjusted life year

**Figure E4. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Cloud for Incremental Cost and QALYs for Roxadustat vs. ESAs, DI-CKD, Commercial Perspective**



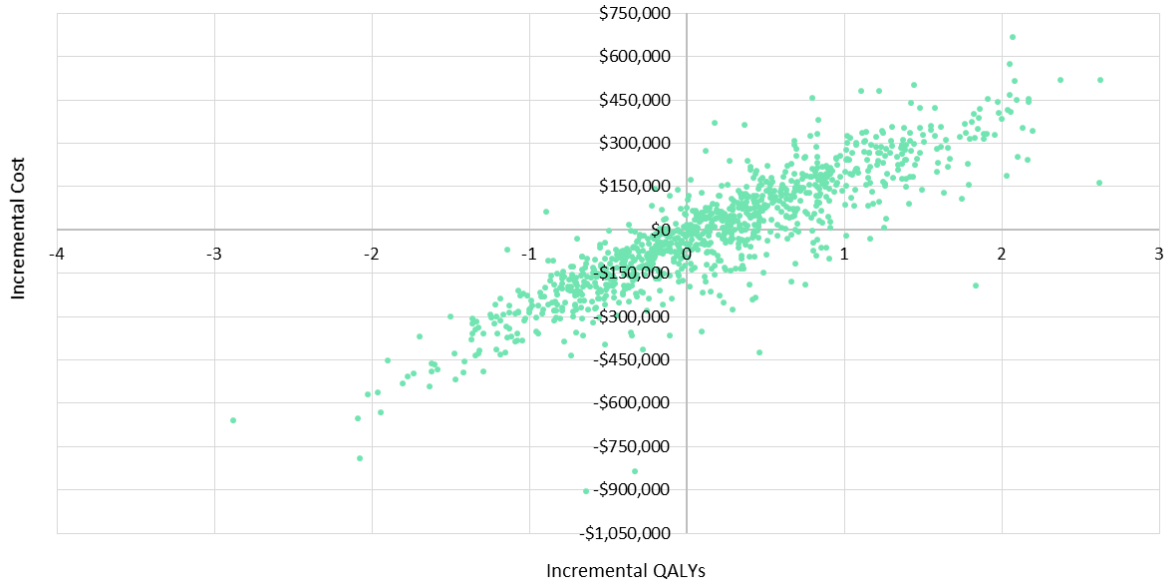

QALY: quality-adjusted life year

**Figure E5. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Cloud for Incremental Cost and QALYs for Roxadustat vs. ESAs, DD-CKD, Commercial Perspective**




QALY: quality-adjusted life year

**Figure E6. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Cloud for Incremental Cost and QALYs for Roxadustat vs. ESAs, DD-CKD, Medicare Perspective**




QALY: quality-adjusted life year

# E5. Scenario Analyses

## Scenario 1: Modified Societal Perspective

We conducted a modified societal perspective scenario analysis to include indirect costs of anemia, anemia treatment, CKD, and MACE+ a summarized in the *Indirect Cost* section above.

**Table E19. Results for Modified Societal Perspective Scenario**

| Treatment | Drug Cost | Total Cost | Life Years | QALYs | evLYs |
|---|---|---|---|---|---|
| **DI-CKD** | | | | | |
| **ESAs** | $54,000 | $599,000 | 7.64 | 5.38 | 5.38 |
| **Roxadustat** | $46,000 | $590,000 | 7.64 | 5.38 | 5.38 |
| **Incremental*** | -8,000 | -$9,000 | 0.00 | <0.01 | <0.01 |
| **DD-CKD, Commercial** | | | | | |
| **ESAs** | $29,000 | $1,190,000 | 6.35 | 3.84 | 3.84 |
| **Roxadustat** | $30,000 | $1,160,000 | 6.18 | 3.75 | 3.75 |
| **Incremental*** | $1,000 | -$29,000 | -0.17 | -0.09 | -0.09 |
| **DD-CKD, Medicare** | | | | | |
| **ESAs** | $0 | $1,330,000 | 6.35 | 3.84 | 3.84 |
| **Roxadustat** | $14,000 | $1,310,000 | 6.18 | 3.75 | 3.75 |
| **Incremental*** | $14,000 | -$21,000 | -0.17 | -0.09 | -0.09 |

DD-CKD: dialysis-dependent chronic kidney disease, DI-CKD: dialysis-independent chronic kidney disease, ESA: erythropoiesis-stimulating agent, evLY: equal-value life year, LY: life year, QALY: quality-adjusted life year.
*Rounding within treatment-specific findings may produce differences when compared to the incremental findings.

## Scenario 2: Inclusion of Impact on MACE+ in DI-CKD Population

We conducted a scenario including a potential impact on MACE+ versus ESAs based on the point estimates in the DOLOMITES trial. In this scenario, roxadustat resulted in 0.46 more QALYs due to reduction in mortality and MACE at an incremental cost of $24,000 versus ESAs higher cost ($24,000) compared with ESAs. Higher costs were driven by the potential reduction in mortality with roxadustat combined with CKD health state costs. When considering the uncertainty around the point estimates for all-cause mortality in DOLOMITES, HR=0.83, 95% CI 0.50, 1.38, the resulting incremental QALYs could range from 1.20 additional QALYs gained using the lower bound of the 95% CI to 0.37 fewer QALYs gained using the upper bound of the 95% CI.

**Table E20. Scenario Analysis Inputs for Inclusion of Impact on MACE+ in DI-CKD Population**

| Parameter | Input (95% CI) | Source |
|---|---|---|
| RR for All-Cause Mortality for Roxadustat vs. ESAs | 0.83 (0.50, 1.38) | [78] |
| RR for Stroke for Roxadustat vs. ESAs | 0.48 (0.14, 1.67) | [78] |
| RR for MI for Roxadustat vs. ESAs | 0.96 (0.41, 2.27) | [78] |
| RR for Unstable Angina Hospitalization for Roxadustat vs. ESAs | 1.00 (1, 1) | [78] |
| HR for CHF Hospitalization for Roxadustat vs. ESAs | 1.08 (0.6, 1.95) | [78] |

CHF: congestive heart failure, CI: confidence interval, DI-CKD: dialysis-independent chronic kidney disease, ESA: erythropoiesis-stimulating agent, HR: hazard ratio, MACE+: major cardiovascular event, MI: myocardial infarction.

