HIF PHI Trials in CKD non-dialysis and dialysis: What do the data really show?

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Korean Society of Nephrology

Disclosures: Honoraria and/or consultancy fees from Amgen, AstraZeneca (ongoing), Boehringer Ingelheim, Bayer, GlaxoSmithKline, Janssen, Napp, Mundipharma, Merck Sharp and Dohme, Takeda, and Vifor Fresenius.

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Anaemia Management in CKD

- 1950s Transfusions
- 1990s Erythropoiesis Stimulating Agents (ESAs)\textsuperscript{1-4}
- 2000s IV and oral Iron\textsuperscript{5-8}
- 2020s HIF stabilizers (Prolyl hydroxylase inhibitors)\textsuperscript{9-13}

Advanced information

Scientific Background:
How cells sense and adapt to oxygen availability (pdf)

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How cells sense and adapt to oxygen availability
Hypoxia mediated gene expression via hypoxia inducible factor (HIF):

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Inhibiting HIF-PHs stimulates endogenous EPO production, reduces hepcidin, and improves iron metabolism, ultimately increasing Hb levels.

DMT1 = divalent metal transporter 1  
HIF = hypoxia-inducible factor;  
PHI = prolyl hydroxylase inhibitor

HIF-PHIs activate the HIF pathway and the coordinated response ensures sufficient iron availability for effective erythropoiesis to occur in the presence of physiologic levels of EPO.²

Adapted from Prabhakar NR, Semenza GL. Physiol Rev 2012;92:967–1003;  
Effect of Prolyl-Hydroxylase Inhibitors ("HIF stabilizers") Mimicking Hypoxia:

Inhibiting HIF-PHs stimulates endogenous EPO production, reduces hepcidin, and improves iron metabolism, ultimately increasing Hb levels.

DMT1 = divalent metal transporter
HIF = hypoxia-inducible factor;
PHI = prolyl hydroxylase inhibitor

HIF-PHIs activate the HIF pathway and the coordinated response ensures sufficient iron availability for effective erythropoiesis to occur in the presence of physiologic levels of EPO.

Increase in plasma EPO after HIF stabilisation

24 hour kinetics of plasma Erythropoietin after a single dose of FG-2216 (individual patient data, n=18)

HIF target genes

- **Cell Survival**
  - ADM
  - EPO
  - IGFBP1-3
  - TGFα

- **Transcriptional regulation**
  - ETS1
  - DEC1-2

- **Erythropoiesis**
  - Epo

- **Iron metabolism**
  - Ceruloplasmin
  - TRF
  - TRFR

- **Extracellular matrix metabolism**
  - PAI1
  - MMP2
  - FN
  - UPAR

- **Angiogenesis**
  - VEGF
  - VEGFR1
  - LEP
  - EGF

- **Mitochondrial function**
  - FDK
  - COX4-1
  - LON

- **Vascular tone**
  - ADM
  - iNOS
  - ET1
  - BNP

- **Cell motility**
  - CXCR4
  - c-Met

- **Glucose metabolism**
  - GLUT1
  - HK
  - LDH1
  - PGK
  - ENO1

- **pH regulation**
  - CA9
  - MCT4
  - NHE1

- **Apoptosis**
  - BNIP3
  - NIX

Courtesy Iain Macdougall

Adapted from Schofield & Ratcliffe, Nat Rev Mol Cell Biol 2004
Pharmacokinetic properties of HIF-PHIs
Daprodustat, Roxadustat, and Vadadustat

<table>
<thead>
<tr>
<th>Compound</th>
<th>Effective Daily Oral Doses in Phase 2 Trials</th>
<th>Dosing Schedule</th>
<th>Half-Life, h</th>
<th>Plasma EPO, IU/L</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daprodustat (GSK-12278863)</td>
<td>5-25 (also examined 50 and 100 mg)</td>
<td>1×/d</td>
<td>~1-7</td>
<td>24.7(^a) and 34.4(^b)</td>
<td>CYP2C8 with minor CYP3A4</td>
</tr>
<tr>
<td>Roxadustat (FG-4592, ASP1517)</td>
<td>0.7-2.5 mg/kg</td>
<td>3×/wk</td>
<td>12-15</td>
<td>113(^c) and 397(^d)</td>
<td>CYP2C8</td>
</tr>
<tr>
<td>Vadadustat (AKB-6548, MT-6548)</td>
<td>150-600 mg</td>
<td>1×/d (3×/wk)</td>
<td>4.7-9.1</td>
<td>32</td>
<td>NR</td>
</tr>
</tbody>
</table>

