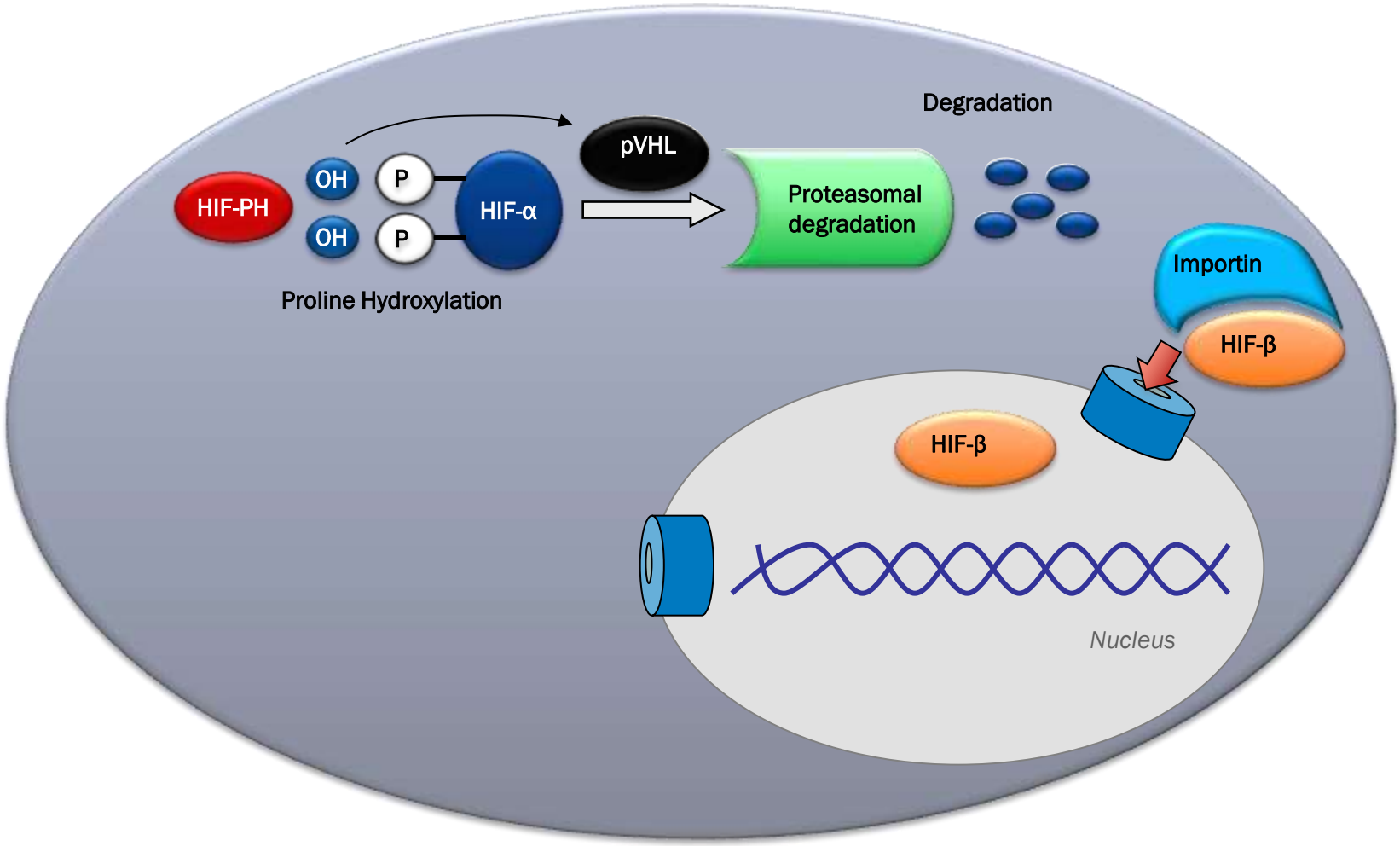
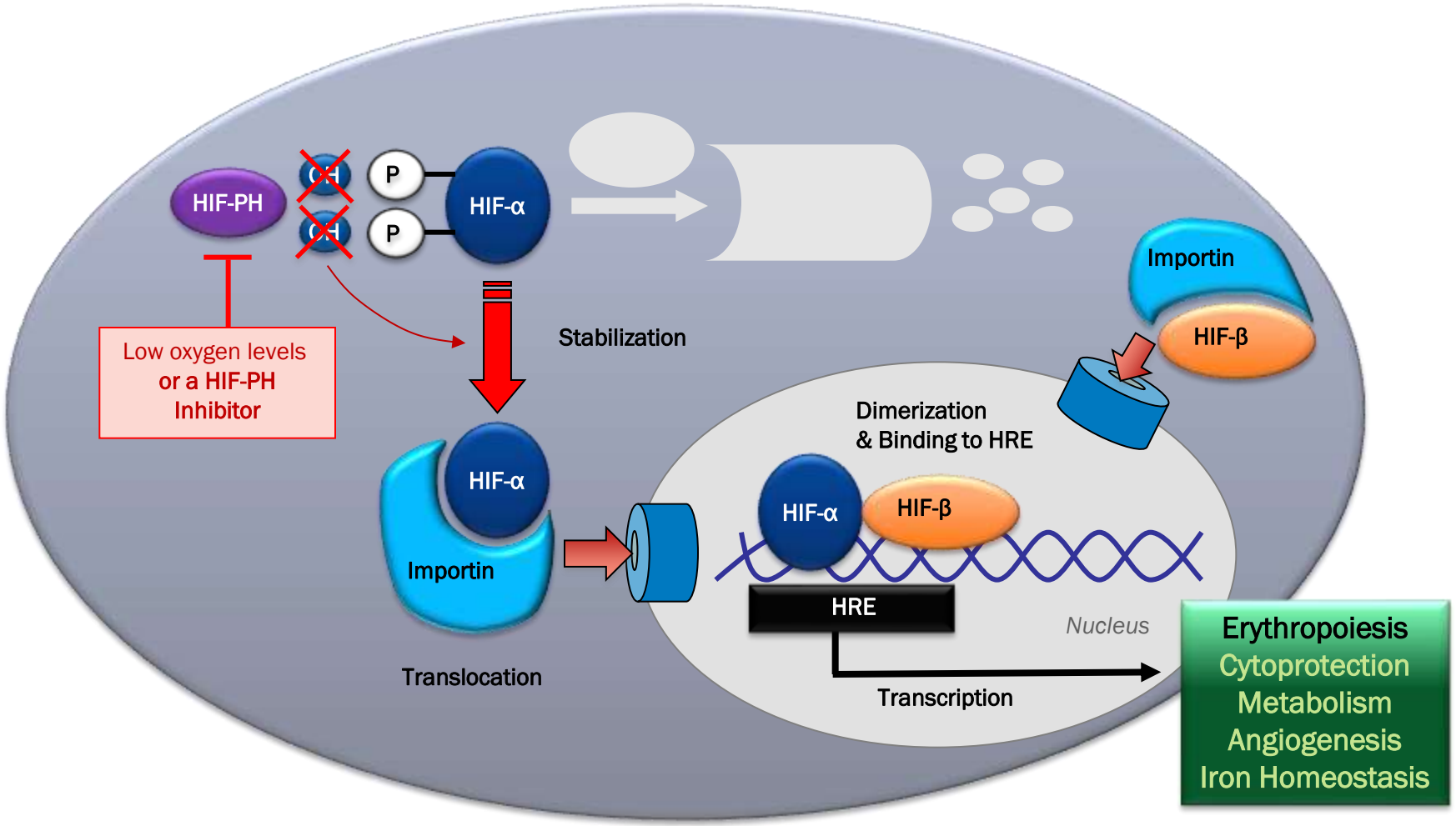
FIBROGEN

Roxadustat
PHI-PHI for Treating CKD-Anemia

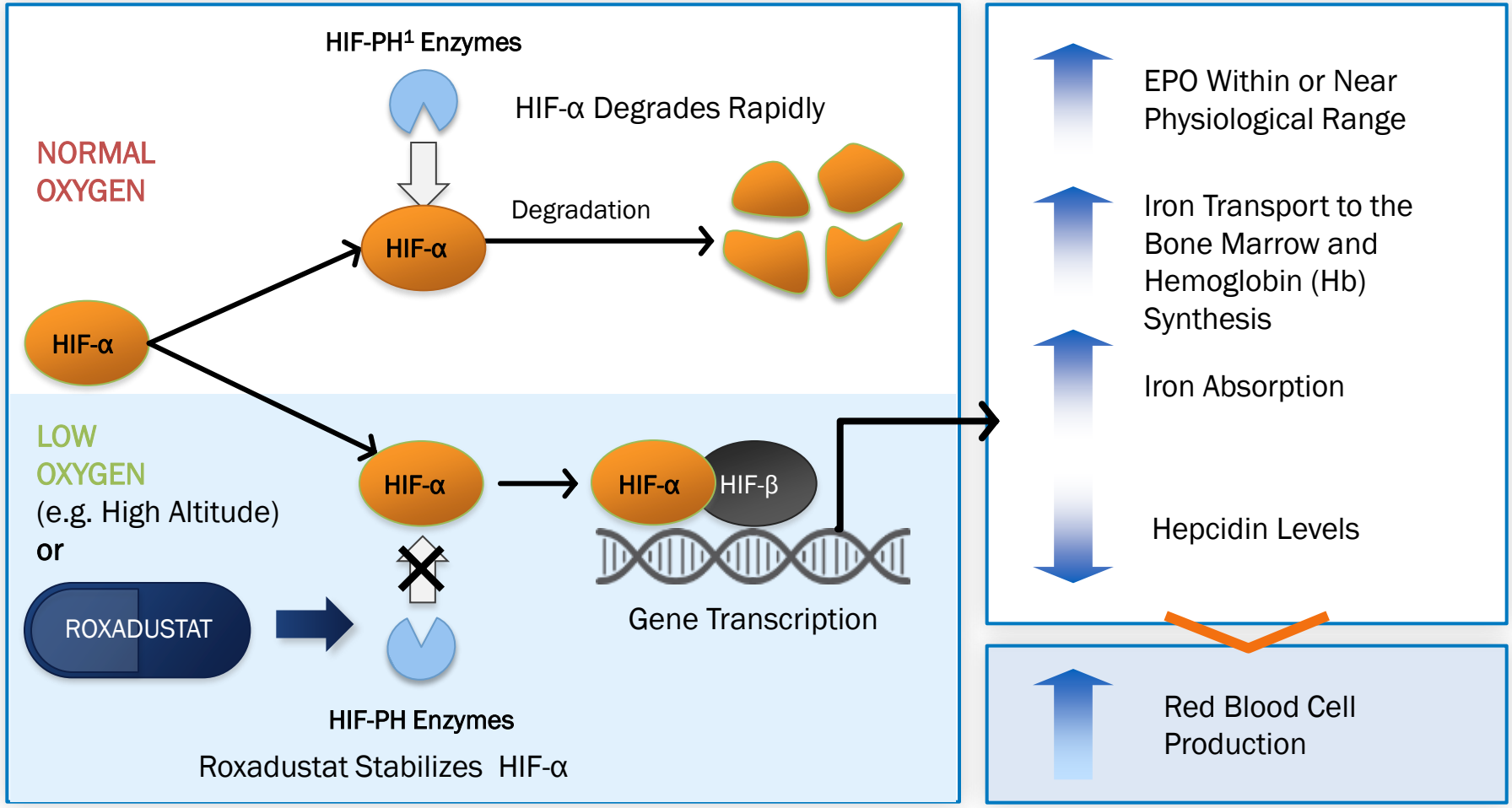
Control of HIF Levels By Prolyl Hydroxylation



