



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?

The image shows a Google search interface. The search bar contains the text "viable meaning". Below the search bar, there are navigation options: "All", "News", "Images", "Videos", "Books", "More", and "Tools". The search results show "About 8,840,000,000 results (0.58 seconds)". A "Dictionary" section is highlighted, with the text "Definitions from Oxford Languages · Learn more". Below this is a search input field with the placeholder "Search for a word". The word "viable" is displayed with a speaker icon and the phonetic transcription "/ˈvaɪəb(ə)l/". Underneath, it says "See definitions in:" followed by buttons for "All", "Biology", and "Medicine". The word "adjective" is written below the buttons. A red-bordered box highlights the definition: "capable of working successfully; feasible." and the example sentence: "the proposed investment was economically viable". To the right of the dictionary section, there is a green-bordered box containing the text "Yes!".

Google viable meaning

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Dictionary
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Search for a word

viable
/ˈvaɪəb(ə)l/

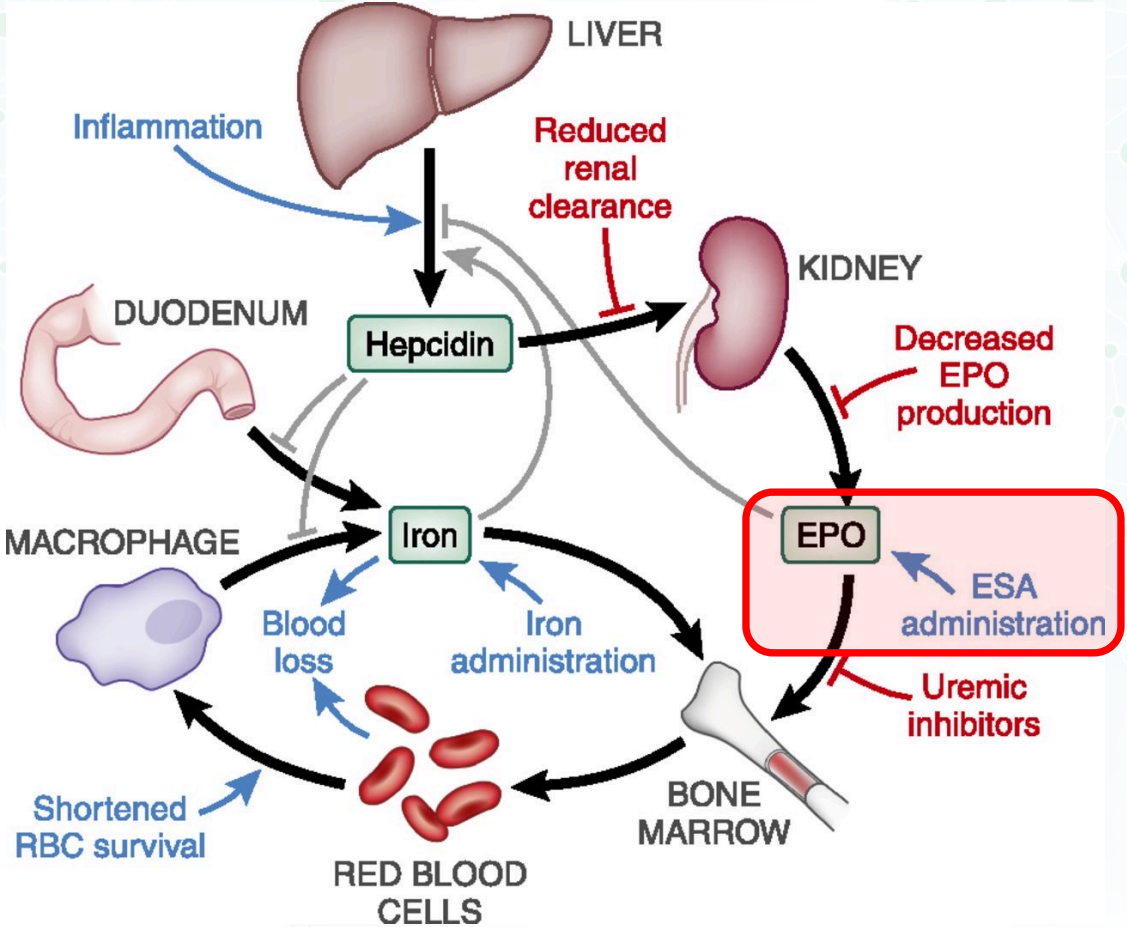
See definitions in:
All Biology Medicine