Adapted with permission from Sanghani and Haase\(^{11}\); original content ©2019 National Kidney Foundation. Abbreviations: CKD, chronic kidney disease; CYP, cytochrome P450; EPO, erythropoietin; HIF, hypoxia-inducible factor; NR not reported/not published.

\(^a\)CKD patients receiving dialysis.

\(^b\)CKD patients not requiring kidney replacement therapy.

\(^c\)For 1 mg/kg dose.

\(^d\)For 2 mg/kg dose.

Wish JB et al.
NKF Scientific Workshop Report on HIF.
# HIF stabilisers: Development Programmes

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Roxadustat&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Vadadustat&lt;sup&gt;2-3&lt;/sup&gt;</th>
<th>Daprodustat&lt;sup&gt;4-5&lt;/sup&gt;</th>
<th>Enarodustat&lt;sup&gt;6&lt;/sup&gt;</th>
<th>Molidustat&lt;sup&gt;7&lt;/sup&gt;</th>
<th>Desidustat&lt;sup&gt;8&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>FibroGen/AstraZeneca</td>
<td>Akebia</td>
<td>GlaxoSmithKline</td>
<td>Japan Tobacco</td>
<td>Bayer</td>
<td>Zydus</td>
</tr>
<tr>
<td>AstraZeneca Astellas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area</td>
<td>Global</td>
<td>Global</td>
<td>Global</td>
<td>Japan only</td>
<td>Japan only</td>
<td>Australia, India, China only</td>
</tr>
<tr>
<td>Status</td>
<td>Launched Japan/China, Approved EU &amp; launched</td>
<td>Launched Japan, Global Phase 3 published</td>
<td>Launched Japan, Global Phase 3 published</td>
<td>Approved in Japan Phase 3 published</td>
<td>Approved Japan, Phase 3 published</td>
<td>Approved in India Phase 3 published</td>
</tr>
<tr>
<td>Half-life</td>
<td>12–13 hours</td>
<td>4.5 hours</td>
<td>4 hours</td>
<td>9 hours&lt;sup&gt;9&lt;/sup&gt;</td>
<td>5-10 hours&lt;sup&gt;10&lt;/sup&gt;</td>
<td>7-13 hours&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anticipated dosing</td>
<td>Oral; 3x week</td>
<td>Oral; once daily</td>
<td>Oral; once daily</td>
<td>Oral; once daily</td>
<td>Oral; once daily</td>
<td>Oral; 3x week</td>
</tr>
<tr>
<td>CVOT data</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

CVOT, Cardiovascular Outcome Trial

Phase 3 studies of HIF-PHIs

Populations: Non-dialysis CKD, Incident dialysis, Stable dialysis.
Intervention: HIF-PHI
Comparator: No treatment or standard ESA
Outcomes: Haemoglobin target and MACE
Roxadustat phase 3 study

305 dialysis patients on ESAs (China)
Roxadustat vs Epoetin alpha (2:1)
26 weeks. IV iron “rescue”.
Primary endpoint = Hb from baseline to average 23-27 weeks


Roxadusatat vs EPO:
• Higher transferrins
• Better maintained serum iron and TSAT
• Lower cholesterol
Roxadustat phase 3 study

