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

July 15, 2021

FibroGen

Cardiovascular and Renal Drugs Advisory Committee

Introduction

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Patients with Anemia of CKD Need Options Beyond Existing Therapies

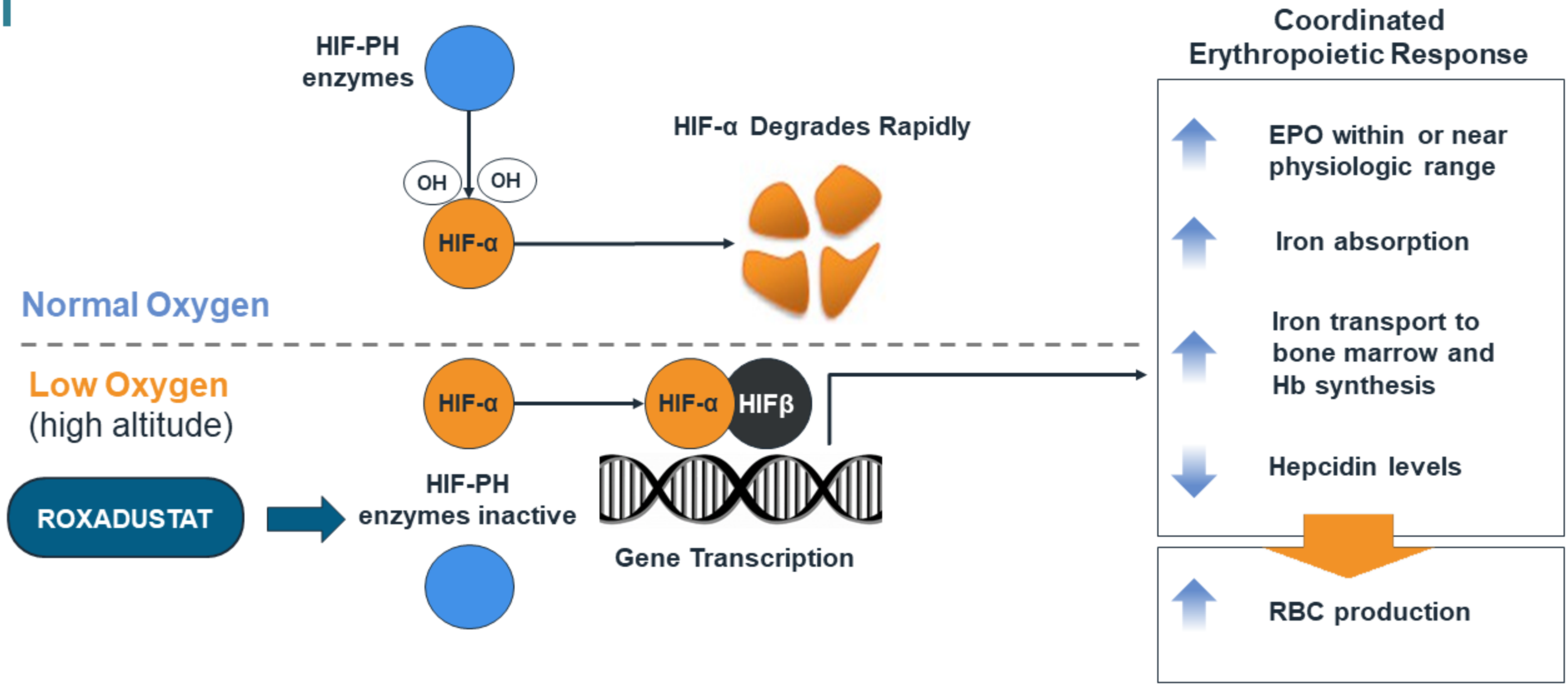
- Anemia is a common and burdensome complication of CKD
  - Associated with undesirable clinical outcomes
- Many patients underserved due to
  - Complexities of injectable treatments
  - Lack of alternative options for those with inadequate treatment response or on home dialysis

Patients would benefit from having the choice of an oral treatment option that can be continued throughout their entire clinical course

Roxadustat: First in Class Oral Therapy for Patients with Anemia of CKD

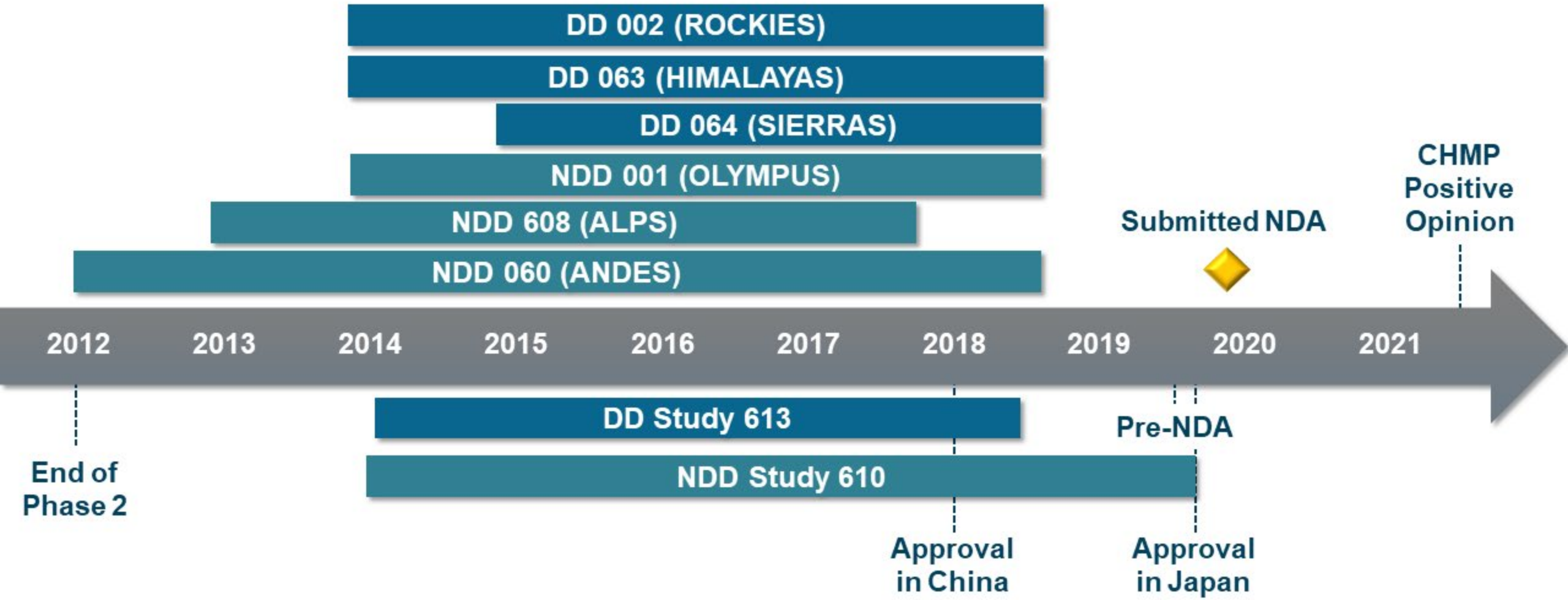
- Consistently corrects and maintains hemoglobin (Hb) across spectrum of patients
- Novel mechanism of action based on Nobel Prize-winning scientific discovery
- Small molecule inhibitor of hypoxia-inducible factor prolyl hydroxylase (HIF-PH) enzymes
  - Regulates HIF activity
  - Coordinates physiologic response to decreased oxygen
- Increases Hb by mimicking natural response to low oxygen

Roxadustat: Novel Mechanism of Action to Treat Patients with CKD Anemia



HIF-PH = hypoxia-inducible factor prolyl hydroxylase

Roxadustat Regulatory History



> 13,000 Patients in Roxadustat CKD Development Program

	Phase 2 Studies (N=9)			Phase 3 Studies US & Global (N=8)			Additional Phase 3 Studies (N=8)		
	Study	Region	N	Study	Region	N	Study	Region	N
Non-Dialysis Dependent (NDD)	017	US	116	001	Global	2782	310	Japan	325
	041	US	145	060	Global	922	314	Japan	100
	047	China	91	608	Global	597	808	China	151
	303	Japan	107	610	Global	616			
	059	Global	15						
Dialysis Dependent (DD)	040	US	161	002	Global	2133	302	Japan	56
	048	China	96	063	Global	1043	307	Japan	303
	053	Global	60	064	US	741	308	Japan	75
	304	Japan	134	613	EU	838	312	Japan	164
							806	China	304

Roxadustat Efficacy and Safety Consistently Demonstrated Across Spectrum of Patients with CKD

- Consistent efficacy results in NDD and DD patients including Incident Dialysis (ID-DD) and Stable / Prevalent Dialysis (SDD)
  - Independent of inflammation and iron status
- Primary efficacy endpoint (Hb) met in all 6 pivotal studies
  - NDD trials: statistically significant and clinically meaningful treatment differences favoring roxadustat vs placebo
  - DD trials: roxadustat comparable to ESA
- Reduction in red blood cell transfusions
- CV safety comparable to placebo in NDD and epoetin alfa in DD
- Acceptable general safety profile

Proposed Indication

Treatment of anemia due to chronic kidney disease (CKD) in adult patients not on dialysis and on dialysis.

Agenda

Unmet Need

Roberto Pecoits-Filho, MD, PhD
Nephrologist and Senior Research Scientist
Arbor Research Collaborative for Health

Efficacy Results

Lynda Szczech, MD
Vice President
Clinical Development and Medical Affairs
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Safety Results

Dustin Little, MD
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Clinical Perspective

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Additional Experts

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AstraZeneca

Lars Frison, PhD
Statistical Science Director
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Mats Någård, PhD
Director Clinical Pharmacology
AstraZeneca

Khalil G Saikali, PhD
Vice President, Head of Biometrics
FibroGen

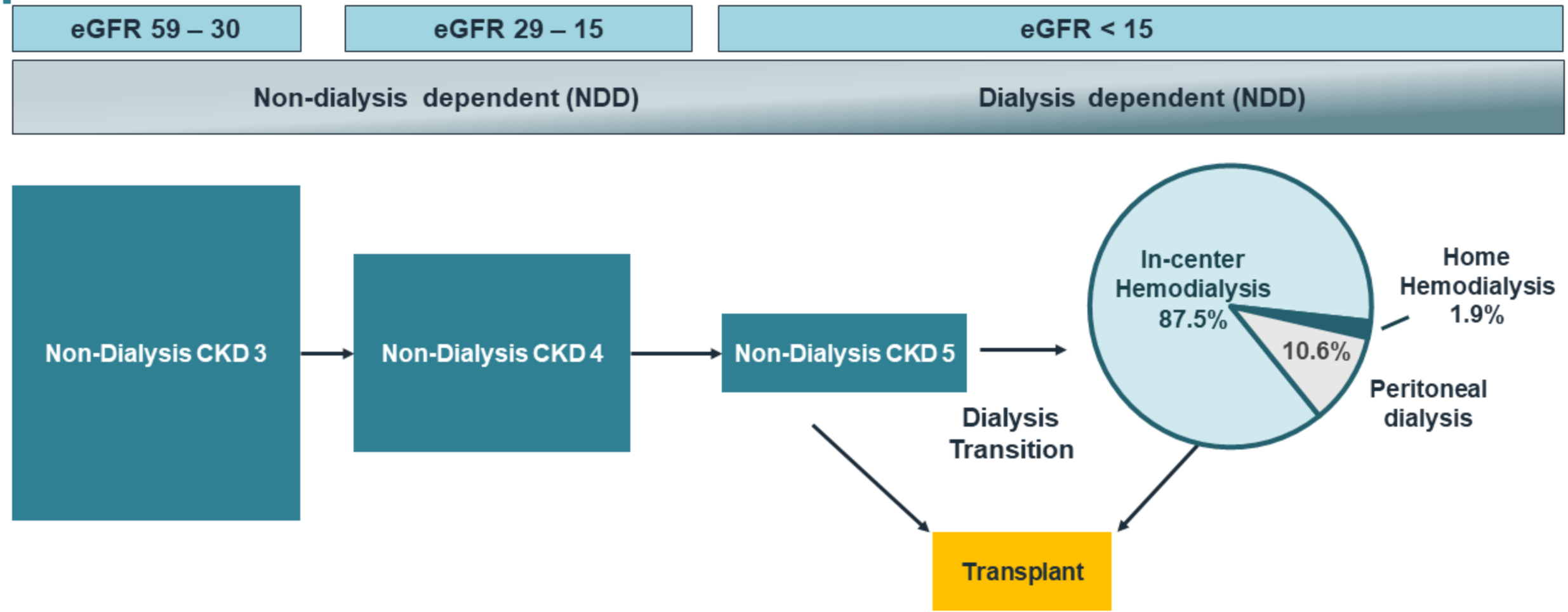
Gail Walkinshaw, PhD
Vice President, Research
FibroGen

Unmet Need

Roberto Pecoits-Filho, MD, PhD

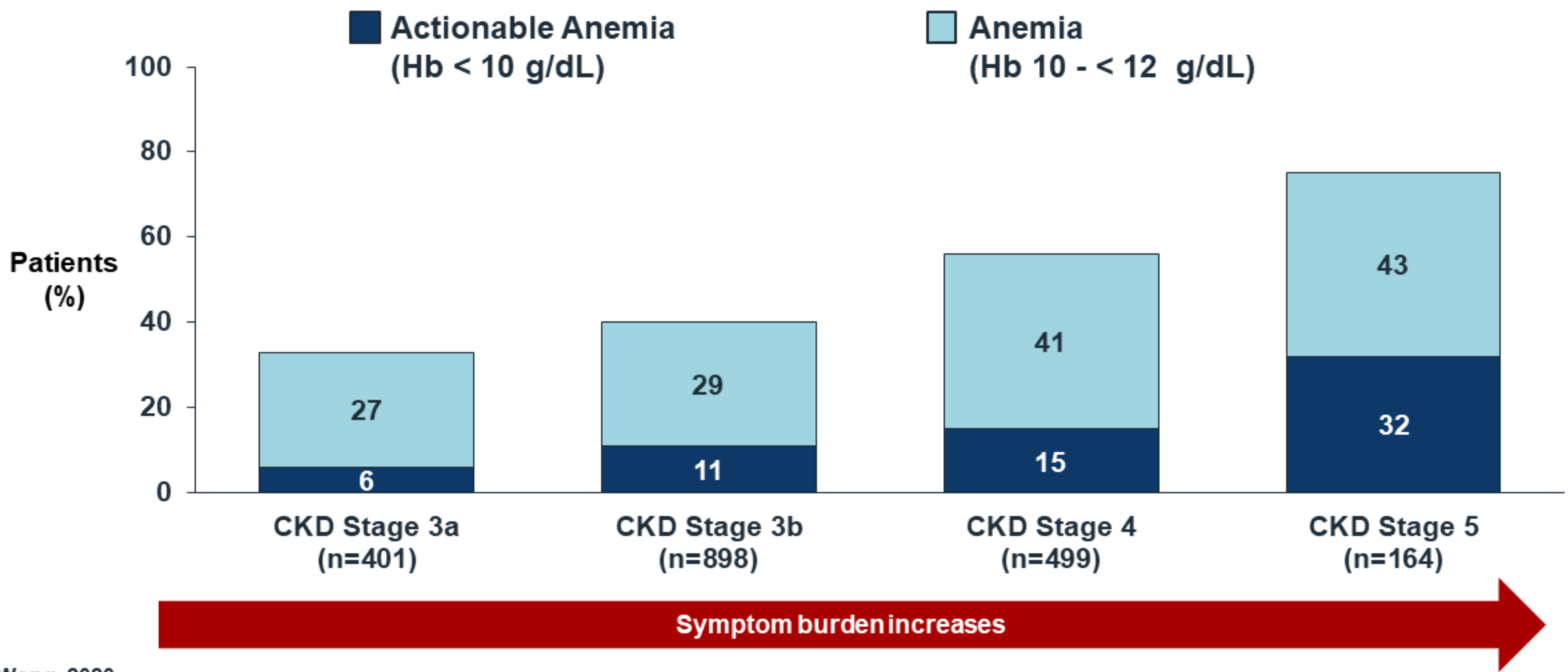
Nephrologist and Senior Research Scientist,
Arbor Research Collaborative for Health
Ann Arbor, USA

Individual Patient Journey with CKD



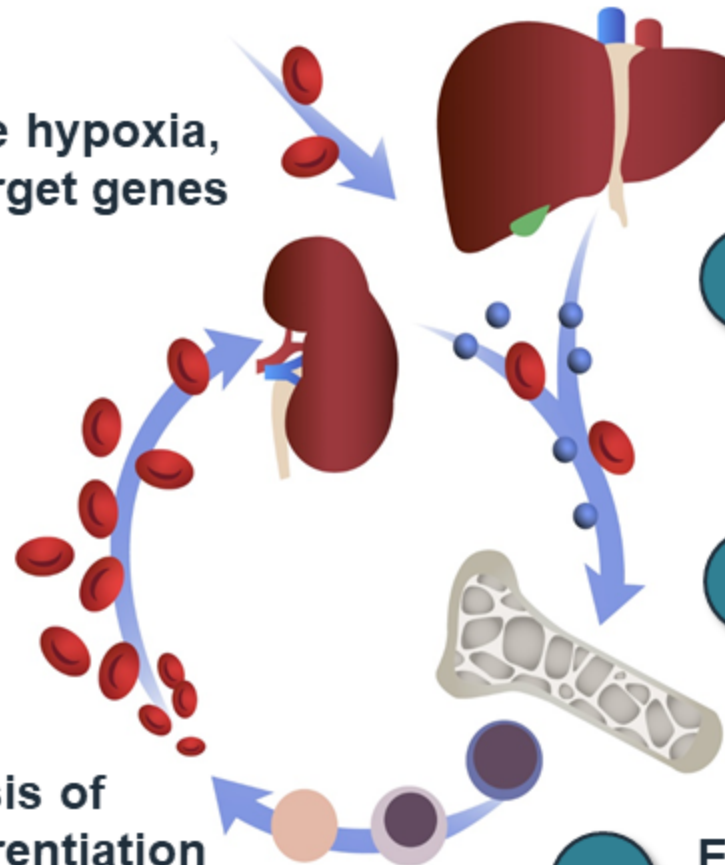
US Renal Data System (USRDS) Annual Data Report, 2020

Anemia Becomes More Prevalent as CKD Progresses



Wong, 2020

Current Understanding of the Pathophysiology of Anemia in CKD



1. Liver and kidneys sense hypoxia, HIF is stabilized, and target genes are transcribed
2. HIF promotes production of EPO by the kidney and extra-renal sites
3. HIF stabilization is associated with a reduction in hepcidin that promotes iron release into circulation
4. EPO promotes survival of proerythrocytes in the bone marrow
5. Iron supports synthesis of hemoglobin and differentiation into mature RBCs

Murilo Guedes, 2020

Current Therapies Do Not Fully Address Needs of Patients With CKD Anemia

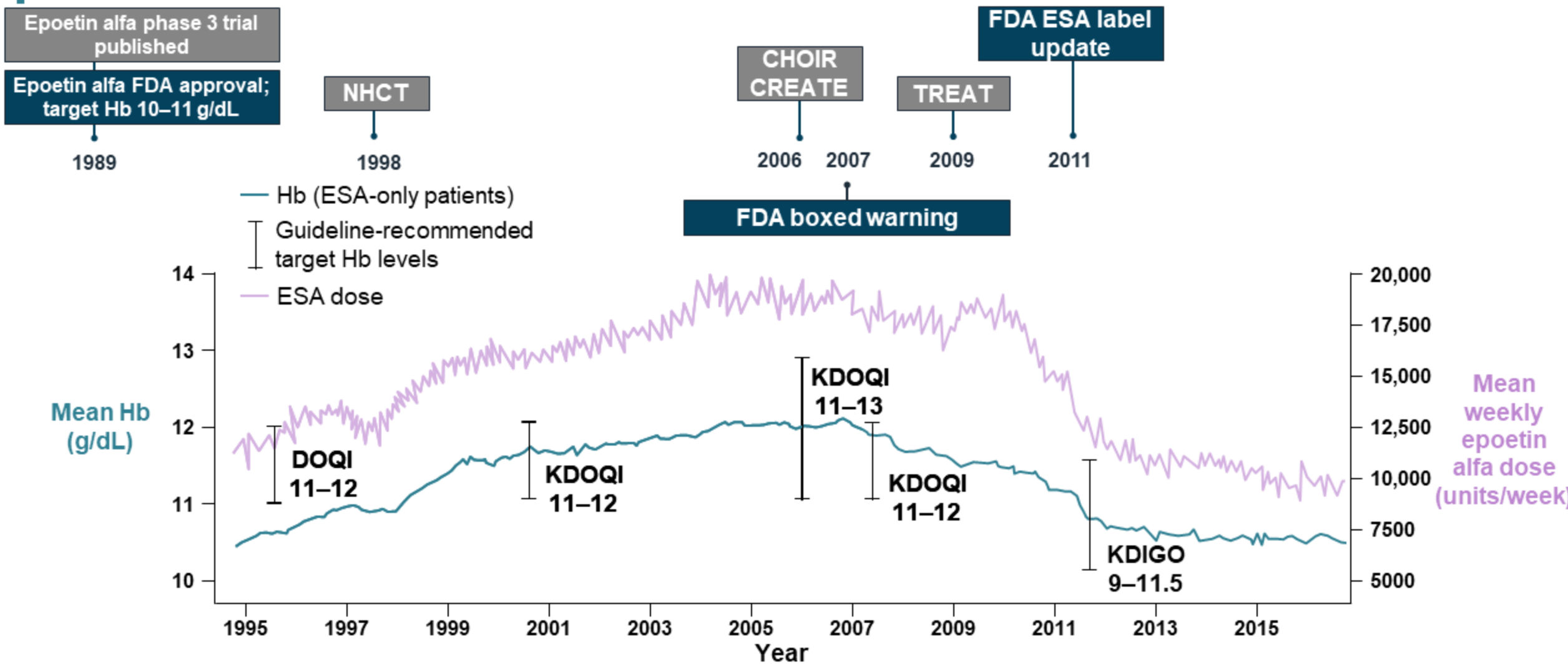
ESAs
Erythropoiesis Stimulating Agents

Iron Therapy

Blood Transfusion

- No MOA alternatives
- Logistically complex treatments lead to many NDD patients being left untreated
- IV iron therapy represent potential harm
- A group of patients are hyporesponsive (inflamed and/or iron deficient)
- Transfusion is currently a common treatment across CKD spectrum, can compromise future transplant