Control of HIF Levels By Prolyl Hydroxylation



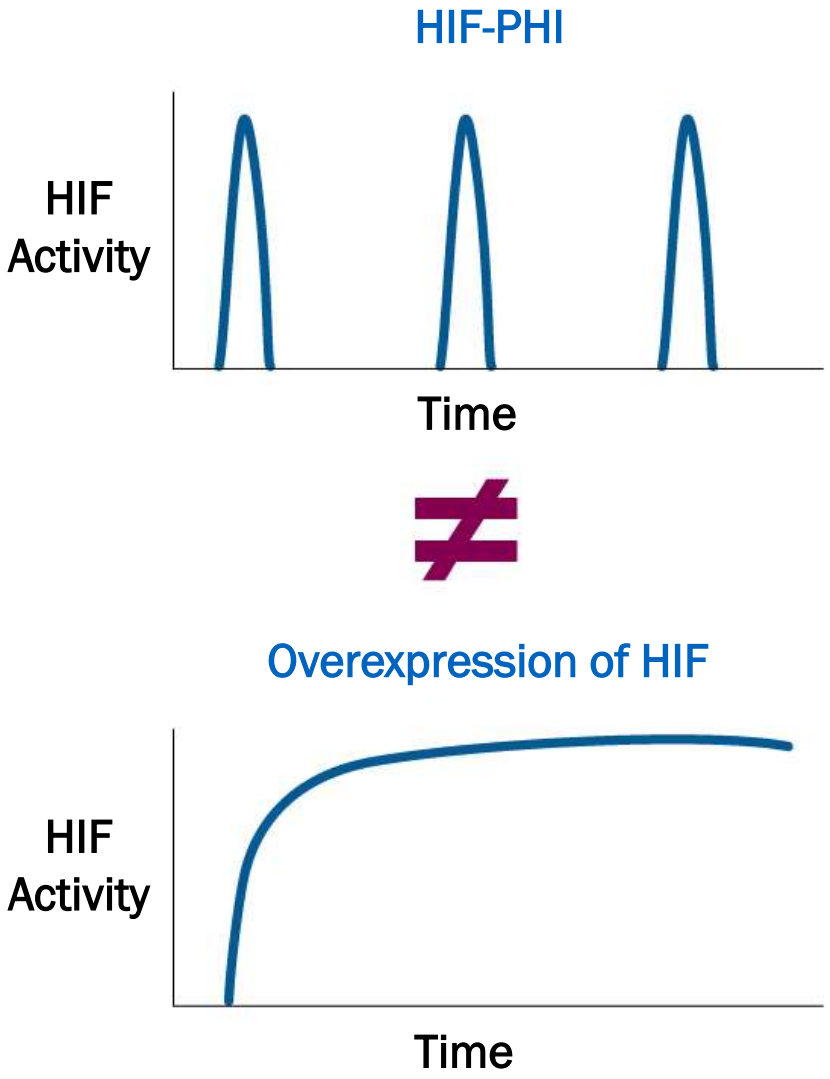
Roxadustat Affects the Multifactorial and Natural Pathway that Contributes to the Development of Anemia



[1]HIF-PH - hypoxia-inducible factor prolyl hydroxylase

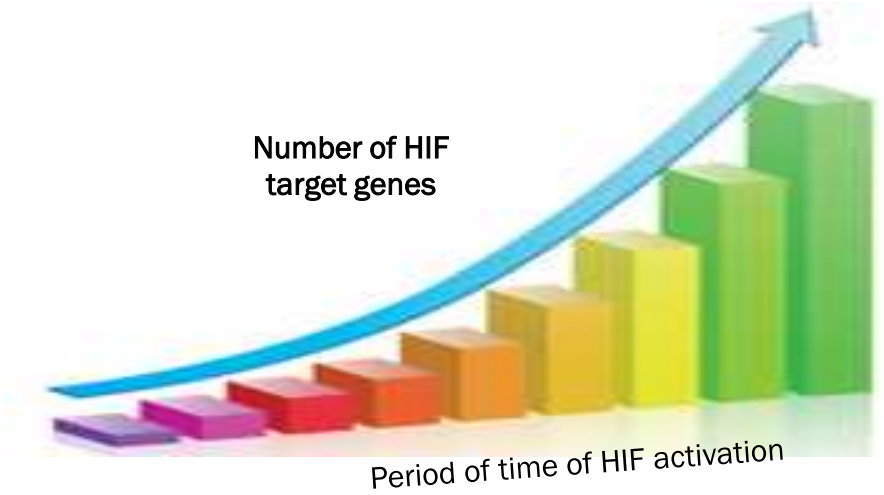
Roxadustat Thrice Weekly (TIW) - Transient HIF Activation by Intermittent Dosing of HIF-PHI Is Not the Same as Chronic HIF Activation

- Roxadustat has a half life of 10 to 12 hours, dosed TIW →no dose accumulation.
- With TIW dosing, HIF system has enough time to fully reset to basal levels between doses.
  - Ensures durability of effect over time.
  - Transient HIF-activation of early response gene for anemia therapy, avoid chronic HIF activation.
- Fundamentally different from experimental models of hereditary conditions where HIF is genetically overexpressed, i.e. constant HIF activation.

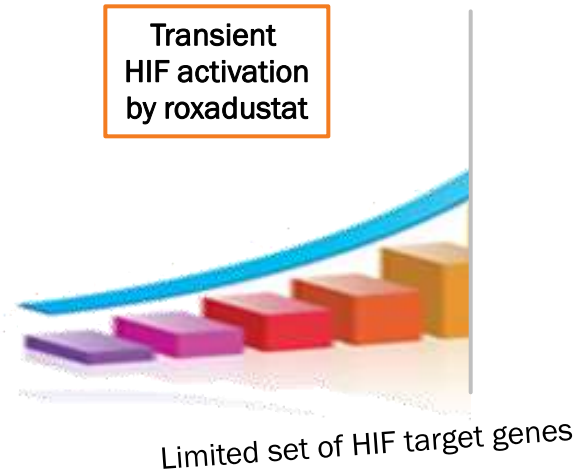


Transient HIF Activation Limits the HIF Target Gene Response

- HIF target genes respond differently following HIF activation
- Some genes are switched on quickly whereas other genes require longer periods of HIF stabilization

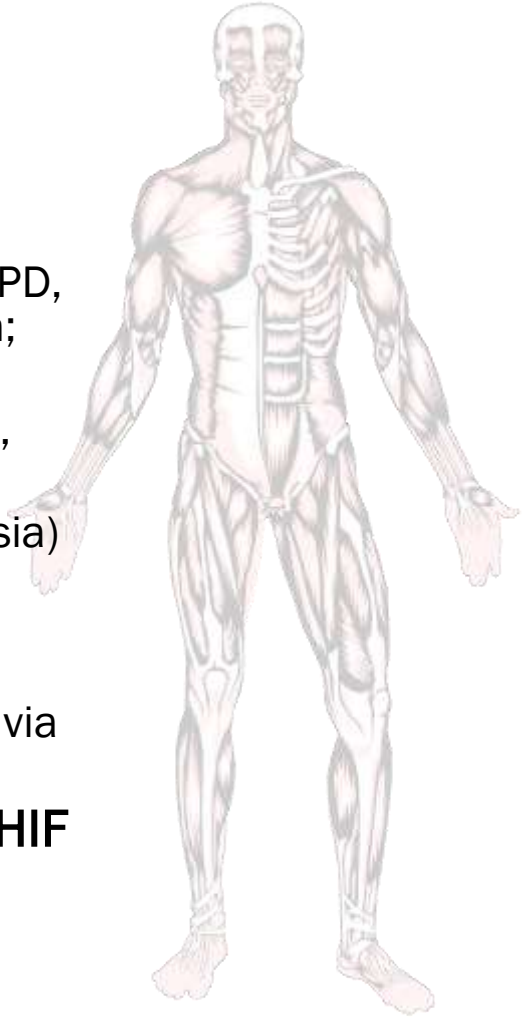


- HIF-PHI such as roxadustat only transiently activate the HIF system
- As the drug is cleared by the body, the HIF response is rapidly switched off
- This transient activation of HIF limits the number of HIF target genes that are regulated



Pharmacologic Activation of HIF is Easily Distinguished from Other Stimuli Associated with HIF Activation

- The unique effects of HIF-PHI exposure cannot be easily anticipated from the literature.
- The pharmacology of HIF-PHI is very different from pathologic settings where HIF is known to be activated.
  - Systemic hypoxia (exercise, altitude, respiratory insufficiency - COPD, apnea, asphyxia) - HIF-PHI treated cells are not starved for oxygen; pathologic consequences of O_2 deprivation do not occur.
  - Hemorrhage (trauma, phlebotomy) - HIF-PHI improve iron balance, promote RBC formation.
  - Ischemia (vasoconstriction/occlusion, embolism, trauma, neoplasia) – HIF-PHI do not recapitulate the profound effects of ischemia on local glucose depletion or metabolite accumulation.
  - Somatic and germ line mutation (congenital polycythemias, neoplasia) – HIF-PHI permit HIF activation to be closely regulated via dose level and regimen, treatment effects are fully reversible.
- **Unlike mutation, the duration, magnitude and interval of HIF stabilization by HIF-PHI is pharmacologically controlled.**
  - Roxadustat dosing regimens allow HIF to be fully reset between doses.



