New Drugs for Treating Anaemia of CKD Patients

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Currently available ESAs

• Recombinant human erythropoietin (rHuEPO)
  – Epoetin alfa
  – Epoetin beta
  – Epoetin theta

• Longer-acting ESA
  – Darbepoetin alfa
  – CERA

• Biosimilars
  - HX575
  - Epoetin zeta

All ESAs act on the same target receptors

EPO, rHuEPO

Darbepoetin alfa

C.E.R.A. Peg-rHuEPO

EPO mimetic peptide

Signal transduction

Survival, differentiation, proliferation, and maturation of RBC progenitors and precursors

Gene activation

C.E.R.A., continuous erythropoietin receptor activator; ESA, erythropoiesis-stimulating agent; EPO, erythropoietin; Jak, Janus Kinase; RBC, red blood cell

Current and future chemical therapies for treating anaemia in chronic kidney disease

Francesco Locatelli, Lucia Del Vecchio & Maria Carmen Luise

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To link to this article: https://doi.org/10.1080/14656566.2017.1323872
EPO-mimetic peptides
Small Peptides as Potent Mimetics of the Protein Hormone Erythropoietin

Wrighton NC, Farrell FX, Chang R, Kashyap AK, Barbone FP, Mulcahy LS, Johnson DL, Barrett RW, Jolliffe LK, Dower WJ.

- Random phage display peptide libraries and affinity selective methods were used to isolate small peptides that bind to and activate the EPO receptor.
- EPO mimetic peptide 1 (EMP1) was chosen.
- This is a cyclic oligopeptide of 20 aminoacids, joined by a disulphide bridge between two cystein residues.

Science 1996 Jul 26;273(5274):458-64
Peginesatide (Omontys, Hematide)

- **Synthetic peptide** *(two identical, covalently-linked 21 amino acid chains covalently linked to polyethylene glycol)*
- Binds to and activates EPO receptor
- Amino acid sequence unrelated to EPO
Peginesatide in patients with anemia undergoing hemodialysis

The EMERALD 1 and 2 Studies

Mean Hemoglobin Level, According to Study Week

Kaplan–Meier Curves for the Event-free Rate of the Composite Safety End Point

EMERALD 1 AND 2


Hazard ratio, 0.95 (95% CI, 0.77–1.17)
Peginesatide as a new approach for treating anemia of CKD patient: is it like a falling star?

Francesco Locatelli† & Lucia Del Vecchio

“Alessandro Manzoni” Hospital, Department of Nephrology, Dialysis and Renal Transplantation, Lecco, Italy
February 2013

IMPORTANT DRUG INFORMATION

Subject: Affymax and Takeda are instituting a voluntary product recall of OMONTYS following serious hypersensitivity reactions, including life threatening and fatal events, reported in patients receiving OMONTYS
Anaphylaxis and Hypotension after Administration of Peginesatide


61,482 doses in 19,540 patients
Potential induction of anti-PEG antibodies and complement activation
WHAT'S NEXT?
Investigational hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI) for the treatment of anemia associated with chronic kidney disease

Lucia Del Vecchio & Francesco Locatelli

To cite this article: Lucia Del Vecchio & Francesco Locatelli (2018): Investigational hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI) for the treatment of anemia associated with chronic kidney disease, Expert Opinion on Investigational Drugs, DOI: 10.1080/13543784.2018.1493455

To link to this article: https://doi.org/10.1080/13543784.2018.1493455
High-altitude physiology

At high altitude blood viscosity increase

Such change is due to an increase in red cells in the circulation

Mexico, Pico de Orizaba (5.610 m a.s.l.)
Expedition to the Peruvian Andes, 1890

Discovery:

Low oxygen partial pressure (pO2) induced increased erythropoiesis

Professeur François-Gilbert Viault,
Professeur ‘Anatomie Générale et d’Histologie
à l’Université de Bordeaux, France
Hypoxia-inducible nuclear factors bind to an enhancer element located 3′ to the human erythropoietin gene