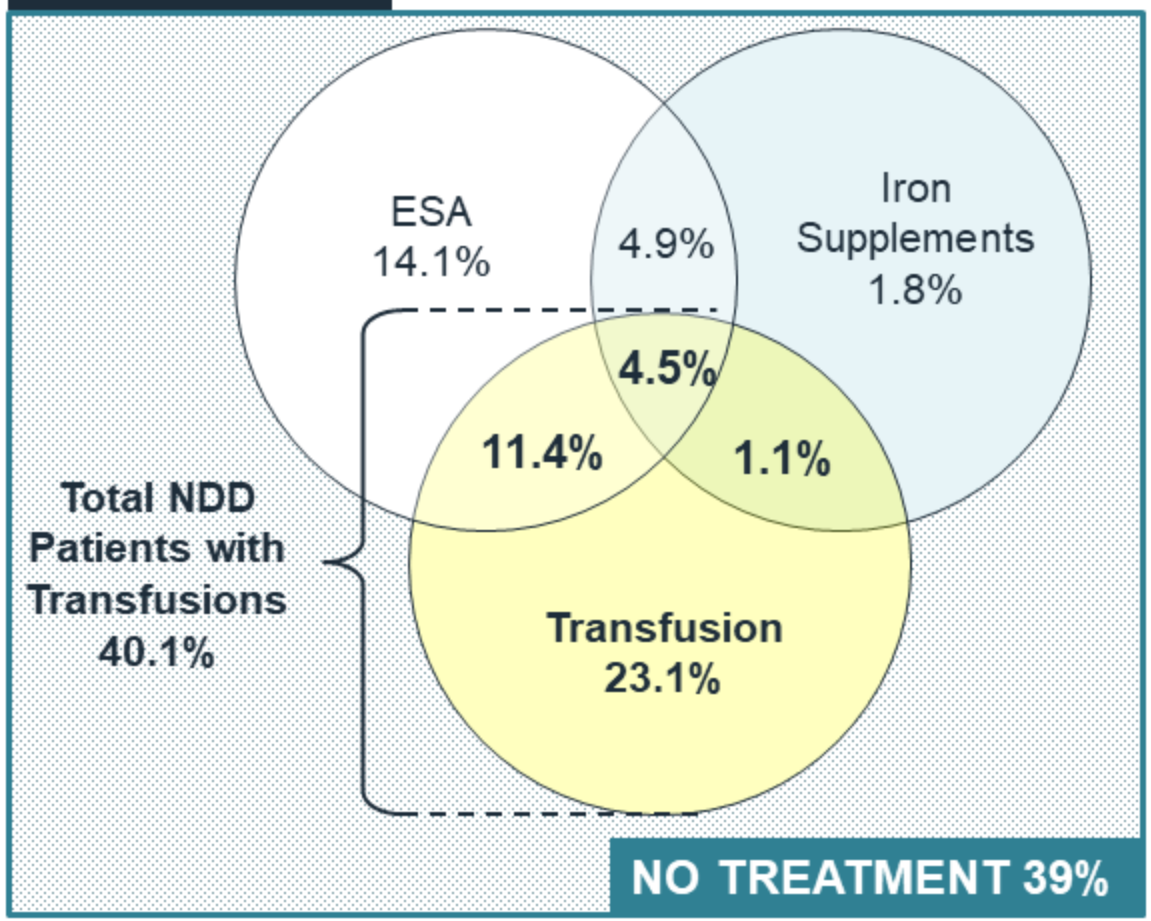
CV Safety Trials Led to ESA Labeling Changes and Decreased Hb Target Levels



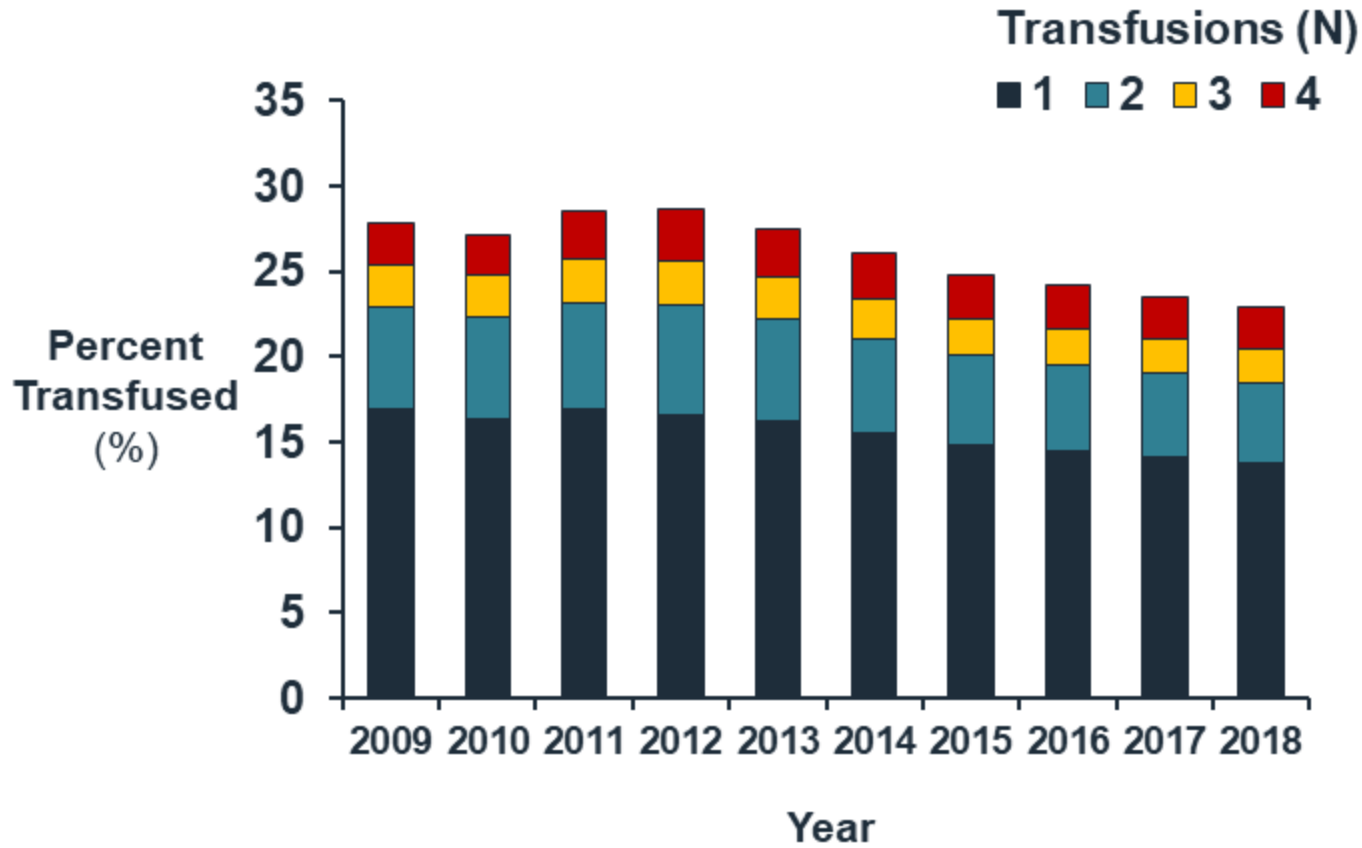
USRDS Annual Data Report, 2018; KDOQI, 2006; US FDA Safety, 2017

Transfusions are Very Common in NDD- and DD-CKD Populations

NDD Patients



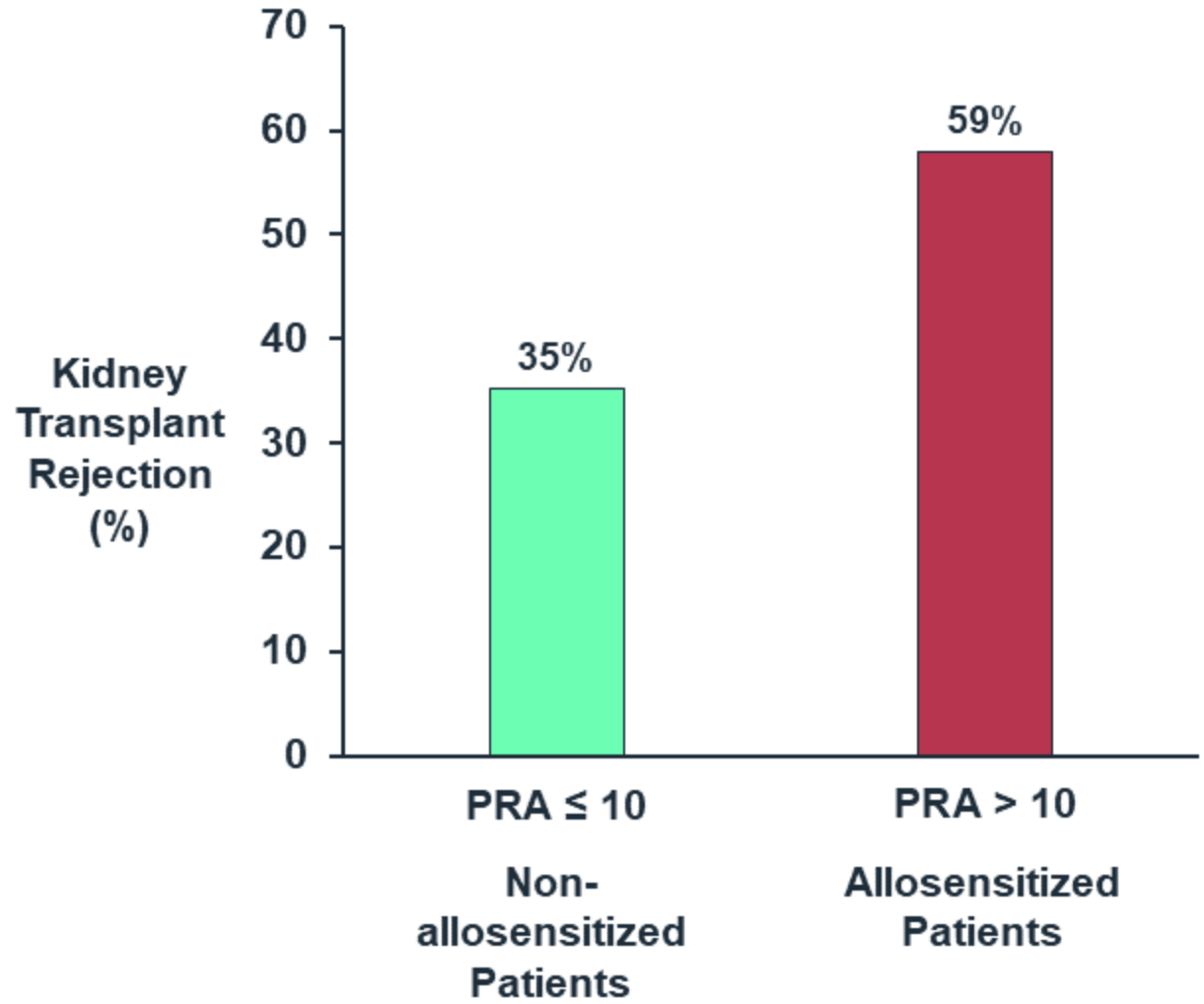
DD Patients



Winkelmeyer, 2014; USRDS Annual Data Report, 2020

Transfusions Substantially Impact Transplant Outcomes

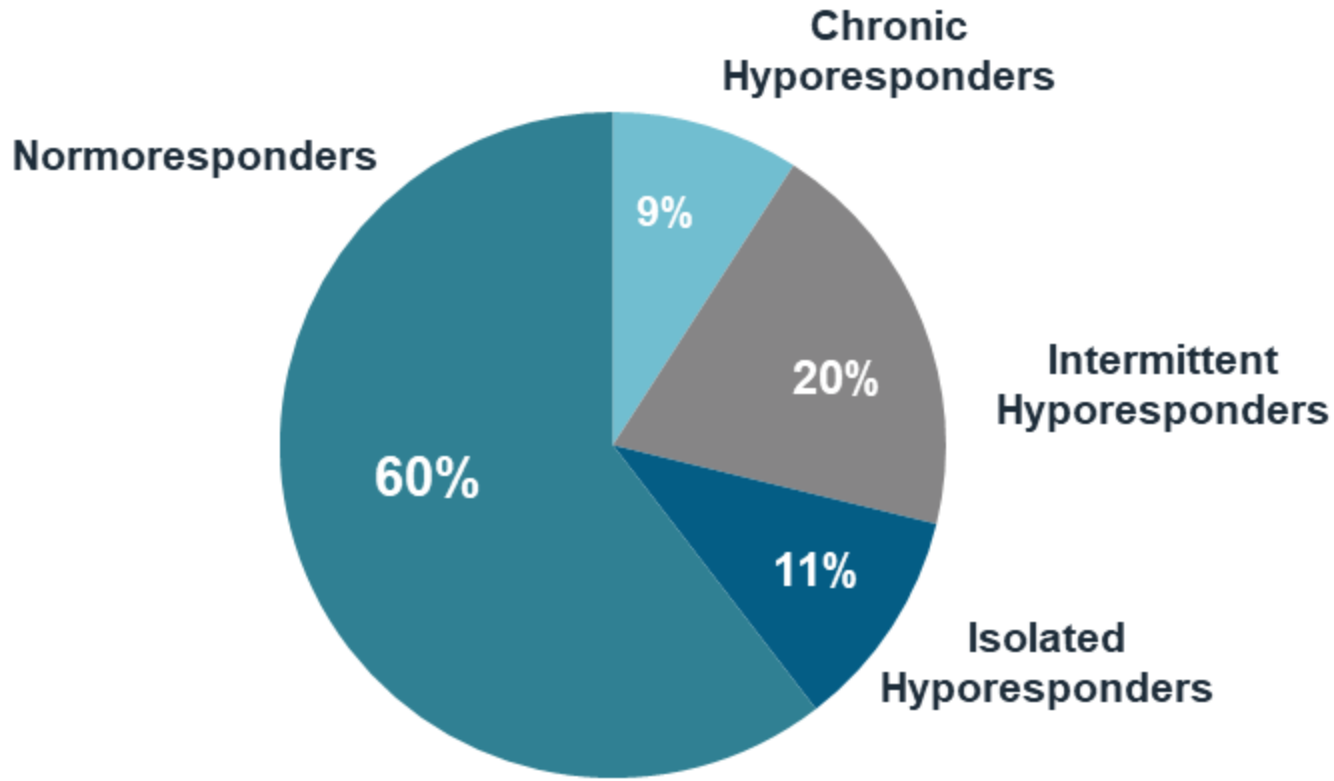
- Transfusion results in clinically significant increases in antibody production and allosensitization
  - Longer wait, may never receive transplant[1]
  - Increased risk of rejection and poorer graft survival[2]
- Highly sensitized patients require complex and costly treatments[3]



PRA = panel-reactive antibody

1. Marfo, 2011; 2. Bostock, 2013; 3. Kuppachi and Axelrod, 2020

ESA Hyporesponsiveness is Common and Related with Poor Outcomes



ESA-hyporesponsive dialysis patients have higher mortality, hospitalization rates, and healthcare costs as compared with ESA-normoresponsive patients

Cizman, 2020

My Patients' Unmet Needs in Anemia of CKD

- Oral therapy that stimulates a coordinated erythropoiesis, represents a choice for ESA-hyporesponders and **addresses logistical challenges of anemia treatment**
- **Spares** IV iron requirement and resultant high ferritin levels
- Optimizes anemia treatment in home dialysis setting
- Enables **continuous** therapy in outpatients with NDD-CKD to dialysis
- Facilitates transplant status by lowering the risk of transfusions

Efficacy Results

Lynda Szczech, MD

Vice President

Clinical Development and Medical Affairs

FibroGen

Pivotal Studies Enrolled Broad Spectrum of Patients with Chronic Kidney Disease

	Phase 2 (N=9)			Phase 3 US & Global (N=8)			Additional Phase 3 (N=8)		
	Study	Region	N	Study	Region	N	Study	Region	N
Non-Dialysis Dependent (NDD)	303	Japan		001	Global	2782	310	Japan	325
	017	US	Pooled NDD	060	Global	922	314	Japan	100
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	053	Global	60	613	EU	838	307	Japan	303
							806	China	304

Non-Dialysis-Dependent (NDD)

Study 001 [OLYMPUS]

Study 060 [ANDES]

Study 608 [ALPS]

Similar Study Designs for Three Pivotal Studies in Patients with NDD-CKD

	Pivotal Phase 3 NDD Studies		
	Study 001 OLYMPUS	**Study 060** ANDES	**Study 608** ALPS
Region	**Global**	**Global**	**Global**
Randomized, double-blind	**Yes**	**Yes**	**Yes**
Control	**Placebo**	**Placebo**	**Placebo**
Baseline Hb	**< 10.0 g/dL**	**≤ 10.0 g/dL**	**≤ 10.0 g/dL**
Randomization scheme	**1:1**	**2:1**	**2:1**
Duration (years)	**1 – 4**	**1 – 4**	**1 – 2**

NDD: Primary Efficacy Endpoint Consistent Across Pivotal Phase 3 Studies

- **Primary Endpoint**
  Mean change from baseline in Hb averaged over Week 28 to Week 52 regardless of rescue therapy

NDD: Select Secondary and Additional Endpoints

Hb-related

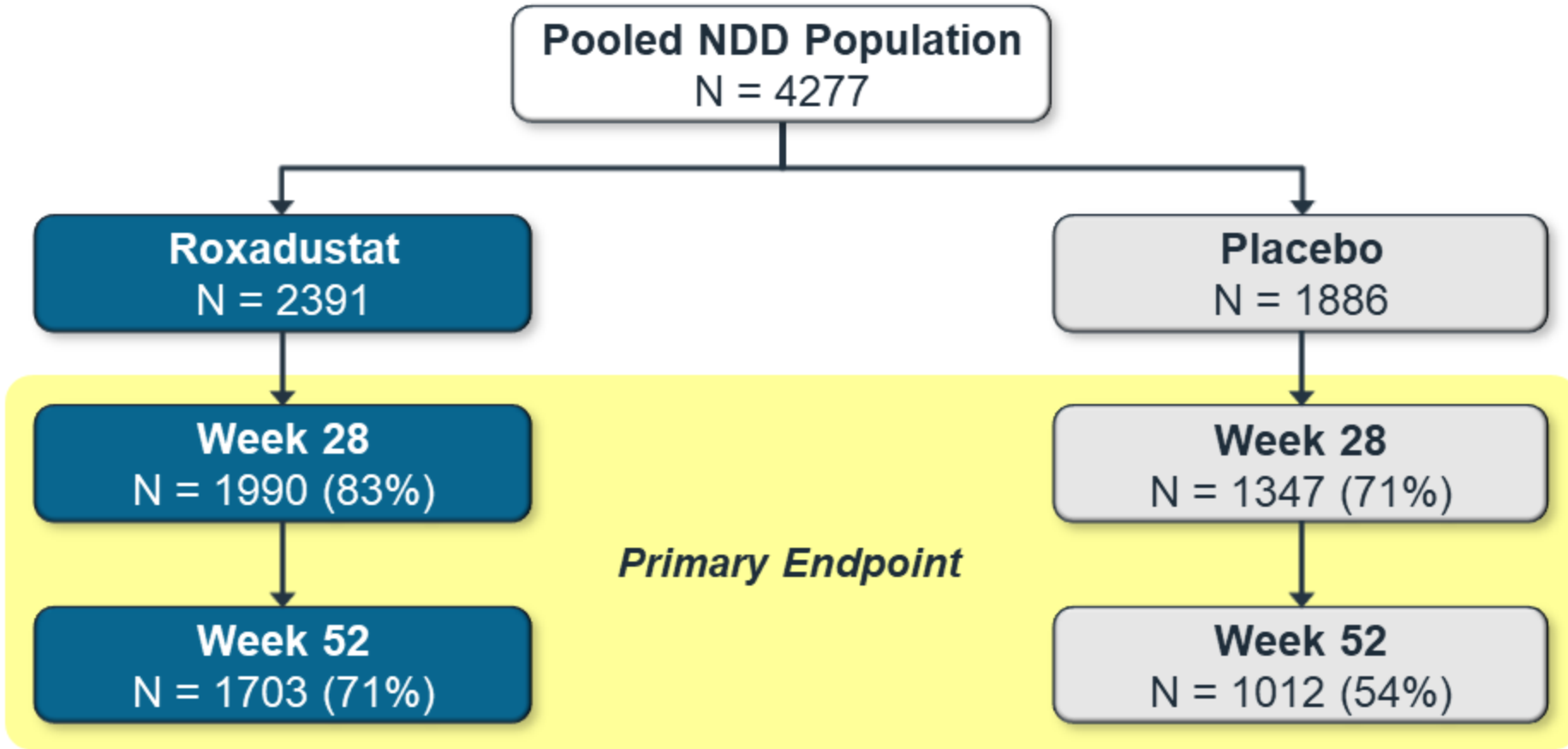
1. % Hb responders
2. % requiring rescue therapy*
3. % requiring RBC transfusion**

Non Hb-related

4. Change in hepcidin and iron parameters

*Secondary Endpoint. **Secondary endpoint in studies 001 and 060, not in study 608.

NDD: Patient Disposition up to 1 Year for Primary Efficacy Assessment



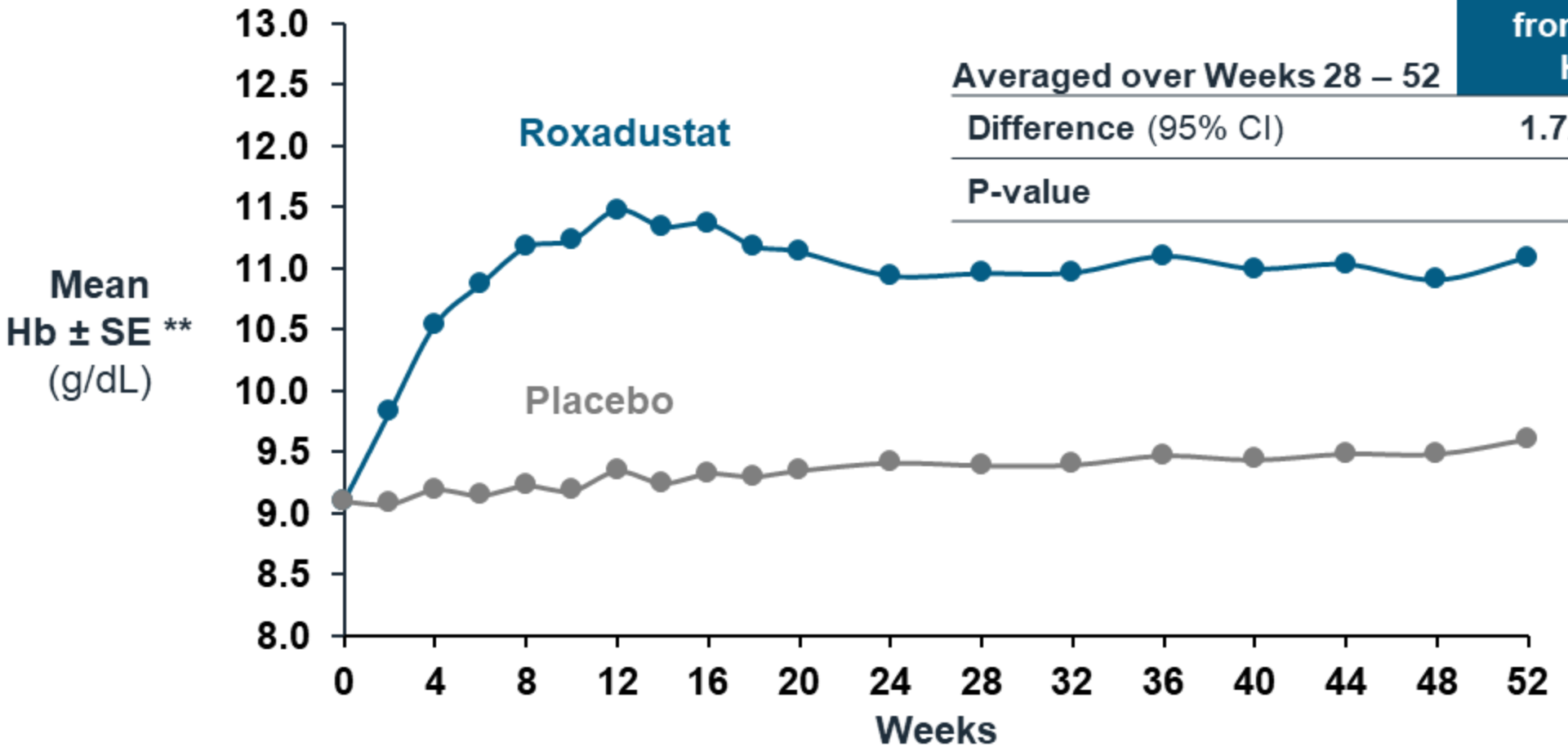
NDD: Baseline Demographics and Characteristics Reflective of NDD-CKD Population