**Table E21. Results for Scenario Analysis of Inclusion of Impact on MACE+ in the DI-CKD Population**

| Treatment | Drug Cost | Total Cost | Life Years | QALYs | evLYs |
|---|---|---|---|---|---|
| ESAs | $54,000 | $430,000 | 7.64 | 5.38 | 5.38 |
| Roxadustat | $49,000 | $457,000 | 8.33 | 5.87 | 5.99 |
| Incremental* | -$4,000 | $28,000 | 0.70 | 0.61 | 0.62 |

DI-CKD: dialysis-independent chronic kidney disease, ESA: erythropoiesis-stimulating agent, evLY: equal-value life year, LY: life year, MACE+: major cardiovascular event, QALY: quality-adjusted life year.
*Rounding within treatment-specific findings may produce differences when compared to the incremental findings.

## Scenario 3: Exclusion of Impact on MACE+ in DD-CKD Population

We conducted a scenario excluding any potential impact on MACE+ versus ESAs in the DD-CKD population due to uncertainty in the pooled estimates and lack of statistical significance of the individual MACE+ events.

**Table E22. Results for Scenario Analysis of Exclusion of Impact on MACE+ in the DD-CKD Population**

| Treatment | Drug Cost | Total Cost | Life Years | QALYs | evLYs |
|---|---|---|---|---|---|
| Commercial Perspective | | | | | |
| ESAs | $29,000 | $834,000 | 6.35 | 3.84 | 3.84 |
| Roxadustat | $31,000 | $835,000 | 6.35 | 3.85 | 3.85 |
| Incremental* | $2,055 | $1,500 | 0.00 | 0.01 | 0.01 |
| Medicare Perspective | | | | | |
| ESAs | $0 | $978,000 | 6.35 | 3.84 | 3.84 |
| Roxadustat | $14,000 | $992,000 | 6.35 | 3.85 | 3.85 |
| Incremental* | $14,000 | $14,000 | 0.00 | 0.01 | 0.01 |

DI-CKD: dialysis-independent chronic kidney disease, ESA: erythropoiesis-stimulating agent, evLY: equal-value life year, LY: life year, MACE+: major cardiovascular event, QALY: quality-adjusted life year.
*Rounding within treatment-specific findings may produce differences when compared to the incremental findings.

# E6. Heterogeneity and Subgroups

## ESA Normo-Responsive vs. Hyporesponsive

**Table E23. Results for Subgroup Analysis of ESA Normo-Responsive vs. Hyporesponsive, DD-CKD Population, Commercial Perspective**

| Treatment | Drug Cost | Total Cost | Life Years | QALYs | evLYs |
|---|---|---|---|---|---|
| **Normo-Responsive** | | | | | |
| **ESAs** | $16,000 | $821,000 | 6.35 | 3.84 | 3.84 |
| **Roxadustat** | $30,000 | $804,000 | 6.18 | 3.75 | 3.75 |
| **Incremental*** | $14,000 | -$18,000 | -0.17 | -0.09 | -0.09 |
| **Hyporesponsive** | | | | | |
| **ESAs** | $47,000 | $852,000 | 6.35 | 3.84 | 3.84 |
| **Roxadustat** | $31,000 | $804,000 | 6.18 | 3.75 | 3.75 |
| **Incremental*** | -$16,000 | -$48,000 | -0.17 | -0.09 | -0.09 |

DD-CKD: dialysis-dependent chronic kidney disease, ESA: erythropoiesis-stimulating agent, evLY: equal-value life year, LY: life year, QALY: quality-adjusted life year.

*Rounding within treatment-specific findings may produce differences when compared to the incremental findings.

# E7. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and Supplemental Materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were like our analysis, with comparable populations, settings, perspective, and treatments.

## Prior Economic Models

A review of the literature for prior economic models was conducted comparing the cost effectiveness of ESAs or roxadustat treatments in CKD patients with anemia. We found nine peer reviewed publications, most of which (six) were outside the US.[97-104] Among studies comparing ESAs to other treatments in the US, Dahl et al. evaluated health outcomes and costs associated with ferumoxytol monotherapy, oral iron monotherapy, and in combination with ESAs in adult non-DD CKD patients.[103] The five-week treatment cost was $2,489, $5,216, $1,298, and $4,263 per patient for ferumoxytol, ferumoxytol with ESAs, oral iron, and oral iron with ESAs, respectively. The

corresponding incremental costs per g/dL increase in Hb for ferumoxytol with ESAs, oral iron, and oral iron with ESAs, relative to ferumoxytol alone, was $398, $3,558, and $4,768 per patient. More recently, Yarnoff et al. used a CKD Health Policy Model to create a cohort of patients with CKD stages III-IV and explored the most cost-effective Hb target for anemia treatment.[97] They found that targeting a Hb between 10-11 g/dl resulted in an incremental cost-effectiveness ratios below $35,000/QALY, any treatment target above 11 g/dl increased medical costs and decreased QALYs. This study used a lifetime time horizon and health care sector perspective.

Only one study, Hu et al. evaluated roxadustat treatment for anemia in patients with CKD.[102] This study was performed in patients not receiving dialysis from perspective of the Chinese medical system. This study developed a Markov model with five-year time horizon to evaluate the cost effectiveness of roxadustat compared with placebo. QALY gains were entirely driven by elevation of Hb for roxadustat compared with placebo. Impact on CKD health states, mortality, and MACE were not considered. They found that roxadustat treatment (70 mg, three times per week) provided an additional 0.49 QALYs at a cost of $12,526 in the time horizon of five years, resulting in an incremental cost-effectiveness ratio of $25,563 per QALY. This study differs from our analysis due to the choice of comparator (placebo vs. ESAs). Other key differences include the cost of roxadustat ($21.20 USD three times per week, equating to $3,307 per year, approximately half of the placeholder price in our analysis) and health state utility derivation starting from the assumption of a 0.028 decrease in utility per 1 g/dL loss in Hb, more than twice that assumed in our analysis (0.0114).

