The open-label, single-arm study assessed the efficacy and safety of roxadustat in correcting/maintaining hemoglobin (Hb) goal of 11 g/dL over 24 weeks in adult patients with anemia of CRF receiving in-center or home dialysis for end-stage renal disease at nine US sites.

The aims of the trial were two fold:

- To obtain information on the use of roxadustat in patients with COVID-19 and anemia via a semi-pragmatic evaluation of incorporation into protocol at a large US dialysis organization (Prevención Medical Care).

**Methods**

The open-label, single-arm study assessed the efficacy and safety of roxadustat in correcting/maintaining hemoglobin (Hb) goal at 11 g/dL over 24 weeks in adult patients with anemia of CRF receiving in-center or home dialysis for end-stage renal disease at nine US sites.

**Roxadustat starting dose:**
- Subjects taking MenQ®6-8 weeks (stable ESA) were converted to roxadustat using a predefined dose-conversion algorithm.
- Subjects taking MenQ®6-8 weeks or who had never used ESA before (ESA-naïve) were given a roxadustat-dose based on body weight and sex.
- Subjects were excluded if they had received a red blood cell (RBC) transfusion within 4 weeks prior to enrollment or had anemia due to causes other than CRD.

Roxadustat dose was titrated every 4 weeks based on Hb level or rate of change. Roxadustat dose reductions occurred if Hb level was >12 g/dL, for 4 weeks. Dose was then placed on hold if Hb level 11.0-12.0 g/dL, regardless if Hb was ≥11.0 or ≤12.0 g/dL.

**Efficacy endpoints:**
- Mean Hb change from baseline to average Hb over weeks 16-24
- Proportion of patients achieving mean Hb over 11.0 g/dL from weeks 16 through Weeks 24

**Safety endpoints:**
- Incidence of treatment-emergent adverse events (TEAEs) and serious TEAEs
- Clinically significant changes in laboratory values from baseline and vital signs
- Vascular access thrombosis as defined by TEAE of special interest
- COVID-19 positivity was reported as an AE
- Demographics, baseline characteristics, and all efficacy analyses were evaluated using the full analysis set (FAS), which consisted all patients who signed informed consent, who were enrolled and received at least one dose of roxadustat, and who provided data for baseline and at least one post-baseline Hb time point.

**Methods (contd.)**

**Study Design**

**Roxadustat TREATMENT PERIOD**

- Study visits were biweekly until Week 8, and every 4 weeks thereafter until Week 24. At each visit, Hb was checked prior to dialysis to determine the need for a dose adjustment including assessment of excessive rate of rise of Hb.
- Due to the COVID-19 pandemic, investigators could adjust study visit frequency for home-dialysis patients, including dose titration, based on schedule and method of data (e.g., use of telemedicine) in consideration of clinical circumstances and convenience of the patient.
- If not recommended by protocol to be considered for patients with ferritin <200 mg/L or TSAT <20%, iron could be administered without restriction, with dose and frequency to be determined by the investigator.
- Throughout the treatment period under the following conditions:
  - If Hb level rose >2 g/dL in the first 8 weeks after start of roxadustat, dose was increased by ±1 mg/kg.
  - If no clear cause of Hb rise was identified and not due to the risk of allograft dysfunction in transplant-eligible subjects, or
  - Reduction of other treatment-related effect was a goal.
- Subjects permanently discontinuing roxadustat were able to receive ESA at least 3 days after last roxadustat dose.

**Patient Disposition**

Patients randomized: n=201
- 84% of patients achieved Hb goal 10.0-11.0 g/dL, averaged over weeks 16-24.
- 80.9% of initially enrolled (ESA naïve) patients.
- 88.5% of initially enrolled (ESA naïve) patients.

**Full Analysis Set (FAS)**

- Mean change in Hb from baseline averaged over weeks 16-24, regardless of TEAE severity was 0.5 g/dL.
- Subjects who had a mean Hb level increase >5.0 g/dL during conversion and treatment were excluded from final analysis.
- TEAEs were assessed using the safety analysis set (SAF): all enrolled patients who received at least one dose of study drug.
- All analyses were performed using SAS v9.1.3 or higher.

**Results (contd.)**

**Efficacy Endpoints: Hb Response**

**Mean Hemoglobin Over Time (FAS)**

- 84.7% of patients achieved mean Hb 10.0-11.0 g/dL over weeks 16-24 over 46 patients over 24.
- 87.9% (ESA naïve) patients.
- 88.5% of initially enrolled (ESA naïve) patients.

**Explanatory Endpoints**

- The proportion of patients achieving mean Hb 10.0-11.0 g/dL in the first 8 weeks after initiation of treatment was 81.1% (122/150).
- Six patients (3%) received RBC transfusion during the study.
- There was no significant incidence rate for 100 patient-years (PY), PEF for each patient (total dose - first dose date - 1)/0.25.
- Mean (±SD) treatment adherence (total amount of actual dose administration)/total amount of expected dose administration (ID) was 94.2±4.9%.

**Mean Weekly Roxadustat Dose Over (FAS)**

- Mean (±SD) treatment duration was 26.8±4.7 weeks.

**Adverse Event Summary**

Overall summary of TEAEs (SAF)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>6 (3.4)</td>
<td>5 (2.9)</td>
<td>3 (1.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>2 (1.0)</td>
<td>2 (1.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>24 (12.4)</td>
<td>18 (9.8)</td>
<td>9 (4.9)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

**Serious TEAEs Occurring in ≥1% of Patients (SAF)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>9 (4.9) (in 1 patient)</td>
</tr>
<tr>
<td>RBC transfusion</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>3 (1.5)</td>
</tr>
</tbody>
</table>

**Conclusions**

- This trial added to phase 3 studies of roxadustat by elucidating its use in treating anemia of CKD in home-in-center dialysis patients during the COVID-19 pandemic, while providing a view on patient operationalization and ease of real-world use.
- The pragmatic design of the DENALI trial allowed the ability to evaluate the switch from an traditional oral anemia therapy to the nephrology-dedicated dialysis nurses administered roxadustat in center during hemodialysis and experienced management of a flock-weeks’ worth of anemia medication for the care of home dialysis patients.
- Roxadustat was effective in correcting/maintaining Hb levels within the target range during dialysis and throughout 24 weeks of maintenance therapy in a patient cohort converting from a long-acting ESA.
- The safety data are consistent with the known safety profile of roxadustat and background risk of adverse clinical events in US dialysis patients.
- Roxadustat doses decreased over treatment: exploratory analyses showed high dosing adherence.