ARE HIF STABILIZERS A VIABLE ALTERNATIVE TO ESAs IN THE MANAGEMENT OF ANEMIA IN CKD?

PRO

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DISCLOSURES

• GlaxoSmithKline – ASCEND program steering committee member
  – Consultancy fees

• Vifor Pharma – Consultancy fees
DISCLOSURES

• I am intentionally adopting an extreme position for the purposes of making an interesting debate and do not necessarily fully subscribe to this position myself
ARE HIF STABILIZERS a **Viable** ALTERNATIVE TO ESAS IN THE MANAGEMENT OF ANEMIA IN CKD?

**Yes!**

Definition of viable:

*capable of working successfully; feasible.*

*the proposed investment was economically viable*
MECHANISMS OF ANEMIA IN CKD

Erythropoietin Receptor

STAT-5 Homodimerization

RAS-MAPK

PKB/AKT1

Differentiation

Proliferation

Prevention of Apoptosis/Cell Survival

Gene Transcription

Erythropoiesis

The Erythropoietic Response is Mediated by HIF

LONDON TO BERLIN BY LAND

ESA therapy

HIF stabilizers
The erythropoietic response is mediated by HIF

HIF-PHIs more likely to improve anemia in patients resistant to or hyporesponsive to “conventional” ESA therapy

Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis

ERYTHROPOIETIN CONCENTRATION-TIME PROFILES

Erythropoiesis range

Three 40 U/kg SC doses/week
Two 60 U/kg SC doses/week
One 120 U/kg SC dose/week

Erythropoietin concentration-time profiles

EPO has non-erythropoietic actions

High EPO levels

- ↑ VSMC $[Ca^{2+}]_i$
- ↑ RAS activation
- ↑ ET-1
- ↑ Thromboxane
- ↓ Prostacycline
- ↑ ADMA
- ↓ NO

Hypertension

VSMC proliferation
- EC proliferation
- Angiogenesis

Blood access stenosis
- Proliferative retinopathy
- Vascular remodeling
- Tumor growth

Platelet production
- ↑ Platelet activity
- ↑ E selectin
- ↑ P selectin
- ↑ vWF
- ↑ PAI-1

Thrombosis

ERYTHROPOIETIN CONCENTRATION-TIME PROFILES

Three 40 U/kg SC doses/week
Two 60 U/kg SC doses/week
One 120 U/kg SC dose/week

Erythropoiesis range

HIF-PHI strategy

Physiological levels of EPO

Hypoxia-Inducible Factor Stabilization as an Emerging Therapy for CKD-Related Anemia: Report From a Scientific Workshop Sponsored by the National Kidney Foundation

Jay B. Wish, Kai-Uwe Eckardt, Csaba P. Kovácsdy, Steven Fishbane, Bruce S. Spinowitz, and Jeffrey S. Berns

Table 1. Pharmacokinetic properties of 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&lt;sup&gt;a&lt;/sup&gt; and 34.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CYP2C8 with minor CYP3A4</td>
</tr>
<tr>
<td>Roxadustat (FG-4592, ASPI517)</td>
<td>0.7-2.5 mg/kg</td>
<td>3×/wk</td>
<td>12-15</td>
<td>113&lt;sup&gt;c&lt;/sup&gt; and 397&lt;sup&gt;d&lt;/sup&gt;</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<sup>11</sup>; 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.
<sup>a</sup>CKD patients receiving dialysis.
<sup>b</sup>CKD patients not requiring kidney replacement therapy.
<sup>c</sup>For 1 mg/kg dose.
<sup>d</sup>For 2 mg/kg dose.
DIRECT TRANSCRIPTIONAL TARGETS OF HIF

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Box 1. Summary of Recommendations for Future Research

- Further evaluation of potential adverse effects of HIF-PHI therapy
  - Evidence examined in phase 3 clinical trials
    - Major adverse cardiovascular events
    - Thrombotic events
    - Effects on blood lipids and their consequences
  - Evidence not sufficiently examined in phase 3 clinical trials
    - Malignancies
    - Diabetic retinopathy
    - Pulmonary arterial hypertension
    - Infection risk
    - Kidney fibrosis
    - Cyst growth in polycystic kidney disease
    - Hyperkalemia