# F. Potential Other Benefits and Contextual Considerations

## QALY Shortfalls

One important contextual consideration to consider is the argument that society should give preference to treatments for patients with more severe conditions,[105] and that giving priority to treatments according to "lifetime burden of illness" or "need" best represents the ethical instincts of a society or other decision-makers.[106,107] To inform this contextual consideration, ICER provides empirical results for the absolute QALY shortfall and proportional QALY shortfall. The absolute QALY shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[108] The ethical consequences of using absolute QALY shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute QALY shortfall.

The proportional QALY shortfall is measured by calculating the proportion of the total QALYs of remaining life expectancy that would be lost due to untreated illness.[109,110] The proportional QALY shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute QALY shortfall, rapidly fatal conditions of childhood have high proportional QALY shortfalls, but the highest numbers can also often arise from severe conditions among the elderly who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment.

For the DI-CKD population, the absolute shortfall was estimated to be 19.23 QALYs, with a proportional shortfall of 0.75, representing a loss of 75% of total quality-adjusted life expectancy (QALE) relative to individuals without the condition. For the DD-CKD population, the absolute shortfall was estimated to be 20.86 QALYs, with a proportional shortfall of 0.81, representing a loss of 81% of total QALE relative to individuals without the condition. To provide some anchoring of these results, we also present a league table of absolute and proportional QALY shortfalls for a variety of conditions from prior ICER reports (Table F1), using a burden of disease calculator developed by Dutch investigators (https://imta.shinyapps.io/iDBC/) that allows for calculation of absolute and proportional QALY shortfalls under different assumptions.[107]

**Table F1. League Table of Absolute and Proportional QALY Shortfalls for Selected Conditions**

| | From ICER Reports | | | From iDBC tool[111] | |
|---|---|---|---|---|---|
| Condition | Age | % Male | Total Undiscounted QALYs with Standard of Care | Absolute Shortfall | Proportional Shortfall |
| DI-CKD | 50 | 50% | 6.52 | 19.23 | 0.75 |
| DD-CKD | 50 | 50% | 4.89 | 20.86 | 0.81 |
| Heterozygous FH with ASCVD | 62 | 50 | 14.1 | 3.09 | 0.18 |
| Secondary Prevention for ASCVD | 66 | 61 | 13.9 | 0.54 | 0.04 |
| Cystic Fibrosis | 2 | 52 | 25.8 | 42.3 | 0.62 |
| Secondary Progressive Multiple Sclerosis | 48 | 39 | 3.0 | 24.5 | 0.89 |
| Hemophilia A | 18 | 100 | 38.6 | 13.3 | 0.26 |
| Treatment-Resistant Major Depression | 46 | 33 | 20.5 | 8.7 | 0.30 |
| Moderate-to-Severe Ulcerative Colitis | 40 | 59 | 27.4 | 6.2 | 0.19 |
| BCG-Unresponsive High-Risk NMIBC | 72 | 80 | 4.94 | 5.7 | 0.54 |

ASCVD: atherosclerotic cardiovascular disease, BCG: Bacillus Calmette-Guerin, FH: familial hypercholesterolemia, iDBC: Individual Driving Cycle Builder, NMIBC: non-muscular invasive bladder cancer, PTSD: post-traumatic stress disorder, QALY: quality-adjusted life year

# G. Potential Budget Impact: Supplemental Information

## Methods

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[112] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year-time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2019-2020, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $819 million per year for new drugs.

# References


1. World Health Organization. Anemia. https://www.who.int/health-topics/anaemia#tab=tab_1. Published 2020. Accessed July 13, 2020.
2. World Health Organization. *Worldwide prevalence of anaemia 1993-2005 : WHO global database on anaemia.* Geneva: World Health Organization; 2008 2008. 9789241596657.
3. Chapter 1: Diagnosis and evaluation of anemia in CKD. *Kidney Int Suppl (2011).* 2012;2(4):288-291.
4. Kidney Disease Outcomes Quality Initiative (KDOQI). KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2006;47(5 Suppl 3):S11-145.
5. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Annals of internal medicine.* 2003;139(2):137-147.
6. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney international.* 2005;67(6):2089-2100.
7. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney international.* 2011;80(1):17-28.
8. Chapter 1: Definition and classification of CKD. *Kidney Int Suppl (2011).* 2013;3(1):19-62.
9. Stevens LA, Levey AS. Measured GFR as a Confirmatory Test for Estimated GFR. *Journal of the American Society of Nephrology.* 2009;20(11):2305.
10. Levey AS, Titan SM, Powe NR, Coresh J, Inker LA. Kidney Disease, Race, and GFR Estimation. *Clinical Journal of the American Society of Nephrology.* 2020:CJN.12791019.
11. Stevens LA, Coresh J, Greene T, Levey AS. Assessing Kidney Function — Measured and Estimated Glomerular Filtration Rate. *New England Journal of Medicine.* 2006;354(23):2473-2483.
12. KDIGO. Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl (2011).* 2012;4(2):279-335.
13. National Institute for Health and Care Excellence. Chronic kidney disease: managing anaemia [NG8]. Published 2015. Accessed November 12, 2020.
14. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Annals of internal medicine.* 1997;126(5):376-380.
15. Higgins J, Thomas, J, Chandler, J, Cumpston, M, Li, T, Page, MJ, Welch, VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). https://training.cochrane.org/handbook/current. Published 2020. Accessed.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine.* 2009;6(7):e1000097.
17. Agency for Healthcare Research and Quality. U.S. Preventive Services Task Force Procedure Manual. Published 2008. Accessed.
18. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.
19. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. https://icer-review.org/methodology/icers-methods/icer-evidence-ratingmatrix/. . Published 2020. Updated January 31, 2020. Accessed.