Pooled NDD Population	Roxadustat N = 2391	Placebo N = 1886
Age; mean (range)	**62** (19-100)	**63** (18-93)
White	**47%**	**47%**
Asian	**36%**	**37%**
Black*	**8%**	**8%**
Diabetes mellitus	**56%**	**58%**
Hb level (g/dL)**; mean**	**9.10**	**9.10**
eGFR (ml/min/1.73 m^2)**; median**	**16.9**	**17.0**
hsCRP (mg/L)	**7.4**	**7.2**
Iron non-replete (TSAT < 20% or ferritin < 100 ng/mL)	**40%**	**40%**

*Of 552 Roxadustat-treated patients in the US, 31.7% were Black or African American

NDD: Significant Improvement in Hb Levels Over Time with Roxadustat vs. Placebo

Averaged over Weeks 28 – 52	Mean Change from Baseline in Hb (g/dL) *
Difference (95% CI)	**1.72** (1.65, 1.79)
P-value	**< 0.001**

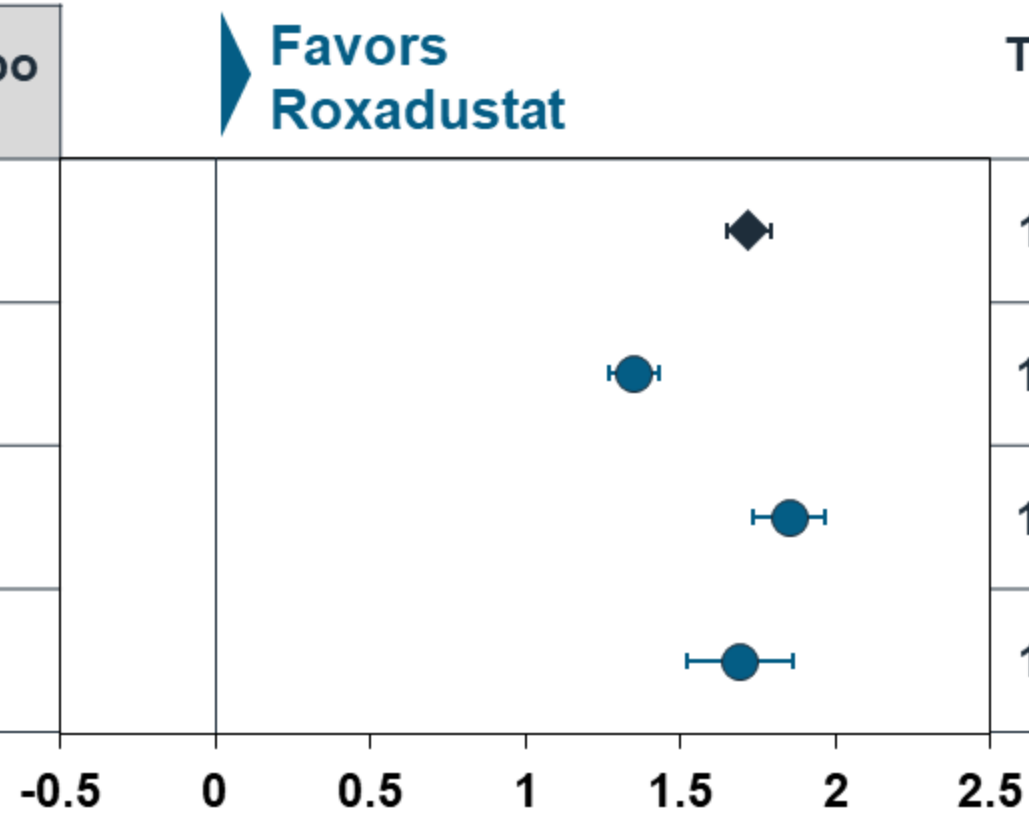


Roxadustat	2368	2229	2162	2104	2060	2028	1994	1947	1907	1850	1845	1799	1766	1730
Placebo	1865	1751	1686	1597	1519	1451	1385	1340	1265	1216	1160	1115	1060	1041

* ITT; ** FAS

NDD: Consistent Hb Improvement with Roxadustat Across Pivotal Phase 3 Studies

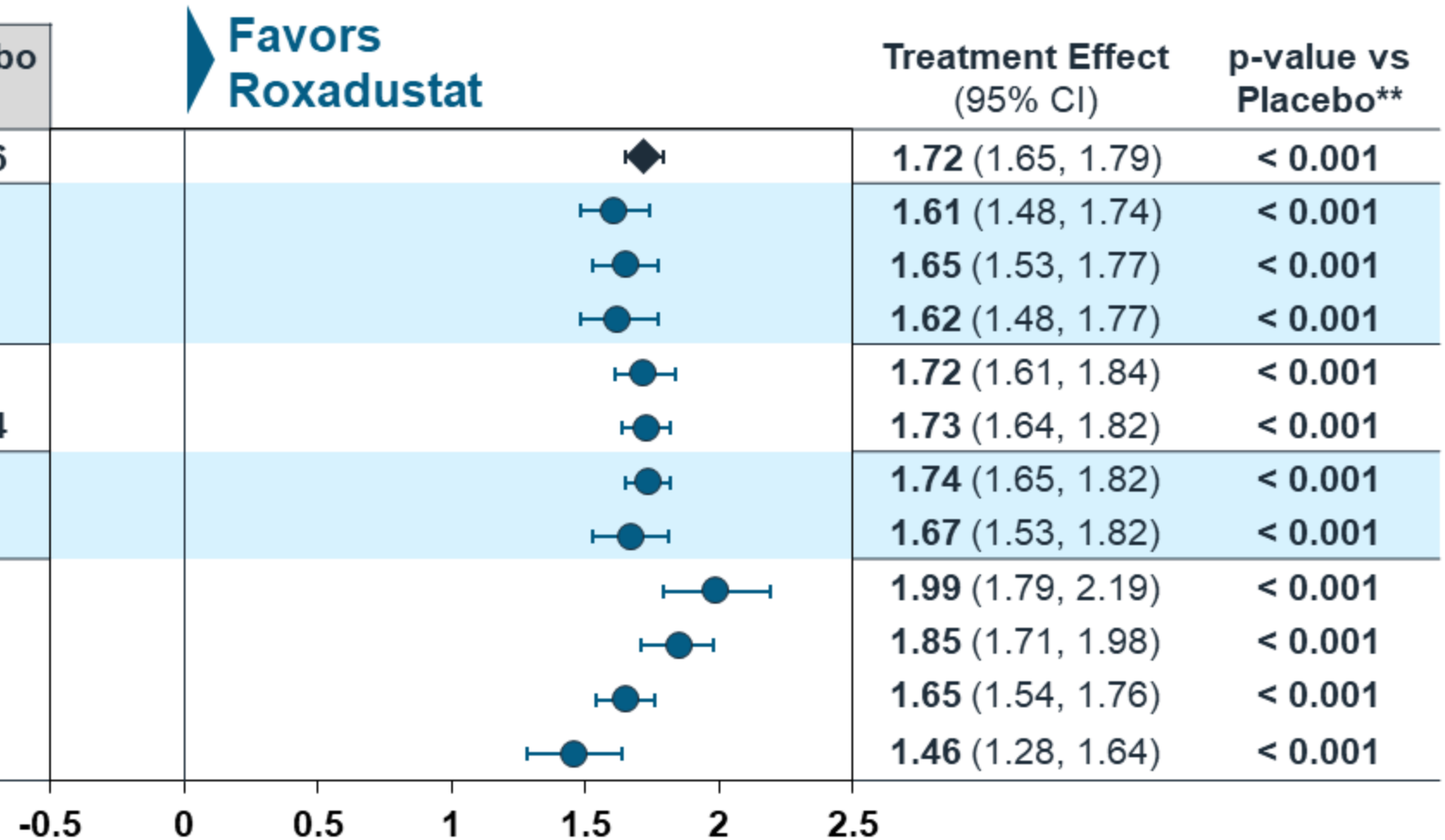
	Roxa N	Placebo N	Treatment Effect (95% CI)	p-value vs Placebo
Pooled NDD	2391	1886	**1.72** (1.65, 1.79)	**< 0.001**
Study 001	1384	1377	**1.35** (1.27, 1.43)	**< 0.001**
Study 060	616	306	**1.85** (1.74, 1.97)	**< 0.001**
Study 608	391	203	**1.69** (1.52, 1.86)	**< 0.001**



ITT for pooled NDD
Using the prespecified methods for each individual study (ITT: 001, OT+7: 060 and 608)

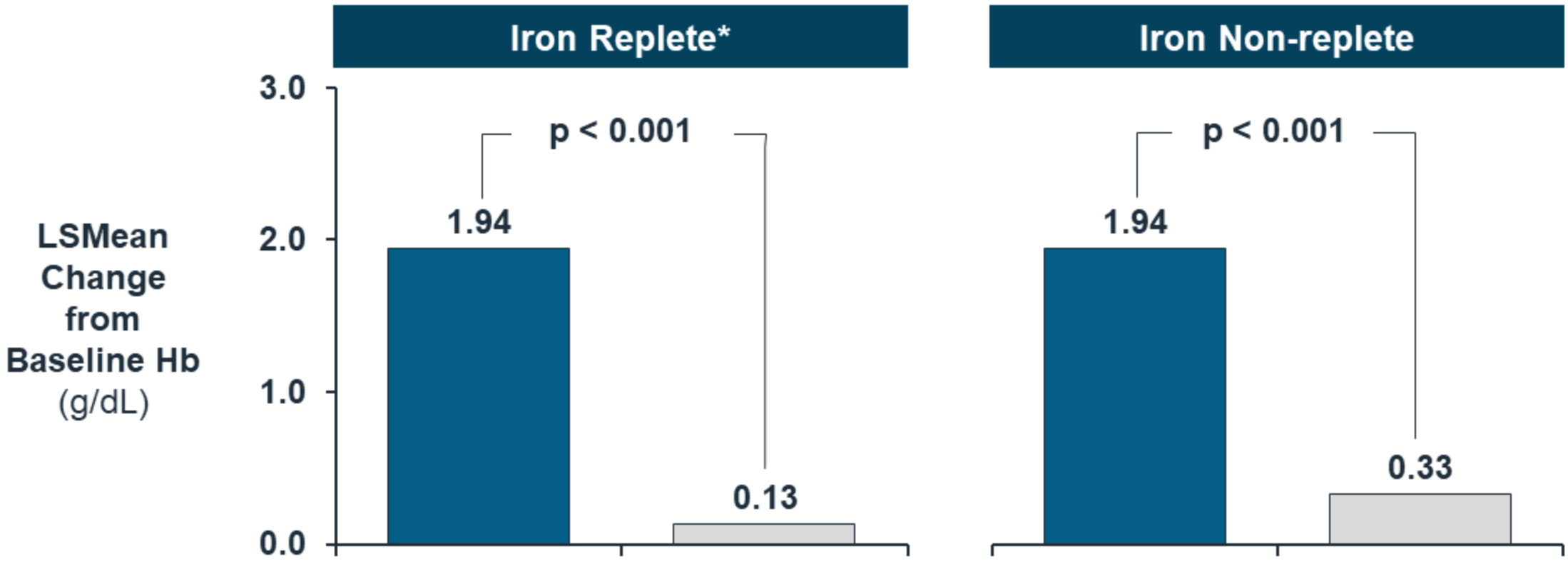
NDD: Roxadustat Treatment Effect by Subgroup

	Roxa N	Placebo N	Treatment Effect (95% CI)	p-value vs Placebo**
Pooled NDD	2391	1886	**1.72** (1.65, 1.79)	< 0.001
US	552	441	**1.61** (1.48, 1.74)	< 0.001
Europe	597	447	**1.65** (1.53, 1.77)	< 0.001
Other	1242	998	**1.62** (1.48, 1.77)	< 0.001
Male	974	832	**1.72** (1.61, 1.84)	< 0.001
Female	1417	1054	**1.73** (1.64, 1.82)	< 0.001
CRP ≤ ULN	1222	855	**1.74** (1.65, 1.82)	< 0.001
CRP > ULN	526	357	**1.67** (1.53, 1.82)	< 0.001
eGFR < 10*	481	359	**1.99** (1.79, 2.19)	< 0.001
eGFR 10 - < 15*	526	452	**1.85** (1.71, 1.98)	< 0.001
eGFR 15 - < 30*	954	724	**1.65** (1.54, 1.76)	< 0.001
eGFR ≥ 30*	430	351	**1.46** (1.28, 1.64)	< 0.001



ITT
*ml/min/1.73 m^2
**p-value not controlled for multiplicity

NDD: Treatment Effect of Roxadustat Regardless of Iron Repletion Status at Baseline

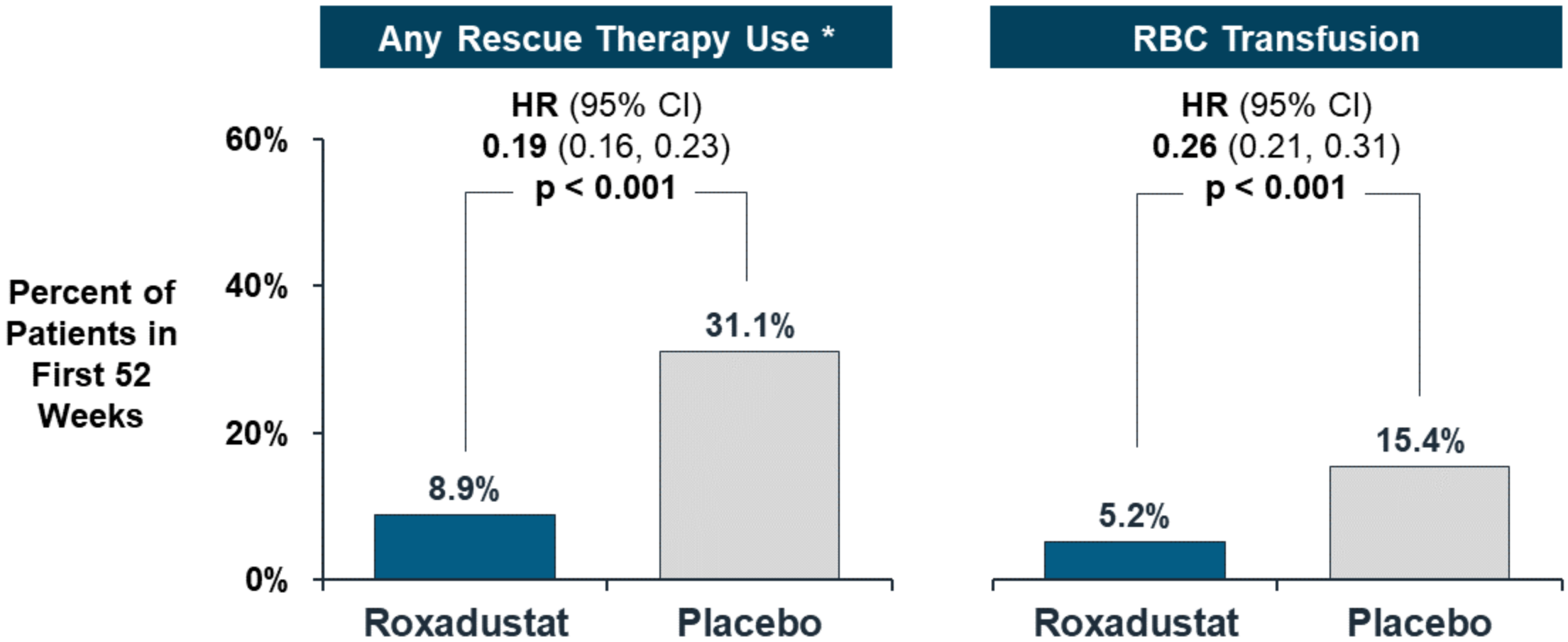


Mean Weekly Dose	Roxadustat n = 1433	Placebo n = 1127	Roxadustat n = 956	Placebo n = 755
52-week average	2.99 mg/kg	-	3.00 mg/kg	-

Post hoc analysis

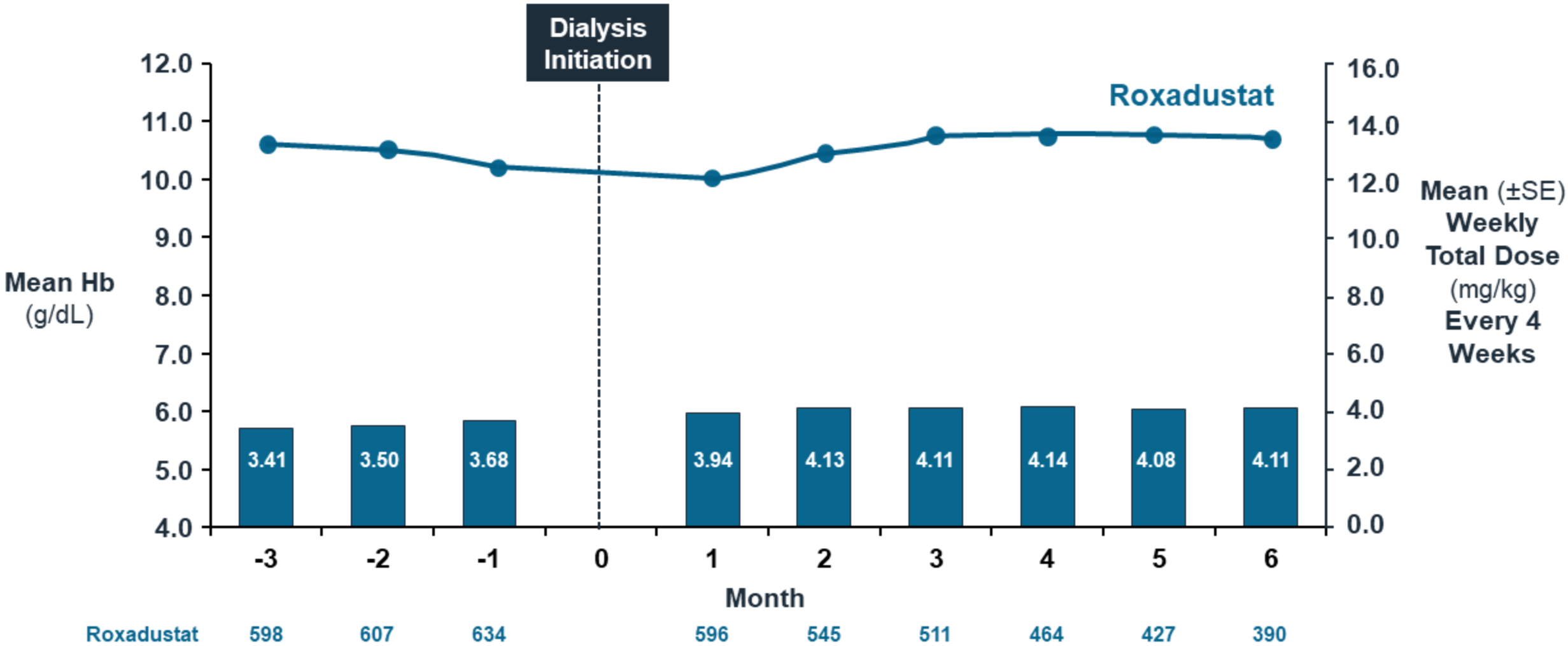
*Iron replete defined as TSAT ≥ 20% and ferritin ≥ 100 ng/mL; ITT, mean change from baseline to average of weeks 28 – 52

NDD: Fewer Roxadustat Patients Required Any Rescue or Transfusion



* Any Rescue = Transfusion, IV Iron or ESA rescue
RBC transfusion prespecified secondary endpoint in Study 001 and Study 060

Mean Hb and Weekly Roxadustat Dose Prior to and After Chronic Dialysis Initiation in NDD-ID



Roxadustat Corrects and Maintains Hb in NDD Patients with Anemia of CKD

Non-Dialysis-Dependent

- Statistically significant and clinically meaningful treatment differences in Hb favoring roxadustat compared to placebo
  - Increases in Hb regardless of baseline iron repletion status
  - Reduces RBC transfusions and the administration of IV iron

Dialysis-Dependent (DD)

Study 002 [ROCKIES]

Study 063 [HIMALAYAS]

Study 064 [SIERRAS]

Design of Pivotal Phase 3 Studies in Patients with Dialysis- Dependent CKD

	Pivotal Phase 3 DD Studies		
	Study 002 ROCKIES	**Study 063** HIMALAYAS	**Study 064** SIERRAS
Region	Global	Global	United States
Design	Open-label	Open-label	Open-label
Control	Epoetin alfa	Epoetin alfa	Epoetin alfa
Randomization scheme	1:1	1:1	1:1
Duration (years)	≤ 4	≤ 4	≤ 4
Baseline Hb (g/dL)	< 12 if on ESA or < 10	≤ 10	9.0 – 12 (DD) 8.5 – 12 (ID-DD)

DD: Primary Efficacy Endpoint Consistent Across Pivotal Phase 3 Studies

- **Primary Endpoint**
  Mean change from baseline in Hb averaged over Week 28 to Week 52 regardless of rescue therapy

DD: Select Secondary and Additional Endpoints

Hb-related

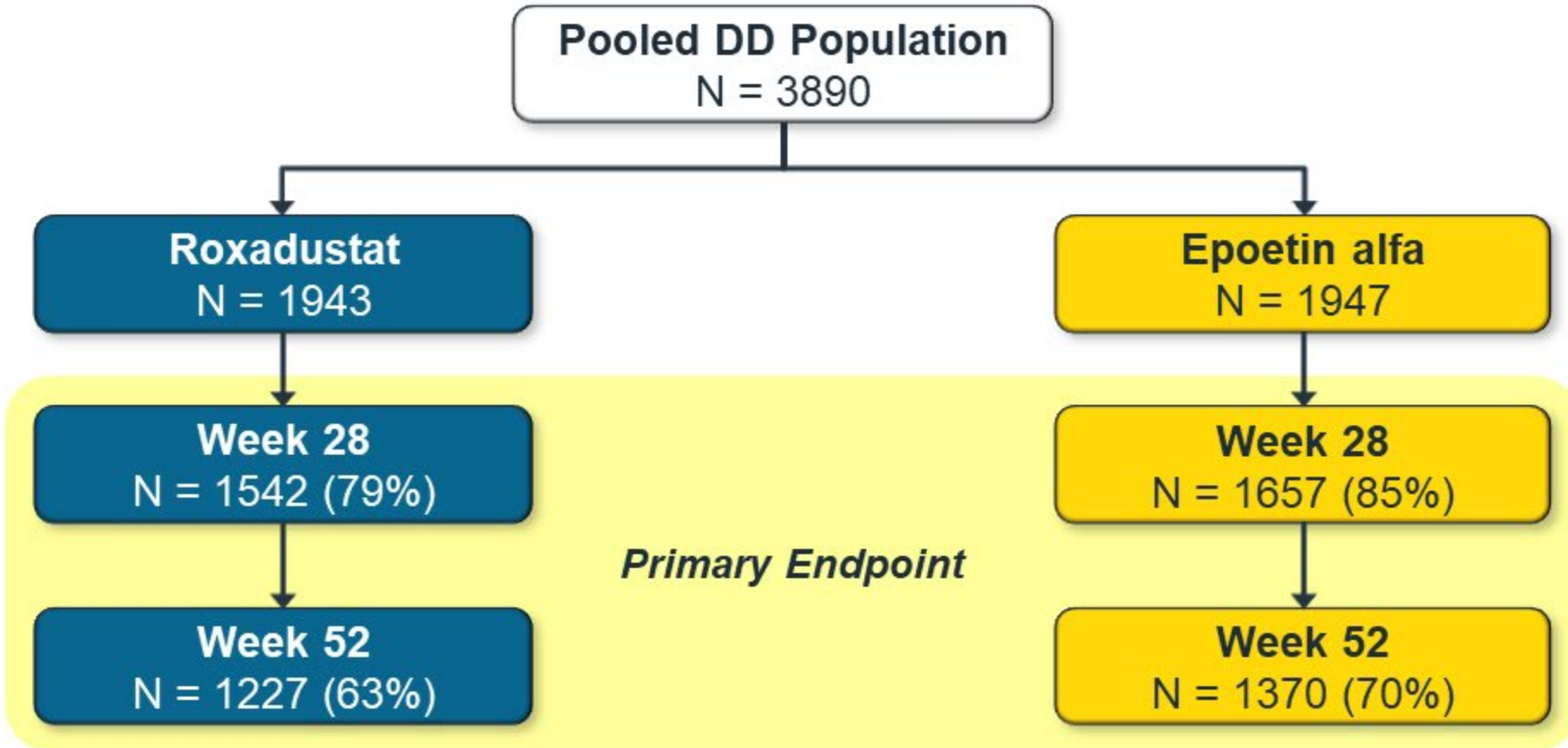
1. Hb by inflammation status*
2. % requiring RBC transfusion*
3. IV iron use*

