Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors: Potential New Treatment for Anemia in Chronic Kidney Disease

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Outline

- Discuss the mechanism of action of hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs).
- Provide an overview of ongoing and completed trials for roxadustat, vadadustat and daprodustat.
- Review current efficacy and safety data for the HIF-PHIs.
- Summarize the pharmacokinetics and pharmacodynamics of roxadustat, vadadustat and daprodustat.
- Compare the advantages and disadvantages of HIF-PHIs over erythropoietin stimulating agents.

HIF-PH Inhibitors (HIF-PHIs)

Generic Name	Investigational Name	Sponsor
Roxadustat	FG-4592	FibroGen, Astellas, & AstraZeneca (Canada)
Vadadustat	AKB-6548	Akebia, Otsuka (Canada), Mitsubishi Tanahe Pharma Corporation (Japan)
Daprodustat	GSK-12788863	GlaxoSmithKline
Molidustat	BAY-85-3934	Bayer

Pipeline Approval of HIF-PHIs

HIF-PHIs	Pipeline
Roxadustat	• Approved December 2018 for DD-CKD (China) • Approved August 2019 for NDD-CKD (China) • Approved September 2019 for DD-CKD (Japan) • FDA submission anticipated Fall 2019 and Health Canada after US filing
Vadadustat	• New drug application submitted July 2019 (Japan) • Health Canada submission anticipated 2020/2021
Daprodustat	• Health Canada submission anticipated 2020/2021

Effect of Altitude on Dosing and Response to Erythropoietin in End Stage Renal Disease

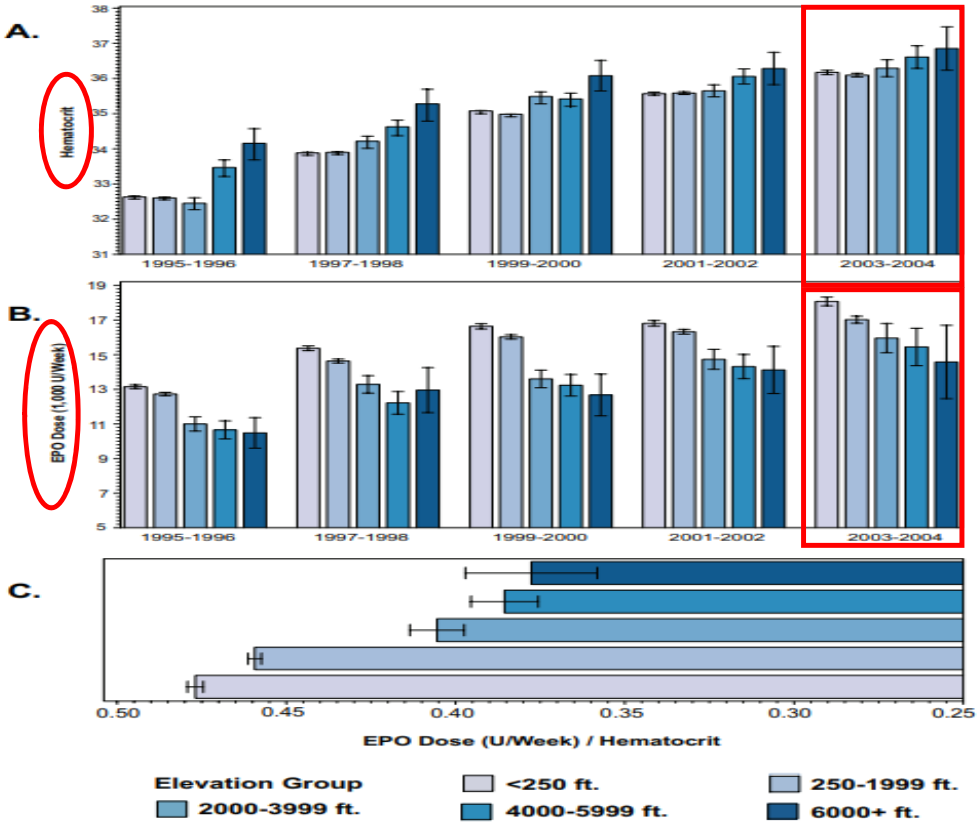


Figure 2. (A) Average hematocrit by elevation group and time period. (B) Average EPO dose by elevation group and time period. (C) EPO resistance (EPO dose/hematocrit) by elevation group.

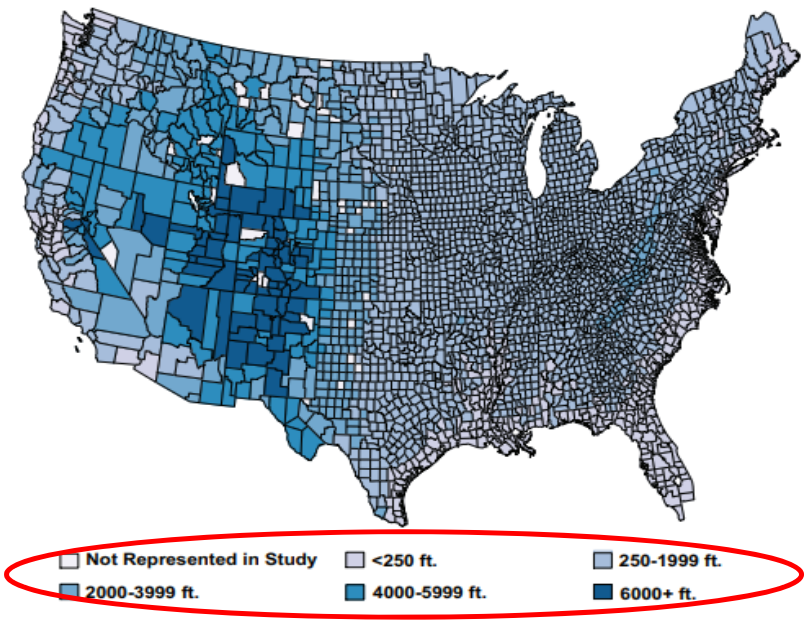


Figure 1. Map of average county-level elevation of patients in study cohort.