GREGG L. SEMENZA, MARY K. NEJFELT, SUZIE M. CHI, AND STYLIANOS E. ANTONARAKIS

Center for Medical Genetics, Departments of Pediatrics and Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD 21205

A Nuclear Factor Induced by Hypoxia via De Novo Protein Synthesis Binds to the Human Erythropoietin Gene Enhancer at a Site Required for Transcriptional Activation

GREGG L. SEMENZA* AND GUANG L. WANG

Center for Medical Genetics, Departments of Pediatrics and Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205
HIF Stabilizers

- Hypoxia-inducible factors (HIFs) are transcription factors that respond to changes in available oxygen in the cellular environment.
- They have been defined as “oxygen sensors”.
- They are regulated by a family of prolyl hydroxilase enzymes (PHD1, PHD2, PHD3).
Hypoxia-Inducible Factor (HIF) Stabilizers

<table>
<thead>
<tr>
<th>DRUG</th>
<th>COMPANY</th>
<th>STAGE OF CLINICAL DEVELOPMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>FG-4592 (ROXADUSTAT)</td>
<td>FIBROGEN*</td>
<td>Phase II studies completed (ND CKD, HD, PD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase III studies ongoing (ND CKD, HD, PD)</td>
</tr>
<tr>
<td>AKB-6548</td>
<td>AKEBIA THERAPEUTICS</td>
<td>Phase II studies completed (ND CKD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase II studies ongoing, but not recruiting (HD)</td>
</tr>
<tr>
<td>GSK1278863</td>
<td>GLAXO SMITH KLINE</td>
<td>Phase IIa studies completed (ND CKD, HD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase IIb studies ongoing, but not recruiting (ND CKD)</td>
</tr>
<tr>
<td>BAY 85-3934 (MOLIDUSTAT)</td>
<td>BAYER PHARMA</td>
<td>Phase IIb studies ongoing (ND CKD, HD) DIALOGUE studies</td>
</tr>
<tr>
<td>JTZ-951</td>
<td>AKROS PHARMA</td>
<td>Phase I study completed (HD)</td>
</tr>
<tr>
<td>DS-1093a</td>
<td>DAIICHI SANKYO</td>
<td>Phase I study ongoing (CKD 3b or 4)</td>
</tr>
<tr>
<td>JNJ-42905343</td>
<td>JOHNSON &amp; JOHNSON</td>
<td>Experimental studies in rats</td>
</tr>
</tbody>
</table>

Targeting Hypoxia-Inducible Factors for the Treatment of Anemia in Chronic Kidney Disease Patients

Francesco Locatelli, Steven Fishbane, Geoffrey A. Block, Iain C. Macdougall

*Department of Nephrology, Alessandro Manzoni Hospital, Lecco, Italy; *Department of Medicine, Hofstra Northwell School of Medicine, Great Neck, NY; †Department of Nephrologists, Denver, CO, USA; ‡Department of Renal

Fig. 2. a, b HIF activity under normoxic/hypoxic conditions and HIF-PHI inhibition, and its effects on erythropoiesis. DCytB, duodenal cytochrome B; DMT1, Divalent metal transporter 1; EPO, erythropoietin; HIF, hypoxia-inducible factor; HIF-PH, hypoxia-inducible factor-prolyl-4-hydroxylase domain; HRE, HIF-responsive element; Pro, proline.
What hypoxia-inducible nuclear factors (HIF) are?

- Hypoxia-inducible factors (HIFs) are transcription factors that respond to changes in available oxygen in the cellular environment.

- They have been defined as “oxygen sensors”.

- They are regulated by a family of prolyl hydroxilase enzymes (PHD1, PHD2, PHD3).

  - **HIF-1α** facilitates O2 delivery and cellular adaptation to hypoxia by stimulating a wide spectrum of biological processes that include angiogenesis, anaerobic glucose metabolism, mitochondrial biogenesis.