Non Hb-related

4. Change in hepcidin and iron parameters

*Secondary Endpoint

DD: Patient Disposition up to 1 Year for Primary Efficacy Assessment



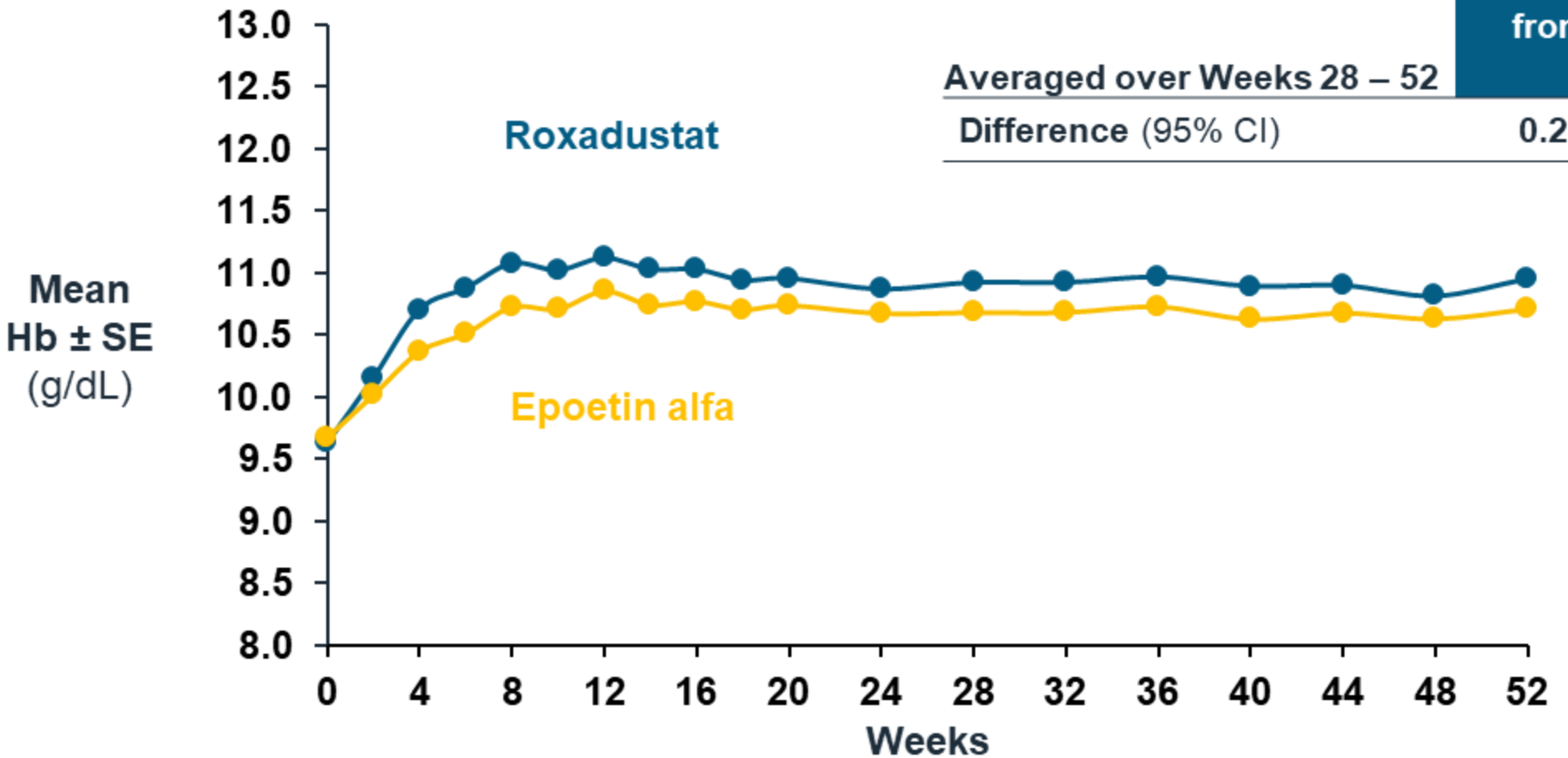
DD: Baseline Demographics Reflective of Dialysis-Dependent CKD Population

Pooled DD Population	Roxadustat N = 1943	Epoetin alfa N = 1947
Age (years); **mean** (range)	**54** (18-93)	**55** (18-94)
White	**61%**	**61%**
Black*	**18%**	**19%**
Asian	**14%**	**14%**
Diabetes	**47%**	**47%**
Hemodialysis	**91%**	**90%**
Hb level (g/dL); **mean**	**9.63**	**9.66**
hsCRP (mg/L); **mean**	**10.5**	**10.2**
TSAT (%); **mean** [< 20% considered iron deplete]	**33%**	**33%**
Ferritin (ng/mL); **mean** [normal values 100 to 300]	**610.6**	**603.2**

*Of 882 Roxadustat-treated patients enrolled in the US, 39% were Black or African American

DD: Roxadustat Comparable to Epoetin in Increasing Hb (Primary Endpoint)

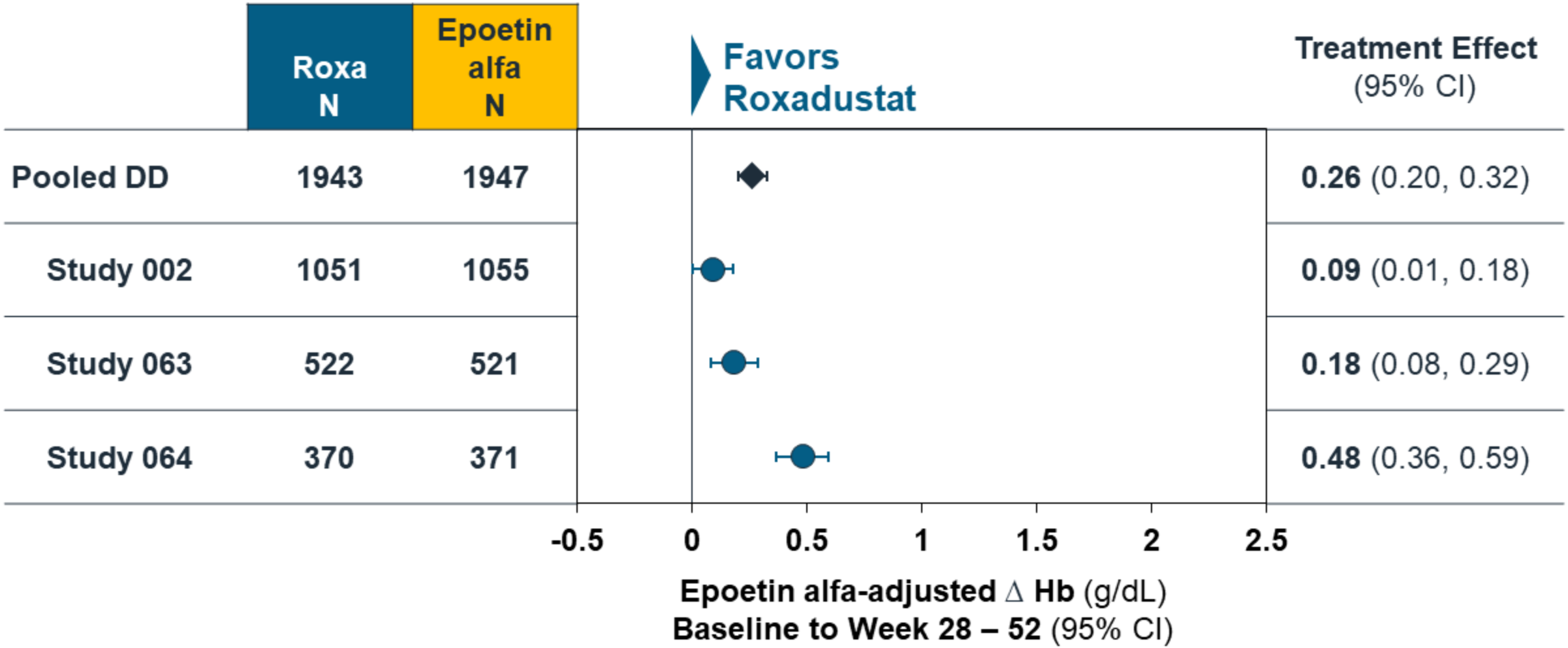
Averaged over Weeks 28 – 52	Mean Change from Baseline in Hb (g/dL)
Difference (95% CI)	**0.26** (0.20, 0.33)



Roxadustat	1929	1909	1835	1783	1729	1678	1566	1531	1485	1425	1387	1323	1271	1226
Epoetin alfa	1928	1907	1882	1849	1805	1777	1654	1634	1594	1538	1501	1458	1394	1344

ITT

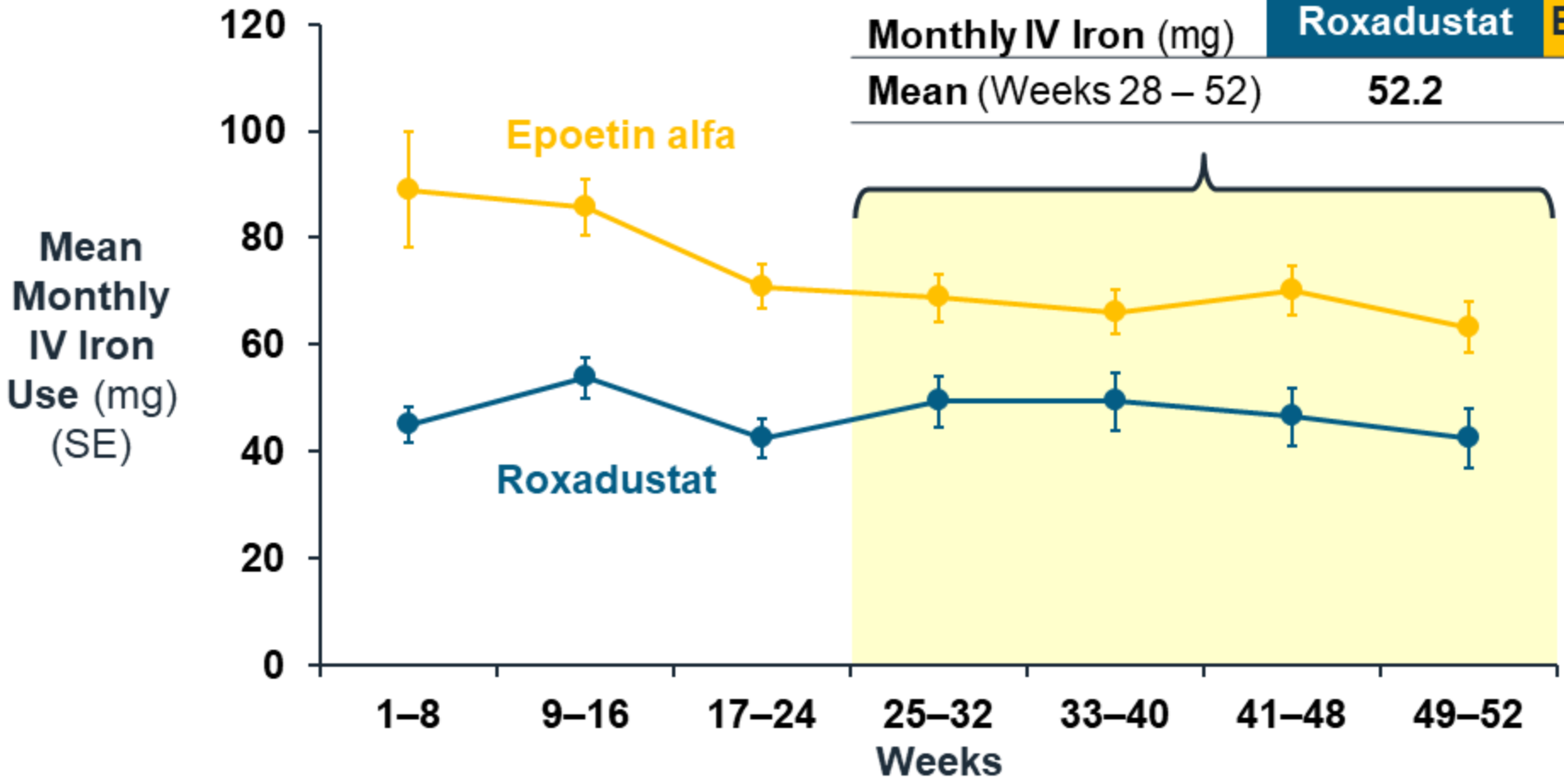
DD: Hb Improvement Consistently Observed Across Pivotal Phase 3 Studies



Using the prespecified methods for each individual study (ITT: 002, OT+7: 063 and 064)
Non-inferiority margin = -0.75

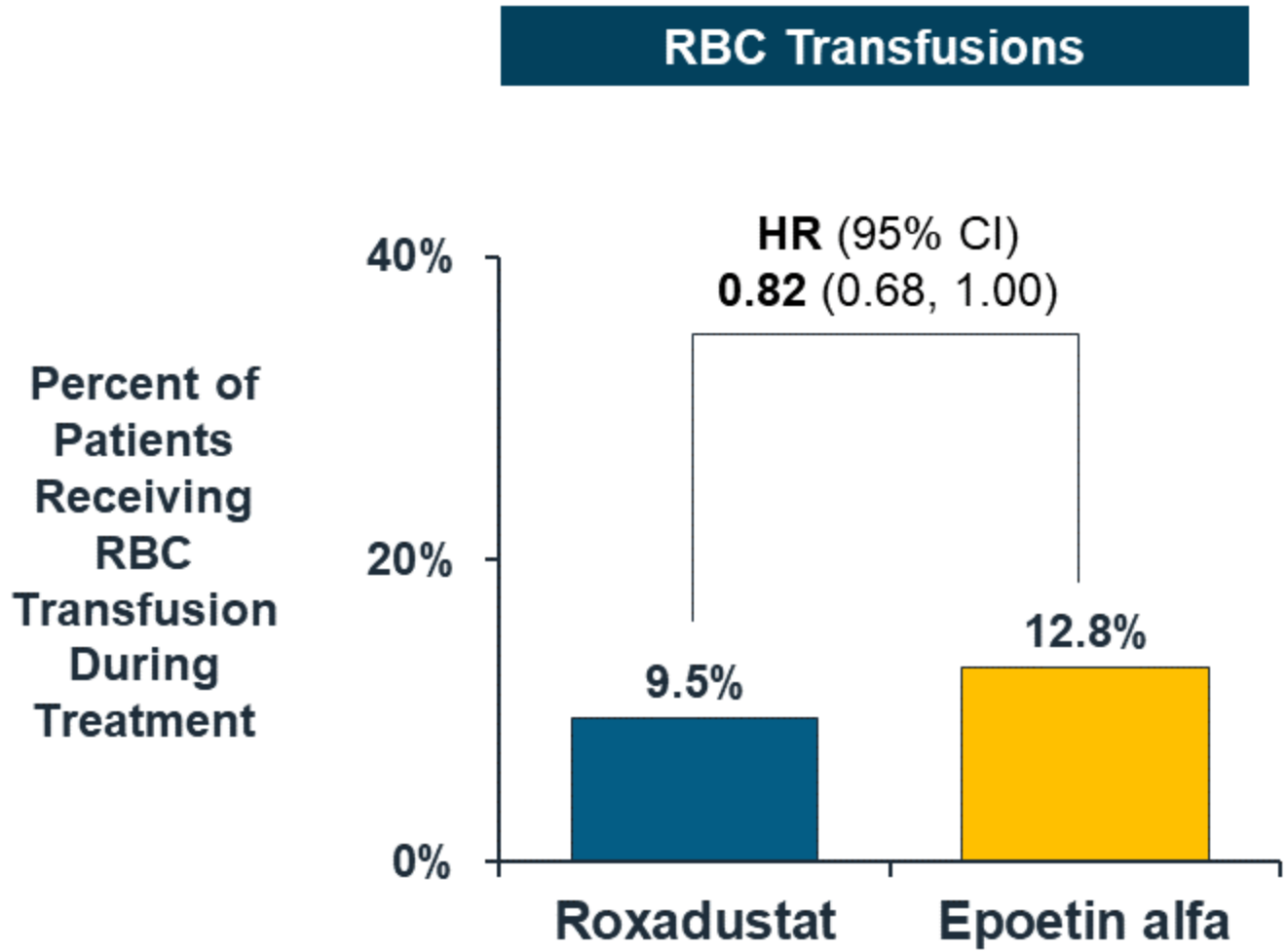
DD: Roxadustat Patients Required Less Monthly IV Iron Use

Monthly IV Iron (mg)	Roxadustat	Epoetin alfa
Mean (Weeks 28 – 52)	52.2	66.8



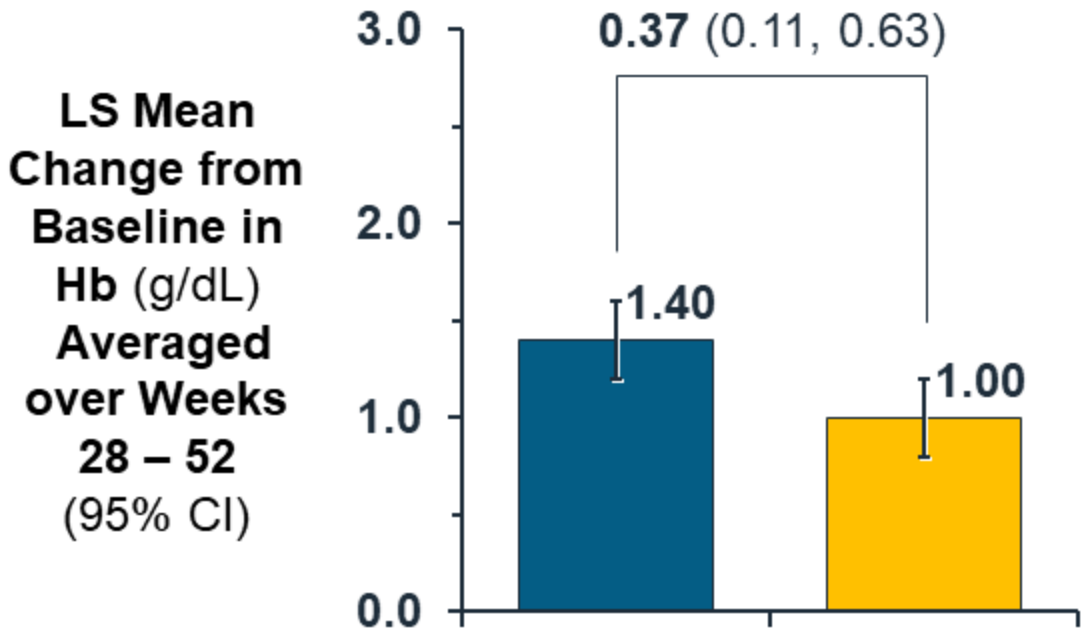
	1–8	9–16	17–24	25–32	33–40	41–48	49–52
Roxadustat	1929	1847	1761	1681	1590	1499	1406
Epoetin alfa	1928	1885	1823	1736	1659	1582	1485

DD: Fewer Roxadustat Patients Required RBC Transfusions



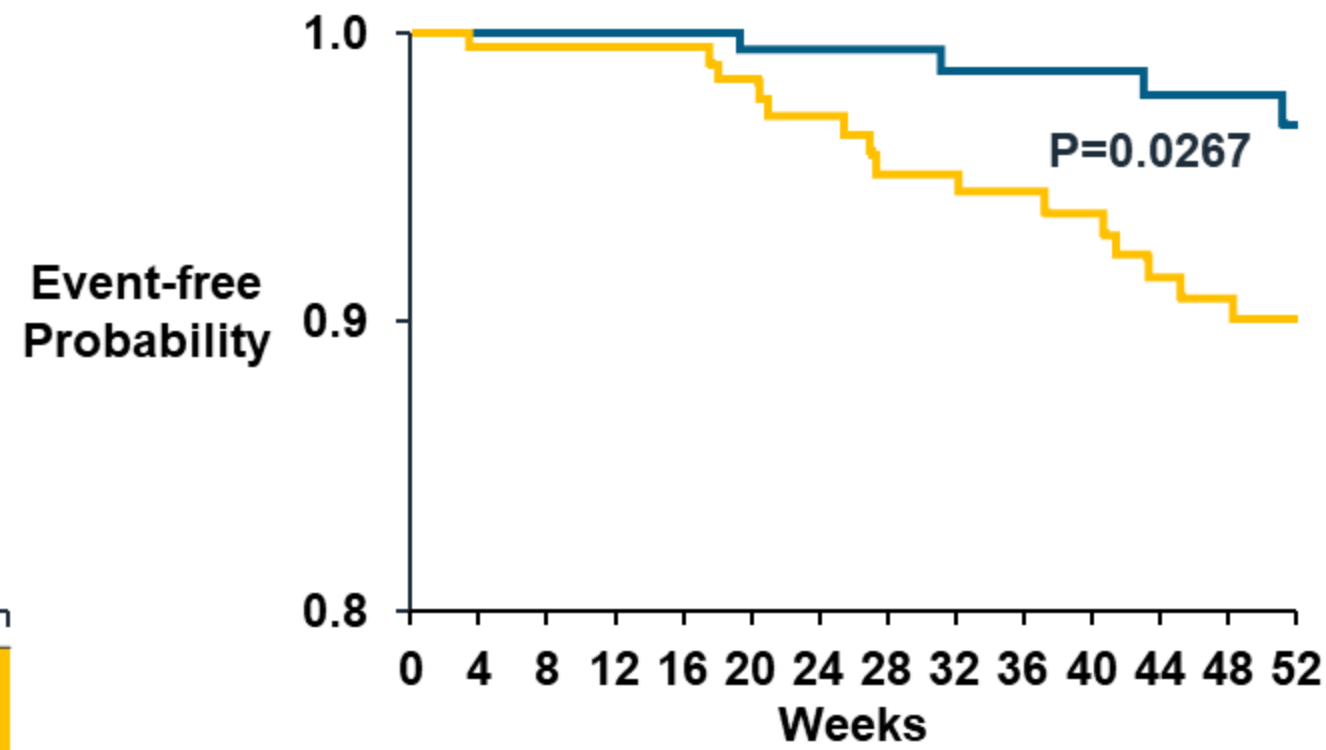
Patients Receiving Home Peritoneal Dialysis (N=372) Had Benefits Across Endpoints

Hb Change



Mean Hb (g/dL)	Roxadustat N = 180	Epoetin alfa N = 192
Baseline	9.58	9.56
Week 28 – 52 (averaged)	11.00	10.64