J Am Soc Nephrol 2008; 19: 1389-95.

HIF-PHI increases Erythropoietin Production in ESRD

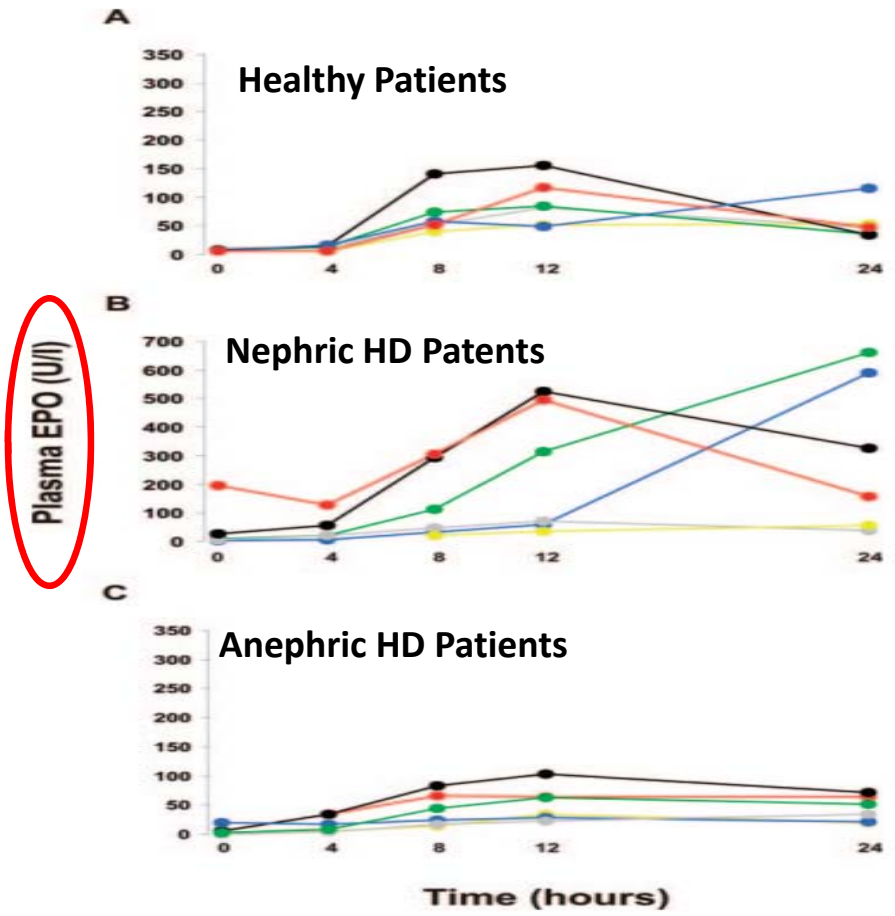


Figure 1 FG-2216 increases plasma-EPO levels in healthy controls and in HD patients with and without remaining renal tissue. Twenty-four-hour kinetics of plasma EPO levels after a single dose of FG-2216. (A through C) Individual values are depicted for control subjects (A), nephric HD patients (B), and anephric HD patients (C). All individuals except one received FG-2216 at a dosage of 20 mg/kg; patient 4 in the anephric group (blue line in C) was accidentally underdosed with approximately 4 mg/kg.

J Am Soc Nephrol 2010; 21: 2151-6.