adjective

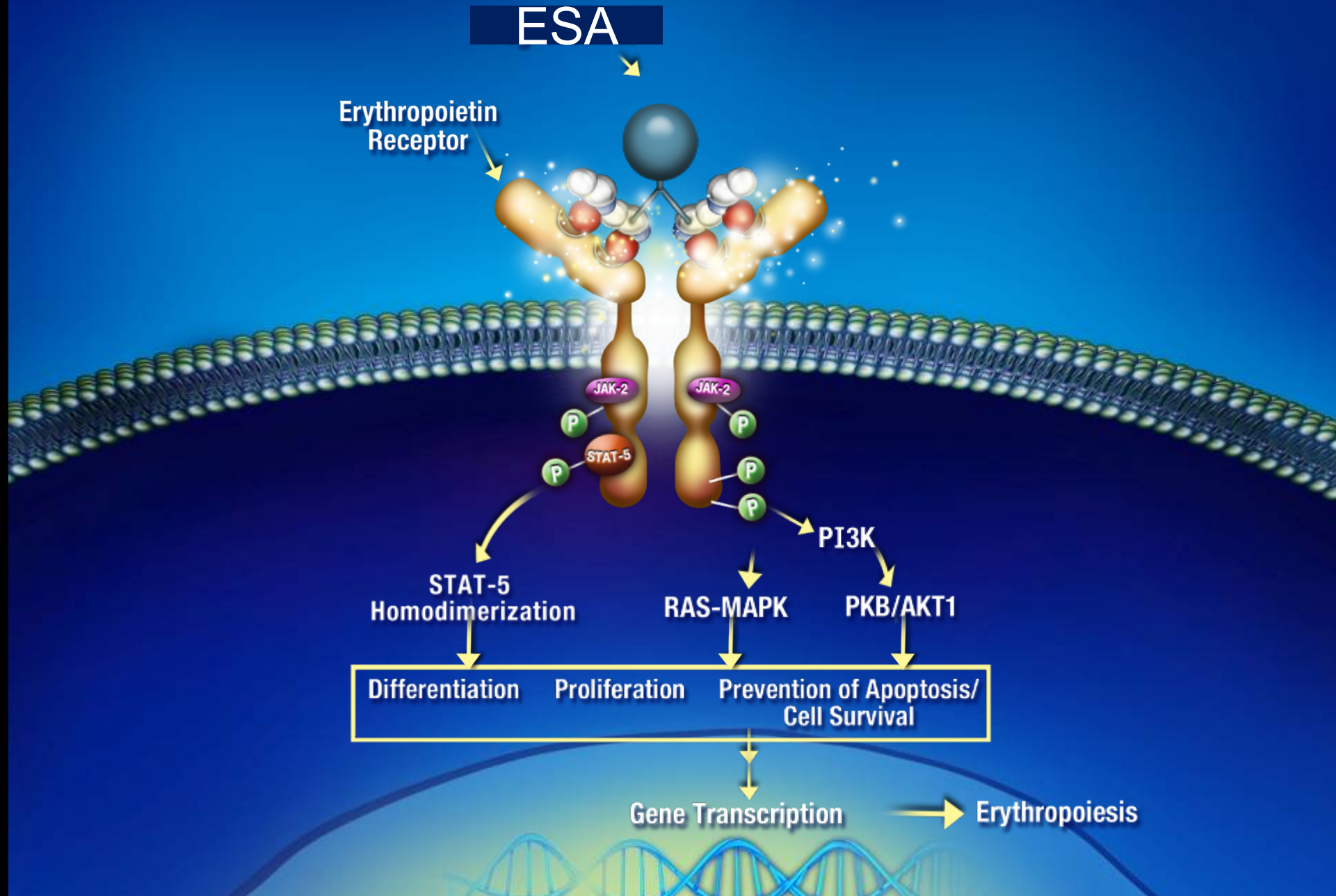
capable of working successfully; feasible.
"the proposed investment was economically viable"

Yes!

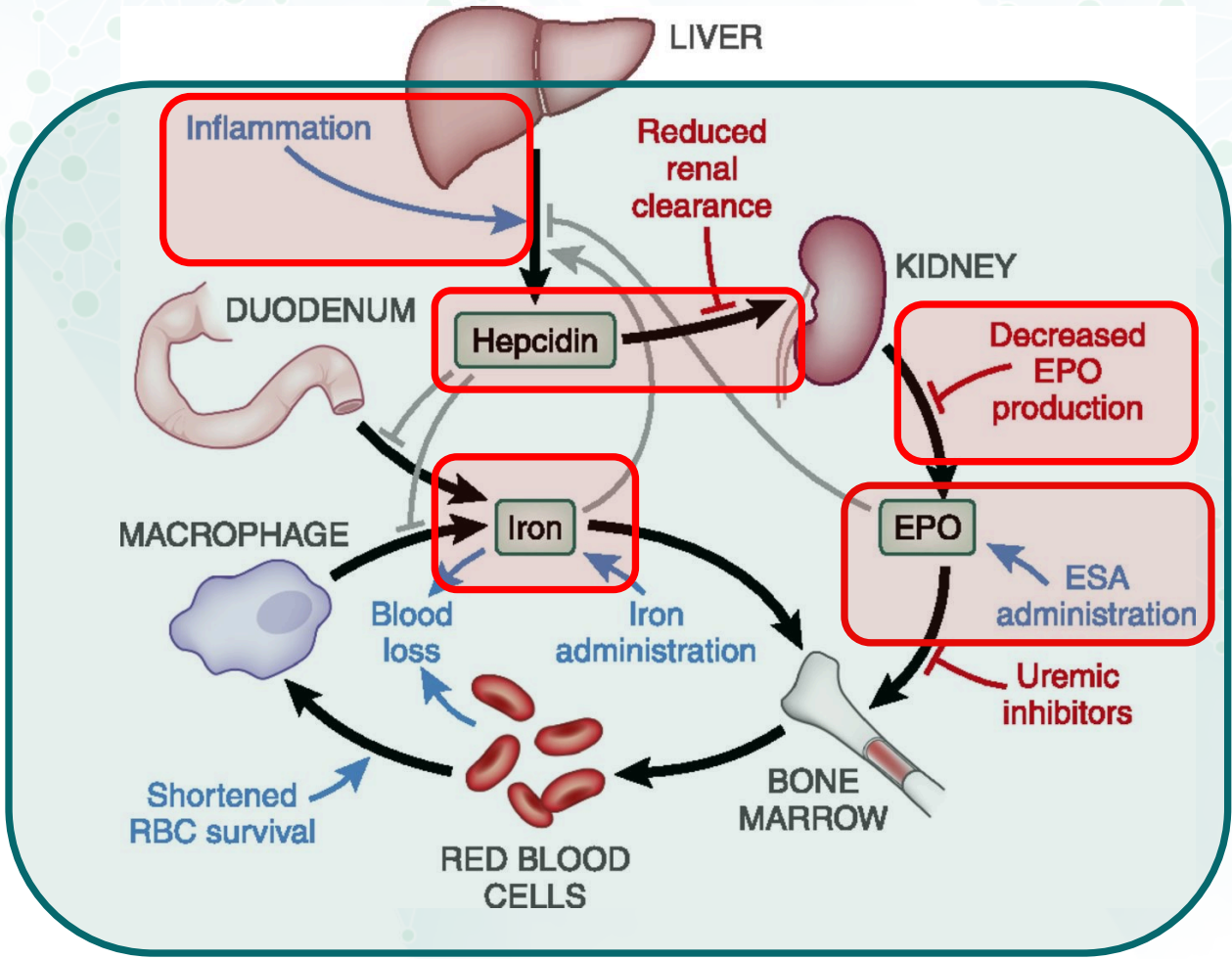
MECHANISMS OF ANEMIA IN CKD



Babitt JL, Lin HY.
Mechanisms of anemia in CKD.
J Am Soc Nephrol. 2012; **23**: 1631-1634