Roxadustat CKD Anemia Development Program

Phase 1

Completed 22- clinpharm studies

- PK/PD similar in Caucasians, Japanese, and Chinese
- PK not impacted by hemodialysis
- TQT study: no QT prolongation

Phase 2

6- completed
(4-US-global & 2-China)

2- ongoing (Japan)

- Efficacious in CKD-ND, CKD-DD, inflamed or not, no IV iron
- Independent data monitoring committee: no safety signals
- No hypertension
- No liver safety concerns
- Reduces hepcidin
- No thrombocytosis
- Lowers cholesterol

Phase 3

8 Global phase 3 studies: ongoing

China Ph 3- also will start 2015

- Multiple independent regulatory pathways: China, EU, US
- Address FDA requirement of CV composite endpoint
- Patient recruitment by FibroGen, Astellas, & AstraZeneca

> 1100 subjects exposed to roxadustat in completed Ph 1& 2 clinical studies

Exposure up to 4 years in open label extension study

Phase 3 with enrollment target 7300 well-underway, started since 2012

Pharmacologic Activation of HIF Does Not Resemble Tumor Hypoxia

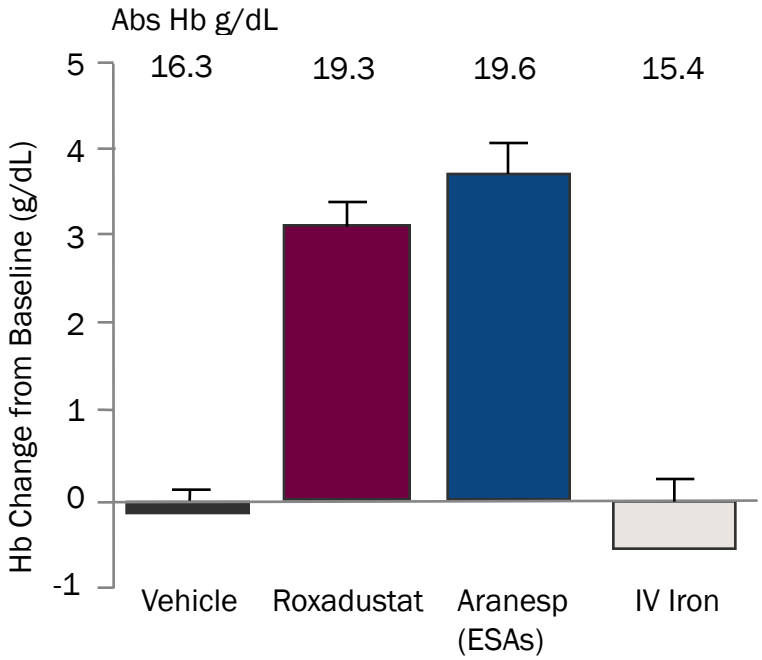
- To investigate the relation between HIF-PHI and tumor progression, a total of six HIF-PH inhibitors have been examined in 35 studies total, in 18 models:
  - Including but not limited to cancers relevant to CIA populations.
  - Models of xenograft, syngeneic, or spontaneous tumors.
  - Models widely recognized as dependent on vascular endothelial growth factor (VEGF).
  - Selected combination anti-tumor treatment models to assess interference, if any.
- No effects on tumor initiation, promotion or metastasis observed in any study.
- No effect on efficacy of anti-tumor therapy in models.
- Two year carcinogenicity studies completed in 2 species with roxadustat & with another HIF-PHI: No carcinogenic effect.

No evidence exists to suggest tumor risk association with use of roxadustat

ESAs Ineffective or Require High Doses in Presence of Inflammation in Preclinical Model

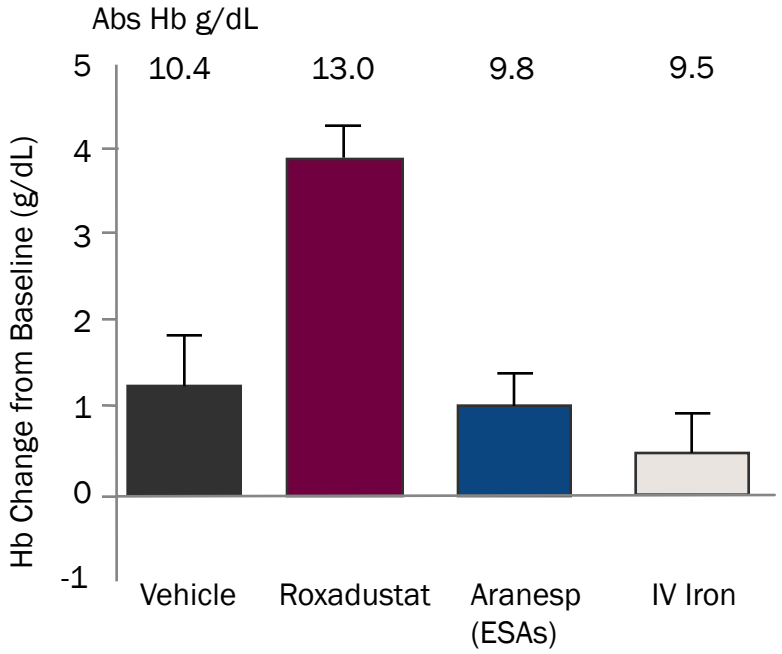
Normal Animals

- Roxadustat Increased Hb
- Aranesp® Increased Hb but Reduced Mean Cell Volume (Depletes Iron)b
- IV Iron Ineffective



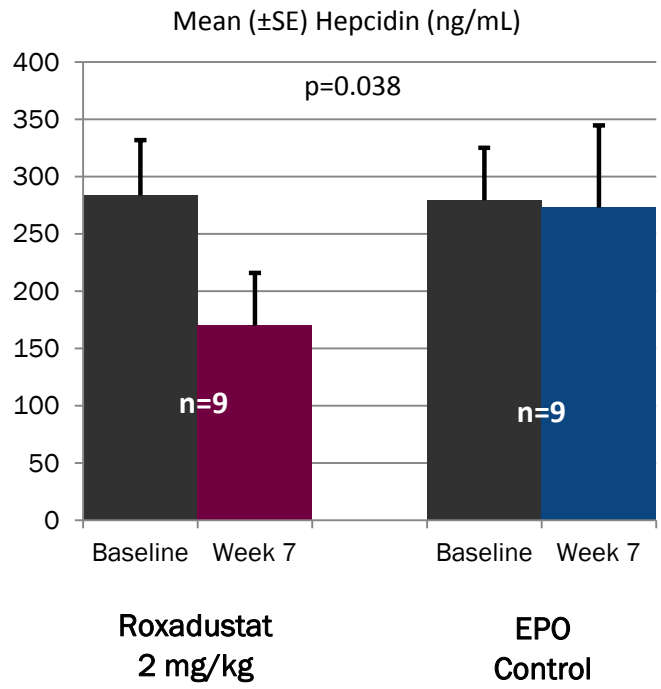
Anemia of Inflammation

- Roxadustat Increased Hb
- Aranesp® or IV Iron Ineffective for Anemia of Inflammation

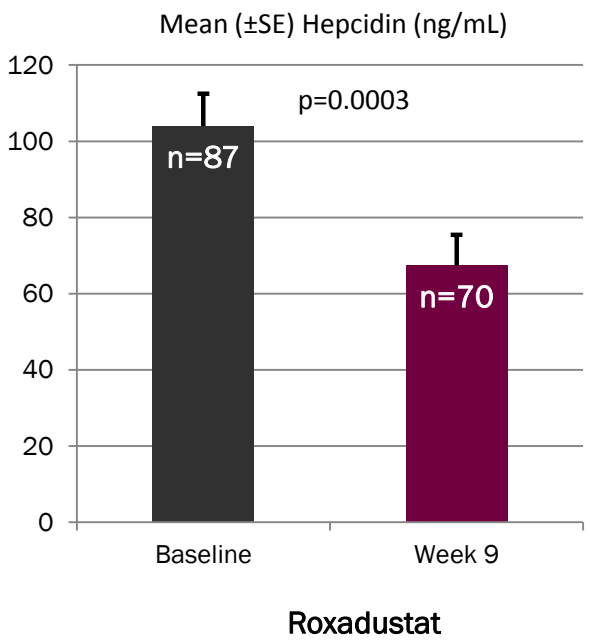


Roxadustat Reduces Hepcidin in Both CKD and ESRD Patients

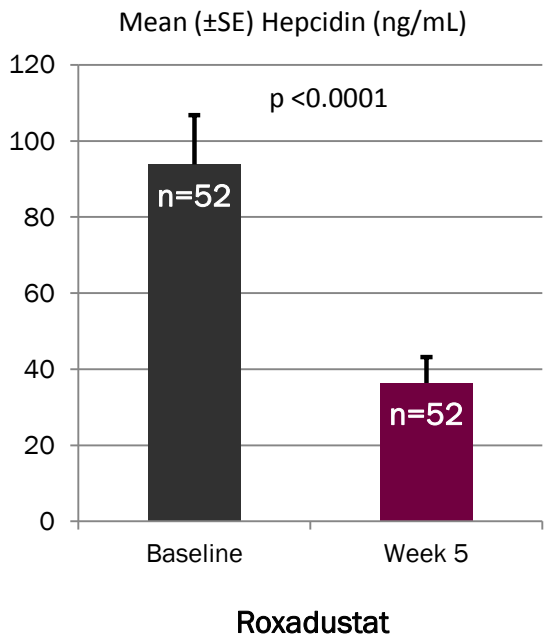
CKD-DD patients previously treated with EPO and randomized (Study 040 A)



CKD-ND (Study 041)



CKD-DD newly initiated dialysis (Study 053)



Hepcidin reduction in CKD patients on dialysis & not on dialysis:

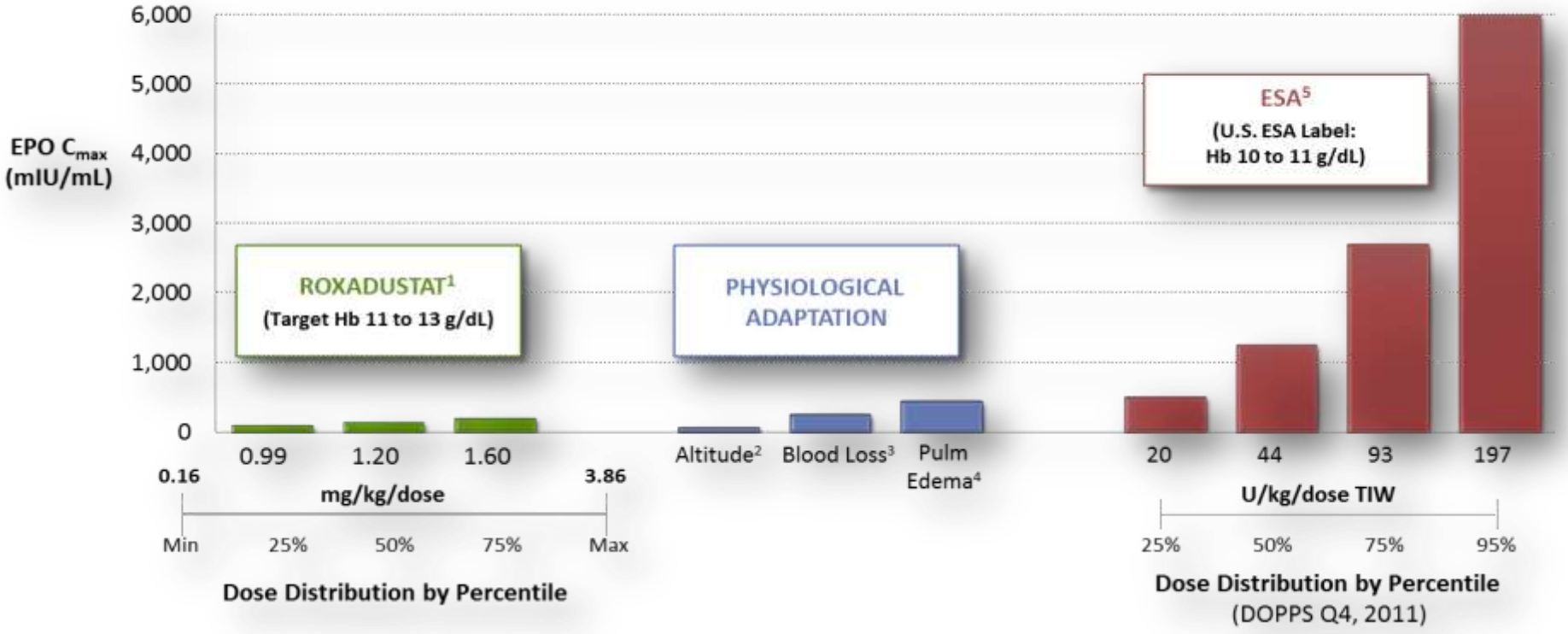
1. Iron available for making RBC, potential for remove need for IV iron;
2. Effective regardless of inflammation (unlike ESA's dampened/no effect in inflammation);
3. Lower Hepcidin level – potential for better patient outcome: "Hepcidin-25 in diabetic CKD is predictive for mortality and progression to end stage renal disease"*

*Wagner et al., PLoS One. 2015 Apr 20;10(4):e0123072

AND Roxadustat Corrects Anemia With Only Physiologic Levels of Endogenously Produced Erythropoietin

Roxadustat:
Doses used in phase 2 studies are associated with EPO elevations within/near physiologic range

IV ESA: Majority of ESA treated patients are exposed to supraphysiologic range of EPO



[1] C_{max} data for roxadustat estimated for a subset of 243 patients who achieved Hb response and were dosed at expected therapeutic doses.
[2] Milledge & Cotes (1985) J Appl Physiol 59:360.
[3] Goldberg et al. (1993), Clin Biochem 26:183, Maeda et al. (1992) Int J Hematol 55:111.
[4] Kato et al. (1994) Ren Fail 16:645.
[5] Based on Flaherty et al. (1990) Clin Pharmacol Ther 47:557.

Phase 2 Program Conducted Across Different CKD Populations

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STUDY		PATIENTS	WEEKS	DOSE LEVELS	TIER WEIGHTS	CONTROL	KEY RESULTS
Placebo-Controlled Pre-Dialysis							
017	Dose Range Finding, NDD	116	4	4	No	Placebo	• Reduction in Hepcidin • Dose-dependent Increase in Hb
047	Pre-dialysis	91	8	2	3	Placebo	• Encouraging Safety Data • Validation of Tier Weight-based Dosing
ESA-Controlled Dialysis Conversion							
048	Dialysis (Converted)	96	6	3	3	ESA	• Encouraging Safety Data • Successful Conversion from ESA IV & SQ
040a	Dialysis	60	6	3	No	ESA	• Successful Conversion, Includes ESA Hyporesponsive Patients • Dose Dependent Decrease in Hepcidin
Phase 2b Key Proof of Concept Studies							
041	Pre-dialysis (Six Correction and Maintenance Dose Cohorts)	145	16 and 24	6	3		• Both tier weight and fixed starting doses can initiate Hb correction • Maintained Hb with TIW, BIW, QW • Decrease in Blood Pressure Observed (Subgroup) • Reduced Total Cholesterol Levels
040b	Dialysis* (Conversion)	101	19	5	3	ESA	• Maintenance • Reduced Total Cholesterol Levels
053	Dialysis (Newly Initiated)	60	12	1	3		• Oral Iron ≈ IV Iron • Oral Iron HD ≈ oral Iron PD

* Many patients were ESA hyporesponsive. Higher doses of ESA are generally needed to treat such patients.

Study 017: Placebo-Controlled Proof of Concept Study in Pre-Dialysis

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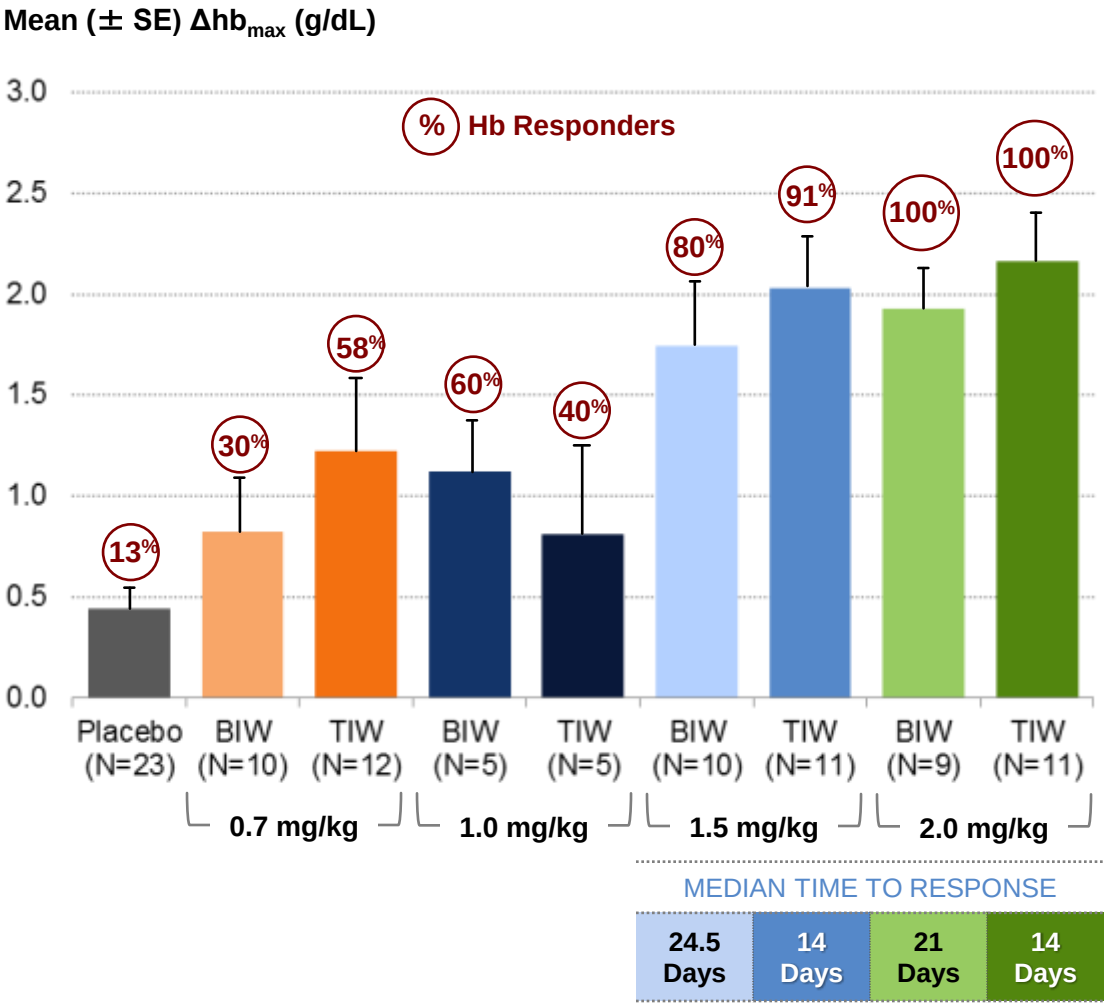
DESIGN

- Anemic Pre-dialysis Patients not Receiving ESA
- Randomized to Placebo or Roxadustat, BIW or TIW
  - 4-week Dose Ranging Study Evaluating 4 Weight-based Doses
  - Responder = Hb rise ≥1 g/dL

OBSERVATIONS

- Statistically significant, dose-dependent Hb increase for all 4 doses and for all assessments from Day 8 (p=0.025) to end of treatment (Day 22 p=0.0001; Day 26-29 p<0.0001)
- 100% Response Rate at Highest Dose
- Hepcidin reduction in 1.5 mg/kg cohort (p=0.048) and in 2.0 mg/kg cohort (p=0.001)