Mechanism of Action of HIF-PHIs

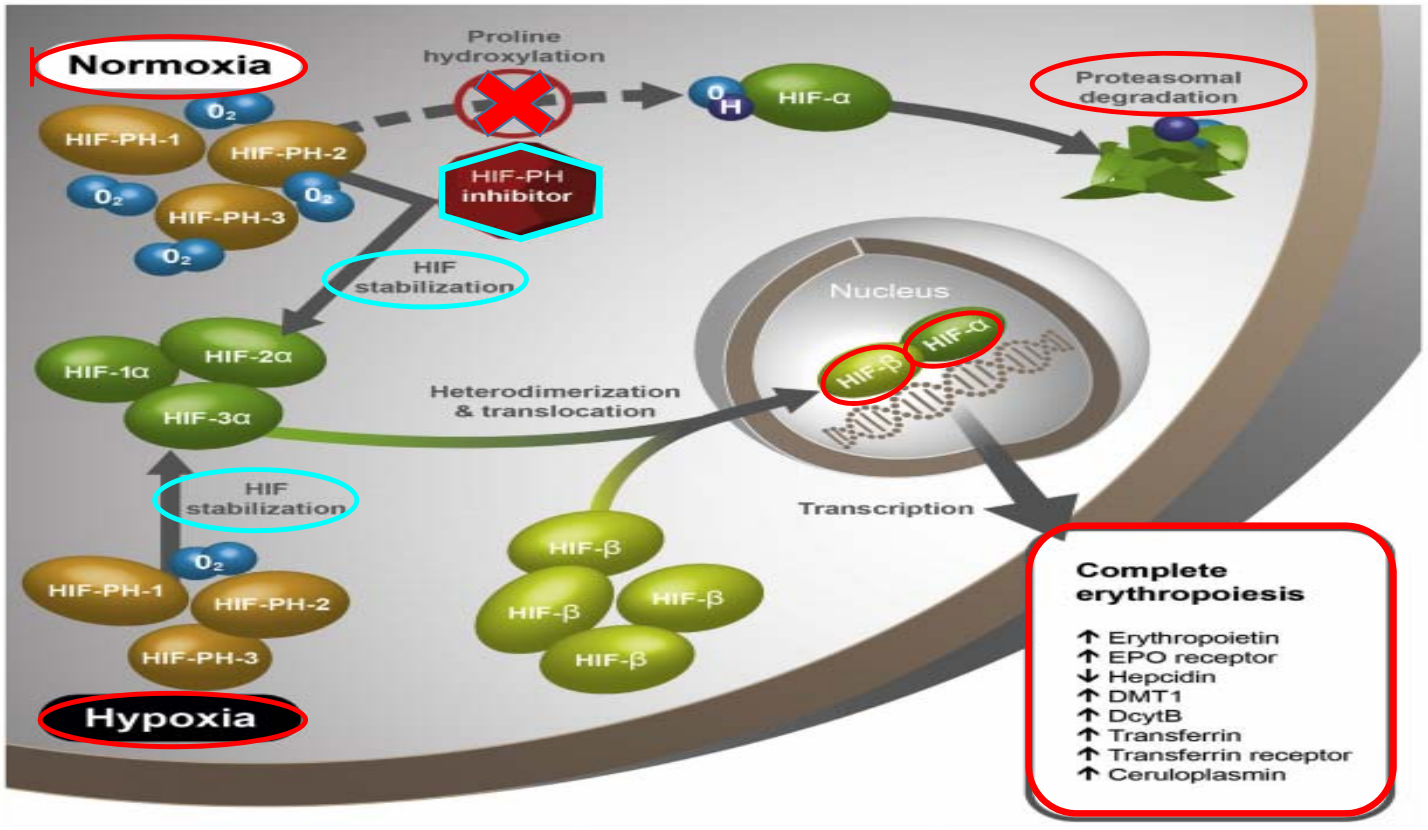
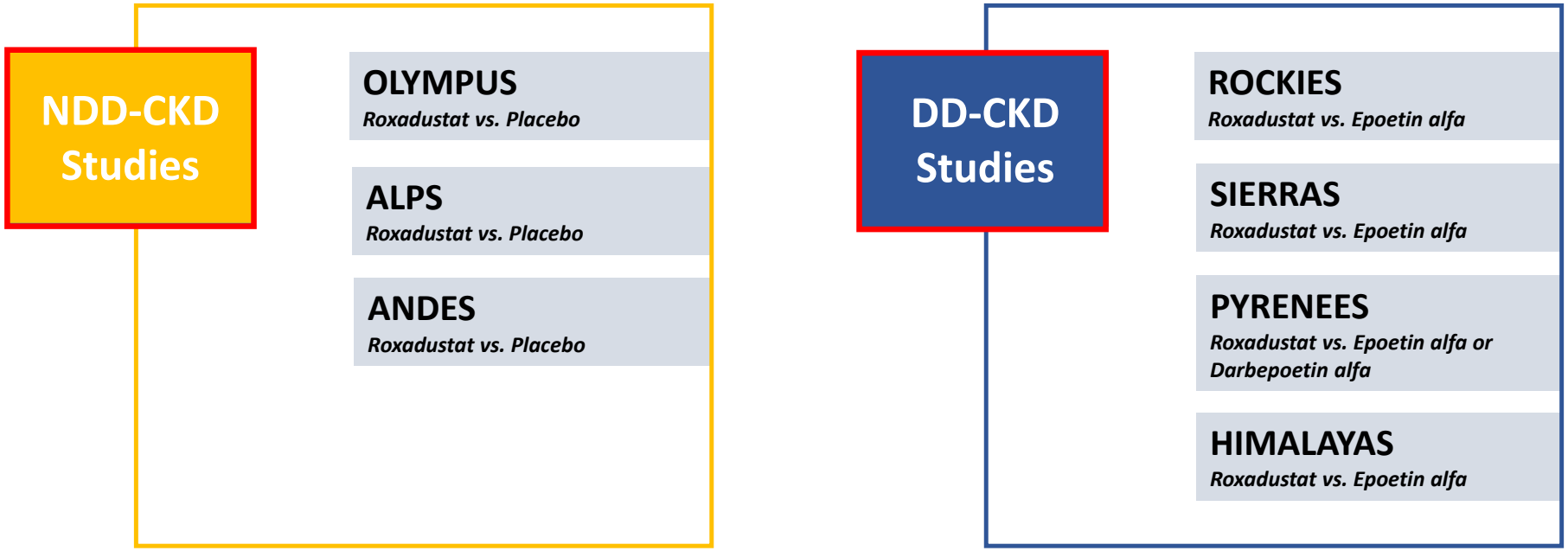


Figure 1. Hypoxia-inducible factor (HIF) pathway. Abbreviations: DcytB, duodenal cytochrome B; DMT1, divalent metal transporter 1; EPO, erythropoietin; PH, prolyl hydroxylase.

Am J Kidney Dist 2017; 69(6): 815-26.