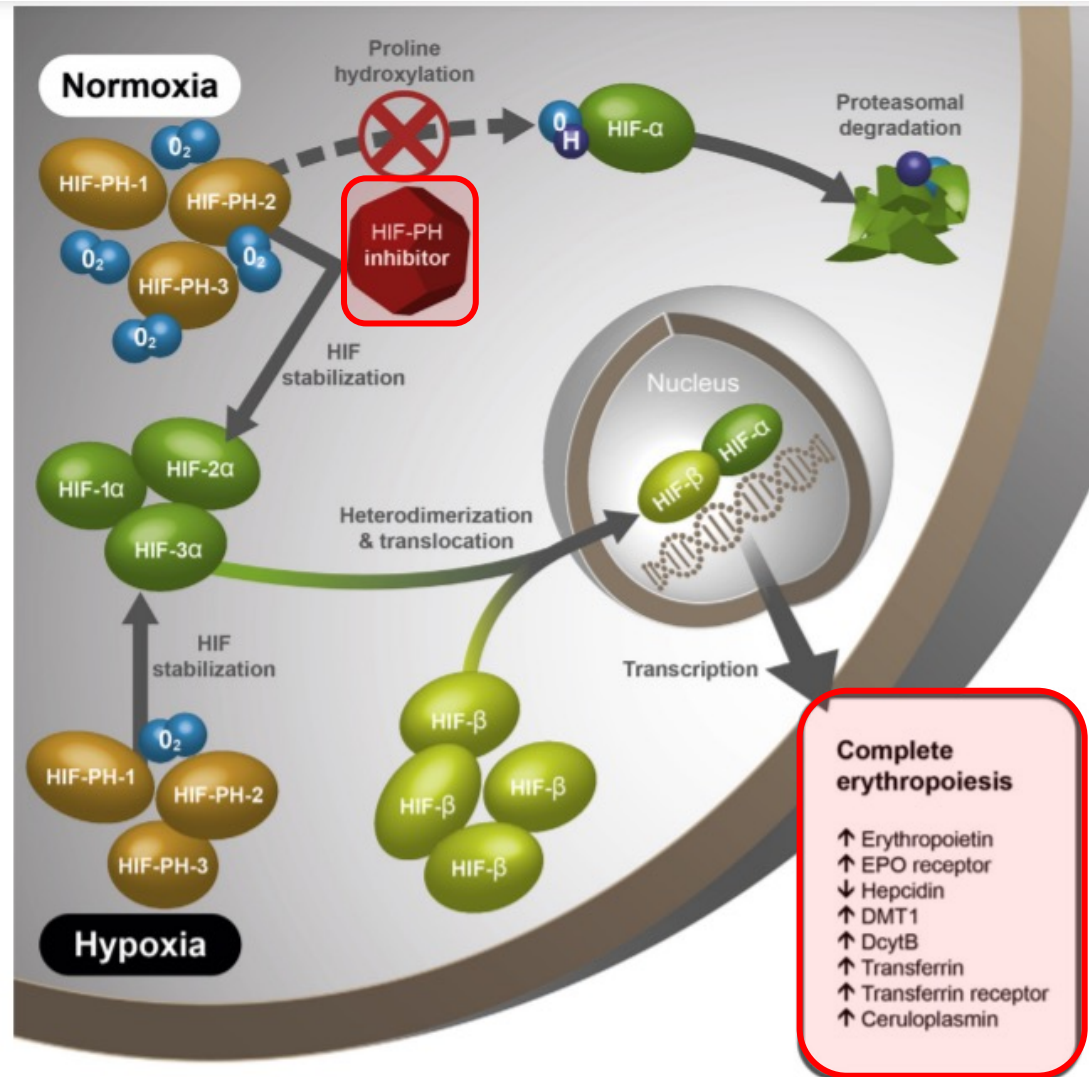


MECHANISMS OF ANEMIA IN CKD



Babitt JL, Lin HY.
Mechanisms of anemia in CKD.
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THE ERYTHROPOIETIC RESPONSE IS MEDIATED BY HIF



- Complete erythropoiesis**
- ↑ Erythropoietin
 - ↑ EPO receptor
 - ↓ Heparin
 - ↑ DMT1
 - ↑ DcytB
 - ↑ Transferrin
 - ↑ Transferrin receptor
 - ↑ Ceruloplasmin

Special Report

AJKD

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. Kovesdy, Steven Fishbane, Bruce S. Spinowitz, and Jeffrey S. Berns

Wish JB et al.
NKF Scientific Workshop Report on HIF.
Am J Kidney Dis 2021 Nov; 78: 709-718.