20. Barratt J. Roxadustat for the Treatment of Anaemia in Chronic Kidney Disease Patients Not on Dialysis: A Phase 3, Randomised, Open-Label, Active-Controlled Study. ERA-EDTA; June 6-9, 2020, 2020.
21. Akizawa T, Iwasaki M, Otsuka T, Yamaguchi Y, Reusch M. A Phase 3, Multicenter, Randomized, Open-Label, Active Comparator Conversion Study of Roxadustat in Non-Dialysis-Dependent (NDD) Patients with Anemia in CKD. ASN 2020; 22-25 October, 2020, 2020.
22. Astellas I. A Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis (ISN 1517-CL-0608). https://astellasclinicalstudyresults.com/study.aspx?ID=363. Published 2019. Accessed October 29, 2020.
23. AstraZeneca. Investor science call: American Society of Nephrology Kidney Week 2019. https://www.astrazeneca.com/content/dam/az/Investor_Relations/events/AZN%20Investor%20science%20conference%20call%20ASN%202019%20Presentation.pdf. Published 2019. Accessed.
24. AstraZeneca. *Roxadustat: AMCP Unapproved Product Dossier.* 2020.
25. Chen N, Hao C, Peng X, et al. Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis. *New England Journal of Medicine.* 2019;381(11):1001-1010.
26. Besarab A, Provenzano R, Hertel J, et al. Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients. *Nephrology Dialysis Transplantation.* 2015;30(10):1665-1673.
27. Chen N, Qian J, Chen J, et al. Phase 2 studies of oral hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for treatment of anemia in China. *Nephrology Dialysis Transplantation.* 2017;32(8):1373-1386.
28. Akizawa T, Iwasaki M, Otsuka T, Reusch M, Misumi T. Roxadustat Treatment of Chronic Kidney Disease-Associated Anemia in Japanese Patients Not on Dialysis: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial. *Advances in Therapy.* 2019;36(6):1438-1454.
29. Astellas I. A Phase 3, Randomized, Open-Label, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in End Stage Renal Disease Subjects on Stable Dialysis. https://astellasclinicalstudyresults.com/study.aspx?ID=364. Published 2019. Accessed.
30. Chen N, Hao C, Liu B-C, et al. Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis. *New England Journal of Medicine.* 2019;381(11):1011-1022.
31. Akizawa T, Iwasaki M, Yamaguchi Y, Majikawa Y, Reusch M. Phase 3, Randomized, Double-Blind, Active-Comparator (Darbepoetin Alfa) Study of Oral Roxadustat in CKD Patients with Anemia on Hemodialysis in Japan. *Journal of the American Society of Nephrology.* 2020;31(7):1628-1639.
32. Provenzano R, Besarab A, Wright S, et al. Roxadustat (FG-4592) Versus Epoetin Alfa for Anemia in Patients Receiving Maintenance Hemodialysis: A Phase 2, Randomized, 6- to 19-Week, Open-Label, Active-Comparator, Dose-Ranging, Safety and Exploratory Efficacy Study. *American Journal of Kidney Diseases.* 2016;67(6):912-924.
33. Astellas I. A Japanese, Phase 2, Multicenter, Randomized, 4-arm Parallel, Double-blind (Arms 1-3), Open-label (Arm 4), Active-comparator (Darbepoetin Alfa) Study of Intermittent Oral Dosing of ASP1517 in Hemodialysis-dependent Chronic Kidney Disease Patients with Anemia. https://astellasclinicalstudyresults.com/study.aspx?ID=355. Published 2018. Accessed.
34. Provenzano R, Shutov E, Liubov E, et al. HIMALAYAS: A Phase 3, Randomized, Open-Label, Active-Controlled Study of the Efficacy and Safety of Roxadustat in the Treatment of Anemia in

Incident-Dialysis Patients. fibrogen.com. http://investor.fibrogen.com/static-files/8720f26b-e86f-4770-bfb9-0fb1e45da3a1. Published 2019. Accessed.
35. clinicaltrials.gov. Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients With Chronic Kidney Disease (CKD), Not on Dialysis. https://clinicaltrials.gov/ct2/show/NCT02174627. Published 2019. Updated December 16, 2019. Accessed.
36. Provenzano R, Fishbane S, Wei L-J, et al. Pooled Efficacy and CV Safety Results of Roxadustat in the Treatment of Anemia in Chronic Kidney Disease (CKD) Patients On and Not on Dialysis. https://fibrogen.gcs-web.com/static-files/c456ad75-05bd-4b48-915c-84c3743dc3fb. Published 2019. Accessed.
37. Provenzano R, Szczech L, Zhong M, et al. Pooled Analyses of the Phase 3 Roxadustat Studies: Congestive Heart Failure Hospitalization Rates in Dialysis and Non-Dialysis Patients with Anemia Treated with Roxadustat vs. Comparators. ASN 2020; 22-25 October, 2020, 2020.
38. Maruish ME. *User's Manual for the SF-36v2 Health Survey.* Quality Metric Incorporated; 2011.
39. 5Q-5D. About. https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/. Published 2017. Accessed October 29, 2020.
40. Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. *Semin Hematol.* 1997;34(3 Suppl 2):13-19.
41. Guy W. ECDEU Assessment Manual for Psychopharmacology Revised. 1976.
42. Leaf DE, Goldfarb DS. Interpretation and review of health-related quality of life data in CKD patients receiving treatment for anemia. *Kidney international.* 2009;75(1):15-24.
43. Coyne DW, Manllo-Karim R, Pergola PE, et al. Health-Related Quality of Life in Roxadustat-Treated Patients With Anemia and Non-Dialysis-Dependent Chronic Kidney Disease. ASN 2020; 22-25 October, 2020, 2020.
44. Chen P, Lin KC, Liing RJ, Wu CY, Chen CL, Chang KC. Validity, responsiveness, and minimal clinically important difference of EQ-5D-5L in stroke patients undergoing rehabilitation. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2016;25(6):1585-1596.
45. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health and quality of life outcomes.* 2007;5:70.
46. Zanini A, Aiello M, Adamo D, et al. Estimation of minimal clinically important difference in EQ-5D visual analog scale score after pulmonary rehabilitation in subjects with COPD. *Respiratory care.* 2015;60(1):88-95.
47. Finkelstein FO, van Nooten F, Wiklund I, Trundell D, Cella D. Measurement properties of the Short Form-36 (SF-36) and the Functional Assessment of Cancer Therapy - Anemia (FACT-An) in patients with anemia associated with chronic kidney disease. *Health and quality of life outcomes.* 2018;16(1):111.
48. Fishbane S, Provenzano, R., Rastogi, A., Coyne, D., Pecoits-Filho, R., Charytan, C., Pola, M., Poole, L., Saha, G. Chou, W., Lee, T., Yu, KHP. Roxadustat Lowers Risk of Red Blood Cell Transfusion in Patients with Anemia of CKD. NKF 2020; 2020.
49. Levey AS, Cattran D, Friedman A, et al. Proteinuria as a surrogate outcome in CKD: report of a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2009;54(2):205-226.
50. Fishbane S, Charytan C, Little D, Tham S, Leong R, Pergola PE. Hemoglobin (Hb) Correction with Roxadustat Is Associated with Improved Iron Homeostasis in Patients with Non-Dialysis-Dependent CKD (NDD-CKD). ASN 2020; 22-25 October 2020, 2020.