Study 047: Placebo-Controlled Study in Pre-dialysis

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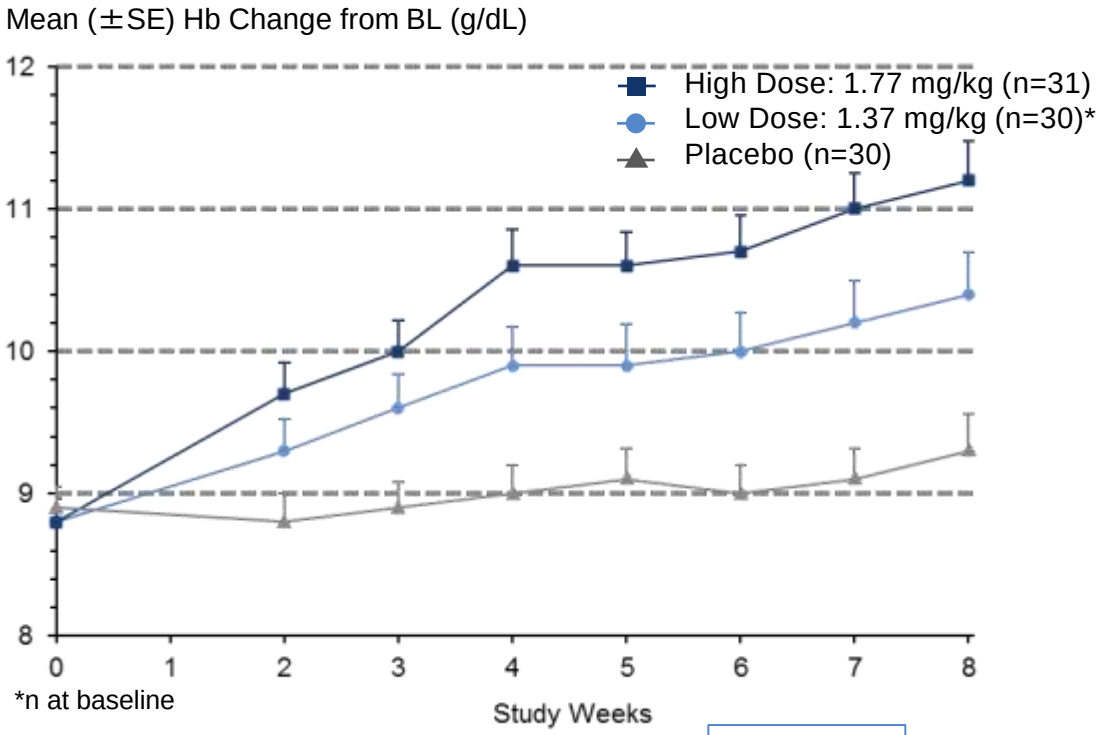
DESIGN

- Anemic Pre-dialysis Patients not Receiving ESA
- Randomized to Placebo or Roxadustat TIW
  - Two Tier Weight-based Doses
  - 8 Weeks Dosing

OBSERVATIONS

- Statistically Significant, Dose-dependent Hb Increase for Both Cohorts
- 93.1% Hb response rate at highest dose



TREATMENT	N	BASELINE HB	MAX CHANGE IN HB	P-VALUE VS PLACEBO	PATIENTS WITH HB INCREASE ≥ 1 G/DL	P-VALUE VS PLACEBO
High Dose	31	8.9	2.4	<0.0001	93.1%	<0.0001
Low Dose	30	8.8	1.6	<0.0001	88.5%	<0.0001
Placebo	30	9.0	0.4		25.9%	

* Hb increase ≥ 1 g/dL and Hb ≥11.0 g/dL at end of treatment

Studies 048 and 040a: ESA Comparator Study in Stable Dialysis Patients when Switched from Epoetin α (Conversion)

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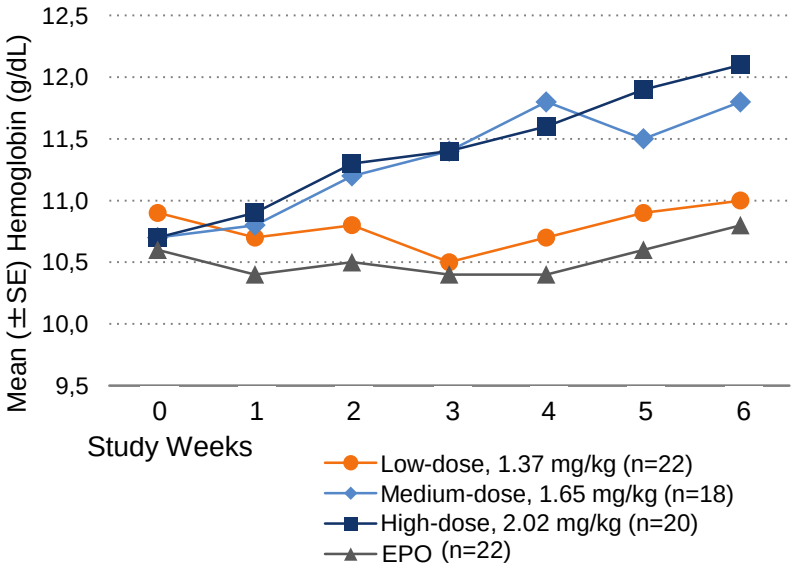
DESIGN
Studies 048 and 040

- Hemodialysis Patients with Hb Corrected on Stable Doses of ESA
  - For Study 048, approximately 50:50 split between SC and IV
- Randomized to Roxadustat TIW or Continuation of EPO for 6 Weeks of Treatment

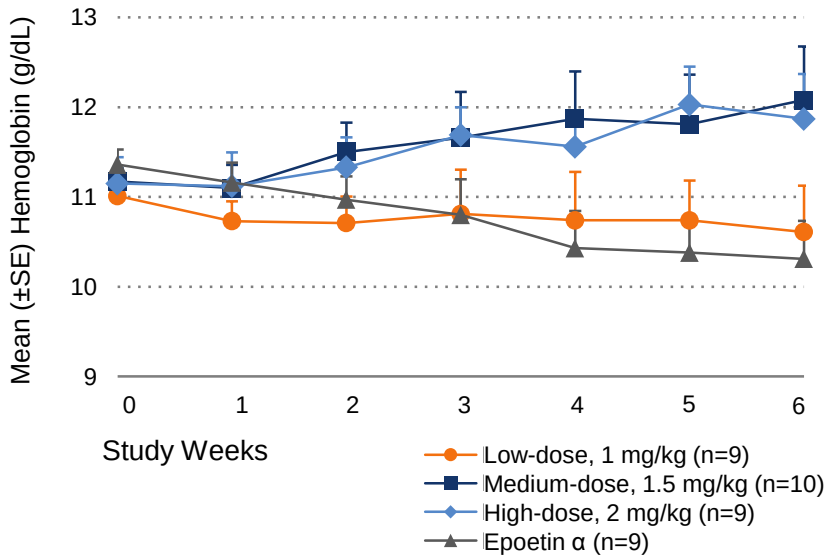
OBSERVATIONS – Study 048

- Roxadustat Maintained Hb in All Cohorts
- Hb Response Rates*
  - Low Dose (59.1%), Mid Dose (88.9%), High Dose (100%)
  - EPO (50%), p=0.005 (Mid Dose), p=0.0002 (High Dose)



OBSERVATIONS – Study 040a (6 wks)

- Successful in Wide Range of Patients, Includes EPO Hyporesponsive Patients



* % of Patients Maintaining Hb Level No Lower than 0.5 g/dL below Baseline at Both Week 6 and Week 7

Study 040b: ESA Comparator Study in Stable Dialysis Patients when Switched from Epoetin α (Conversion)

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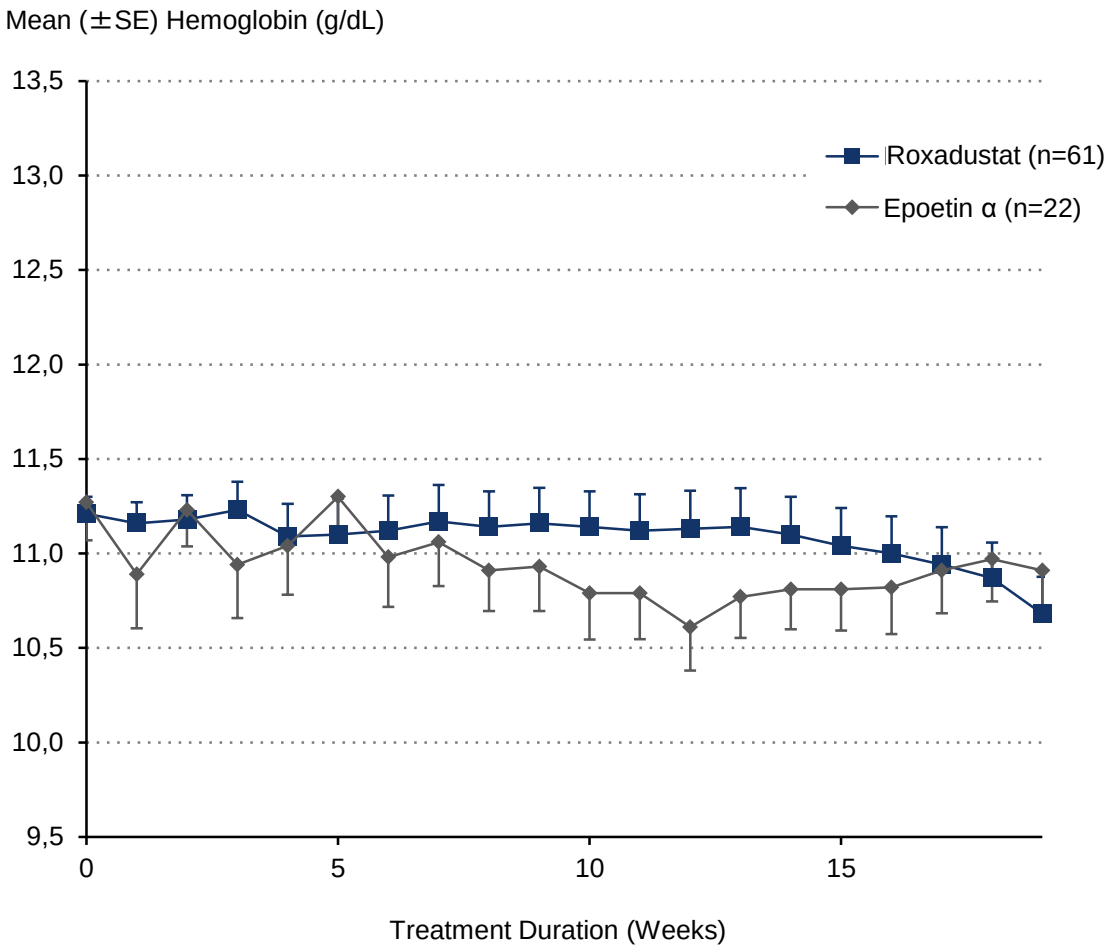
DESIGN – Stable Dialysis Conversion from ESA