LONDON TO BERLIN BY LAND

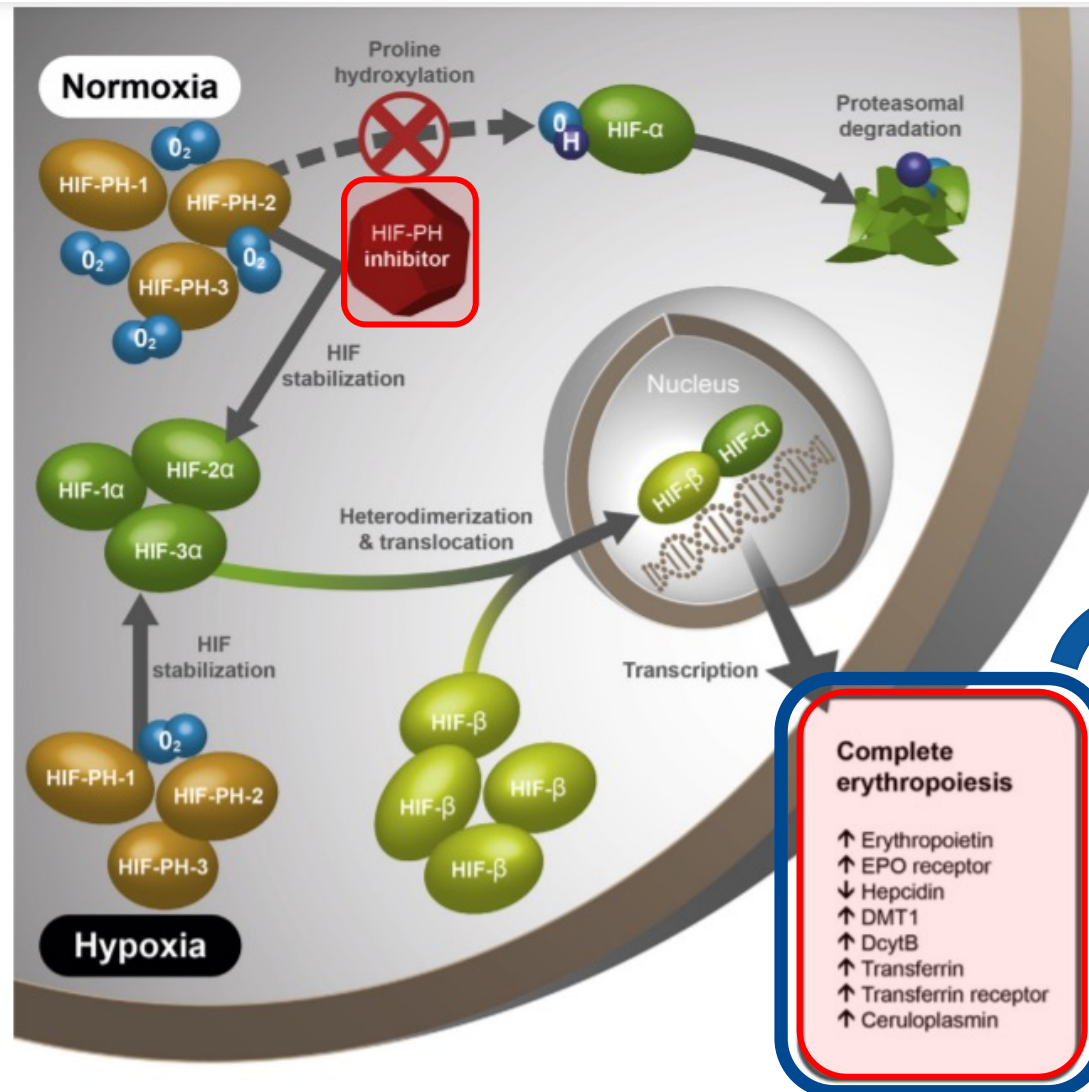


ESA therapy

HIF stabilizers



THE ERYTHROPOIETIC RESPONSE IS MEDIATED BY HIF



Special Report

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Complete erythropoiesis

- ↑ Erythropoietin
- ↑ EPO receptor
- ↓ Heparin
- ↑ DMT1
- ↑ DcytB
- ↑ Transferrin
- ↑ Transferrin receptor
- ↑ Ceruloplasmin

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

ORIGINAL ARTICLE

Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis

N. Chen, C. Hao, B.-C. Liu, H. Lin, Caili Wang, C. Xing, X. Liang, G. Jiang, Zhengrong Liu, X. Li, L. Zuo, L. Luo, J. Wang, M. Zhao, Zhihong Liu, G.-Y. Cai, L. Hao, R. Leong, Chunrong Wang, C. Liu, T. Neff, L. Szczech, and K.-H.P. Yu