51. Roger SD, El-Shahawy MA, Pollock CA, et al. Roxadustat Lowers Low-density Lipoprotein Cholesterol in Patients With Anemia of Chronic Kidney Disease. ASN 2020; 22-25 October, 2020, 2020.
52. clinicaltrials.gov. Roxadustat in the Treatment of Anemia in End Stage Renal Disease (ESRD) Patients on Stable Dialysis (Pyrenees). https://clinicaltrials.gov/ct2/show/NCT02278341?term=Pyrenees&draw=2&rank=3. Published 2020. Updated August 26, 2020. Accessed.
53. Clinicaltrials.gov. Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients With Chronic Kidney Disease, on Dialysis. https://clinicaltrials.gov/ct2/show/results/NCT02174731?view=results. Published 2019. Accessed November 12, 2020.
54. Pergola PE, Charytan C, Little D, Tham S, Szczech L, Fishbane S. Hemoglobin (Hb) Correction with Roxadustat Is Associated with Improved Iron Homeostasis in Patients with Dialysis-Dependent CKD (DD-CKD). ASN 2020; 22–25 October 2020, 2020.
55. The Pharmaceuticals and Medical Devices Agency. Report on the Deliberation Results. https://www.pmda.go.jp/files/000234811.pdf. Published 2019. Accessed.
56. Provenzano R, Fishbane, S., Coyne, D., Pollock, C., Pola, M., Chou, W., Saikali, K., YU, KHP. Roxadustat Treatment of Anemia in Non-Dialysis Dependent Chronic Kidney Disease is Not Influenced by Iron Status. NKF 2020; 2020.
57. Coyne DW, El-Shahawy MA, Pecoits-Filho R, et al. Subgroup Analyses of Efficacy of Roxadustat for Treatment of Anemia in Patients With Non-Dialysis-Dependent Chronic Kidney Disease. ASN 2020; 22-25 October 2020, 2020.
58. Pollock CA, Roger SD, Manllo-Karim R, et al. Roxadustat Increases Hemoglobin in Anemic Non-Dialysis-Dependent (NDD) Chronic Kidney Disease (CKD) Patients Independent of Inflammation. ASN 2020; 2020.
59. Provenzano R, Fishbane S, Coyne DW, et al. Roxadustat Treatment of Anemia in Non-Dialysis-Dependent Chronic Kidney Disease Is Not Influenced by Iron Status. ASN 2020; 22-25 October 2020, 2020.
60. Pecoits-Filho R, Chan TM, Hardy E, Yu KP, Fishbane S. Roxadustat Treatment Results in Consistent Improvements in Hemoglobin (Hb) Versus Placebo: An Analysis of 3 Multinational RCTs in Patients With Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD). ASN 2020; 22-25 October 2020, 2020.
61. El-Shahawy MA, Roger SD, Manllo-Karim R, et al. Roxadustat Increases Hemoglobin in Anemic Dialysis-Dependent (DD) Chronic Kidney Disease (CKD) Patients Independent of Inflammation. ASN 2020; 22–25 October 2020, 2020.
62. Provenzano R, Kumar J, Fishbane S, et al. Subgroup Analyses of Efficacy of Roxadustat for Treatment of Anemia in Patients With Incident Dialysis–Dependent Chronic Kidney Disease. ASN 2020; 22-25 October, 2020, 2020.
63. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama.* 2016;316(10):1093-1103.
64. St Peter WL, Guo H, Kabadi S, et al. Prevalence, treatment patterns, and healthcare resource utilization in Medicare and commercially insured non-dialysis-dependent chronic kidney disease patients with and without anemia in the United States. *BMC Nephrol.* 2018;19(1):67.
65. USDRS. Annual Data Report. https://www.usrds.org/annual-data-report/previous-adrs/. Published 2018. Accessed October 1, 2020.