  - EPO synthesis and iron metabolism are HIF-2-regulated processes.

Hypoxia-inducible factor-1
Hypoxia-inducible factor prolyl hydroxylase inhibitor (HIFPHI)

- HIF stabilization upon hypoxia or by HIF-PHIs, induces activation of a group of early response target genes, including those for EPO, EPO receptor, proteins promoting iron absorption, iron transport and heme synthesis.

- Selective stabilization of HIF with small molecule HIF-PHIs may be an innovative therapeutic approach to anemia treatment.
The size of the EPC pool is regulated in an oxygen-dependent manner and increases under hypoxic conditions.

Erythropoietin Synthesis in Renal Myofibroblasts Is Restored by Activation of Hypoxia Signaling

Tomokazu Souma,*†† Masahiro Nezu,*†† Daisuke Nakano,§ Shun Yamazaki,*† Ikuo Hirano,*† Hiroki Sekine,*† Takashi Dan,‖ Kotaro Takeda,¶ Guo-Hua Fong,¶ Akira Nishiyama,§ Sadayoshi Ito,‡ Toshio Miyata,‖ Masayuki Yamamoto,* and Norio Suzuki†

Activation of the Epo-gene transcription in PHD-deficient myofibroblasts
HIF stabilizers, also called PHD inhibitors, reversibly inhibit PHD catalytic activity by binding to the ferrous-iron-containing active site, thereby blocking entry of the co-substrate 2OG.
Mechanism of action of HIF stabilisers

HIF: hypoxia-inducible transcription factors
PHD: prolyl hydroxylase domain

Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in NDD-CKD patients

Anatole Besarab¹, Robert Provenzano², Joachim Hertel³, Raja Zabaneh⁴, Stephen J. Klaus¹, Tyson Lee¹, Robert Leong¹, Stefan Hemmerich¹, Kin-Hung Peony Yu¹ and Thomas B. Neff¹

117 NDD-CKD subjects with Hb ≤11.0 g/dL, and of 15–59 mL/min/1.73 m²

Randomization to roxadustat or placebo 3:1 for 4 weeks

Four dose cohorts: 1.0, 1.5, 2.0 and then 0.7 mg/kg BIW or TIW

Primary endpoints:
- ΔHb from baseline
- proportion of Hb responders (ΔHb ≥ 1.0 g/dL)
Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in NDD-CKD patients

Mean change from BL in Hb (ΔHb) in TIW cohorts (EE population)

Roxadustat Versus Epoetin Alfa in maintenance HD patients

Pharmacodynamic effects of roxadustat compared to epoetin alfa

![Graph showing mean ± SE plasma erythropoietin levels (mIU/ml) over hours post-dosing for Epoetin alfa IV at screening (n=6) and Roxadustat Day 2 (n=6).](image)

Much Lower Plasma Endogenous EPO Level After FG-4592 Treatment Compared with rhEPO Treatment in Hemodialysis Patient

Subject 1102-4001: A1, 1.0 mg/kg

Responders

Day 2 post-FG-4592 dose (70 mg)

Day 37 of post-FG-4592 dose 70 mg
Hb = 10.8 g/dL

Screening
Hb = 11.0 g/dL
Open-label, randomized correction study

60 anemic (Hb<10.0 g/dl) patients  ESA-naives incident to HD or PD

Treatment with roxadustat (4.0mg/kg thrice weekly) for 12 weeks

Randomization to different iron supplementation regimens:
• no iron
• oral iron
• IV iron