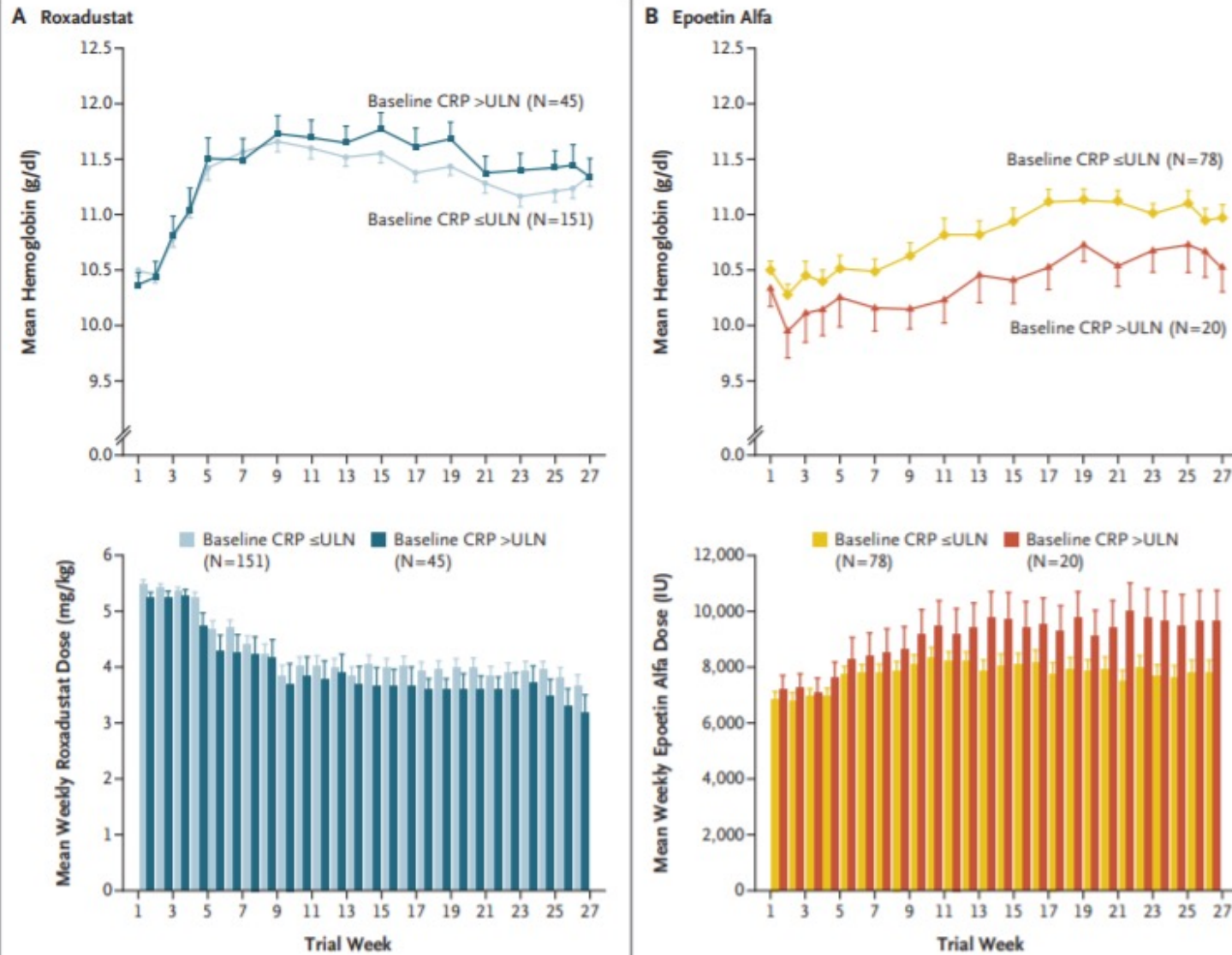
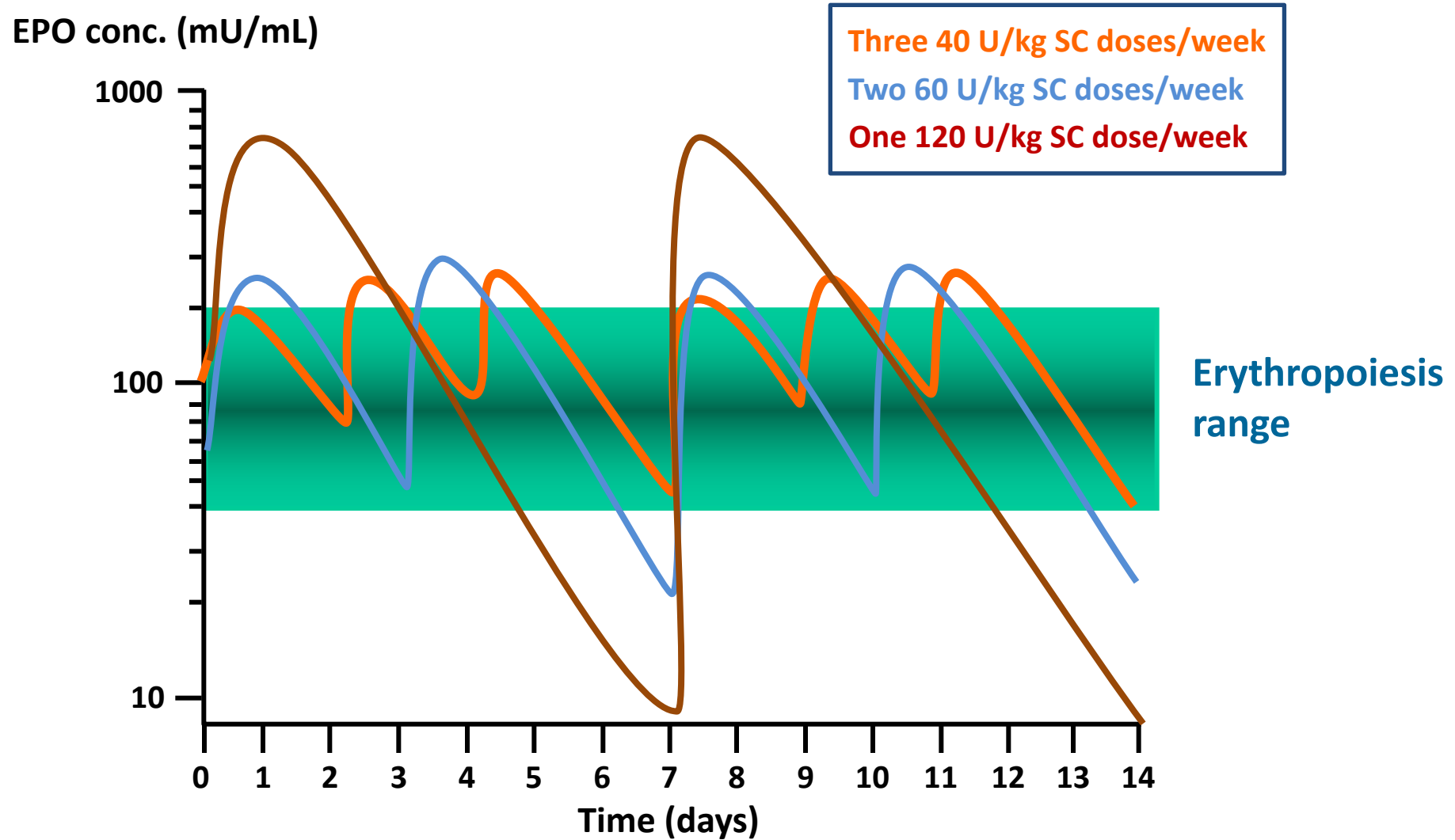