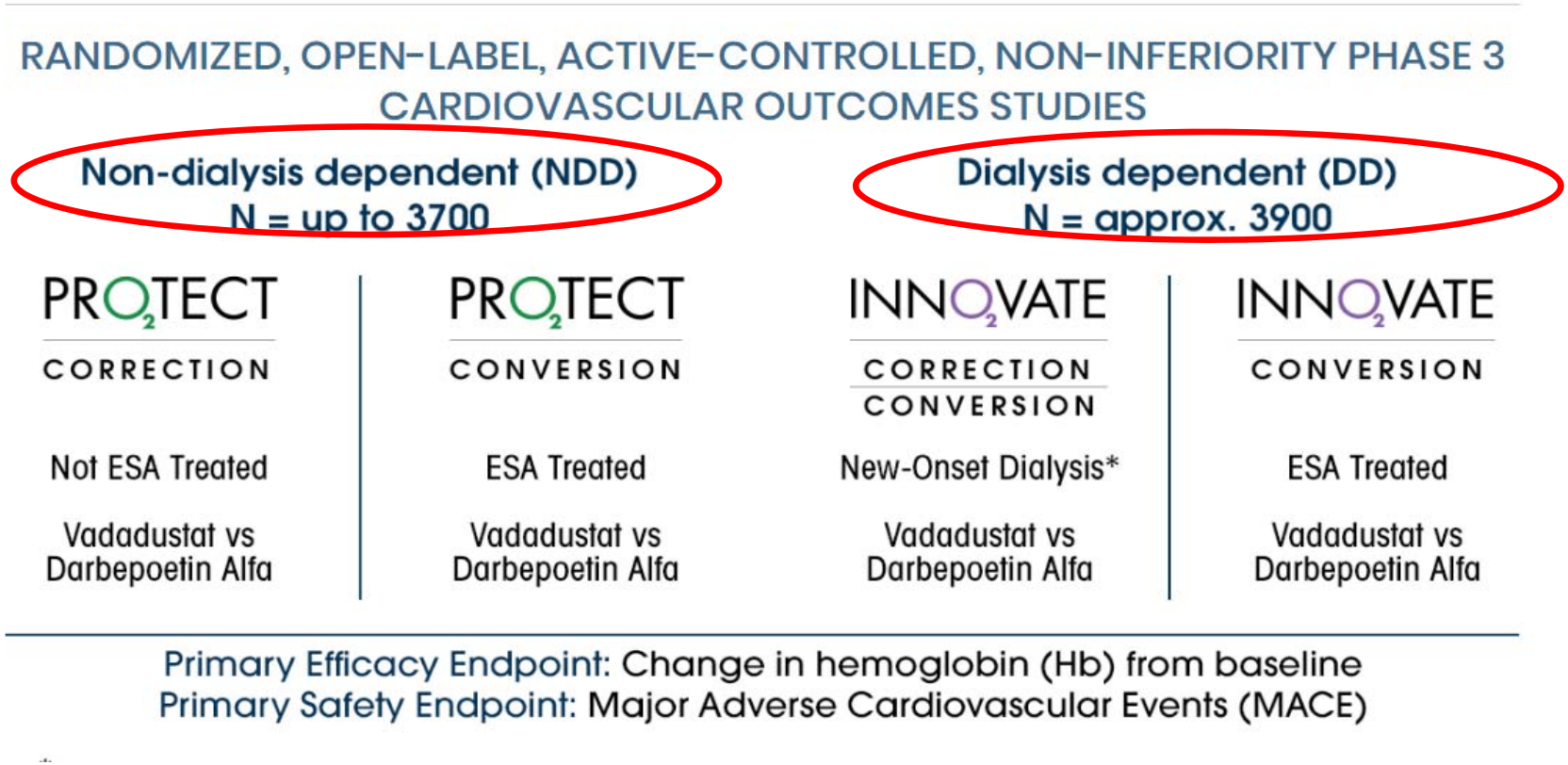
- Provide a summary of ongoing and completed Phase III trials for roxadustat, vadadustat and daprodustat

Roxadustat Phase III (Alpine) Program for Treatment of Anemia Due to CKD



Completed – Top Line Results Available

Vadadustat Phase III Program for Treatment of Anemia Due to CKD



*≤ 16 weeks of dialysis treatment, with or without prior ESA treatment

Daprodustat Phase III Program for Treatment of Anemia Due to CKD

Trial name	Comparator(s)	ClinicalTrials.gov identifier	Estimated primary completion date; estimated enrollment
A Study to Evaluate Efficacy and Safety of Daprodustat Compared to Darbepoetin Alfa in Japanese Hemodialysis (HD)-Dependent Subjects With Anemia Associated With Chronic Kidney Disease (CKD)	Darbepoeitin alfa	NCT02969655	July 2018; 270 patients
A Study to Evaluate the Efficacy and Safety of Daprodustat Compared to Recombinant Human Erythropoietin (rhEPO) in Subjects With Anemia Associated With Chronic Kidney Disease (CKD) Who Are Initiating Dialysis	Darbepoeitin alfa	NCT03029208	November 2019; 300 patients
Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Dialysis (ASCEND-D)	rhEPO	NCT02879305	April 2020; 3000 patients
Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Non Dialysis (ASCEND-ND)	Darbepoetin alfa	NCT02876835	January 2021; 4500 patients