66. Elbasha E, Greaves W, Roth D, Nwankwo C. Cost-effectiveness of elbasvir/grazoprevir use in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and chronic kidney disease in the United States. *J Viral Hepat.* 2017;24(4):268-279.
67. Sugrue DM, Ward T, Rai S, McEwan P, van Haalen HGM. Economic Modelling of Chronic Kidney Disease: A Systematic Literature Review to Inform Conceptual Model Design. *Pharmacoeconomics.* 2019;37(12):1451-1468.
68. Charytan C, Manllo-Karim R, Martin ER, et al. SIERRAS: A Phase 3, Open-Label, Randomized, Active-Controlled Study of the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in Subjects with ESRD on Stable Dialysis. ASN 2019; 2019; Washington, D.C.
69. Sud M, Tangri N, Pintilie M, Levey AS, Naimark D. Risk of end-stage renal disease and death after cardiovascular events in chronic kidney disease. *Circulation.* 2014;130(6):458-465.
70. Cizman B, Smith HT, Camejo RR, et al. Clinical and Economic Outcomes of Erythropoiesis-Stimulating Agent Hyporesponsiveness in the Post-Bundling Era. *Kidney Med.* 2020;2(5):589-599 e581.
71. Amgen. Conversion Dosing Guide: From epoetin alfa to Aranesp® in patients with anemia due to CKD on dialysis. https://www.anemiahub.com/~/media/amgen/full/www-anemiahub-com/files/brochures/_aranesp-dosing-conversion-guide.ashx. Published 2019. Accessed November 2, 2020.
72. Vifor. MIRCERA® (methoxy polyethylene glycol-epoetin beta) Injection, For Intravenous or Subcutaneous Use. PRODUCT MONOGRAPH. https://mircera.com/themes/custom/mircera_rebuild/images/healthcare/MIRCERA%C2%AE-Monograph.pdf. Published 2019. Accessed November 2, 2020.
73. USDRS. Annual Data Report. https://www.usrds.org/media/1300/2019-referencetables_cost.xlsx. Published 2019. Accessed October 1, 2020.
74. CMS. Acute Inpatient Prospective Payment System Fiscal Year 2020 Final Rule Tables 1A-1E. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/FY2020-IPPS-Final-Rule-Home-Page-Items/FY2020-IPPS-Final-Rule-Tables. Published 2020. Accessed October 1, 2020.
75. CMS. End Stage Renal Disease (ESRD) Prospective Payment System (PPS) Calendar Year (CY) 2021 Proposed Rule (CMS-1732-P) Fact Sheet. https://www.cms.gov/newsroom/fact-sheets/end-stage-renal-disease-esrd-prospective-payment-system-pps-calendar-year-cy-2021-proposed-rule-cms. Published 2020. Accessed November 2, 2020.
76. CMS. Physician Fee Schedule. https://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx. Published 2020. Accessed November 2, 2020.
77. Toner RW, Pizzi L, Leas B, Ballas SK, Quigley A, Goldfarb NI. Costs to hospitals of acquiring and processing blood in the US: a survey of hospital-based blood banks and transfusion services. *Appl Health Econ Health Policy.* 2011;9(1):29-37.
78. Barratt J, Andrić B, Tataradze A, et al. Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: A phase 3, randomised, open-label, active-controlled study. *Nephrology Dialysis Transplantation.* 2020;35(Supplement_3).
79. CMS. Payment Allowance Limits for Medicare Part B Drugs. https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2020-asp-drug-pricing-files. Published 2020. Accessed October 1, 2020.
80. Feraheme®. (ferumoxytol injection) [prescribing information]. In. Waltham, MA: AMAG Pharmaceuticals, Inc.; 2020.

81. Esposito C, Csiky B, Tataradze A, Reusch M, Han C, Sulowicz W. Two Phase 3, Multicenter, Randomized Studies of Intermittent Oral Roxadustat in Anemic CKD Patients on (PYRENEES) and Not on (ALPS) Dialysis. ANS 2019; 2019; Washington, D.C.
82. O'Sullivan AK, Rubin J, Nyambose J, Kuznik A, Cohen DJ, Thompson D. Cost estimation of cardiovascular disease events in the US. *Pharmacoeconomics.* 2011;29(8):693-704.
83. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making.* 2006;26(4):410-420.
84. Shao H, Yang S, Fonseca V, Stoecker C, Shi L. Estimating Quality of Life Decrements Due to Diabetes Complications in the United States: The Health Utility Index (HUI) Diabetes Complication Equation. *Pharmacoeconomics.* 2019;37(7):921-929.
85. BLS. Table B-3. Average hourly and weekly earnings of all employees on private nonfarm payrolls by industry sector, seasonally adjusted. US Bureau of Labor Statistics. https://www.bls.gov/news.release/empsit.t19.htm. Published 2020. Accessed October, 2020.
86. OECD. Average usual weekly hours worked on the main job. OECD Statistics. https://stats.oecd.org/index.aspx?DataSetCode=ANHRS. Published 2019. Accessed September, 2020.
87. van Haalen H, Jackson J, Spinowitz B, Milligan G, Moon R. Impact of chronic kidney disease and anemia on health-related quality of life and work productivity: analysis of multinational real-world data. *BMC Nephrol.* 2020;21(1):88.
88. Ray KN, Chari AV, Engberg J, Bertolet M, Mehrotra A. Opportunity costs of ambulatory medical care in the United States. *The American journal of managed care.* 2015;21(8):567-574.
89. MSKCC. Frequently Asked Questions About Blood Transfusions. https://www.mskcc.org/cancer-care/patient-education/frequently-asked-questions-about-blood-transfusion#:~:text=One%20transfusion%20of%20red%20blood,takes%2030%20to%2060%20minutes. Published 2020. Updated May 25, 2018. Accessed October 7, 2020.
90. Cloutier M, Manceur AM, Guerin A, Aigbogun MS, Oberdhan D, Gauthier-Loiselle M. The societal economic burden of autosomal dominant polycystic kidney disease in the United States. *BMC Health Serv Res.* 2020;20(1):126.
91. Rodrigue JR, Schold JD, Morrissey P, et al. Direct and Indirect Costs Following Living Kidney Donation: Findings From the KDOC Study. *Am J Transplant.* 2016;16(3):869-876.
92. Song X, Quek RG, Gandra SR, Cappell KA, Fowler R, Cong Z. Productivity loss and indirect costs associated with cardiovascular events and related clinical procedures. *BMC Health Serv Res.* 2015;15:245.
93. Astellas I. A Phase 3, Randomized, Open-Label, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in End Stage Renal Disease Subjects on Stable Dialysis. https://ascrstudypdfs.blob.core.windows.net/ascrstudypdfs/1517-cl-0613-clrrs-02-disc01-en-final-02.pdf. Published 2019. Accessed October 14, 2020.
94. Wong W, Yim YM, Kim A, et al. Assessment of costs associated with adverse events in patients with cancer. *PLoS One.* 2018;13(4):e0196007.
95. Mangen MJ, Rozenbaum MH, Huijts SM, et al. Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. *Eur Respir J.* 2015;46(5):1407-1416.
96. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value Health.* 2019;22(8):931-941.
97. Yarnoff BO, Hoerger TJ, Simpson SA, et al. The Cost-Effectiveness of Anemia Treatment for Persons with Chronic Kidney Disease. *PLoS One.* 2016;11(7):e0157323.