- Hemodialysis Patients with Hb Corrected on Stable Doses of ESA
- Randomized to Roxadustat TIW or Continuation of EPO
- 19-week Treatment Duration

OBSERVATIONS

- Mean Baseline EPO Doses: 168 U/kg/wk IV (Dosed TIW)
- Low and High EPO Users
- Roxadustat Maintains Hb Levels Without IV Iron
- Roxadustat Maintains Hb Levels with Lower Cmax EPO Levels than IV Epoetin



Study 041: Dose Finding in Pre-dialysis

Different Targets, Different Dosing Regiments, TIW, BIW, QW, All Effective

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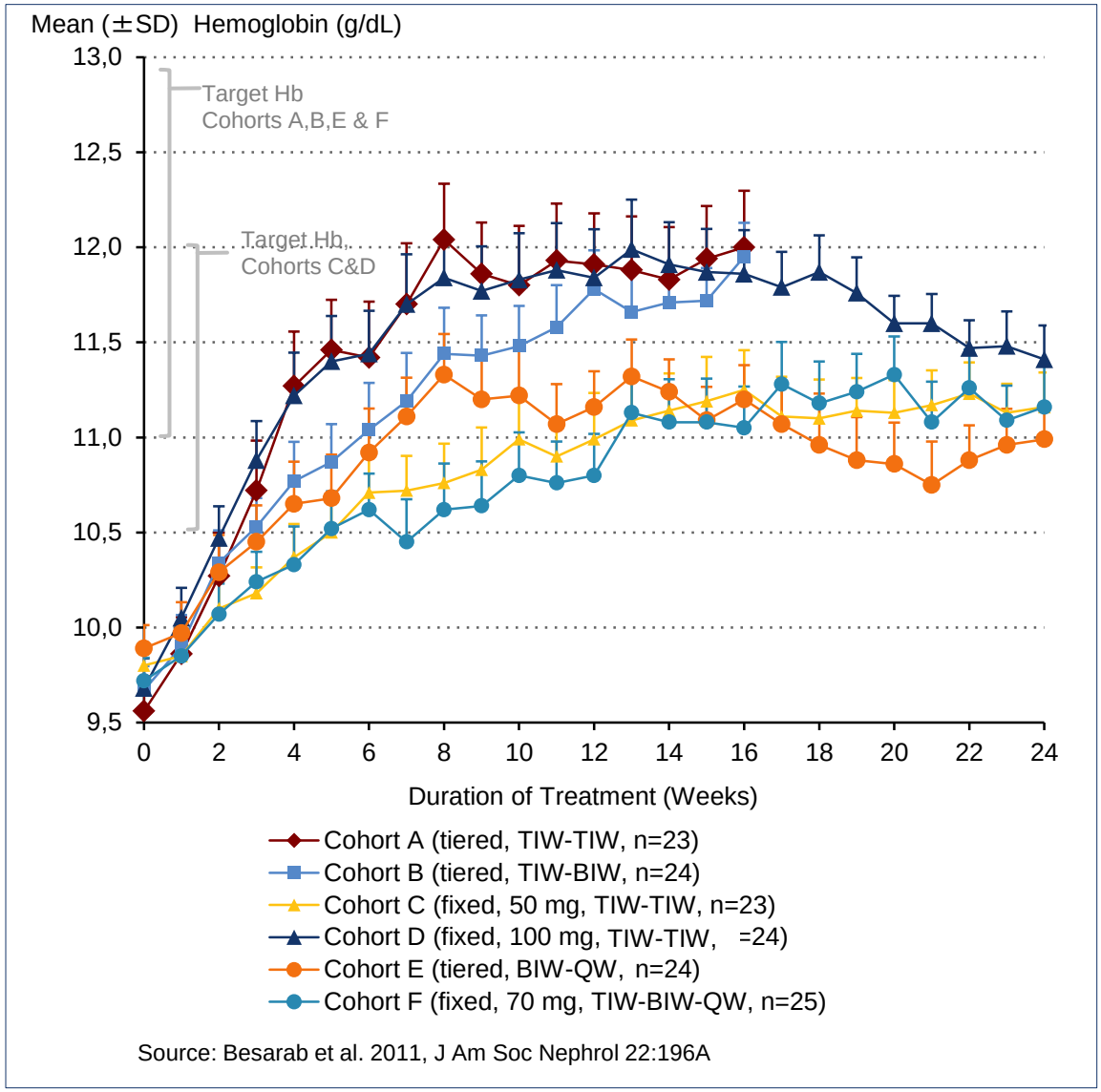
DESIGN

- CKD Patients not on Dialysis
- Roxadustat Starting Doses
  - TIW or BIW
  - Tier Weight Dosing: 3 Sizes
- Dose Titration to Achieve Hb
  - Dose Adjustment Every 4 Wks
- Maintenance Dosing Upon Achieving Hb 11 g/dL
  - TIW, BIW or QW
- Dual Endpoint ΔHb ≥ 1 and Achieved Hb ≥ 11 g/dL
- 16 or 24 Week Treatment

OBSERVATIONS

- 92% Response Rate
- Correction Achieved and Maintained to Ends of Treatment, Regardless of Starting and Maintenance Dose
- Reduction in Serum Hepcidin at Week 9 vs Baseline, p=0.0003



Source: Besarab et al. 2011, J Am Soc Nephrol 22:196A

Study 053: Roxadustat Corrects Anemia in Newly Initiated Dialysis Patients without IV Iron

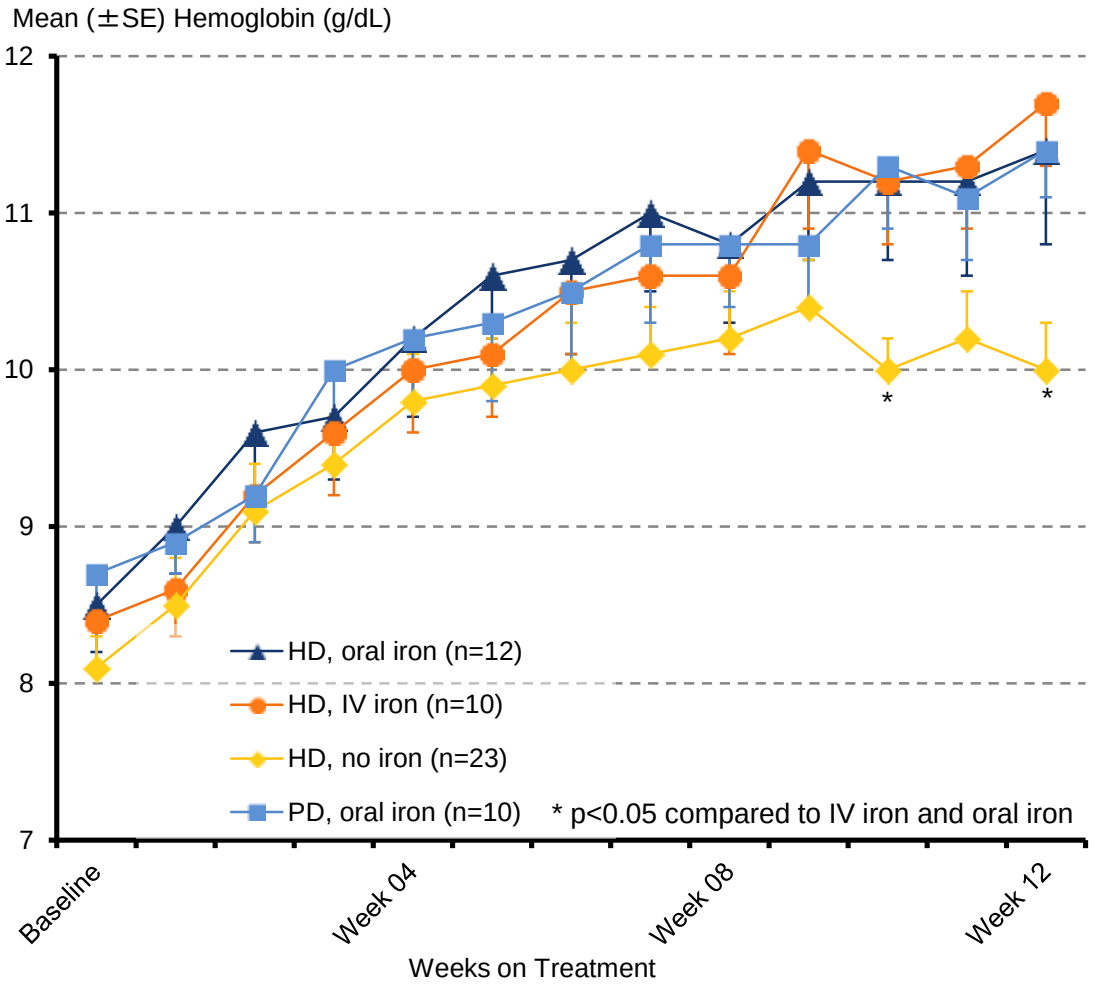
FIBROGEN

DESIGN

- Incident Dialysis (Newly Initiated Dialysis) Patients with Low Hb Levels and not on ESAs
- All Received Roxadustat
- Comparison of Treatment Response Under Different Iron Supplementation Conditions
- HD (Hemodialysis) Randomized to
  - No Iron
  - IV Iron
  - Oral Iron
- PD (Peritoneal) Received Oral Iron

OBSERVATIONS

- Roxadustat Raised Hb as Efficiently with Oral Iron as with IV Iron
- Oral and IV Iron Arms Had Similar Hb Responses in PD and HD
- ≥1 g/dL Hb correction in >90% patients at Week 12



Besarab, et al., J Am Soc Nephrol 23:428A and 24:91A.

Inflammation Increases Dose Requirements of ESAs and Decreases Their Effectiveness

In a cohort of hemodialysis patients, the higher the C-reactive protein, the lower the TSAT and the greater the epoetin dose with in spite of lower hemoglobin levels achieved.