- Review current efficacy and safety data for the HIF-PHIs

The NEW ENGLAND JOURNAL of MEDICINE

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

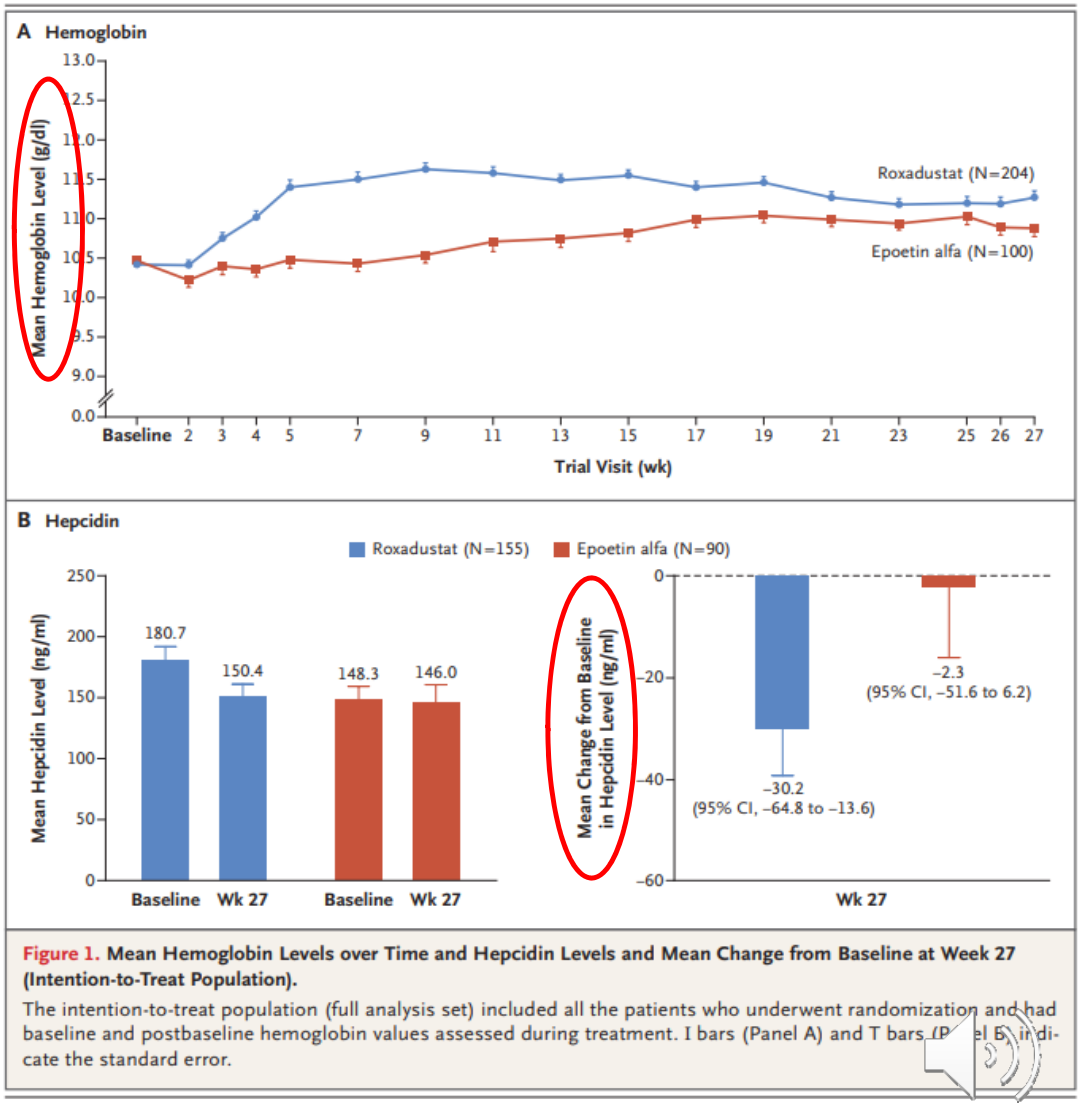


Figure 1. Mean Hemoglobin Levels over Time and Hepcidin Levels and Mean Change from Baseline at Week 27 (Intention-to-Treat Population).

The intention-to-treat population (full analysis set) included all the patients who underwent randomization and had baseline and postbaseline hemoglobin values assessed during treatment. I bars (Panel A) and T bars (Panel B) indicate the standard error.

NEJM 2019; 381: 1011-22.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 12, 2019 VOL. 381 NO. 11

Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis

N. Chen, C. Hao, X. Peng, H. Lin, A. Yin, L. Hao, Y. Tao, X. Liang, Z. Liu, C. Xing, J. Chen, L. Luo, L. Zuo, Y. Liao, B.-C. Liu, R. Leong, C. Wang, C. Liu, T. Neff, L. Szczech, and K.-H.P. Yu

NEJM 2019; 381: 1001-10.