Roxadustat (FG-4592): Correction of Anemia in Incident Dialysis Patients

Mean Hb levels over time in the three iron treatment groups

<table>
<thead>
<tr>
<th>Arm</th>
<th>n</th>
<th>Mean (±SE) ΔHb&lt;sub&gt;max&lt;/sub&gt; (g/dL)</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD, no iron</td>
<td>23</td>
<td>2.8 (±0.2)</td>
<td>95.7%</td>
</tr>
<tr>
<td>HD, oral iron</td>
<td>12</td>
<td>3.5 (±0.5)</td>
<td>91.7%</td>
</tr>
<tr>
<td>HD, IV iron</td>
<td>10</td>
<td>3.5 (±0.4)</td>
<td>100.0%</td>
</tr>
<tr>
<td>PD, oral iron</td>
<td>10</td>
<td>3.3 (±0.2)</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
19-week treatment in 90 individuals in 6 cohorts with various starting doses and adjustment rules
Roxadustat (FG-4592) for the Treatment of Anemia in Patients with CKD

Iron status

- No significant effect of oral iron administration on Hb levels was observed over the first 16 weeks of therapy.

Hb response rate and \( \Delta \text{Hb} \) were independent of baseline iron repletion status.

Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in NDD-CKD patients

Mean change from BL in serum hepcidin (EE population)

Roxadustat (FG-4592): Correction of Anemia in Incident Dialysis Patients

Weekly roxadustat dose during the last 2 weeks and baseline CRP levels

Baseline CRP levels are correlated with pre-enrollment epoetin alfa but not roxadustat maintenance dose requirements.

Roxadustat (FG-4592) Versus Epoetin Alfa for Anemia in Patients Receiving Maintenance Hemodialysis

Hb levels over time (6 weeks) by treatment group

Least squares mean Hb levels over time (19 weeks), roxadustat-treated versus epoetin alfa–treated patients

Roxadustat (FG-4592) for the Treatment of Anemia in Patients with CKD

Hemoglobin over time in the efficacy-evaluable population by cohort
Roxadustat (FG-4592) Versus Epoetin Alfa for Anemia in Patients Receiving Maintenance Hemodialysis

Total cholesterol levels over time

Two phase 2a studies with GSK1278863:

- 73 non-dialysis patients ESA naives (baseline Hb 8.5–11.0 g/dl)
- 83 HD patients on ESA therapy (baseline Hb 9.5–12.0 g/dl)

Randomization to 1:1:1:1 to once-daily GSK1278863 (0.5mg, 2mg, or 5mg) or control (placebo for non-dialysis; continuing on rHuEPO for HD) for 4 weeks
Four-Week Studies of Oral HIF–Prolyl Hydroxylase Inhibitor GSK1278863 for Treatment of Anemia

Study 1: non-dialysis patients

Study 2: HD patients

Observed mean Hb ± SD

Effects of Daprodustat, a Novel Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor on Anemia Management in Japanese Hemodialysis Subjects

- 4-week, phase II, double-blind, placebo-controlled study
- 97 HD patients
- ESA withdrawal between 2 and 8 weeks and a Hb decrease ≥ 0.5 g/dL
- Hb 8.5–10.5 g/dL
- IV or oral iron permitted without changes during the study

RANDOMISATION

PLACEBO

DAPRODUSTAT (GSK1278863)

4, 6, 8, or 10 mg orally once daily

PRIMARY ENDPOINT:
Hemoglobin change from baseline at week 4
### EPO INCREASE

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 18)</th>
<th>Daprodustat 4 mg (n = 19)</th>
<th>Daprodustat 6 mg (n = 20)</th>
<th>Daprodustat 8 mg (n = 19)</th>
<th>Daprodustat 10 mg (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPO, mIU/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, n</td>
<td>18</td>
<td>19</td>
<td>20</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Median</td>
<td>5.6</td>
<td>4.7</td>
<td>7.1</td>
<td>7.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Min, max</td>
<td>2.5, 12.5</td>
<td>2.5, 22.3</td>
<td>2.5, 26.9</td>
<td>2.5, 14.0</td>
<td>2.6, 95.8</td>
</tr>
<tr>
<td>Peak, n</td>
<td>17</td>
<td>18</td>
<td>20</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Median</td>
<td>11.7</td>
<td>33.3</td>
<td>68.0</td>
<td>88.6</td>
<td>82.4</td>
</tr>
<tr>
<td>Min, max</td>
<td>3.4, 23.2</td>
<td>8.2, 111.1</td>
<td>12.2, 513.9</td>
<td>34.3, 554.7</td>
<td>13.1, 838.1</td>
</tr>
</tbody>
</table>