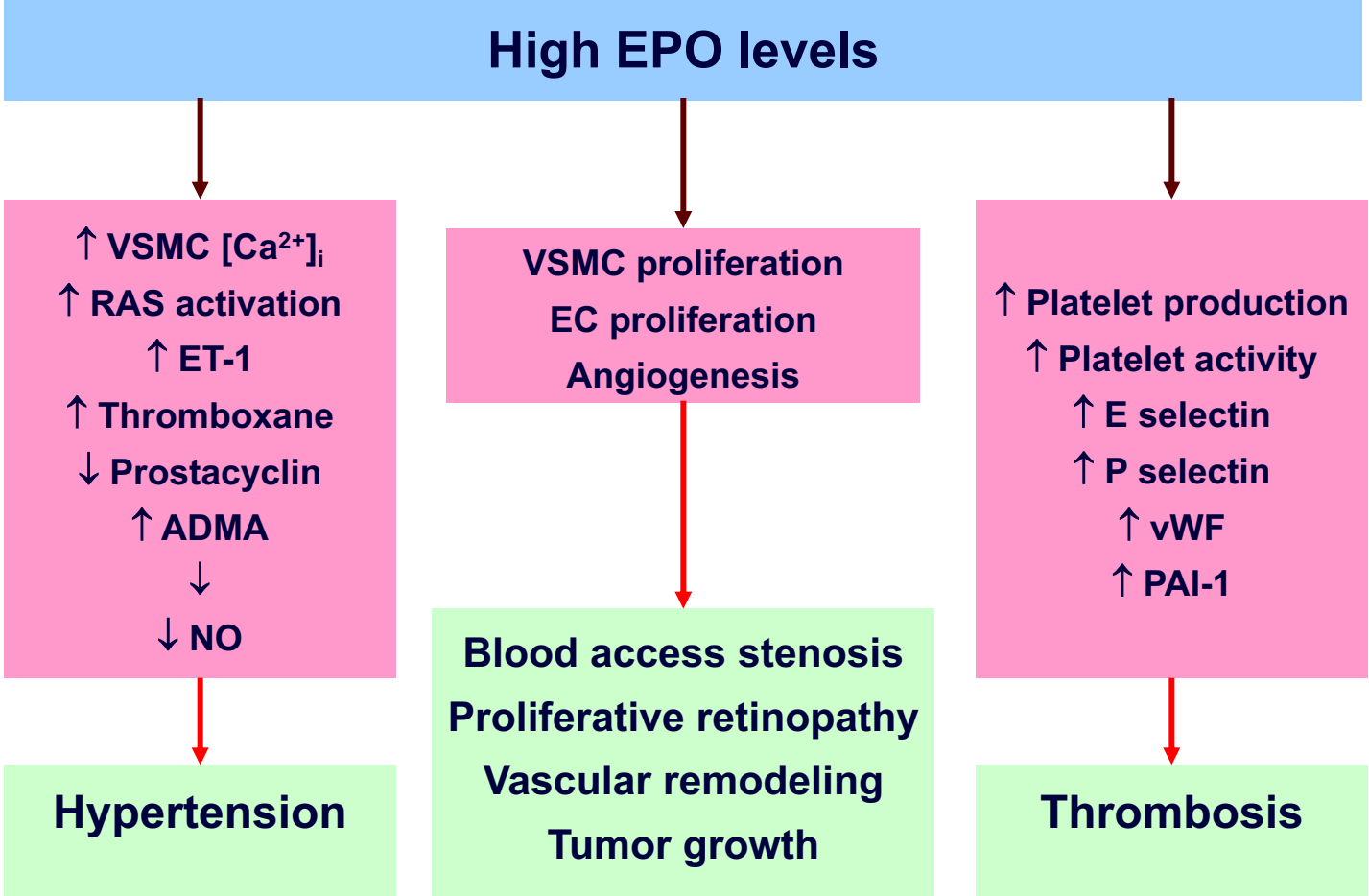
Figure 2. Mean Doses of Roxadustat and Epoetin Alfa and Hemoglobin Levels over Time, According to C-Reactive Protein Subgroup (Per-Protocol Population).

The upper limit of the normal range (ULN) for C-reactive protein (CRP) was 4.9 mg per liter. I bars (top graphs) and T bars (bottom graphs) indicate the standard error of the mean.