## Roxadustat clinical trial overview including 9600 patients

<table>
<thead>
<tr>
<th>NDD-CKD</th>
<th>Incident DD-CKD*</th>
<th>Stable DD-CKD†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESA-untreated patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>0608 ALPS (N = 594)¹,²</td>
<td></td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>00001 OLYMPUS (N = 2760)²,³</td>
<td></td>
</tr>
<tr>
<td>FibroGen</td>
<td>060 ANDES (N = 916)²,⁴</td>
<td></td>
</tr>
<tr>
<td>Astellas</td>
<td>0610 DOLOMITES (N = 616)²,⁵</td>
<td></td>
</tr>
<tr>
<td><strong>ESA-treated patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FibroGen</td>
<td>063 HIMALAYAS (N = 1039)¹,²,⁶</td>
<td></td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>00002 ROCKIES (N = 2101)¹,²,⁷</td>
<td></td>
</tr>
<tr>
<td>Astellas</td>
<td>0613 PYRENEES (N = 834)§,²,⁸</td>
<td></td>
</tr>
<tr>
<td>FibroGen</td>
<td>064 SIERRAS (N = 740)¹,²,⁹</td>
<td></td>
</tr>
</tbody>
</table>

The NDD studies are pooled, as are the DD studies.
*Subset of patients with ≥ 2 weeks and ≤ 4 months of dialysis at the time of randomisation; †Subset of patients with > 4 months of dialysis at the time of randomisation; ‡Darbepoetin alfa active comparator; ¶Epoetin alfa active comparator; §Darbepoetin alfa and epoetin alfa active comparator.

CKD, chronic kidney disease; DD, dialysis-dependent; ESA, erythropoiesis-stimulating agent; NDD, non-dialysis-dependent; SmPC, Summary of Product Characteristics.
Roxadustat was effective at achieving and maintaining target Hb levels comparable with ESA in patients with NDD-CKD

Mean (95% CI) concentrations of Hb (per protocol set)

BL, baseline; CI, confidence interval; DA, darbepoetin alfa; EOS, end of study; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; NDD, non-dialysis-dependent.

Roxadustat was effective at achieving and maintaining target Hb levels comparable with ESA in patients on dialysis

Incident dialysis was defined as ≥2 weeks and ≤4 months, and stable dialysis as >4 months.

*Subset of patients from ROCKIES and SIERRAS with ≤ 4 months of dialysis at the time of randomisation; †Subset of patients from ROCKIES and SIERRAS with > 4 months of dialysis at the time of randomisation.

Mean (SE) Hb over 52 weeks (FAS)

Mean Hb was comparable over time with roxadustat vs ESA in incident DD-CKD patients and stable DD-CKD patients previously treated with ESA

Incident dialysis was defined as ≥2 weeks and ≤4 months, and stable dialysis as >4 months.

*Subset of patients from ROCKIES and SIERRAS with ≤ 4 months of dialysis at the time of randomisation; †Subset of patients from ROCKIES and SIERRAS with > 4 months of dialysis at the time of randomisation.

CKD, chronic kidney disease; DD, dialysis-dependent; ESA, erythropoiesis-stimulating agent; FAS, full analysis set; Hb, haemoglobin; IDD, incident dialysis-dependent; SDD, stable dialysis-dependent; SE, standard error.

EVRENZO SmPC, August 2021.
Global Phase 3 PRO$_2$TECT Program

Studies of Vadadustat for Treatment of Anemia due to Chronic Kidney Disease (CKD) in Adult Patients Not on Dialysis

PRO$_2$TECT Consists of Two Randomized, Open-Label, Active-Controlled, Non-Inferiority Phase 3 Cardiovascular Outcomes Studies

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** PRIMARY EFFICACY ENDPOINTS:**

- Mean change in hemoglobin (Hb) between baseline and the primary evaluation period (weeks 24 to 36)
- Non-inferiority margin of -0.75 g/dL

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** PRIMARY SAFETY ENDPOINT:**

- Time to first occurrence of major adverse cardiovascular events (MACE) which is the composite of all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke
- Non-inferiority margin for hazard ratio 1.25

---

Darbepoetin alfa is an erythropoiesis-stimulating agent (ESA). Non-inferiority margins referenced are regulatory agency-approved non-inferiority margins.
Effect of Vadadustat in patients with anaemia and CKD (NDD)

Global Phase 3 INNO₂VATE Program

Studies of Vadadustat for Treatment of Anemia due to Chronic Kidney Disease (CKD) in Adult Patients on Dialysis

INNO₂VATE Consists of Two Randomized, Open-Label, Active-Controlled, Non-Inferiority Phase 3 Cardiovascular Outcomes Studies