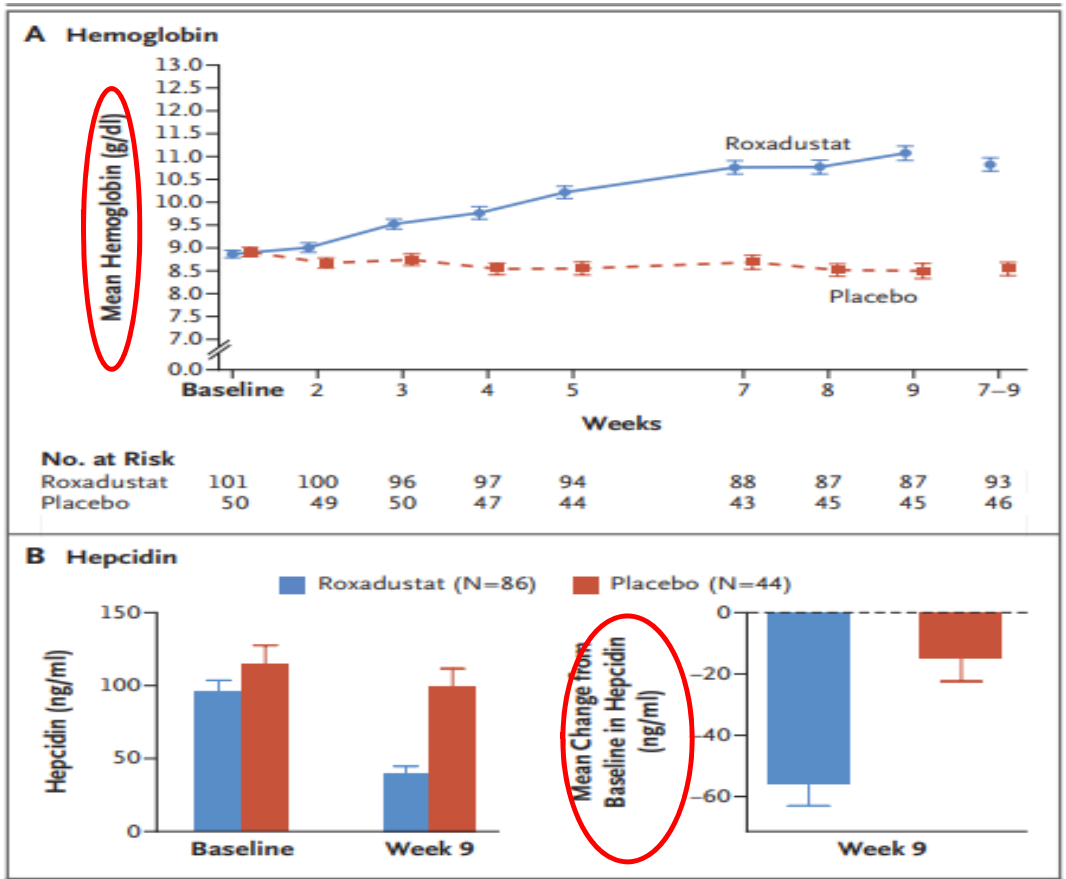


Figure 1. Hemoglobin and Hepcidin Levels.

Shown are the mean hemoglobin levels (Panel A) and mean hepcidin levels and the change from baseline (Panel B) during the 8-week double-blind period. The least-squares mean difference in hemoglobin values was 1.9±0.2 g per deciliter (95% confidence interval [CI], 1.4 to 2.4); the least-squares mean difference in hepcidin values was −49.77 (95% CI, −66.75 to −32.79). In Panel A, the average for weeks 7 through 9 (the measure that was used in the primary end point) is shown to the right of the graph. In Panel B, hepcidin measurements were not available for one patient in the roxadustat group. The error bars in the two panels indicate standard errors.

Roxadustat Phase III (Alpine) Program – Top line results

NDD-CKD Studies

- Demonstrated significantly greater efficacy vs. Placebo for change in Hb from baseline over weeks 28-52 in ALPs, ANDES, and OLYMPUS

DD-CKD Studies

- ROCKIES, SIERRAS, HIMALAYAS demonstrated superiority vs. epoetin alfa for mean change in Hb from baseline averaged over weeks 28-52.

FibroGen

Source: *FibroGen, Inc*

May 09, 2019 16:43 ET

FibroGen Announces Positive Topline Results from Pooled Safety Analyses of Roxadustat Global Phase 3 Program

MACE/MACE+ endpoints evaluated across CKD patients not on dialysis and on dialysis Superiority in time to first MACE+ versus epoetin alfa in incident dialysis patients

Pooled MACE/MACE+ in NDD patients

In the pooled analysis of over 4,300 patients, and based on the totality of the adjudicated evidence, the MACE/MACE+ analyses between roxadustat and placebo showed no clinically-meaningful difference.

Pooled MACE/MACE+ in ID patients

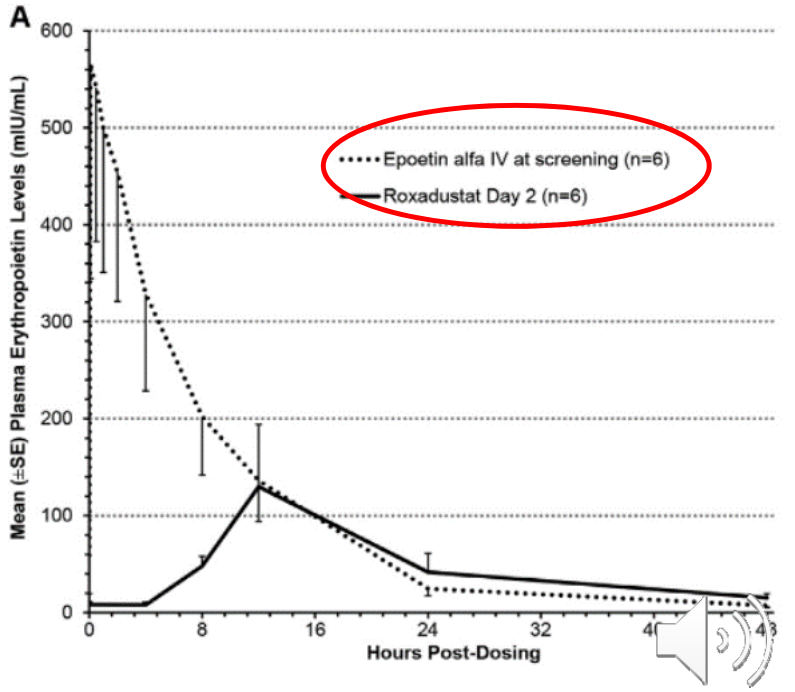
In the pool of 1,500 ID patients, a pre-specified sub-population of DD patients, MACE/MACE+ results indicate that ID patients on roxadustat do better than those who are on epoetin alfa. ID patients are a better population to compare roxadustat vs. epoetin alfa than the stable dialysis population, where patients are stable not only on dialysis but also on erythropoietin.

Pooled MACE/MACE+ in DD patients

In the pooled analysis of around 4,000 patients, and based on the totality of the adjudicated evidence, the MACE/MACE+ analyses between roxadustat and epoetin alfa showed no clinically-meaningful difference.