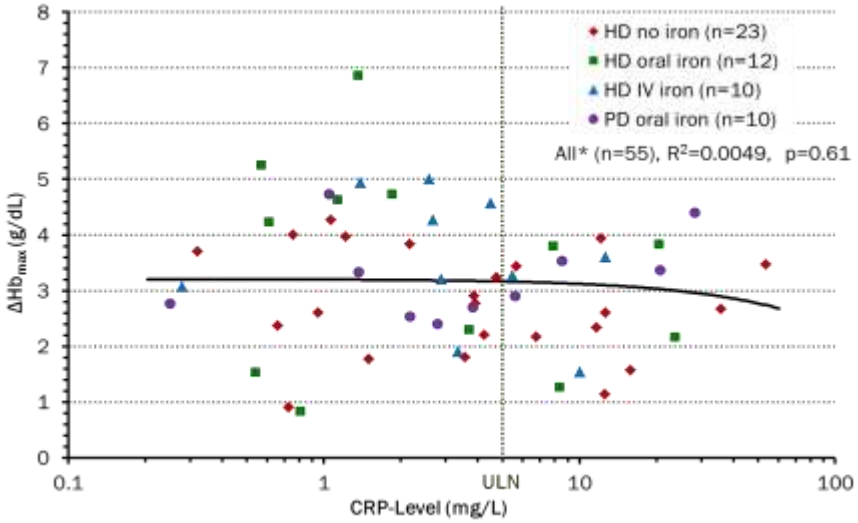
C-reactive protein (mg/L)	<1.3	1.3- 2.04	2.04-3.21	>3.21
TSAT (%)	29.6	28.5	25.4	22.7
Epoetin alfa dose (units per treatment)	7271.9	7386.5	8404.5	11253.5
Hemoglobin (g/dL)	11.6	11.6	11.3	10.8

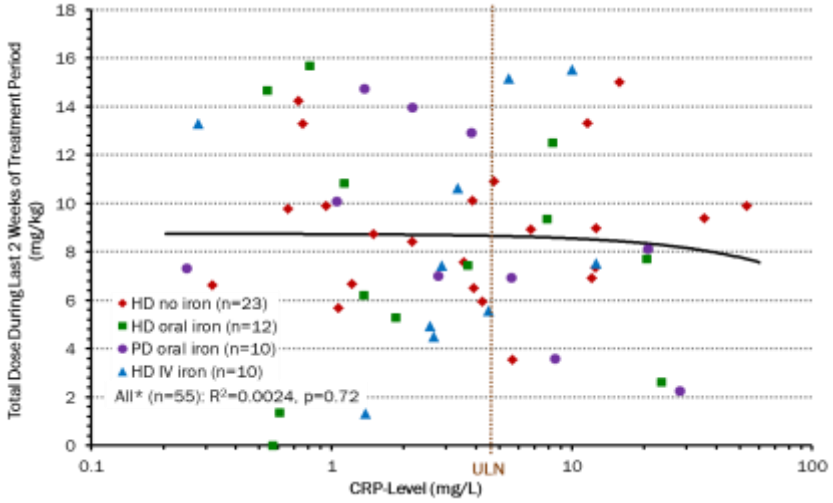
As inflammation (as measured by C-reactive protein) increases, iron stores are less available for erythropoiesis and ESA dose requirements increase in spite of lower hemoglobin gains.

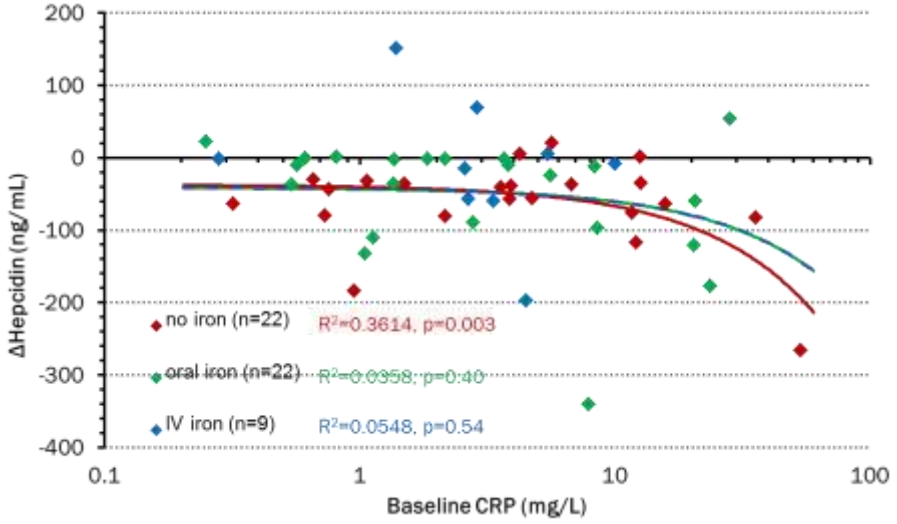
Bradbury et al. Impact of elevated C-reactive protein levels on erythropoiesis-stimulating agent (ESA) dose and responsiveness in hemodialysis patients. NDT 2009; 24; 919- 925

Hb Correction and Maintenance by Roxadustat is Not Impacted by Inflammation (Study 053)

- Hb correction is independent of inflammatory state
- Dose requirement for Hb maintenance is independent of inflammatory state
- Greater reduction in hepcidin level in those with higher baseline hepcidin values







Besarab et al., ASN 2014 poster presentation, "Impact of Iron Regimen on Iron Indices and Hepcidin During Roxadustat Anemia Correction in Incident Dialysis Patients".

CV Risk & Mortality are Associated with High Doses of ESA & IV Fe in Dialysis Patients

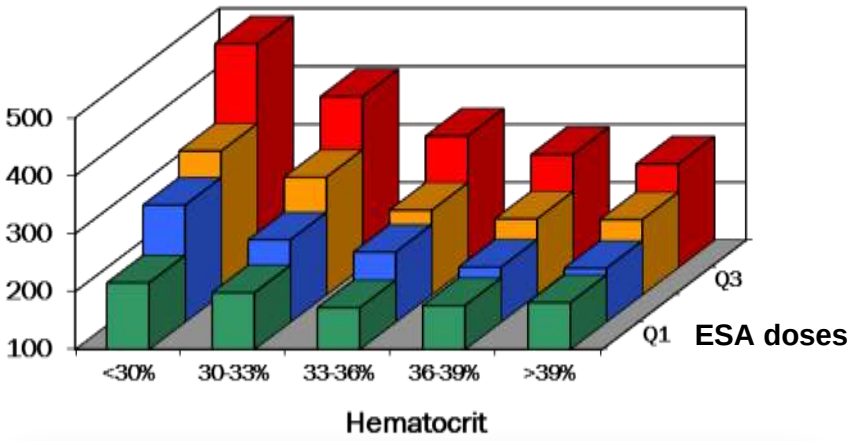
Higher ESA doses is associated with

- Higher mortality rate
- Higher CV event rate
- Increased thrombosis

High Doses of IV Iron is associated with

- Risk of anaphylactic reactions
- Oxidative stress
- Increased mortality

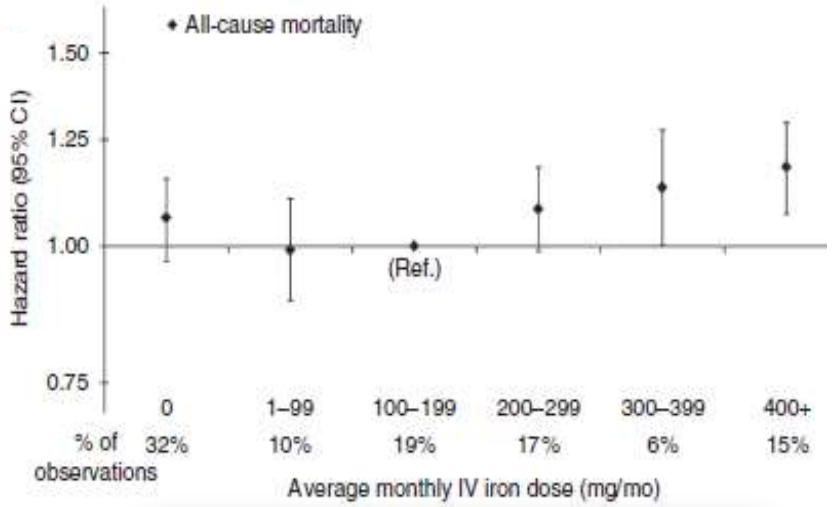
Unadjusted 1-Year Mortality Rates (per 1000) by Hematocrit and EPO dosing quartile (USRDS: 94,569 hemodialysis pts)



IV iron

WARNING: RISK FOR ANAPHYLACTIC-TYPE REACTIONS
Anaphylactic-type reactions, including fatalities, have followed the parenteral administration of iron dextran injection.

Higher mortality & hospitalization rate at Higher IV Iron Doses
(32,435 hemodialysis patients in 12 countries)