**INNO₂VATE**

**CORRECTION**

Incident Dialysis

N = 369

Vadadustat vs Darbepoetin Alfa

**CONVERSION**

ESA Treated

N = 3,554

Vadadustat vs Darbepoetin Alfa

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**PRIMARY EFFICACY ENDPOINTS:**

- Mean change in hemoglobin (Hb) between baseline and the primary evaluation period (weeks 24 to 36)
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**PRIMARY SAFETY ENDPOINT:**

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Effect of Vadadustat in patients with anaemia and CKD (NDD)

ASCEND-D and -ND: Trial Design
Event-driven, open-label, randomized, active-controlled, parallel-group, multicenter, Phase 3 trials
ASCEND-D and ASCEND-ND accepted for publication

ASCEND-D: Key Entry Criteria
- ≥18 years of age
- Randomization Hb criteria:
  - Hb 8.0–11.5 g/dL
- ESA users
- Dialysis (HD/PD) >90 days prior to screening
- Iron replete: Ferritin >100 ng/mL; TSAT >20%

ASCEND-ND: Key Entry Criteria
- ≥18 years of age
- CKD Stage 3–5
- Randomization Hb criteria:
  - Hb 8.0–10.0 g/dL, if not using ESAs
  - Hb 8.0–11.0 g/dL, if using ESAs
- Not on dialysis and no plans to start within 90 days
- Iron replete: Ferritin >100 ng/mL; TSAT >20%

*The sponsor, steering committee and endpoint adjudication committee remained blind to aggregate treatment assignment throughout the trial.
†Epoetin alfa (IV; HD patients) or darbepoetin alfa (SC; PD patients).
‡MACE: composite of all-cause mortality, a non-fatal myocardial infarction, or a non-fatal stroke.
CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HD, hemodialysis; IV, intravenous; MACE, major adverse cardiovascular event; PD, peritoneal dialysis; R, randomization; SC, subcutaneous; TSAT, transferrin saturation.
Co-primary Efficacy Endpoint: ASCEND-D

Mean Hb change from baseline to the evaluation period (Weeks 28–52) – ITT Population

Daprodustat was noninferior to ESA for mean change in Hb from baseline to the evaluation period (Weeks 28–52)

Prespecified NI margin: -0.75 g/dL

Adjusted Mean Treatment Difference (95% CI)*
0.18 (0.12, 0.24)

Noninferiority was achieved because the lower limit of the 95% CI of the treatment difference was greater than the prespecified noninferiority margin of -0.75 g/dL.

*Based on an ANCOVA model using observed and imputed data with terms for treatment, baseline hemoglobin, dialysis type and region. Error bars indicate 95% CI. Post-randomization values include on- and off-treatment values. Visits on or before Day 1 include only pre-treatment values. Horizontal reference lines represent the Hb analysis range (10–11.5g/dL). The Hb target range for dose changes is 10–11g/dL. Vertical dotted lines represent the EP.

CI, confidence interval; EP, evaluation period; EOS, end of study; ESA, erythropoiesis-stimulating agent; FU, follow up; Hb, hemoglobin; ITT, intent-to-treat; NI noninferiority; SCR screening; Wk, week.
Co-primary Efficacy Endpoint: ASCEND-ND

Mean Hb change from baseline to the evaluation period (Weeks 28–52) – ITT Population

Daprodustat was noninferior to darbepoetin alfa for mean change in Hb from baseline to the evaluation period (Weeks 28–52)

Prespecified NI margin: -0.75 g/dL

Adjusted Mean Treatment Difference (95% CI)*
0.08 (0.03, 0.13)

Noninferiority was achieved because the lower limit of the 95% CI of the treatment difference was greater than the prespecified noninferiority margin of ~0.75 g/dL

*Based on an ANCOVA model using observed and imputed data with terms for treatment, baseline hemoglobin, current ESA use and region. Error bars indicate 95% CI. Post-randomization values include on- and off-treatment values. Visits on or before Day 1 include only pre-treatment values. Horizontal reference lines represent the Hb analysis range (10–11.5 g/dL). The Hb target range for dose changes is 10–11 g/dL. Vertical dotted lines represent the EP.