- Summarize the pharmacokinetics and pharmacodynamics of HIF-PHIs
  - Transiently↑endogenouse EPO levels within or near physiologic range
  - Dose-dependently ↑Hgb levels
  - Improves iron utilization
  - ↓hepcidin
  - ↓ cholesterol levels

AJKD



Am J kidney Dis 2016; 67(7) 912-4.

CLINICAL RESEARCH www.jasn.org

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

Anatole Besarab,* Elena Chernyavskaya,† Igor Motylev,‡ Evgeny Shutov,§ Lalathaksha M. Kumbar,‖ Konstantin Gurevich,¶ Daniel Tak Mao Chan,** Robert Leong,* Lona Poole,* Ming Zhong,* Khalil G. Saikali,* Marietta Franco,* Stefan Hemmerich,* Kin-Hung Peony Yu,* and Thomas B. Neff*

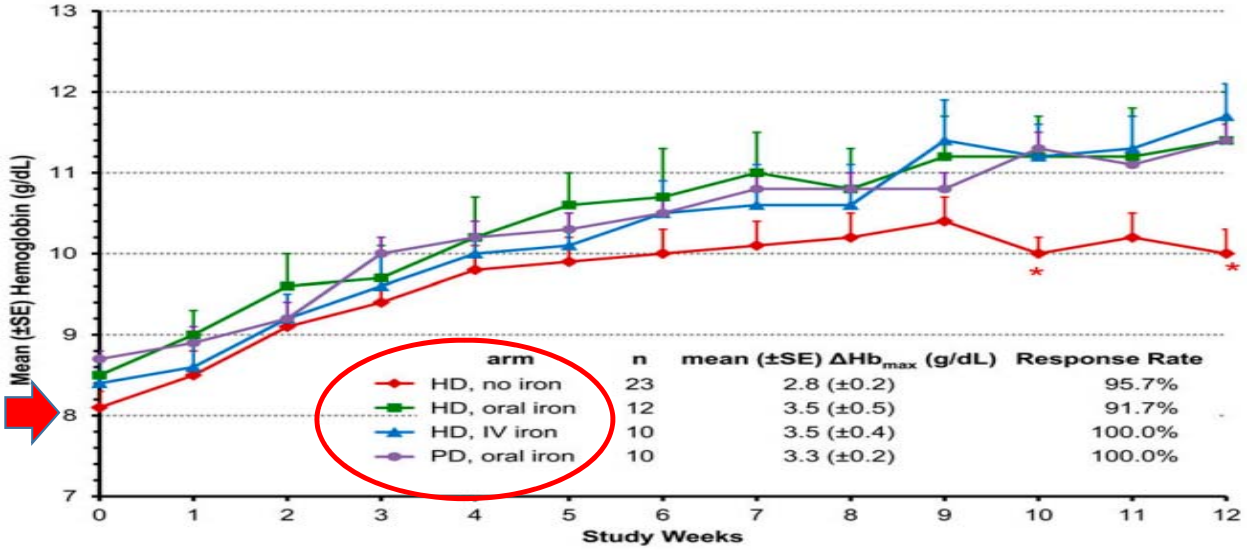


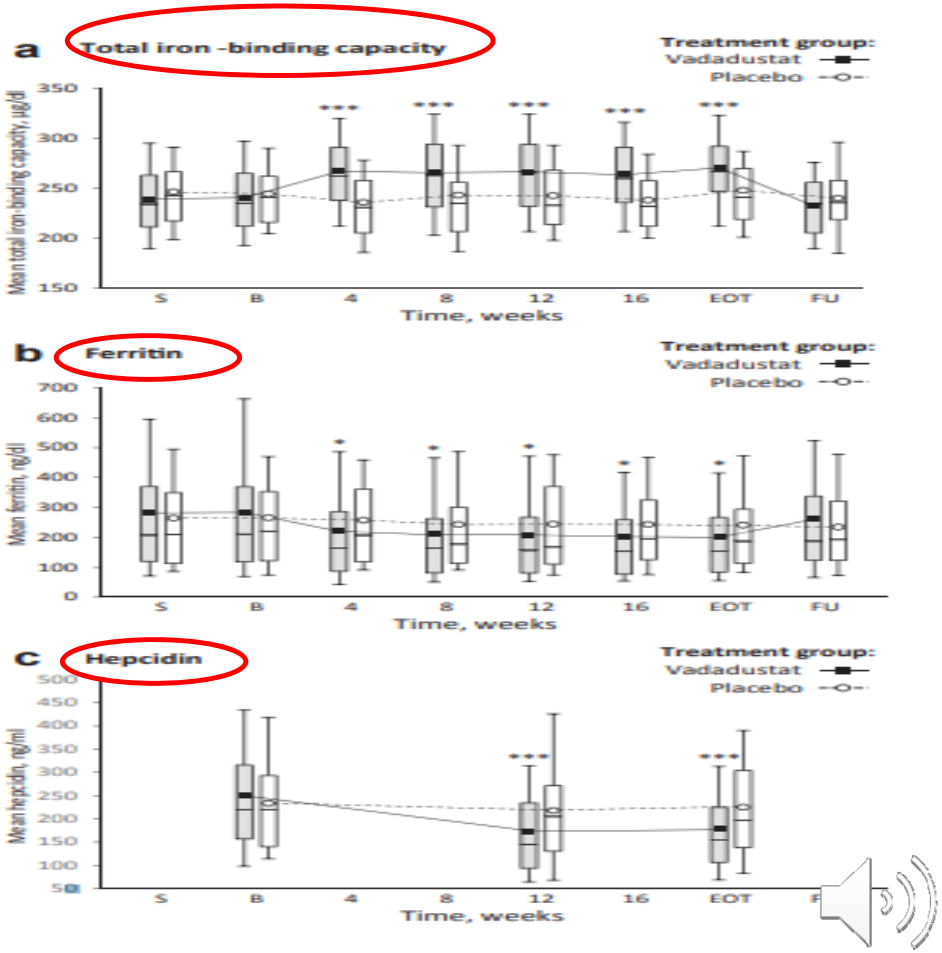
Figure 2. Mean hemoglobin levels over time are similar through 7 weeks for all treatment groups and thereafter lower for the no-iron vs oral or IV iron groups. Data are for the EE population using last-observation-carried-forward imputation for missing data and are expressed as the mean±SEM Hb value at each time point. Week 0 (baseline) is the mean of three predosing Hb values. *$P<0.05$ in comparisons between no-iron cohort to the pooled iron cohorts based on the repeated-measures analysis of covariance model with baseline Hb and iron repletion status as covariates, using all observed data collected during treatment.