Time to First RBC Transfusion*



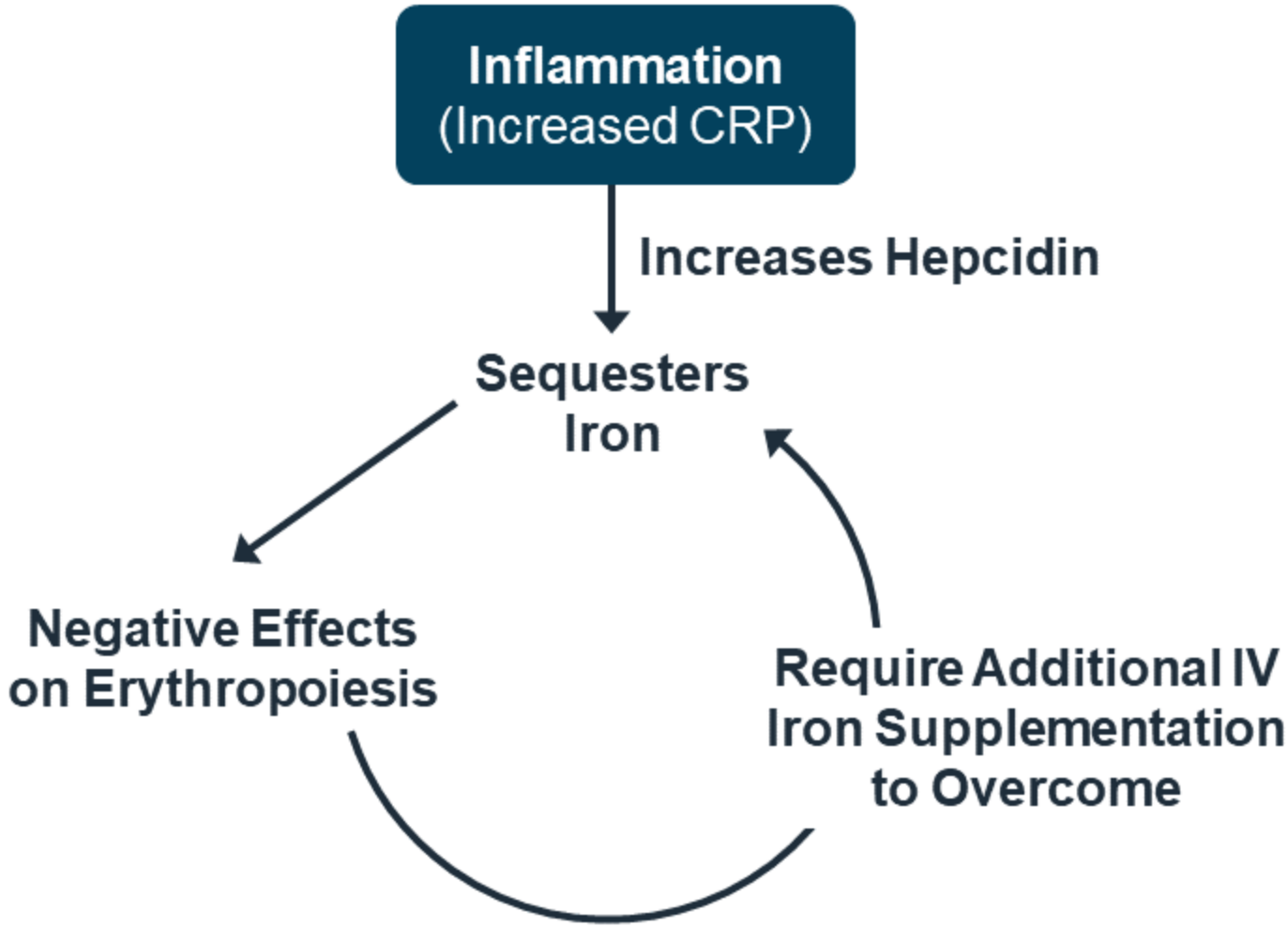
Roxadustat	177	169	163	160	158	151	143	137	129	121	116	109	101	95
Epoetin alfa	188	182	177	174	168	160	151	146	139	133	130	126	116	105

Peritoneal Dialysis (N = 372) – 9.6% of enrolled DD population

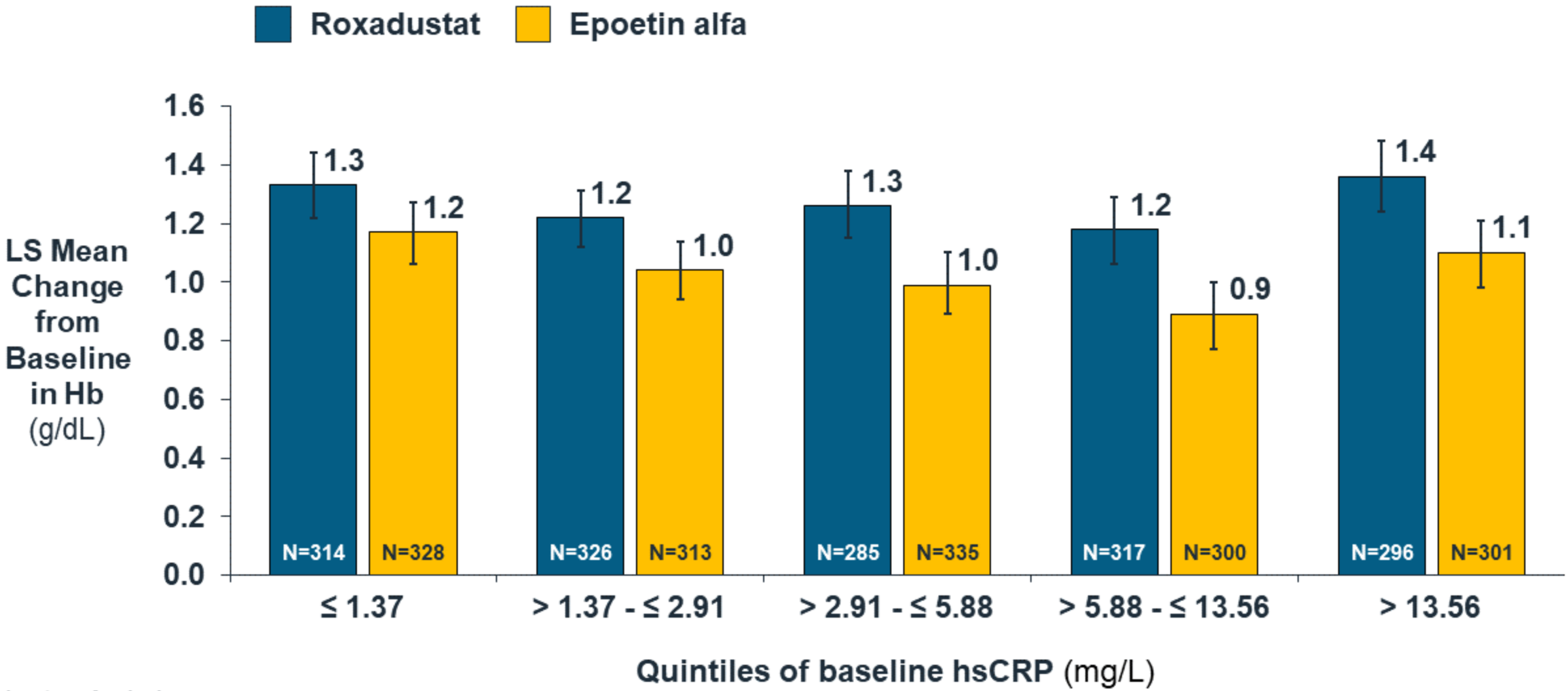
* Not controlled for multiplicity

Inflammation, Hepcidin Reduction, and Iron Mobilization

Effect of Inflammation on Erythropoiesis and Anemia Treatment is Complicated

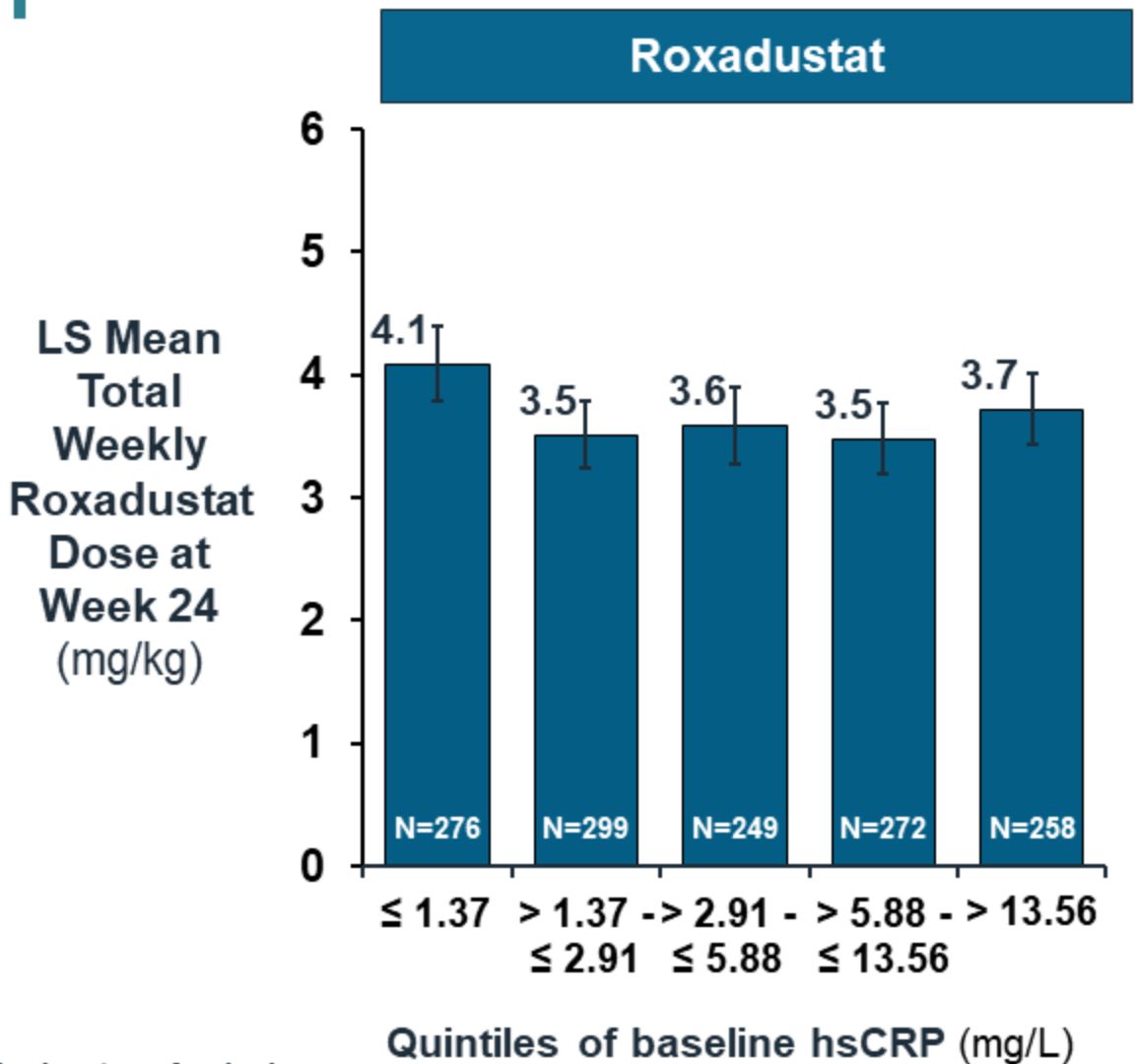


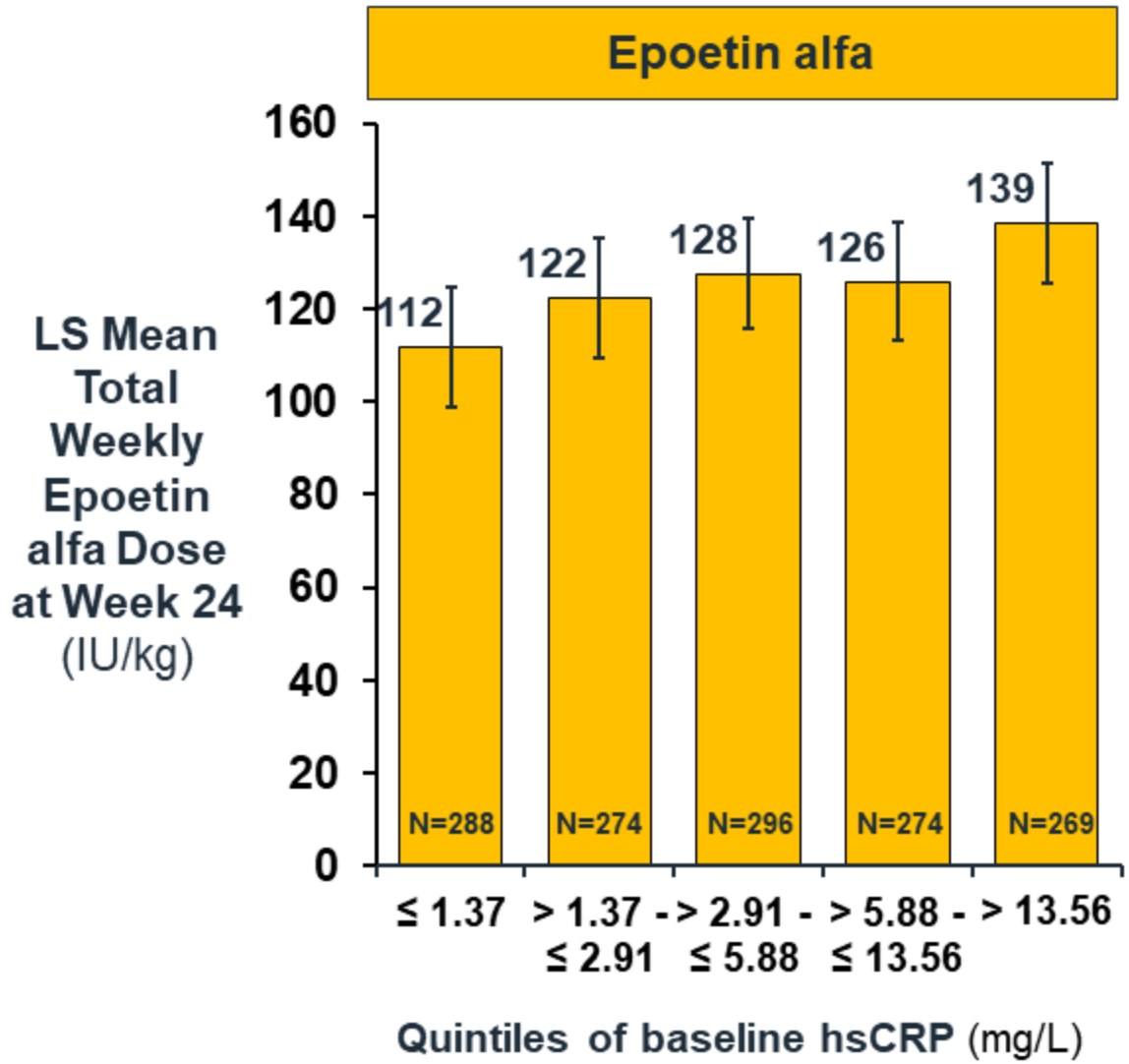
DD: Hb Across Quintiles of Baseline hsCRP



Exploratory Analysis

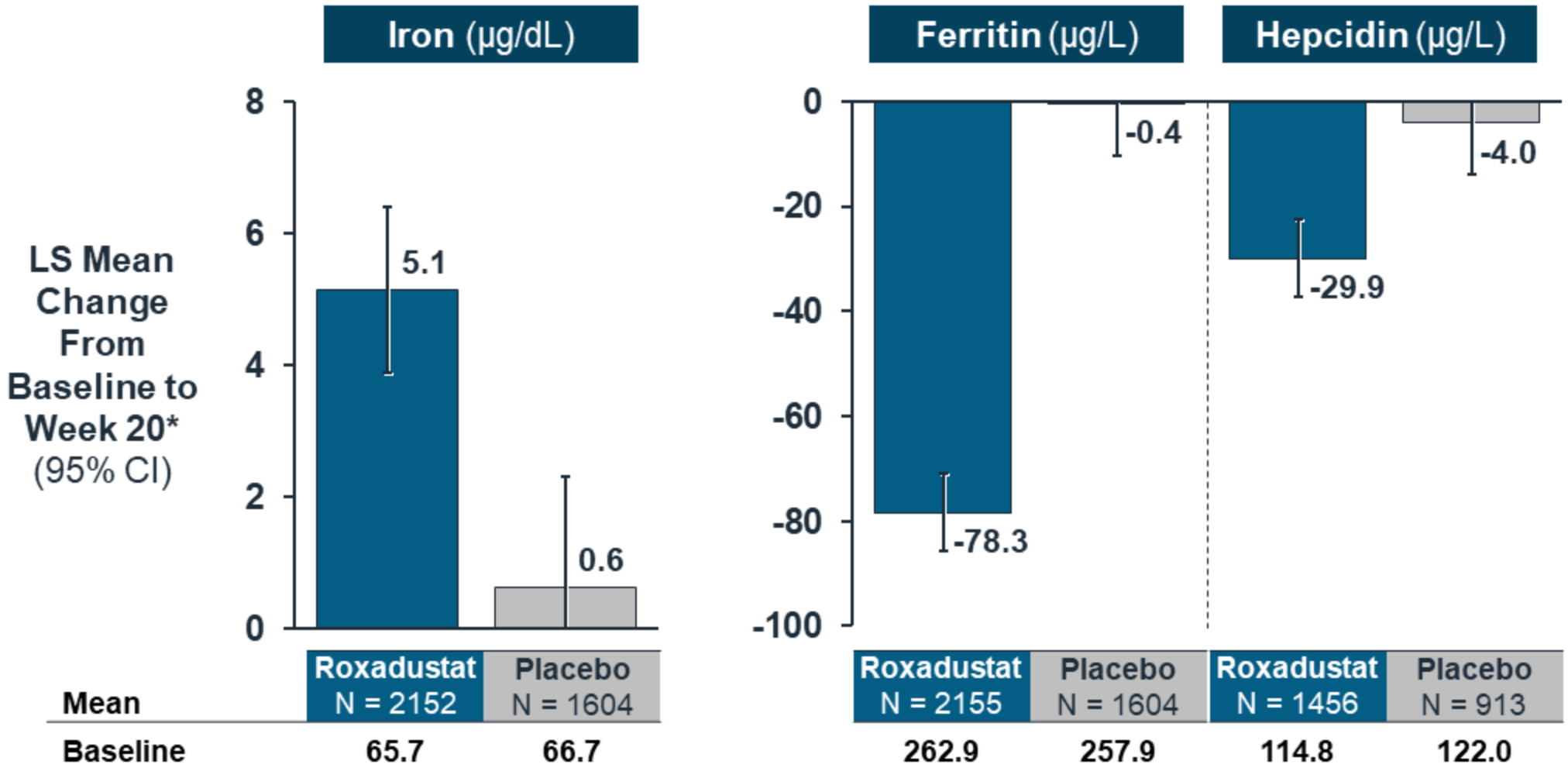
DD: Roxadustat Doses Stable, Whereas Epoetin Alfa Doses Increased Across hsCRP Quintiles





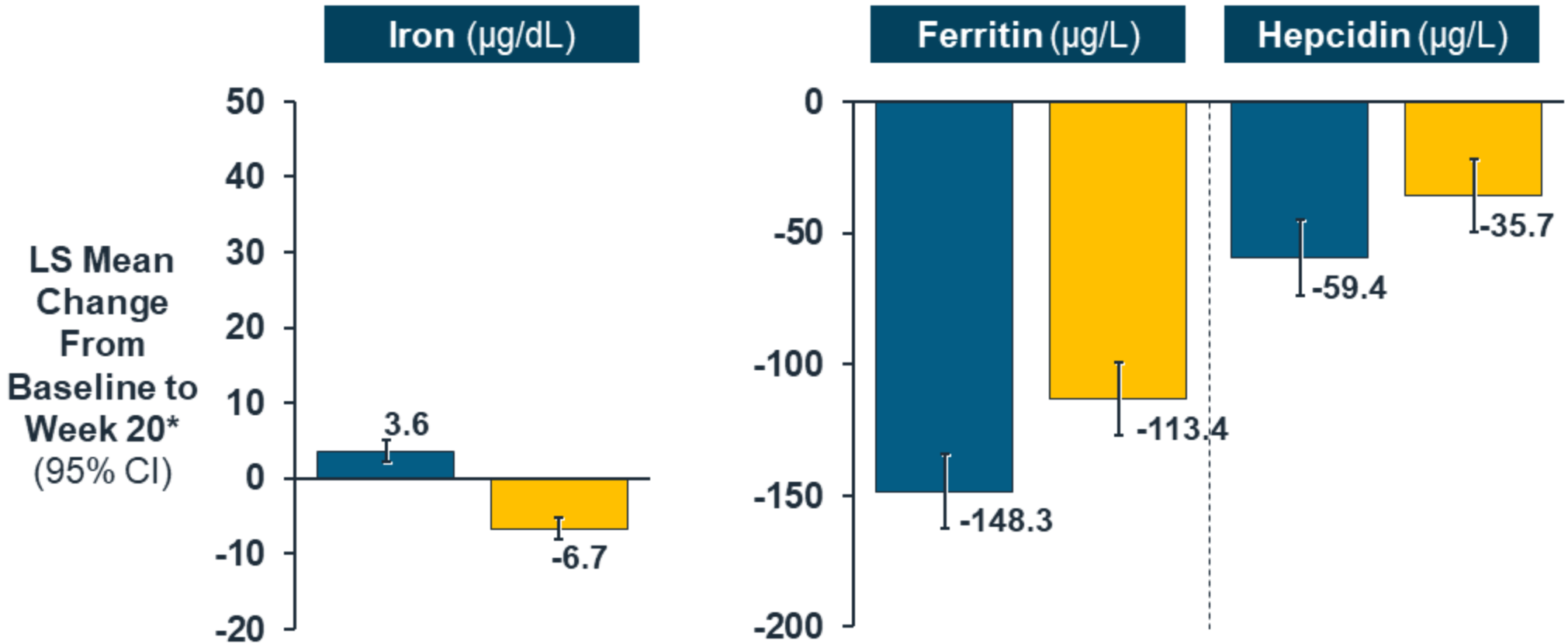
Exploratory Analysis

NDD: Roxadustat Beneficial Effect on Iron Parameters and Hepcidin Levels



*Week 20 = the mean of Weeks 12 – 28; hepcidin data is mean change from BL to Week 24