CI, confidence interval; EP, evaluation period; EOS, end of study; ESA, erythropoiesis-stimulating agent; FU, follow up; Hb, hemoglobin; ITT, intent-to-treat; NI noninferiority; SCR screening; Wk, week.
## Long-term efficacy and safety of hypoxia-inducible factor prolyl hydroxylase inhibitors in anaemia of chronic kidney disease: A meta-analysis including 13,146 patients

Huanhuan Chen, Qingfeng Cheng, Jiuxiang Wang, Xiaofang Zhao, Shenyin Zhu

### Adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>RR (95% CI)</th>
<th>P value</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>1.15 (0.91, 1.43)</td>
<td>0.25</td>
<td>35.80%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.34 (0.95, 1.89)</td>
<td>0.09</td>
<td>51.00%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.30 (1.02, 1.65)</td>
<td>0.03</td>
<td>12.20%</td>
</tr>
<tr>
<td>Headache</td>
<td>1.27 (1.05, 1.53)</td>
<td>0.01</td>
<td>0.00%</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1.14 (0.69, 1.89)</td>
<td>0.61</td>
<td>53.30%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.02 (0.89, 1.17)</td>
<td>0.76</td>
<td>0.00%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0.94 (0.71, 1.25)</td>
<td>0.69</td>
<td>55.70%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1.16 (0.88, 1.52)</td>
<td>0.29</td>
<td>20.90%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.72 (0.51, 1.02)</td>
<td>0.06</td>
<td>0.00%</td>
</tr>
<tr>
<td>Thrombosis events</td>
<td>1.31 (1.05, 1.63)</td>
<td>0.02</td>
<td>44.50%</td>
</tr>
<tr>
<td>MACE</td>
<td>1.02 (0.90, 1.14)</td>
<td>0.80</td>
<td>0.00%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.95 (0.72, 1.26)</td>
<td>0.73</td>
<td>7.00%</td>
</tr>
</tbody>
</table>

Vadadustat, as compared with darbepoetin alfa, met the prespecified noninferiority criterion for hematologic efficacy but not the prespecified noninferiority criterion for cardiovascular safety in patients with NDD-CKD.
<table>
<thead>
<tr>
<th></th>
<th>Population</th>
<th>Primary analysis HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daprodustat</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NDD</td>
<td>1.03 (0.89, 1.19) OS</td>
</tr>
<tr>
<td>2</td>
<td>DD</td>
<td>0.93 (0.81, 1.07) OS</td>
</tr>
<tr>
<td><strong>Vadadustat</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NDD</td>
<td>1.17 (1.01, 1.36) OS</td>
</tr>
<tr>
<td>4</td>
<td>DD</td>
<td>0.96 (0.83, 1.11) OS</td>
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<tr>
<td><strong>Roxadustat</strong></td>
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<td></td>
</tr>
<tr>
<td>6</td>
<td>NDD</td>
<td>0.81 (0.52, 1.25) OT+28</td>
</tr>
<tr>
<td>7</td>
<td>DD</td>
<td>1.09 (0.95, 1.26) OT+7</td>
</tr>
</tbody>
</table>

OT, On-treatment; OS, On-study; NDD, Non-dialysis dependent; DD, Dialysis dependent; HR, Hazard ratio; CI, Confidence interval
What we do know and what are the remaining questions?

Certainties
Efficacy – correct and maintain Hb
Physiological, endogenous EPO doses

Uncertainties
Safety / secondary effects of HIF-PHIs – MACE?, cancer?
Long-term consequences of HIF-PH inhibition
My view on current status of HIF-PHIs May 2022

• Do HIF-PHIs correct anaemia in patients with CKD as effectively as ESAs? Yes, when used in an appropriate dose.

• Do HIF-PHIs maintain haemoglobin levels in patients with CKD as effectively as ESAs? Yes, when used in an appropriate dose.

• Do HIF-PHIs have therapeutic advantages over ESAs? Not sure, possibly less iron required (oral iron instead of IV iron) and may be more effective in inflamed patients. But… and the MoA is physiological

• Do HIF-PHIs have better safety profiles than ESAs? No.

• Are we sure that HIF-PHIs do not have “off target” effects? No.