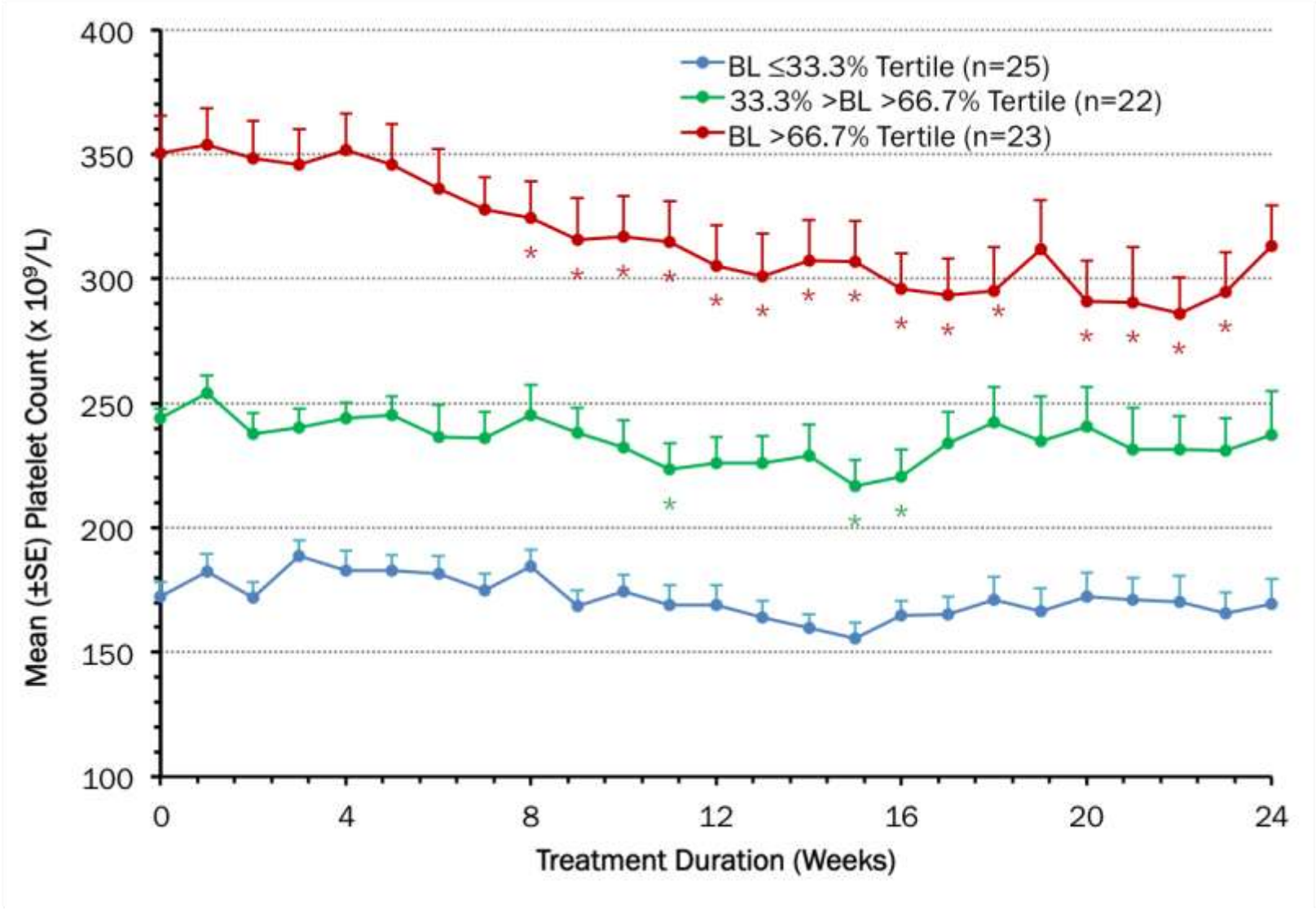


Roxadustat potentially treats anemia w/o excessive EPO

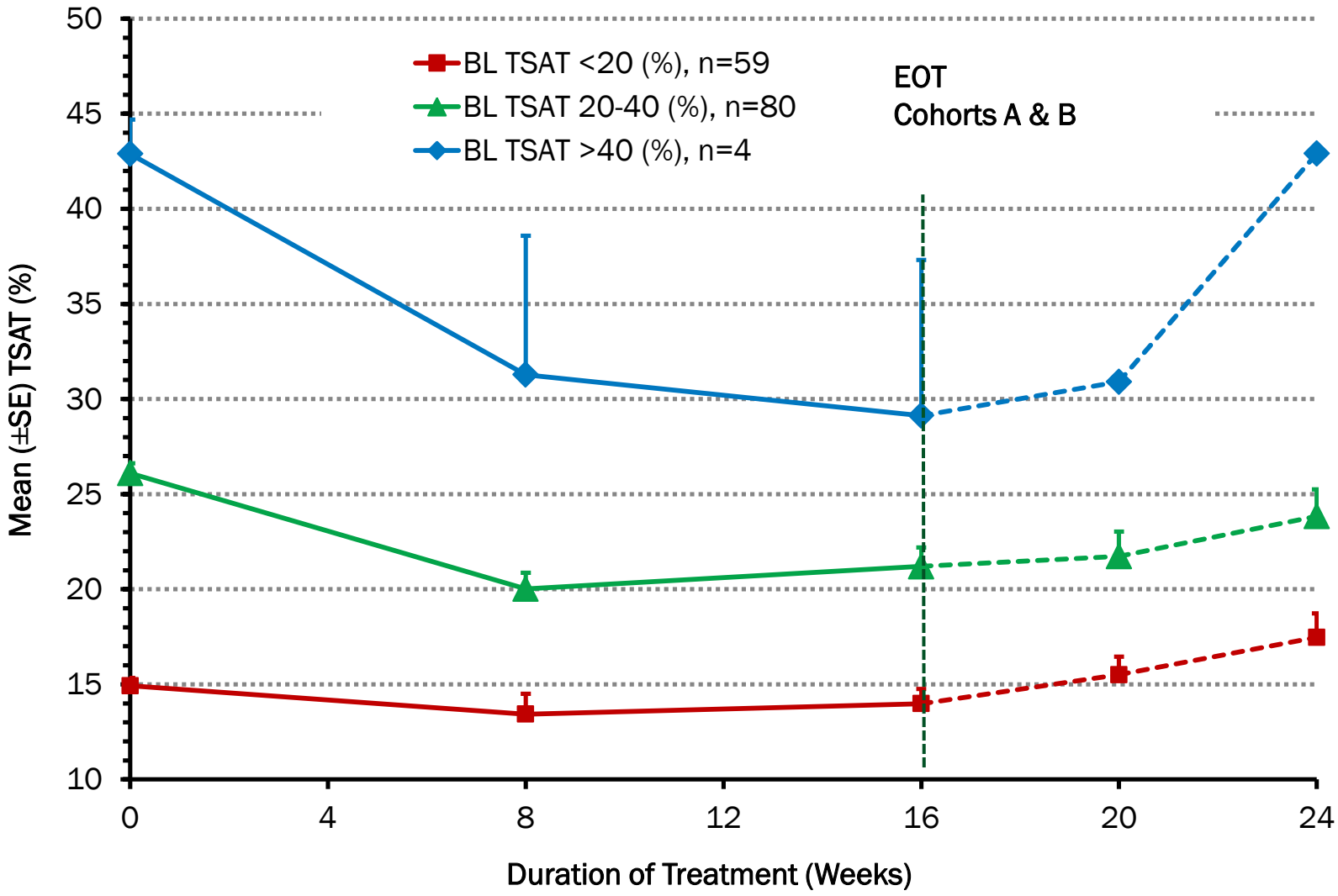
Roxadustat potentially treats anemia w/o IV Iron

1. Zhang et al. *Am J Kidney Dis* 44:866-876.
2. Szczech et al. *Kidney International* (2008) 74, 791–798
3. Koulouridis et al. *Am J Kidney Dis* 2013;61:44-56
4. Bailie et al. *Nephrol Dial Transplant* (2005) 20: 1443–1449
5. Lim et al. *Nephrol Dial Transplant* 1999; 14: 2680- 87.
6. Bailie et al. *Kidney International* (30 July 2014) | doi:10.1038/ki.2014.275

Roxadustat Treatment: Platelet Count Reflecting Homeostasis Evidence Supporting Safety: No Evidence for Thrombocytosis

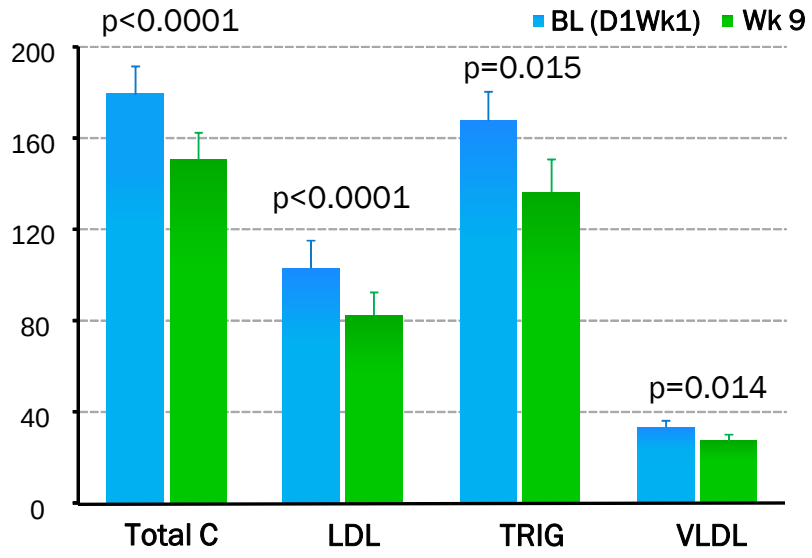


TSAT Over Time By Baseline TSAT Tertiles (041)



IN Addition, Roxadustat Reduces Cholesterol in CKD and ESRD Patients

- High cholesterol is one of the 3 top CV risk factors in CKD patients; CV is the most common cause for mortality.
- Roxadustat reduces cholesterol regardless of taking lipid lowering agents like statins.
- Greater magnitude of cholesterol reduction with higher baseline cholesterol levels.
- Significant reductions in:
  - **LDL**
  - **Triglyceride**
  - **VLDL**
- Improves HDL/LDL ratio.



Overview of Global Phase 3 Clinical Program FibroGen, AstraZeneca, Astellas

Population	Study name	Study code	Sponsor	Comparator	Primary comparison	N
Non Dialysis	Andes	060	FGN	Placebo	Efficacy; superiority	450-600
	Alps	0608	AST	Placebo	Efficacy; superiority	450-600
	Olympus	001	AZ	Placebo	Safety; non-inferiority	2600
Dialysis	Himalayas	063	FGN	Epoetin alfa	Efficacy; non-inferiority	750
	Sierras	064	FGN	Epoetin alfa	Efficacy; non-inferiority	600-750
	Pyrenees	0613	AST	Darbepoetin alfa & Epoetin alfa	Efficacy; non-inferiority	750
	Rockies	002	AZ	Epoetin alfa	Safety; non-inferiority	1425

- 52+ weeks duration (Variable treatment duration)
- Primary efficacy endpoint: Change in Hb from Baseline or % Hb responder
- CV safety endpoints based on data pooled across multiple studies
  - Nondialysis pool- to show as safe as placebo
  - Dialysis pool- powered to show safety superiority

Roxadustat Summary

- **Effective erythropoiesis in CKD anemia.**
- **Oral agent, no IV iron needed.**
- **Intermittent dosing –HIF stabilization with full reset before the next dose.**
  - Preserve durability of efficacy.
  - Minimize risk of stimulating late response HIF genes.
- **MOA: coordinated erythropoiesis.**
  - Hepcidin reduction.
  - Overcoming inflammation.
  - Modest transient eEPO elevation, avoiding supraphysiologic EPO levels.
- **Undergoing extensive safety evaluations in phase 3- a new paradigm for anemia therapy**