5 subjects
(1 subject on 6 mg, 2 subjects on 8 mg, and 2 subjects on 10 mg) exceeding 500 mIU/mL
SECONDARY ENDPOINTS: LIPID CHANGES

Week 4

Total Cholesterol  LDL Cholesterol  HDL Cholesterol

N=18  N=19  N=20  N=19  N=20  N=19  N=20  N=19  N=20

Placebo  4 mg  6 mg  8 mg  10 mg

### SAFETY: VEGF LEVELS

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 18)</th>
<th>Daprodustat 4 mg (n = 19)</th>
<th>6 mg (n = 20)</th>
<th>8 mg (n = 19)</th>
<th>10 mg (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF, ng/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, n</td>
<td>18</td>
<td>19</td>
<td>20</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Median</td>
<td>139.1</td>
<td>149.1</td>
<td>173.3</td>
<td>138.7</td>
<td>151.3</td>
</tr>
<tr>
<td>Min, max</td>
<td>19.1, 415.5</td>
<td>93.6, 478.5</td>
<td>113.4, 255.2</td>
<td>83.9, 373.9</td>
<td>38.8, 297.8</td>
</tr>
<tr>
<td>Peak, n</td>
<td>17</td>
<td>18</td>
<td>20</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Median</td>
<td>169.5</td>
<td>180.3</td>
<td>195.2</td>
<td>177.4</td>
<td>209.3</td>
</tr>
<tr>
<td>Min, max</td>
<td>115.6, 332.4</td>
<td>97.8, 382.8</td>
<td>137.0, 411.4</td>
<td>129.8, 341.3</td>
<td>96.2, 392.1</td>
</tr>
</tbody>
</table>

A Randomized, Placebo- and Positive-Controlled, Single-Dose, Crossover Thorough QT/QTc Study Assessing the Effect of Daprodustat on Cardiac Repolarization in Healthy Subjects

55 healthy adult subjects

In vitro daprodustat inhibited human ether-a-go-go related gene (hERG) current and human sodium channel

The 500-mg daprodustat dose was associated with an increase in heart rate with an unknown mechanism

Vadadustat in Patients with Anemia Secondary to Stage 3 or 4 Chronic Kidney Disease

Mean change in Hb from baseline

Mean Hb change from baseline, g/dL

Primary ANOVA, $p < 0.0001$

<table>
<thead>
<tr>
<th>Vadadustat, mg</th>
<th>240</th>
<th>370</th>
<th>500</th>
<th>630</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Hb change from baseline, g/dL</td>
<td>0.76*, †</td>
<td>0.70*, †</td>
<td>1.15*, †</td>
<td>1.39*, †</td>
</tr>
</tbody>
</table>

Modified intent to treat population

Vadadustat in Patients with Anemia Secondary to Stage 3 or 4 Chronic Kidney Disease

Proportion achieving an Hb increase

![Bar graph showing proportion of subjects with an Hb increase in different treatments.]

- Placebo: 11%
- 240 mg: 31%
- 370 mg: 40%
- 500 mg: 65%
- 630 mg: 78%

Modified intent to treat population

Vadadustat in Patients with Anemia Secondary to Stage 3 or 4 Chronic Kidney Disease

Observed mean ferritin concentration over the trial period

Vadadustat in Patients with Anemia Secondary to Stage 3 or 4 Chronic Kidney Disease

Mean change in hepcidin compared to baseline

First-in-man study with BAY 85-3934 (Moludistat)

- Phase I, randomized, single-blind, placebo-controlled, dose escalation study in 59 healthy male subjects.
- BAY 85-3934 was administered as single oral doses of 5, 12.5, 25, 37.5 and 50 mg to 12 subjects (9 verum, 3 placebo) per dose step.