98. Wong G, Howard K, Hodson E, Irving M, Craig JC. An economic evaluation of intravenous versus oral iron supplementation in people on haemodialysis. *Nephrol Dial Transplant.* 2013;28(2):413-420.
99. Thaweethamcharoen T, Sakulbumrungsil R, Nopmaneejumruslers C, Vasuvattakul S. Cost-Utility Analysis of Erythropoietin for Anemia Treatment in Thai End-Stage Renal Disease Patients with Hemodialysis. *Value Health Reg Issues.* 2014;3:44-49.
100. Tonelli M, Winkelmayer WC, Jindal KK, Owen WF, Manns BJ. The cost-effectiveness of maintaining higher hemoglobin targets with erythropoietin in hemodialysis patients. *Kidney international.* 2003;64(1):295-304.
101. Rognoni C, Ortalda V, Biasi C, Gambaro G. Economic Evaluation of Ferric Carboxymaltose for the Management of Hemodialysis Patients with Iron Deficiency Anemia in Italy. *Adv Ther.* 2019;36(11):3253-3264.
102. Hu Z, Tao H, Shi A, Pan J. The efficacy and economic evaluation of roxadustat treatment for anemia in patients with kidney disease not receiving dialysis. *Expert Rev Pharmacoecon Outcomes Res.* 2020;20(4):411-418.
103. Dahl NV, Kaper RF, Strauss WE, Corvino FA, Zivkovic M. Cost-effectiveness analysis of intravenous ferumoxytol for the treatment of iron deficiency anemia in adult patients with non-dialysis-dependent chronic kidney disease in the USA. *Clinicoecon Outcomes Res.* 2017;9:557-567.
104. Clement FM, Klarenbach S, Tonelli M, Wiebe N, Hemmelgarn B, Manns BJ. An economic evaluation of erythropoiesis-stimulating agents in CKD. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2010;56(6):1050-1061.
105. Clark S, Weale A. Social values in health priority setting: a conceptual framework. *Journal of health organization and management.* 2012;26(3):293-316.
106. Reckers-Droog VT, van Exel NJA, Brouwer WBF. Looking back and moving forward: On the application of proportional shortfall in healthcare priority setting in the Netherlands. *Health policy (Amsterdam, Netherlands).* 2018;122(6):621-629.
107. Versteegh MM, Ramos IC, Buyukkaramikli NC, Ansaripour A, Reckers-Droog VT, Brouwer WBF. Severity-Adjusted Probability of Being Cost Effective. *Pharmacoeconomics.* 2019;37(9):1155-1163.
108. Ottersen T, Førde R, Kakad M, et al. A new proposal for priority setting in Norway: Open and fair. *Health policy (Amsterdam, Netherlands).* 2016;120(3):246-251.
109. van de Wetering EJ, Stolk EA, van Exel NJA, Brouwer WBF. Balancing equity and efficiency in the Dutch basic benefits package using the principle of proportional shortfall. *The European Journal of Health Economics.* 2013;14(1):107-115.
110. Stolk EA, van Donselaar G, Brouwer WB, Busschbach JJ. Reconciliation of economic concerns and health policy: illustration of an equity adjustment procedure using proportional shortfall. *Pharmacoeconomics.* 2004;22(17):1097-1107.
111. *iDBC-iMTA Disease Burden Calculator* [computer program]. 2020.
112. Pearson SD. *2020-2023 Value Assessment Framework.* icer-review.org: Institute for Clinical and Economic Review; January 31, 2020 2020.