- Further evaluation of potential benefits of HIF-PHI therapy
  - Effects in ESA-hyporesponsive patients
  - Effects on iron metabolism
  - Effects on quality of life
  - Reduced rate of loss of kidney function
  - Protection against ischemic events
  - Lowering of blood pressure
  - Glucose tolerance

- Practical considerations for implementation of HIF-PHI into clinical practice
  - Potential normalization of hemoglobin concentration
  - Combination therapy with ESAs
  - Heterogeneity of treatment effects
  - Patient and provider education
  - Cost, formulary, and treatment protocol barriers

- Key recommendations for future studies
  - Patient-level meta-analyses to better define adverse effect profile
  - Patient-level meta-analyses to better define adverse therapeutic response phenotypes
  - Postapproval monitoring (registry) of rare adverse effects
  - Use of data from phase 3 clinical trials to inform design and focus of future clinical trials
**HIF STABILIZERS ON QUALITY-OF-LIFE**

- 614 ND-CKD randomized to dapro vs. placebo (*Baseline Hb 9.73 g/dL dapro, 9.71 g/dL placebo*).
- Adjusted mean difference in Hb change = 1.40 g/dL (95% CI 1.23, 1.56; *P*<0.0001).
- Adjusted mean (SE) SF-36 Vitality score increased by 7.29 (1.1) points (dapro) vs 1.93 (1.2) points (placebo); Adjusted mean difference at Wk 28 was 5.36 (95% CI 2.17, 8.56; *P*=0.0005).

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Johansen et al – “Effects of Daprodustat on Hemoglobin and Quality of Life in Patients with CKD: Results of the ASCEND-NHQ Randomized, Double-Blind, Placebo-Controlled Trial”

-- ASN Kidney Week, Nov. 2021 -- FR-OR53.
HIF Stabilizers in other parts of the World
Roxadustat approved in China for the treatment of anaemia in chronic kidney disease patients on dialysis

18 December 2018

China is the first country to approve roxadustat

AstraZeneca today announced that its partner FibroCin (China) Medical Technology Development Co., Ltd. (FibroCin China) has now received formal marketing authorization from the National Medical Products Administration (NMPA) for roxadustat, a first-in-class erythropoiesis-stimulating factor orally administered (oral-HIF) and novel oral treatment for patients who are anaemic caused by chronic kidney disease (CKD) that are on dialysis. The medicine can be prescribed to patients who use haemodialysis or peritoneal dialysis.

Evrenzo

Table of contents

- Overview
- Authorisation details
- Product information
- Assessment history

GSK’s Duvroq, Akebia’s Vafseo win global first nods in Japan to challenge Astellas’ anemia drug

by Anqua Liu | Jun 30, 2020 12:05pm
DARBEPOETIN ALFA IN INDIA

Darbepoetin Alfa (40mcg) Cresp 40 Injection, Dr Reddy's Laboratories Ltd, Treatment: Anemia

₹ 1,250/ prefilled syringe Get Latest Price

Packaging Size 6 X 40 mcg/0.4 ml single use prefilled syringe
Brand Cresp 40
Manufacturer Dr Reddy's Laboratories Ltd
Composition Darbepoetin alfa (40mcg)
Treatment Anemia
Prescription/Non prescription Prescription

View Complete Details

Fill the quantity to get latest price!

Contact Seller
CASE REPORT (2026)

- 82-year-old Financier in New Delhi
- Advanced CKD due to diabetes and HTN – eGFR 16 ml/min
- Extreme physical fatigue and exhaustion
- Hb 6.4 g/dL (adequate iron status; no other cause for anemia)
- Severe needle phobia
- HIF-PHI cheaper than all injectable ESAs
SUMMARY

- HIF-PHIs have a more “rounded” and complete approach to erythropoiesis
- HIF-PHIs avoid very high circulating levels of EPO
- Possible positive transcriptional benefits of HIF-PHIs, e.g. improving QoL (vital capacity)
- Japanese, Chinese, and European regulators have all approved HIF-PHIs
- In most of the world, HIF-PHIs will be more affordable than conventional ESA therapy
CONCLUSIONS

• We should not throw the baby out with the bathwater

• HIF stabilizers are indeed a viable alternative to ESAs in the management of CKD anemia