All 5 dosages were well tolerated.

Figure 3: Erythropoietin – Concentrations after single oral dose of 5, 12.5, 25, 37.5 and 50 mg BAY 85-3934 and placebo (mean ± SEM; n=58)

Mimicking Hypoxia to Treat Anemia: HIF-Stabilizer BAY 85-3934 (Molidustat) Stimulates Erythropoietin Production without Hypertensive Effects

Ingo Flamme¹*, Felix Oehme², Peter Ellinghaus³, Mario Jeske⁴, Jörg Keldenich⁵, Uwe Thuss⁵

Effects of BAY 85-3934 administration in male Wistar rats treated with gentamicin to induce renal anemia
Pharmacological Characterization of ZYAN1, a Novel Prolyl Hydroxylase Inhibitor for the Treatment of Anemia

M. R. Jain¹, A. A. Joharapurkar¹, V. Pandya², V. Patel¹, J. Joshi², S. Kshirsagar¹, K. Patel¹, P. R. Patel¹, C. Desai²

¹Department of Pharmacology & Toxicology, Zydus Research Centre, Cadila Healthcare Limited, Ahmedabad, India
²Department of Medicinal Chemistry, Zydus Research Centre, Cadila Healthcare Limited, Ahmedabad, India
Phase 2 studies of oral hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for treatment of anemia in China

- Two phase-II studies (ND, placebo and dialysis, open-label)
- 6-8 weeks follow-up
- 91 NND patients and 87 dialysis patients HD patients
- Hb < 10 g/dL (ND) or 9-12 g/dl (dialysis, Epoetin therapy)
- Only oral iron permitted

Dialysis patients:
Roxadustat at three dose groups:
- Low dose: 1.1-1.8 mg/kg
- Medium dose: 1.5-2.3 mg/kg
- High dose: 1.7-2.3 mg/kg

Phase 2 studies of oral hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for treatment of anemia in China

Hb over time and primary efficacy end-point

FibroGen, Inc.), and its subsidiary FibroGen China Medical Technology Development Co., Ltd., today announced that the China Food and Drug Administration (CFDA) has accepted the company’s recently submitted New Drug Application for registration of roxadustat.

The New Drug Application for roxadustat is based on the results of FibroGen’s two Phase 3 multi-center, randomized, controlled studies conducted in China:

- One study in 304 CKD dialysis comparing roxadustat against epoetin alfa for 26 weeks
- One study in 151 CKD non-dialysis comparing roxadustat against placebo for 8 weeks

CKD affects an estimated 119.5 million patients in China.
## Published clinical studies

<table>
<thead>
<tr>
<th>DRUG</th>
<th>AUTHOR</th>
<th>PATIENTS</th>
<th>STUDY</th>
<th>RAND.</th>
<th>DOSE</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>FG-4592 (ROXADUSTAT)</td>
<td>Besarab</td>
<td>117 NDD-CKD</td>
<td>Correction</td>
<td>3:1</td>
<td>1.0, 1.5, 2.0 and then 0.7 mg/kg BIW or TIW</td>
<td>4 weeks</td>
</tr>
<tr>
<td>FG-4592 (ROXADUSTAT)</td>
<td>Besarab</td>
<td>60 ESA-naives</td>
<td>Correction</td>
<td></td>
<td>no iron</td>
<td>12 weeks</td>
</tr>
<tr>
<td>FG-4592 (ROXADUSTAT)</td>
<td>Provenzano</td>
<td>145 ND-CKD</td>
<td>Correction</td>
<td>6 cohorts</td>
<td>1.0, 1.5, 1.8, or 2.0 mg/kg then 1.0-2.0 mg/kg or tiered weight based thrice weekly</td>
<td>19 weeks</td>
</tr>
<tr>
<td>FG-4592 (ROXADUSTAT)</td>
<td>Provenzano</td>
<td>145 ND-CKD</td>
<td>Correction</td>
<td>6 cohorts</td>
<td>60 to 150 mg fixed or weight-based, TIW, BIW or QW</td>
<td>24 weeks</td>
</tr>
<tr>
<td>GSK1278863 (DAPRODUSTAT)</td>
<td>Brigandi</td>
<td>70 ND CKD and 37 HD pts</td>
<td>Correction</td>
<td>1:1:1:1:1</td>
<td>10, 25, 50, or 100 mg once daily</td>
<td>4 weeks</td>
</tr>
<tr>
<td>GSK1278863 (DAPRODUSTAT)</td>
<td>Holdostock</td>
<td>73 ND CKD ESA naives</td>
<td>Correction</td>
<td>1:1:1:1</td>
<td>0.5 mg, 2 mg, or 5 mg once daily</td>
<td>4 weeks</td>
</tr>
<tr>
<td>GSK1278863 (DAPRODUSTAT)</td>
<td>Akawa T</td>
<td>97 HD patients</td>
<td>Correction</td>
<td>1:1:1:1:1</td>
<td>4, 6, 8, or 10 mg once daily</td>
<td>4 weeks</td>
</tr>
<tr>
<td>AKB-6548 (VADADUSTAT)</td>
<td>Pergola</td>
<td>210 ND CKD</td>
<td>Correction</td>
<td>2:1</td>
<td>450 mg once daily</td>
<td>20 weeks</td>
</tr>
</tbody>
</table>