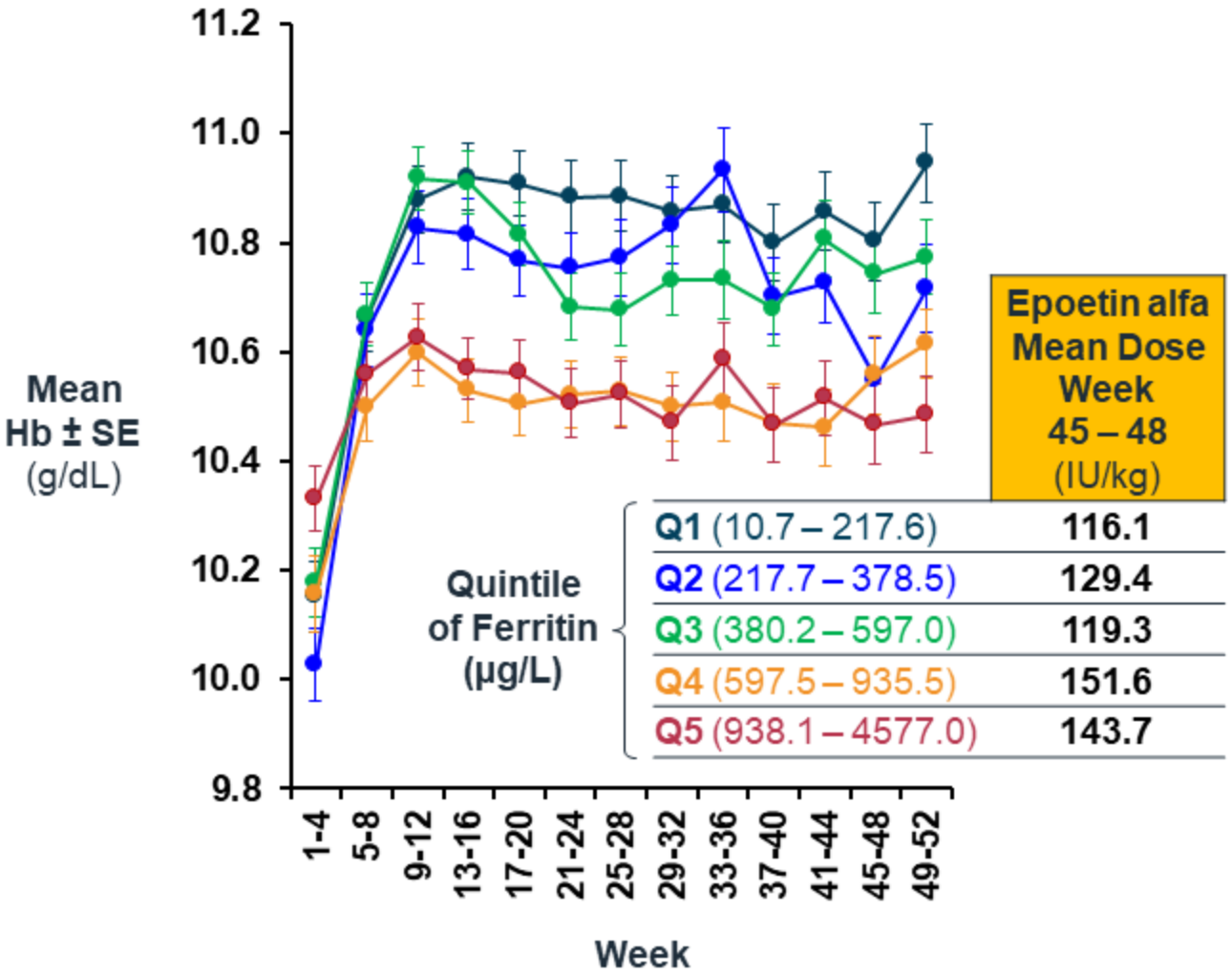
DD: Roxadustat Beneficial Effect on Iron Parameters and Hepcidin Levels

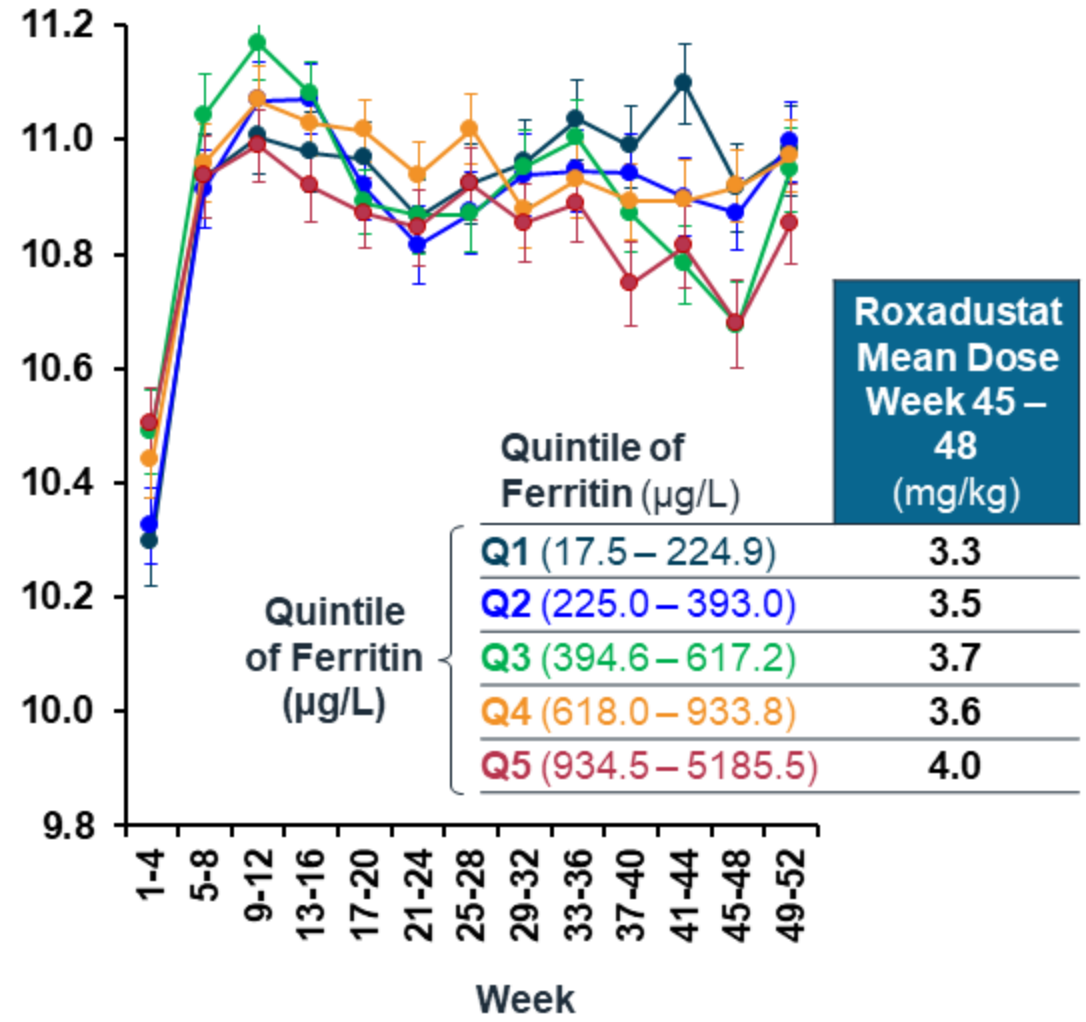


Mean	Roxadustat N = 1737	Epoetin alfa N = 1819	Roxadustat N = 1736	Epoetin alfa N = 1819	Roxadustat N = 1326	Epoetin alfa N = 1361
Baseline	70.2	69.7	608.6	602.2	240.6	236.9

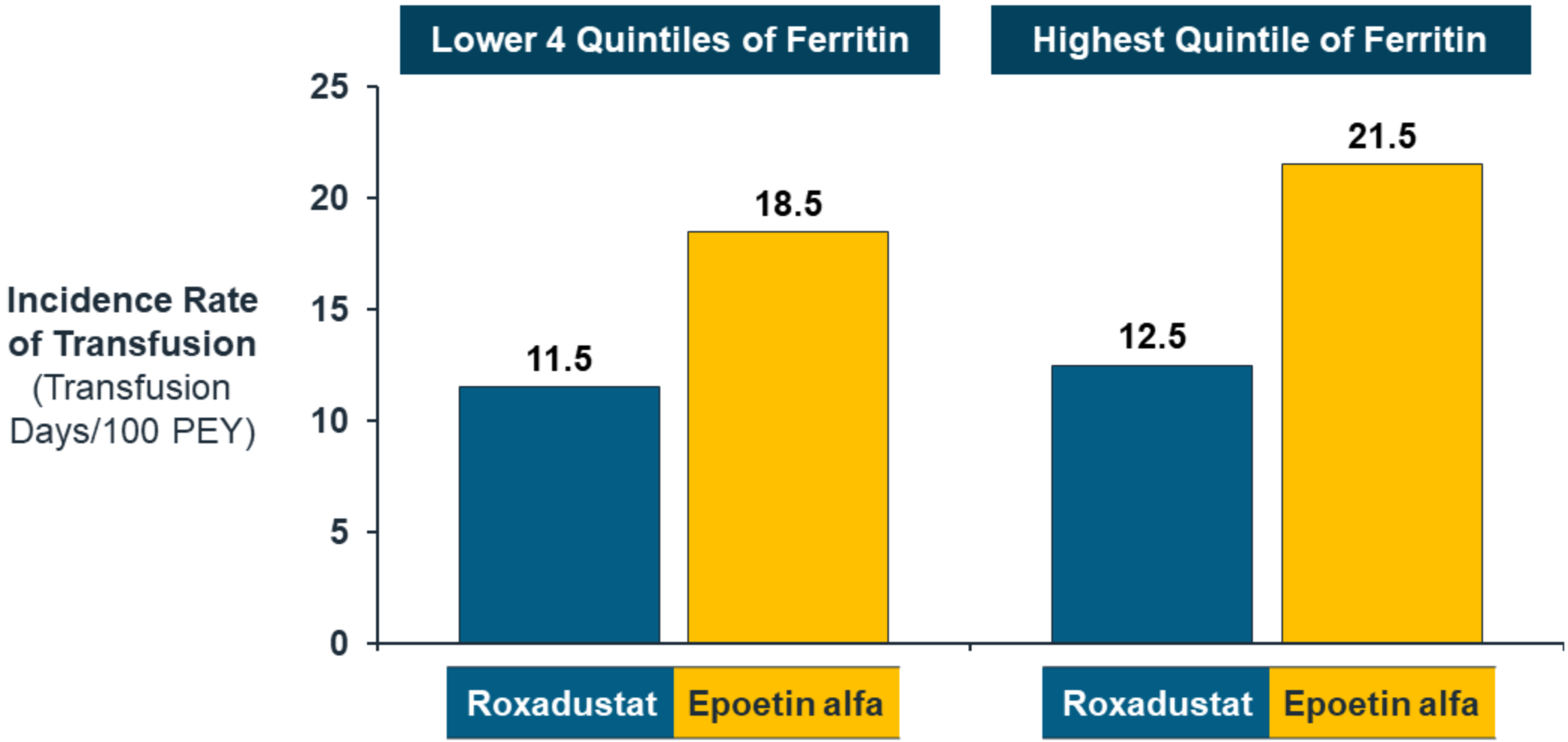
*Week 20 = mean of Weeks 12 – 28; hepcidin data is mean change from BL to Week 24

DD: Patients with Serum Ferritin Levels Reflecting Functional Iron Deficiency have Equally Robust Response to Roxadustat





DD: Roxadustat Reduced Transfusions in Patients with Highest Serum Ferritin Levels



Roxadustat Corrects and Maintains Hb in Dialysis Patients with Anemia of CKD

Dialysis-Dependent

- Roxadustat comparable Hb treatment effect to epoetin alfa
  - Consistent effect regardless of baseline inflammation
  - Fewer Roxadustat patients required RBC transfusions and IV iron use
- Benefits of roxadustat observed
  - Patients transitioning from NDD to DD
  - Incident-Dialysis and Stable-Dialysis patients
  - Patients utilizing home therapy, peritoneal dialysis

Safety Results

Dustin Little, MD

Global Clinical Head

AstraZeneca

Overview of Safety

- Cardiovascular (CV) safety in NDD and DD pools
- Additional safety
  - Seizures
  - Serious infections
  - Thrombosis
    - Vascular access thrombosis (VAT)
    - Deep vein thrombosis (DVT)
- Risk management

Roxadustat CV Safety Meta-Analysis: Background

- Program initially planned to consist of pivotal efficacy trials, without pooled CV safety
- In response to FDA feedback to evaluate cardiovascular safety, 2 large studies were added to the program (Studies 001 and 002), and meta-analysis of CV safety was planned
- Key cardiovascular safety endpoints include
  - MACE (Major adverse cardiovascular events)
    - All-cause mortality, myocardial infarction, and stroke
  - MACE+: MACE plus hospitalization for heart failure or unstable angina

Roxadustat CV Safety Meta-Analysis: High Level Overview

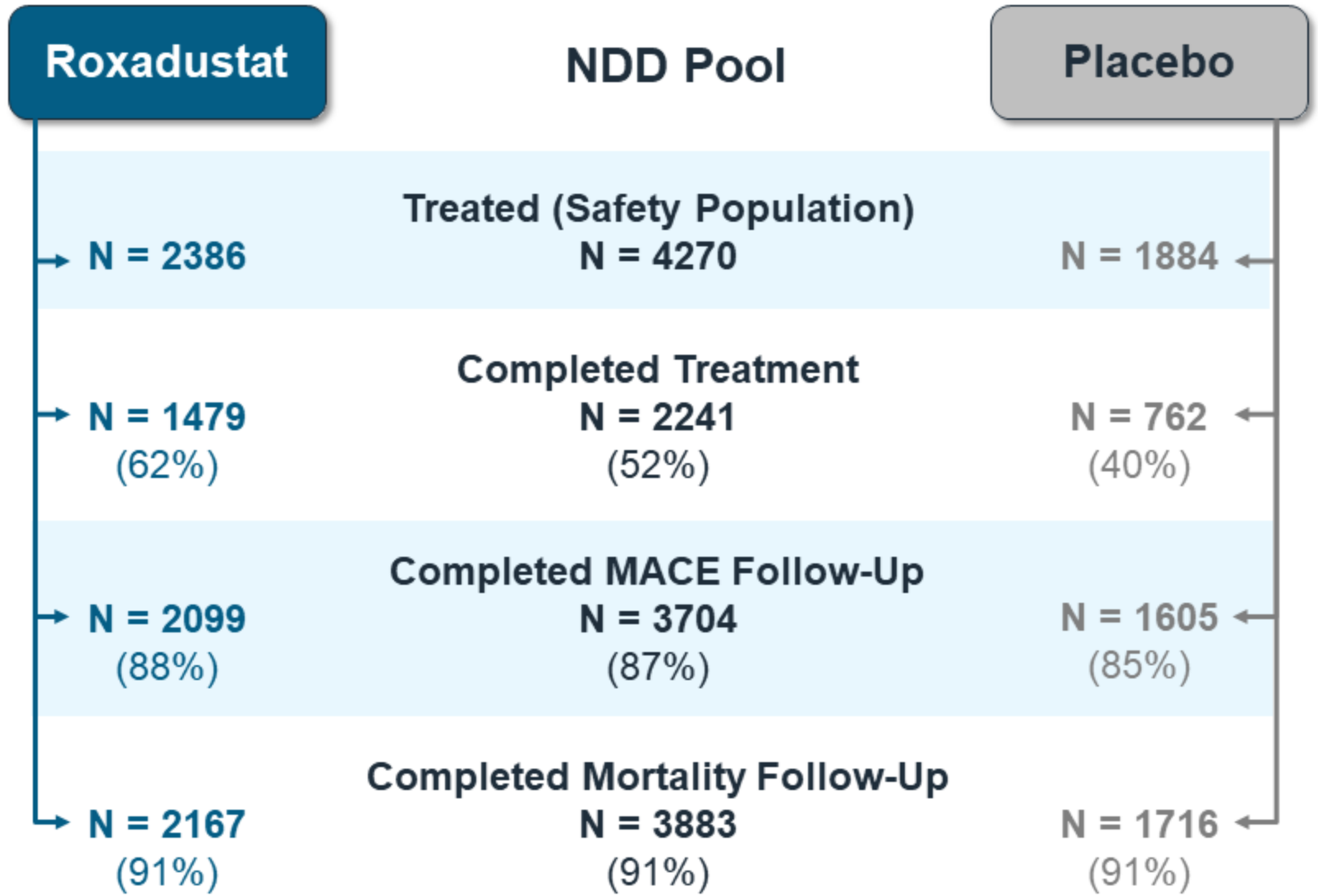
Non-Dialysis Dependent	Dialysis Dependent
Roxadustat vs. Placebo ▪ 4270 patients, 830 with MACE ▪ Asymmetric treatment discontinuation complicates interpretation of CV safety data	**Roxadustat vs. Epoetin Alfa** ▪ 3880 patients, 645 with MACE ▪ Treatment discontinuation more balanced

Methods

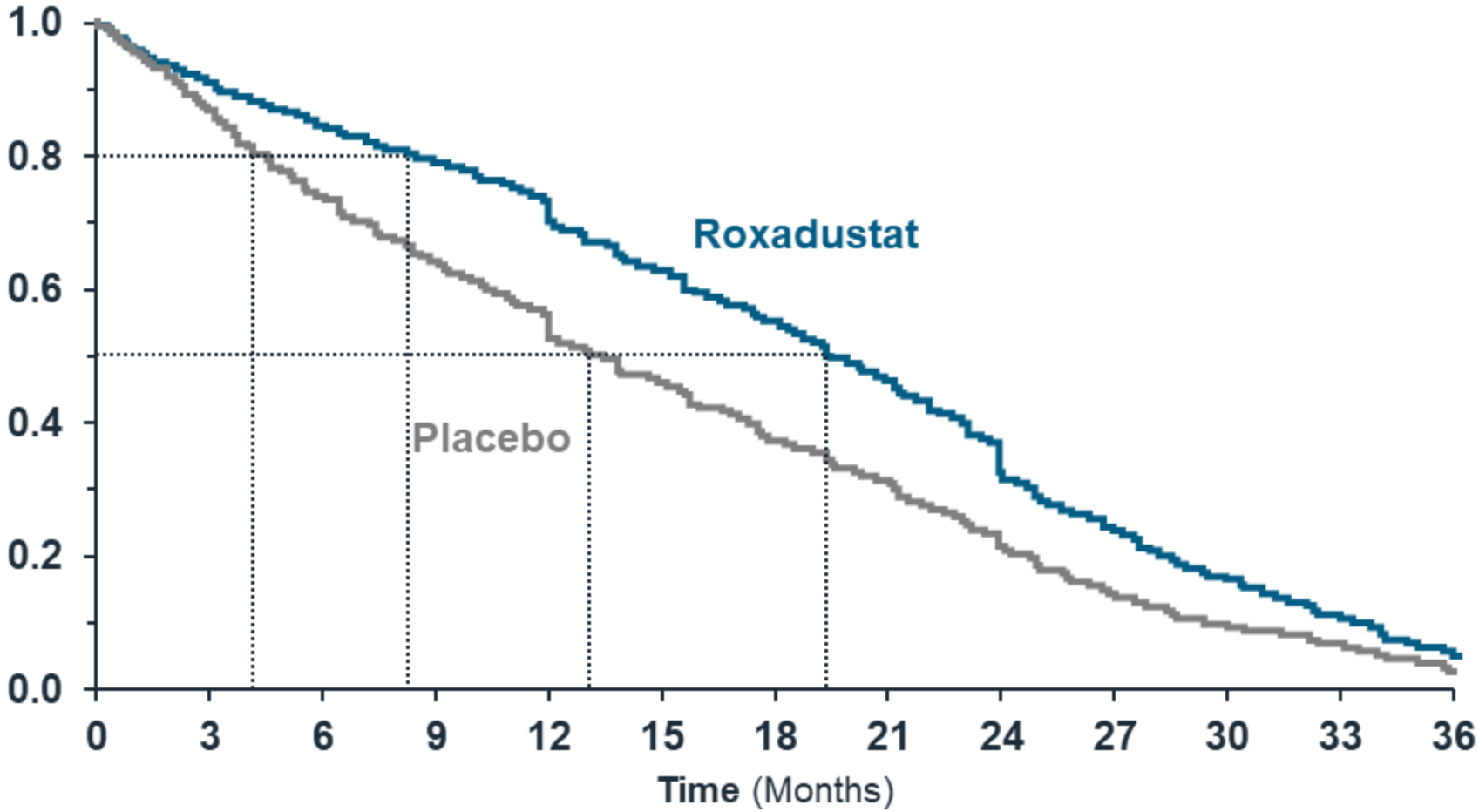
- Adjudication by blinded central Independent Event Review Committee (IERC)
- Monitored by Independent Data Monitoring Committee (IDMC)
- Sufficient precision of MACE HR to ensure 95% CI upper bound < 1.3 in each population