# Evidence Table References


1. Astellas I. A Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis (ISN 1517-CL-0608). https://astellasclinicalstudyresults.com/study.aspx?ID=363. Published 2019. Accessed October 29, 2020.
2. AstraZeneca. *Roxadustat: AMCP Unapproved Product Dossier.* 2020.
3. Barratt J. Roxadustat for the Treatment of Anaemia in Chronic Kidney Disease Patients Not on Dialysis: A Phase 3, Randomised, Open-Label, Active-Controlled Study. ERA-EDTA; June 6-9, 2020, 2020.
4. AstraZeneca. Investor science call: American Society of Nephrology Kidney Week 2019. https://www.astrazeneca.com/content/dam/az/Investor_Relations/events/AZN%20Investor%20science%20conference%20call%20ASN%202019%20Presentation.pdf. Published 2019. Accessed.
5. Chen N, Hao C, Peng X, et al. Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis. *New England Journal of Medicine.* 2019;381(11):1001-1010.
6. Akizawa T, Iwasaki M, Otsuka T, Yamaguchi Y, Reusch M. A Phase 3, Multicenter, Randomized, Open-Label, Active Comparator Conversion Study of Roxadustat in Non-Dialysis-Dependent (NDD) Patients with Anemia in CKD. ASN 2020; 22-25 October, 2020, 2020.
7. Besarab A, Provenzano R, Hertel J, et al. Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients. *Nephrology Dialysis Transplantation.* 2015;30(10):1665-1673.
8. Chen N, Qian J, Chen J, et al. Phase 2 studies of oral hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for treatment of anemia in China. *Nephrology Dialysis Transplantation.* 2017;32(8):1373-1386.
9. Akizawa T, Iwasaki M, Otsuka T, Reusch M, Misumi T. Roxadustat Treatment of Chronic Kidney Disease-Associated Anemia in Japanese Patients Not on Dialysis: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial. *Advances in Therapy.* 2019;36(6):1438-1454.
10. clinicaltrials.gov. Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients With Chronic Kidney Disease (CKD), Not on Dialysis. https://clinicaltrials.gov/ct2/show/NCT02174627. Published 2019. Updated December 16, 2019. Accessed.
11. Provenzano R, Shutov E, Liubov E, et al. HIMALAYAS: A Phase 3, Randomized, Open-Label, Active-Controlled Study of the Efficacy and Safety of Roxadustat in the Treatment of Anemia in Incident-Dialysis Patients. fibrogen.com. http://investor.fibrogen.com/static-files/8720f26b-e86f-4770-bfb9-0fb1e45da3a1. Published 2019. Accessed.
12. Astellas I. A Phase 3, Randomized, Open-Label, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in End Stage Renal Disease Subjects on Stable Dialysis. https://astellasclinicalstudyresults.com/study.aspx?ID=364. Published 2019. Accessed.
13. Chen N, Hao C, Liu B-C, et al. Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis. *New England Journal of Medicine.* 2019;381(11):1011-1022.
14. Akizawa T, Iwasaki M, Yamaguchi Y, Majikawa Y, Reusch M. Phase 3, Randomized, Double-Blind, Active-Comparator (Darbepoetin Alfa) Study of Oral Roxadustat in CKD Patients with Anemia on Hemodialysis in Japan. *Journal of the American Society of Nephrology.* 2020;31(7):1628-1639.

15. Provenzano R, Besarab A, Wright S, et al. Roxadustat (FG-4592) Versus Epoetin Alfa for Anemia in Patients Receiving Maintenance Hemodialysis: A Phase 2, Randomized, 6- to 19-Week, Open-Label, Active-Comparator, Dose-Ranging, Safety and Exploratory Efficacy Study. *American Journal of Kidney Diseases.* 2016;67(6):912-924.
16. Astellas I. A Japanese, Phase 2, Multicenter, Randomized, 4-arm Parallel, Double-blind (Arms 1-3), Open-label (Arm 4), Active-comparator (Darbepoetin Alfa) Study of Intermittent Oral Dosing of ASP1517 in Hemodialysis-dependent Chronic Kidney Disease Patients with Anemia. https://astellasclinicalstudyresults.com/study.aspx?ID=355. Published 2018. Accessed.
17. Clinicaltrials.gov. Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients With Chronic Kidney Disease, on Dialysis. https://clinicaltrials.gov/ct2/show/results/NCT02174731?view=results. Published 2019. Accessed November 12, 2020.
18. clinicaltrials.gov. Roxadustat in the Treatment of Anemia in End Stage Renal Disease (ESRD) Patients on Stable Dialysis (Pyrenees). https://clinicaltrials.gov/ct2/show/NCT02278341?term=Pyrenees&draw=2&rank=3. Published 2020. Updated August 26, 2020. Accessed.
19. Provenzano R, Fishbane S, Wei L-J, et al. Pooled Efficacy and CV Safety Results of Roxadustat in the Treatment of Anemia in Chronic Kidney Disease (CKD) Patients On and Not on Dialysis. https://fibrogen.gcs-web.com/static-files/c456ad75-05bd-4b48-915c-84c3743dc3fb. Published 2019. Accessed.
20. Fishbane S, Charytan C, Little D, Tham S, Leong R, Pergola PE. Hemoglobin (Hb) Correction with Roxadustat Is Associated with Improved Iron Homeostasis in Patients with Non-Dialysis-Dependent CKD (NDD-CKD). ASN 2020; 22-25 October 2020, 2020.
21. Roger SD, El-Shahawy MA, Pollock CA, et al. Roxadustat Lowers Low-density Lipoprotein Cholesterol in Patients With Anemia of Chronic Kidney Disease. ASN 2020; 22-25 October, 2020, 2020.
22. Coyne DW, El-Shahawy MA, Pecoits-Filho R, et al. Subgroup Analyses of Efficacy of Roxadustat for Treatment of Anemia in Patients With Non-Dialysis-Dependent Chronic Kidney Disease. ASN 2020; 22-25 October 2020, 2020.
23. Provenzano R, Fishbane S, Coyne DW, et al. Roxadustat Treatment of Anemia in Non-Dialysis-Dependent Chronic Kidney Disease Is Not Influenced by Iron Status. ASN 2020; 22-25 October 2020, 2020.
24. Pollock CA, Roger SD, Manllo-Karim R, et al. Roxadustat Increases Hemoglobin in Anemic Non-Dialysis-Dependent (NDD) Chronic Kidney Disease (CKD) Patients Independent of Inflammation. ASN 2020; 2020.
25. El-Shahawy MA, Roger SD, Manllo-Karim R, et al. Roxadustat Increases Hemoglobin in Anemic Dialysis-Dependent (DD) Chronic Kidney Disease (CKD) Patients Independent of Inflammation. ASN 2020; 22–25 October 2020, 2020.
26. Provenzano R, Kumar J, Fishbane S, et al. Subgroup Analyses of Efficacy of Roxadustat for Treatment of Anemia in Patients With Incident Dialysis–Dependent Chronic Kidney Disease. ASN 2020; 22-25 October, 2020, 2020.
27. Coyne DW, Manllo-Karim R, Pergola PE, et al. Health-Related Quality of Life in Roxadustat-Treated Patients With Anemia and Non-Dialysis-Dependent Chronic Kidney Disease. ASN 2020; 22-25 October, 2020, 2020.
28. Chan TMD, Pecoits-Filho R, Rastogi A, et al. Roxadustat vs. Placebo or Epoetin Alfa Has No Clinically Meaningful Effect on Blood Pressure in Patients with Anemia of CKD. ASN 2020; 22-25 October, 2020.