ERYTHROPOIETIN CONCENTRATION-TIME PROFILES

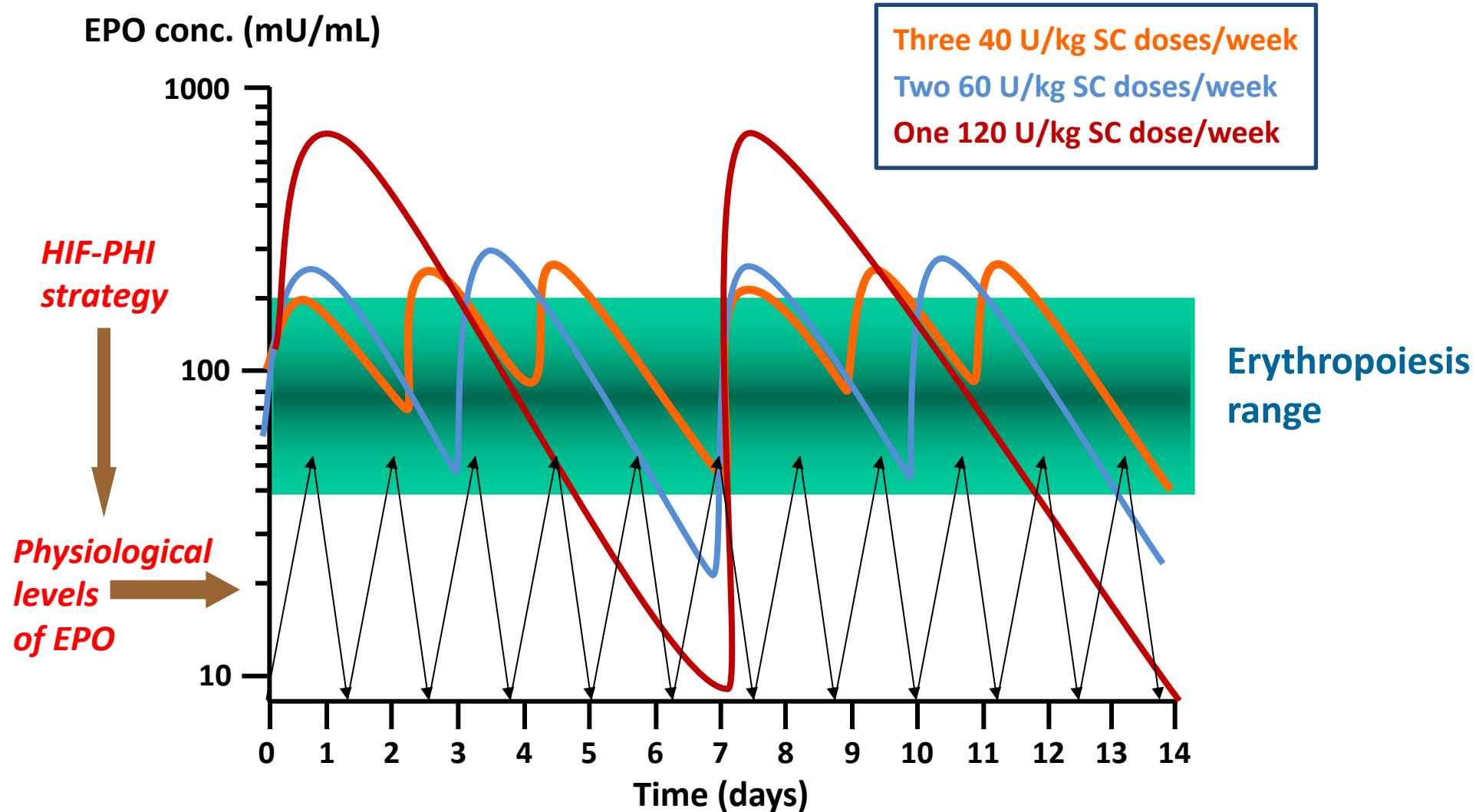


EPO HAS NON-ERYTHROPOIETIC ACTIONS



Vaziri ND & Zhou X. *Nephrol Dial Transplant* 2009; 24: 1082–1088.

ERYTHROPOIETIN CONCENTRATION-TIME PROFILES



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. Kovesdy, Steven Fishbane, Bruce S. Spinowitz, and Jeffrey S. Berns

Table 1. Pharmacokinetic properties of Daprodustat, Roxadustat, and Vadadustat

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

Adapted with permission from Sanghani and Haase¹¹; 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.

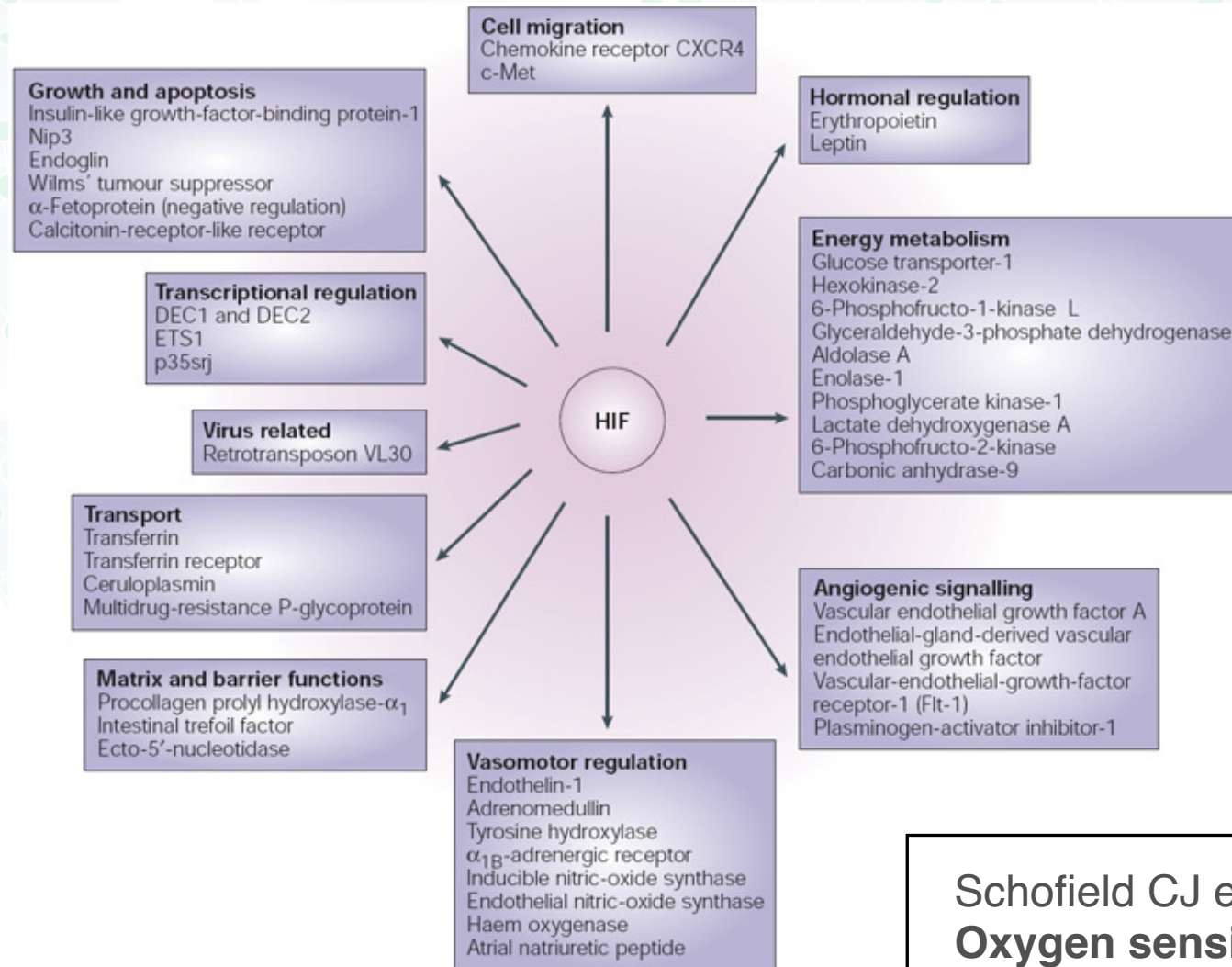
^aCKD patients receiving dialysis.