CV Safety in NDD

Pooled NDD: Retention and Follow-up

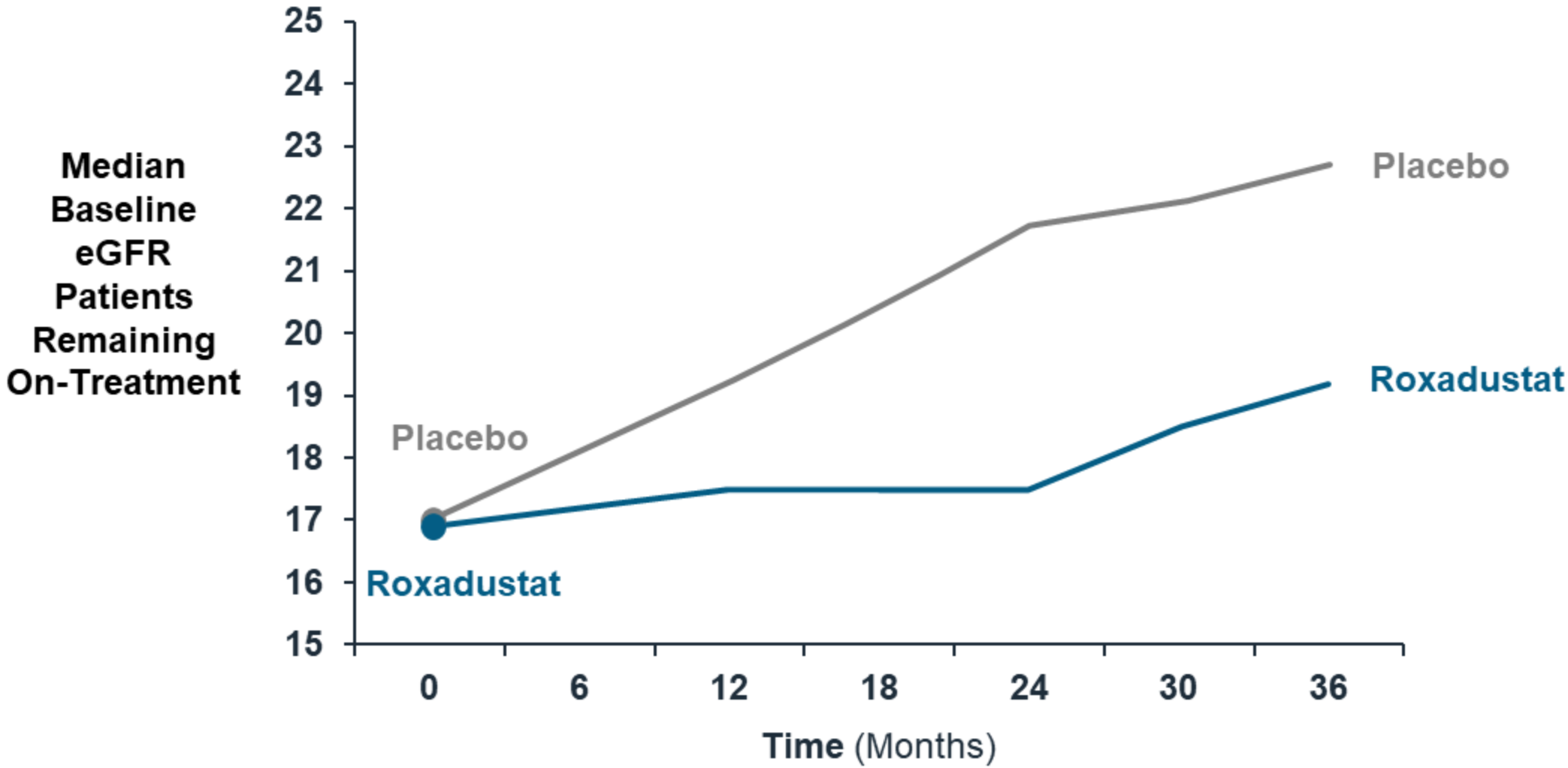


NDD: Higher Rates of Treatment Discontinuation Among Placebo Patients

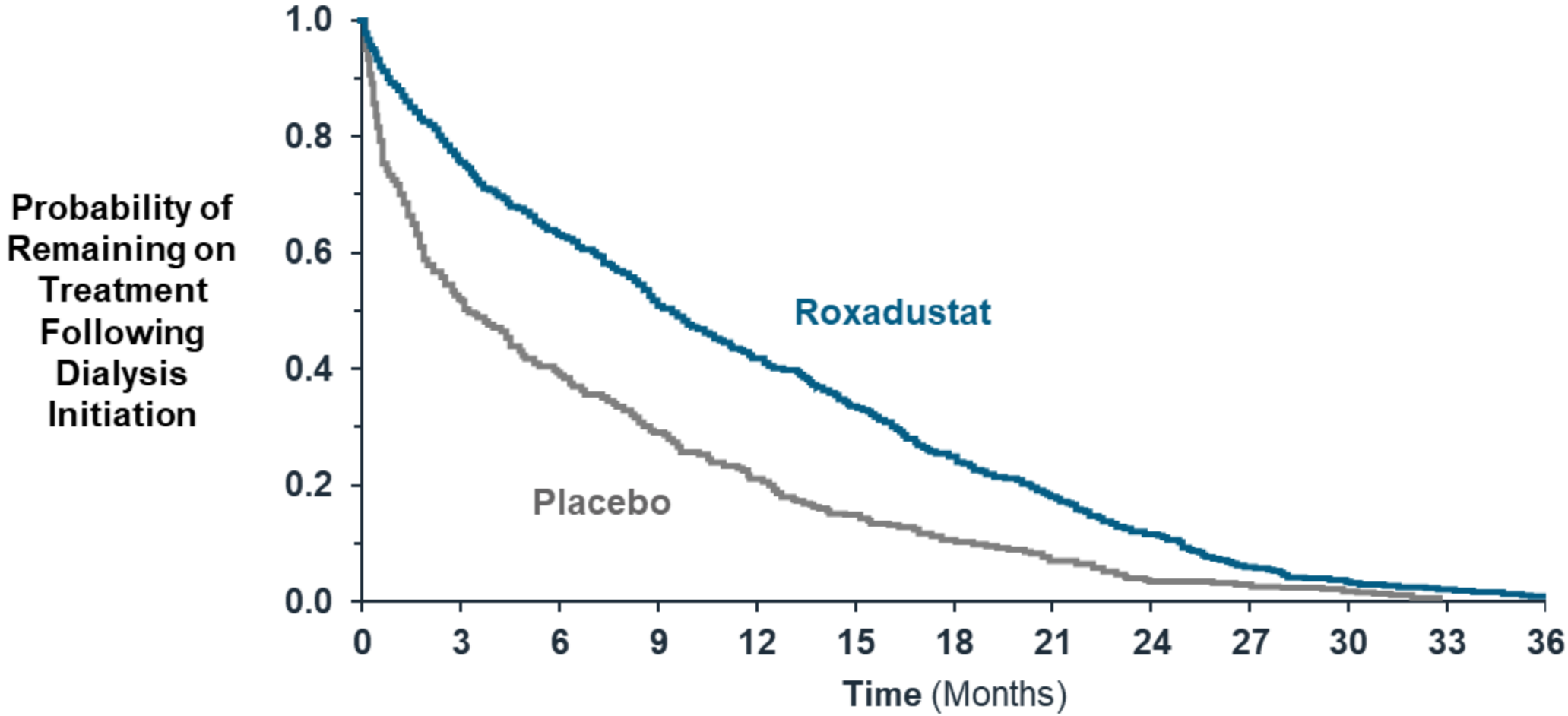


Roxadustat	2386	2020	1684	1333	789	437	165
Placebo	1884	1389	990	696	392	169	39

NDD: Higher Baseline eGFR Among Patients Remaining on Placebo vs. Roxadustat

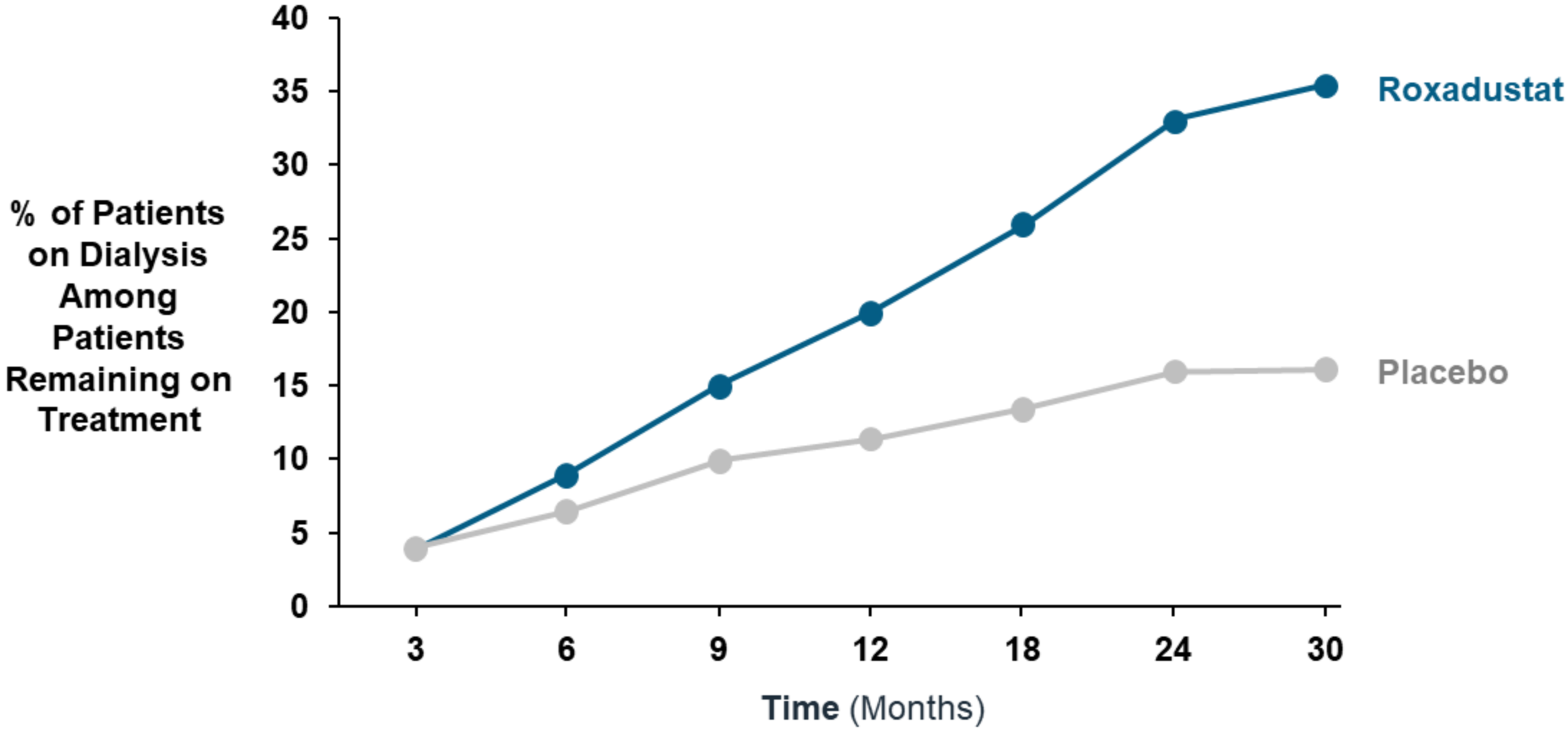


Higher Rates of Treatment Discontinuation for Placebo Patients Starting Dialysis While Receiving Study Drug

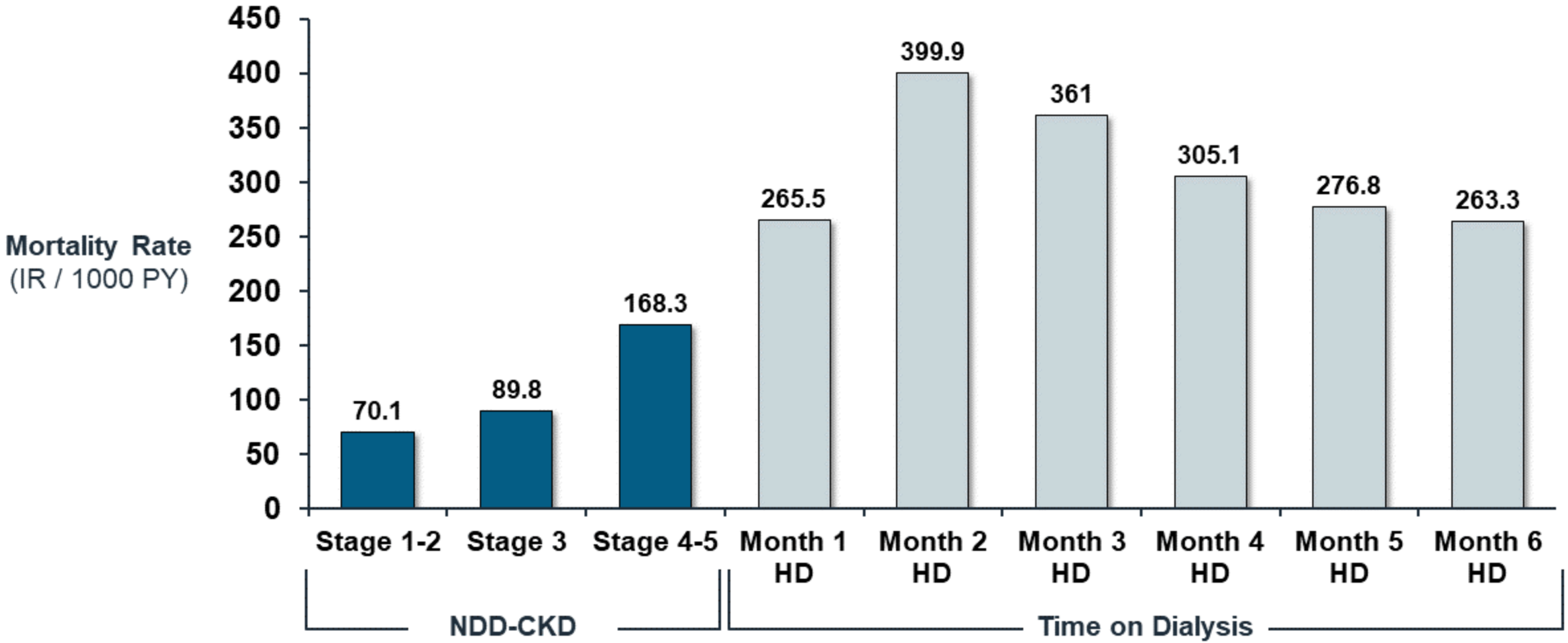


Roxadustat	746	468	310	184	85	26	5
Placebo	351	137	73	36	12	5	0

NDD: Patients Starting Dialysis Continued Roxadustat at Higher Rates



US Data: Higher Mortality Risk with More Severe CKD, Highest After Dialysis Initiation



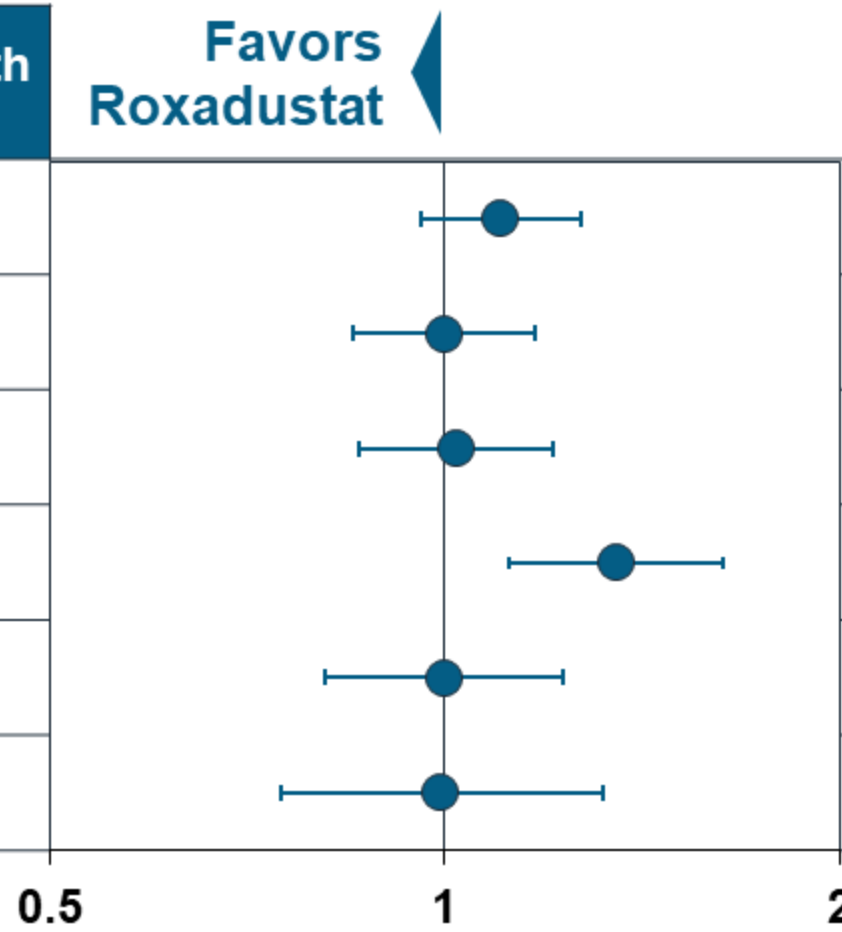
Adapted from USRDS ADR, 2020; ADR, 2015.

Characteristics of Ideal CV Safety Analysis

- Effect of randomization (equal risk by treatment group) preserved
- Minimal missing data
- Minimal time off treatment
- Adequate number of patients with events

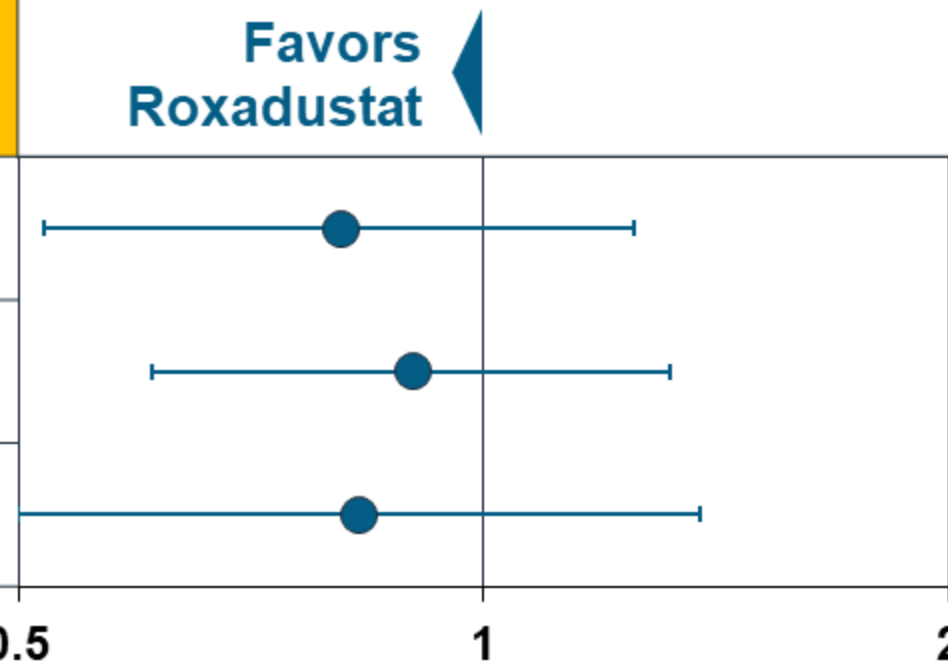
NDD Pool: Multiple Analyses Show Comparable MACE Risk for Roxadustat vs. Placebo

	Patients with Events (N)	Hazard Ratio (95% CI)
ITT / on-study	830	**1.10** (0.96, 1.27)
ITT, eGFR ≥ 10	627	**1.00** (0.85, 1.17)
ITT, censored at dialysis	568	**1.02** (0.86, 1.21)
OT+28	510	**1.35** (1.12, 1.63)
ITT, censored at 1 year	375	**1.00** (0.81, 1.23)
ITT, United States	198	**0.99** (0.75, 1.32)



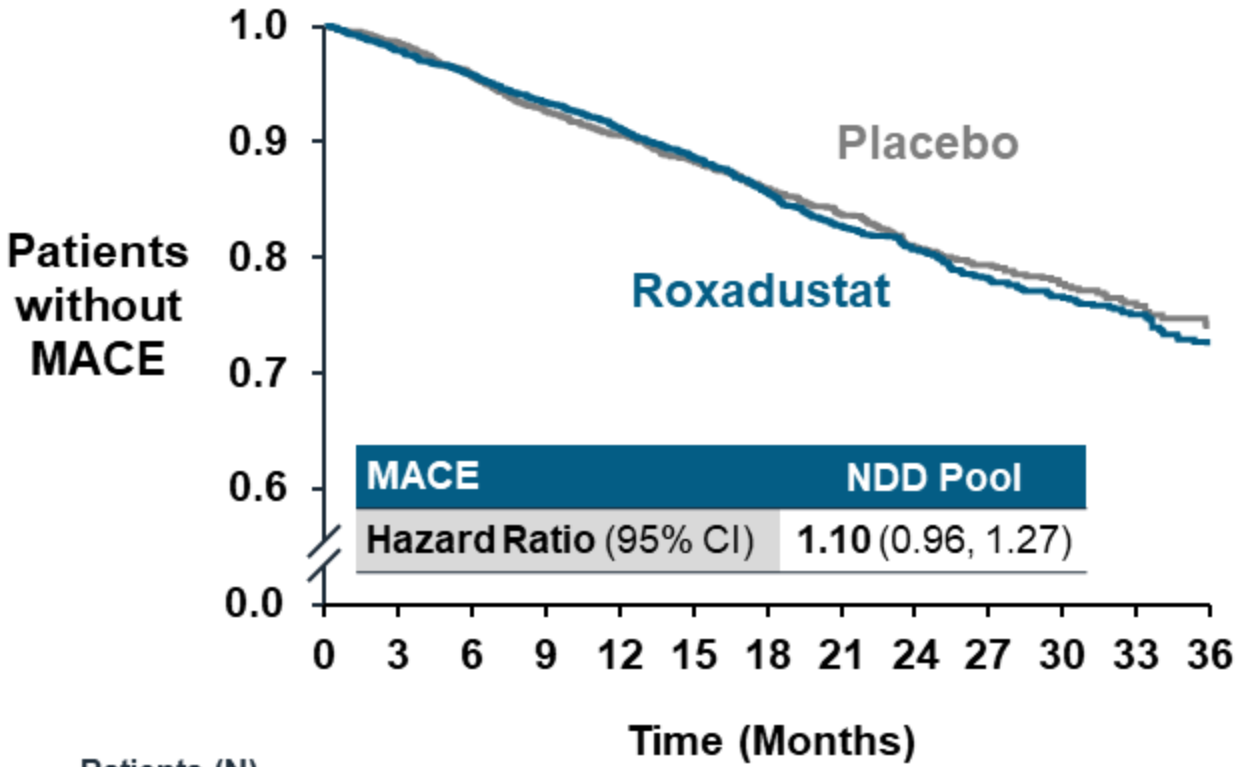
NDD Study 610: Risks of MACE, MACE+, or ACM with Roxadustat Comparable to Darbepoetin Alfa

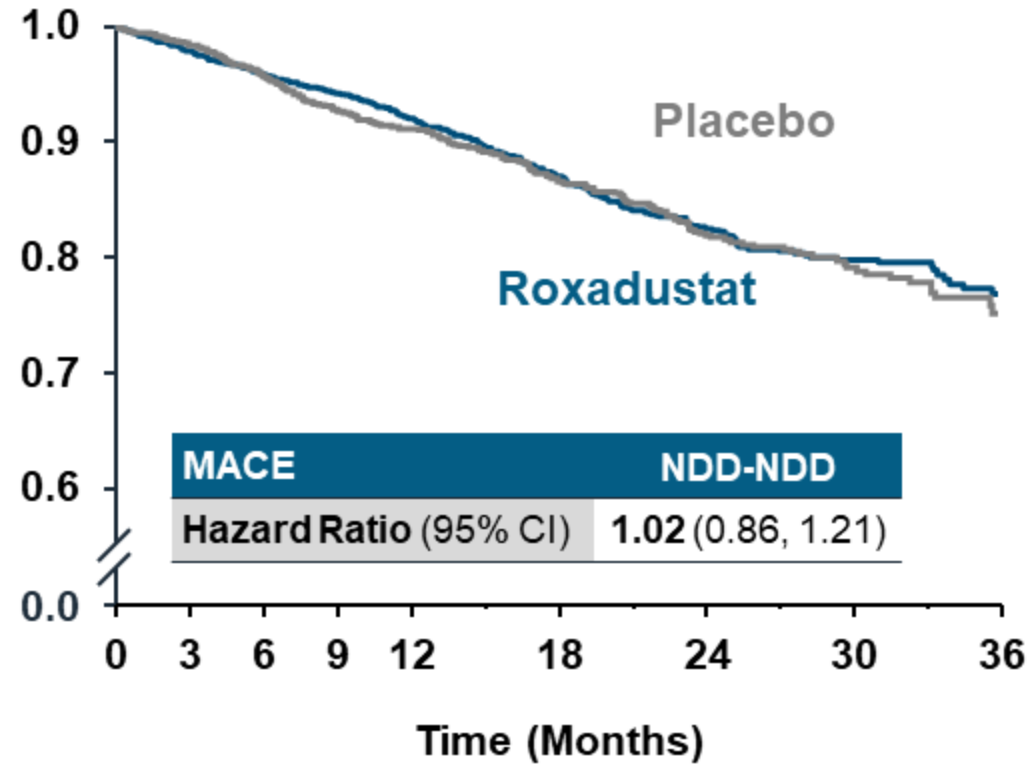
	Roxadustat N = 323	Darbepoetin alfa N = 293	Hazard Ratio (95% CI)
MACE	38 (11.8%)	41 (14.0%)	**0.81** (0.52, 1.25)
MACE +	54 (16.7%)	53 (18.1%)	**0.90** (0.61, 1.32)
ACM	29 (9.0%)	31 (10.6%)	**0.83** (0.50, 1.38)



OT + 28: On-Treatment and within 28 days of last dose of study medication

NDD and NDD-NDD (Censored at Dialysis): MACE Comparable for Roxadustat and Placebo