**Published clinical studies**

- **412 PTS**
  - **FU MAX: 24 WKS**
  - **DOSE: 1.0 -> 4.0 mg/kg OR FIXED REGARDLESS WEIGTH 2 OR 3 TIMES A WEEK**

- **360 PTS**
  - **FU MAX: 4 WKS**
  - **DOSE: 0.2 -> 100 mg ONCE A DAY**

- **210 PTS**
  - **FU MAX: 20 WKS**
  - **DOSE: 450 mg ONCE A DAY**
Several scenarios are possible

HIF inhibitors: pros
- Stimulation of endogenous EPO
- Effective
- Increased iron utilisation
- Not influenced by inflammation
- Cheaper than ESA?

HIF inhibitors: cons
- No long-term data
- Pill burden
- Unexpected effects
- VEGF increase?
Sotatercept (ACE-011)

- Chimeric protein derived from fusion of the extracellular component of the activin receptor 2A to the Fc domain of human IgG1
- It binds to activin, preventing its binding to endogenous receptors and interfering with the SMAD pathway.
- Antitumor activity, it promotes new bone formation
- It increased hematocrit levels in a phase I clinical trial in postmenopausal females

A phase IIa, randomized, double-blind, parallel-group, trial is evaluating sotatercept (starting dose of 0.1 mg/kg sc) on anemia correction in 32 HD
Transforming growth factor-β superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis

Rajasekhar N V S Suragani et al.
A011-08 (double-blind)

Patients with metastatic breast cancer randomized to 2:2:2:1 to sotatercept 0.1, 0.3, or 0.5 mg/kg, or placebo every 28 days

Primary endpoint

Hb increase of ≥1 g/dL from baseline

ACE-011-NSCL-001 (open-label)

Patients with solid tumors treated with platinum-based chemotherapy randomised to sotatercept 15 or 30 mg every 42 days

Support Care Cancer. 2016; 24: 1517–1525
Sotatercept (ACE-011) for the treatment of chemotherapy-induced anemia

55 patients enrolled in the two studies

Exploratory analyses

- Placebo
- Sotatercept 0.1 mg/kg
- Sotatercept 0.3 mg/kg and 15 mg
- Sotatercept 0.5 mg/kg and 30 mg

Mean change in Hb from baseline

Support Care Cancer. 2016; 24: 1517–1525
Will there still be a role for the originator erythropoiesis-simulating agents after the biosimilars and the hypoxia-inducible factor stabilizers approval?

Francesco Locatelli and Lucia Del Vecchio
Are we approaching the end of the recombinant EPO era?

We don’t know the answer yet