^bCKD patients not requiring kidney replacement therapy.

^cFor 1 mg/kg dose.

^dFor 2 mg/kg dose.

DIRECT TRANSCRIPTIONAL TARGETS OF HIF



Schofield CJ et al.

Oxygen sensing by HIF hydroxylases.

Nature Rev Mol Cell Biol 2004; **6**: 343-354.

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

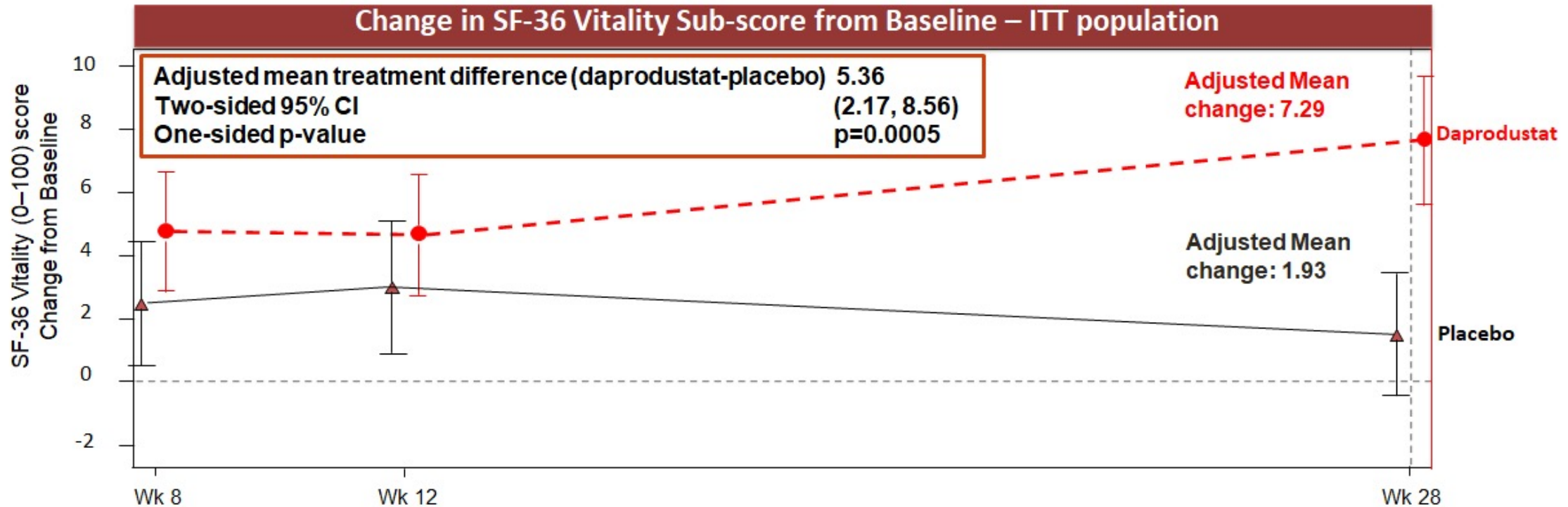
Jay B. Wish, Kai-Uwe Eckardt, Csaba P. Kovesdy, Steven Fishbane, Bruce S. Spinowitz, and Jeffrey S. Berns

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; $P = 0.0005$).



No. of patients

| | | |
|-------------|-----|-----|
| Placebo | 307 | 307 |
| Daprodustat | 307 | 307 |

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”



HIF STABILIZERS IN OTHER PARTS OF THE WORLD

AstraZeneca AstraZeneca Websites Global site

What science can do R&D Our therapy areas Our company Careers Investors **Media** Sustainability Partnering

Roxadustat approved in China for the treatment of anaemia in chronic kidney disease patients on dialysis

PUBLISHED
18 December 2018

18 December 2018 09:00 GMT


China is the first country to approve roxadustat

AstraZeneca today announced that its partner FibroGen (China) Medical Technology Development Co., Ltd. (FibroGen China) has now received formal marketing authorisation from the National Medical Products Administration (NMPA) for roxadustat, a first-in-class hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) and new oral treatment for patients with anaemia caused by chronic kidney disease (CKD) that are on dialysis. The medicine can be prescribed to patients who use haemodialysis or peritoneal dialysis.

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Astellas Receives Approval of EVRENZO® (roxadustat) in Japan for the Treatment of Anemia of Chronic Kidney Disease in Adult Patients Not on Dialysis




Approval by MHLW provides new HIF-PH inhibitor treatment option for healthcare providers and adult patients with anemia of CKD not on dialysis

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

by Angus Liu | Jun 30, 2020 12:05pm



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roxadustat

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- Overview
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- Assessment history

✓ **AUTHORISED**
This medicine is authorised for use in the European Union.

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 pre-refilled syringe |
| Brand | Cresp 40 |
| Manufacturer | Dr Reddy's Laboratories Ltd |
| Composition | Darbepoetin alfa (40mcg) |
| Treatment | Anemia |
| Prescription/Non prescription | Prescription |

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Rohini, Delhi
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84% Response Rate

 Leading Supplier  TrustSEAL Verified

 Wholesale Trader

Ask for more details from the seller

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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