JASN 2016; 27(4): 1225-33.

Change from baseline in Iron Use Parameters

Mean (SD) Levels	Baseline (n=143)	Change from Baseline			
		16 Weeks (n=103)	P-Valuc	EOS (n=122)	P-Value
Hepcidin (ng/mL)[1]	119.7 (107.6)	-27.7 (107.2)	0.004	21.7 (94.9)	0.017
Serum iron (µg/dL)	64.0 (21.7)	1.1 (30.0)	n. s.	14.3 (25.6)	<0.001
TSAT (%)	22.0 (7.7)	−2.7 (8.6)	0.002	4.3 (8.3)	<0.001
Ferritin (ng/mL)[2]	278 (246)	−85.9 (112.6)	<0.001	−45 (113)	<0.001
TIBC (µg/dL)[3]	261.5 (50.7)	40.4 (41.0)	<0.001	5.3 (35.7)	n. s.
MCV (fL)[4]	93.4 (6.1)	1.2 (4.5)	0.001	0.1 (4.6)	n. s.
CHr (pg)[5]	30.7 (2.4)	0.2 (2.0)	n. s.	1.3 (1.7)	<0.001
Platelets (x10^9/L)[6]	255 (88)	−12.5 (61.2)	0.008	-26.0 (52.3)	<0.001

All cohorts were combined. Baseline is defined as the mean of the last three available values pre-1st dose. P-values are from ANOVA model comparing change from BL with zero utilizing the pooled variance from all groups. EOS (end of study) was 4 weeks post-end of treatment. [1]n=137, 102, and 116, respectively. [2]n=143, 103, and 123, respectively. [3]TIBC: total iron binding capacity, n=145, 102, and 122 (Safety Population), respectively. [4]n=143, 128, and 127, respectively. [5]n=136, 96, and 117, respectively. [6]n=143, 128 and 128, respectively.



CJASN 2016; 11:982-91.

Kidney Int. 2016; 90:1115-22.

Property	Roxadustat	Vadadustat	Daprodustat
Half-life, h	10-12	4.5	4
Dosing Frequency	3X/week	Daily	Daily
Dialyzable	No	No	No
Starting Dose (dosing from trials) Dose adjustments Q4 wks	100 mg po TIW (45 to < 60kg) 120 mg po TIW (≥ 60kg) (20 mg, 50 mg capsules) With or without food	300 mg po daily (150 mg tablets) With or without food	2-4 mg po daily (dosed in 2 mg increments) With or without food
Drug Interactions	1 h spacing before or after phosphate binders (sevelamer carbonate, calcium acetate), oral iron, magnesium/ aluminium-containing antacids or other multivalent cation-containing drugs and supplements Probenecid (UGT and OAT1/OAT3 inhibitor) • Teriflunomide (OAT1/OAT3 inhibitor), Valproic acid (UGT inhibitor), Rifampin (UGT inducer) Rosuvustatin Gemfibrozil (CYP2C8 and OATP1B1 inhibitor) • Cyclosporine (OATP1B1), Clopidogrel (CYP2C8), Rifampin (CYP2C8 inducer)	Weak CYP 2C9 inhibitor (atorvastatin, rosuvastatin) Oral Iron	CYP2C8 inhibitor (gemfibrozil) CYP2C8 inducer (rifampin)
Adverse Effects	Nausea, vomiting, diarrhea, hyperkalemia, metabolic acidosis	Nausea, diarrhea, vomiting	Nausea Dyspepsia
Precautions	Moderate hepatic impairment		

- Compare the advantages and disadvantages of HIF-PHIs over erythropoietin stimulating agents

Advantages and Disadvantages of HIF-PHIs over ESAs

HIF-PHIs

- Oral (NDD-CKD, PD)
- Maintain plasma EPO levels within or near normal physiologic range (negating concerns about high EPO levels with ESA agents)
- Improves FID (↓ hepcidin, ↓ ferritin and ↓ TSAT by increasing TIBC) – may require less iron therapy
- May be beneficial in inflamed patients who are hyporesponsive to ESA
- ↓serum cholesterol (↓LDL and ↑HDL) (Roxa)
- Neutral effect on Bp (Roxa), ? ↑ BP (Vada)
- Long-term safety? Activation of HIF system (VEGF , tumor growth, worsening retinopathy), hepatic injury

ESAs

- Parenteral (NDD-CKD, PD)
- $$$
- Refrigeration (Cold Chain requirement)
- 25% of patients have ESA resistance
- Worsening blood pressure
- Cardiovascular, thromboembolic and cancer risk

Questions or Comments?