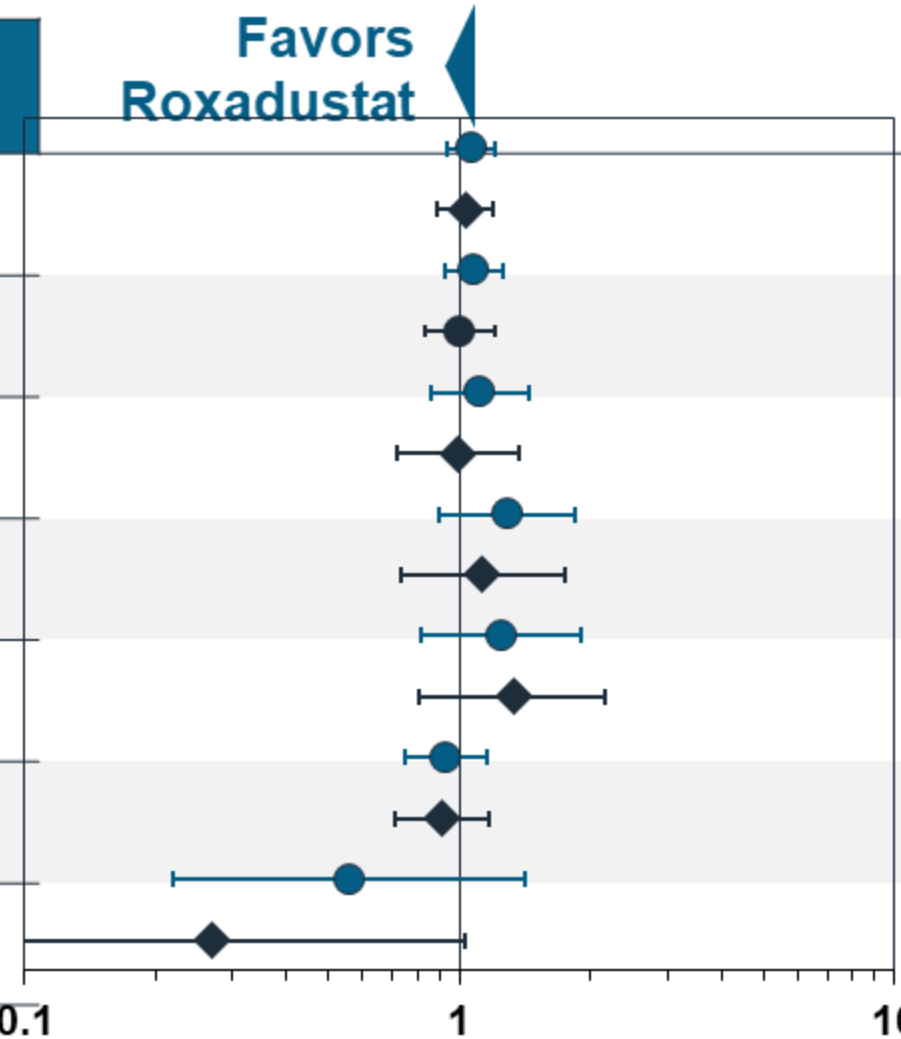
Patients (N)									
Roxadustat	2386	2279	2177	2091	1994	1603	1158	598	246
Placebo	1884	1802	1686	1596	1508	1237	851	428	142

Roxadustat	2386	2178	1957	1756	1551	1129	727	344	142
Placebo	1884	1714	1501	1337	1196	890	557	264	95

On-Study Analysis

NDD and NDD-NDD: MACE+ and Components 95% CIs Cross 1.0

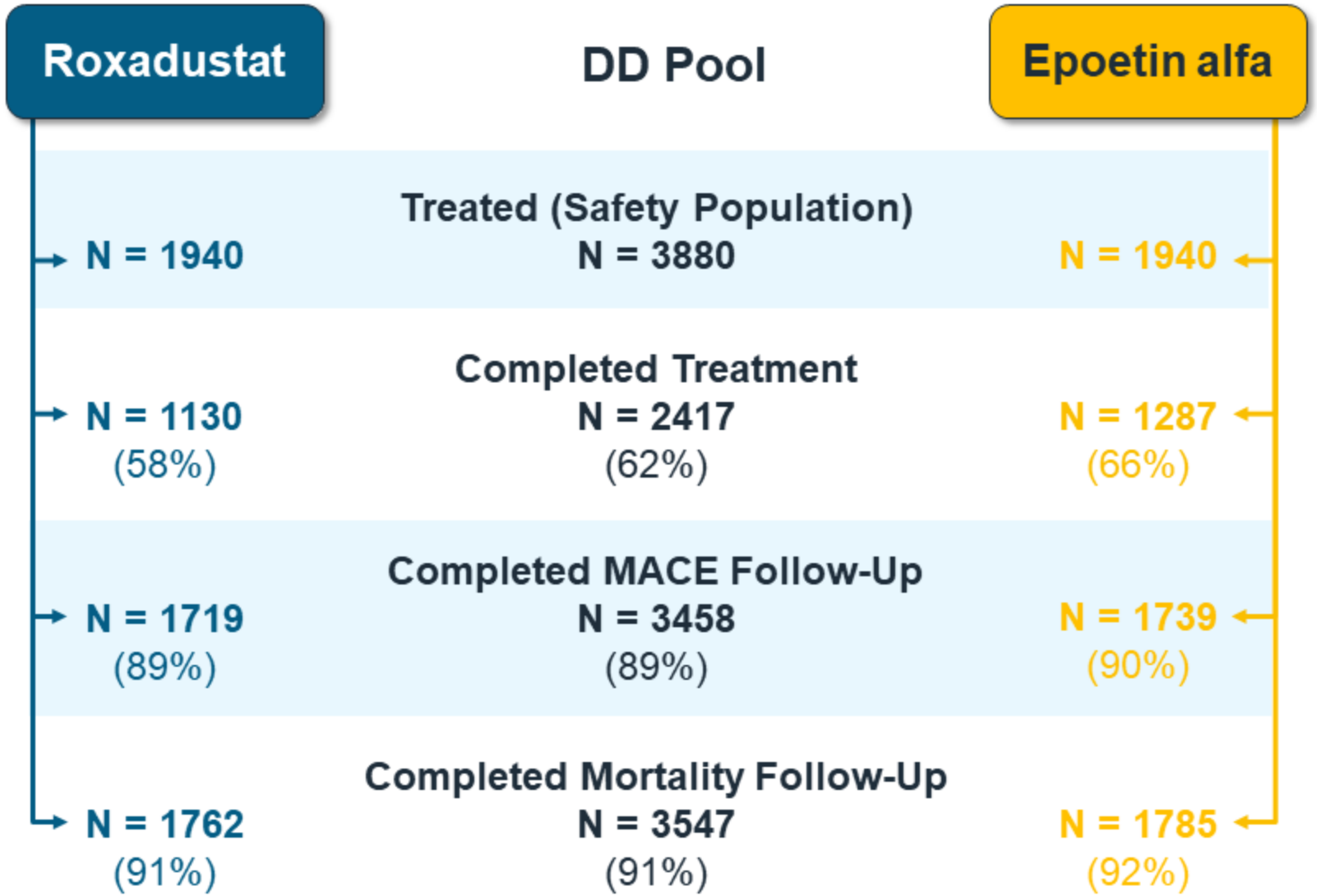
		Events N	Hazard Ratio (95% CI)
MACE+	NDD Pool	1010	1.07 (0.94, 1.21)
	NDD-NDD	731	1.03 (0.89, 1.19)
All-Cause Mortality	NDD Pool	701	1.08 (0.93, 1.26)
	NDD-NDD	464	1.00 (0.83, 1.21)
CV-related mortality	NDD Pool	245	1.11 (0.86, 1.44)
	NDD-NDD	156	0.99 (0.72, 1.37)
Myocardial infarction	NDD Pool	138	1.29 (0.90, 1.85)
	NDD-NDD	91	1.13 (0.73, 1.75)
Stroke	NDD Pool	92	1.25 (0.82, 1.90)
	NDD-NDD	69	1.33 (0.81, 2.17)
Heart failure	NDD Pool	326	0.93 (0.75, 1.16)
	NDD-NDD	247	0.91 (0.71, 1.17)
Unstable angina	NDD Pool	27	0.56 (0.22, 1.42)
	NDD-NDD	20	0.27 (0.07, 1.03)



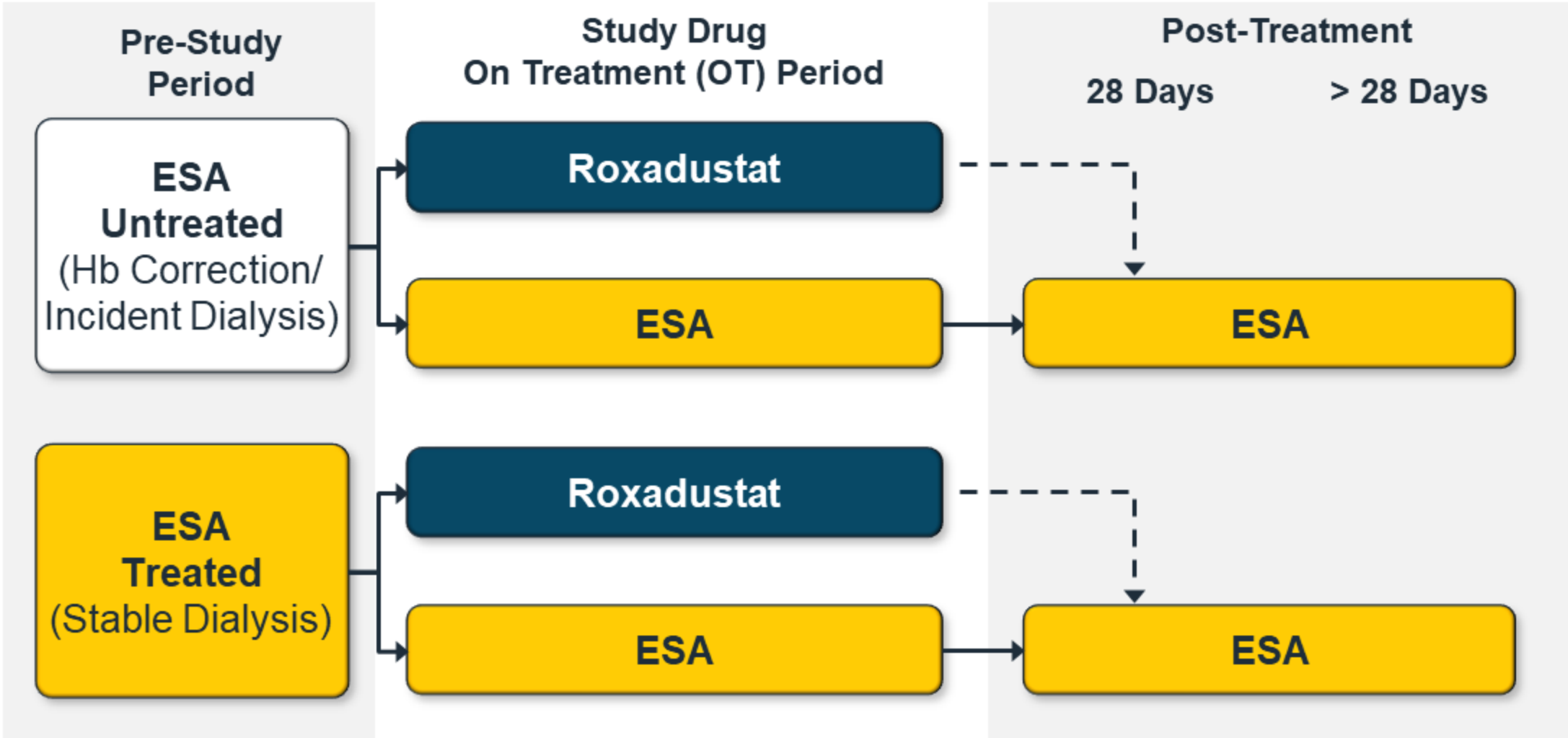
On-study analysis (Studies 001, 060, 608)
*Censored at dialysis initiation

CV Safety in DD

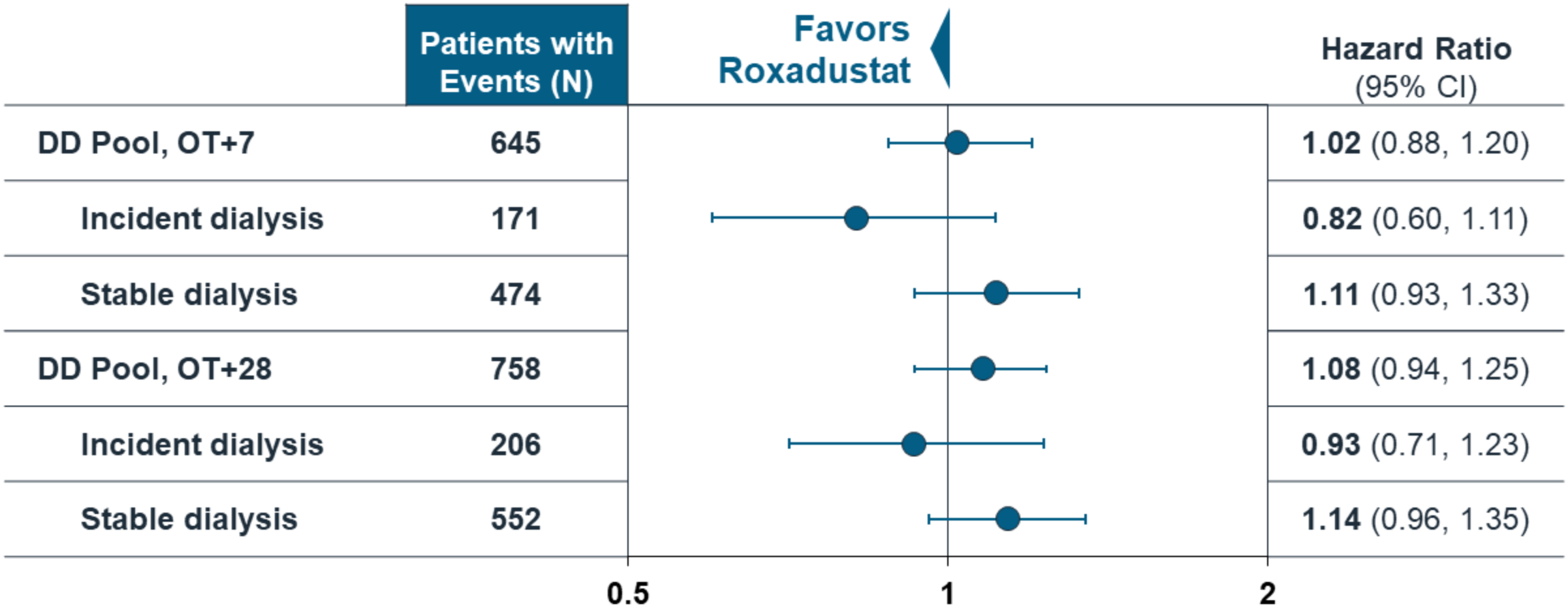
Pooled DD: Retention and Follow-Up



DD: Roxadustat Patients Convert from ESA to Roxadustat and Back; ESA Patients Remain on ESA

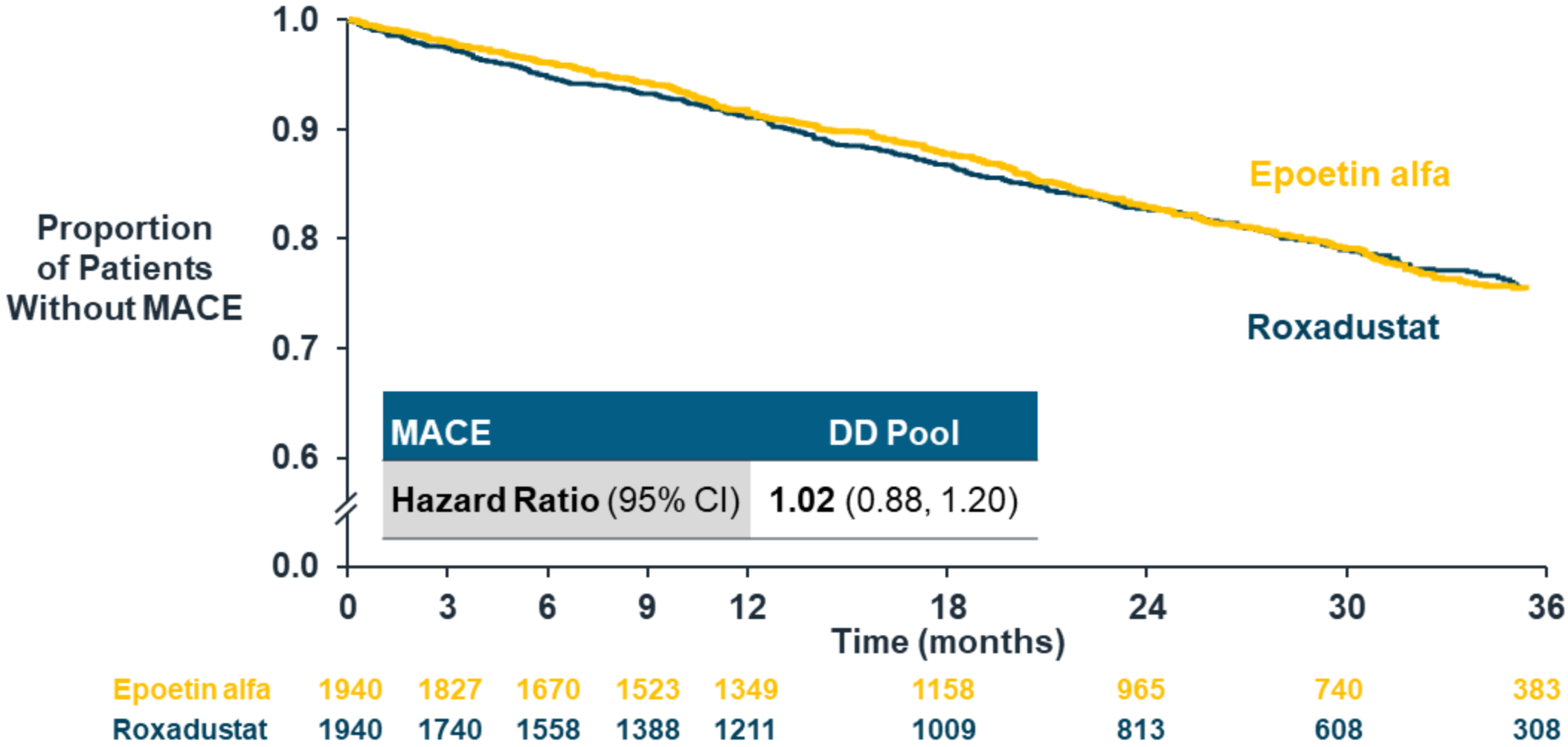


DD: Risk for MACE Comparable for Roxadustat and Epoetin Alfa



OT+7: On-Treatment and within 7 days of last dose of study medication
OT+28: On-Treatment and within 28 days of last dose of study medication

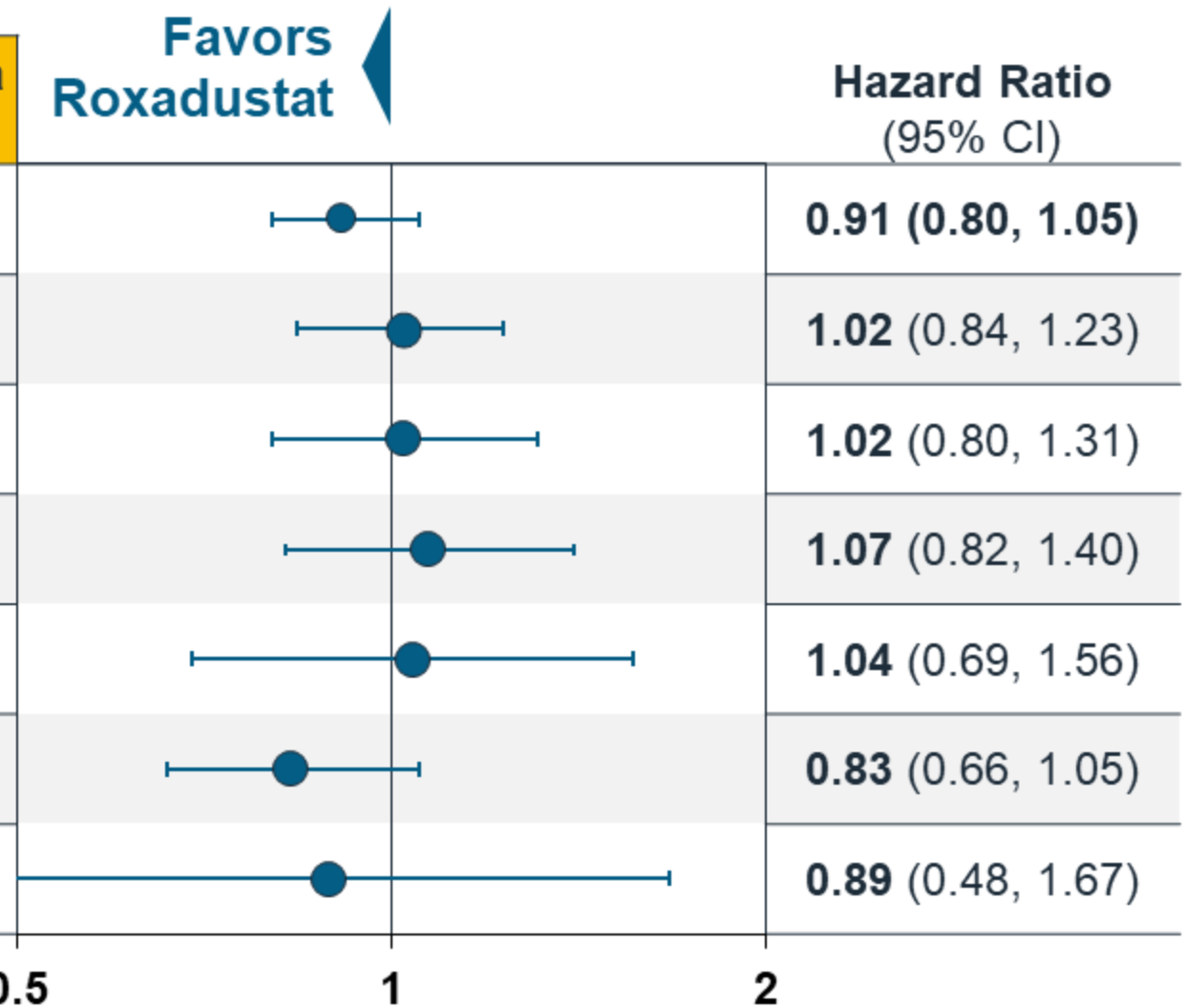
DD: Proportion of Patients Without MACE Comparable Between Groups



OT+7: On-Treatment and within 7 days of last dose of study medication
DD Pool: Studies 002, 063, 064

DD: Incidence of MACE+ Components Comparable to Epoetin Alfa

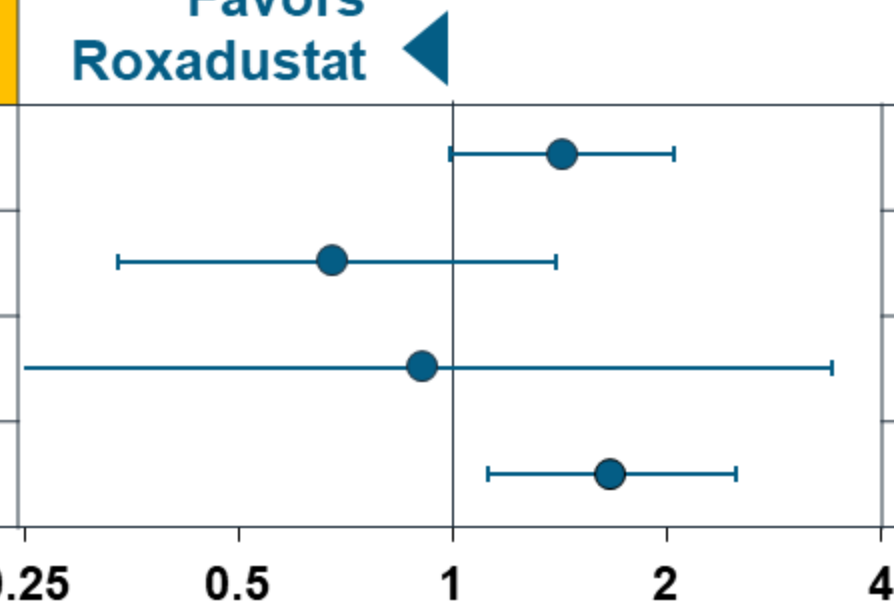
	Roxadustat N = 1940	Epoetin alfa N=1940	Hazard Ratio (95% CI)
MACE+	**373**	**458**	**0.91 (0.80, 1.05)**
All-Cause Mortality	**207**	**232**	**1.02** (0.84, 1.23)
CV-related mortality	**122**	**136**	**1.02** (0.80, 1.31)
Myocardial Infarction	**103**	**109**	**1.07** (0.82, 1.40)
Stroke	**45**	**50**	**1.04** (0.69, 1.56)
Heart failure	**120**	**166**	**0.83** (0.66, 1.05)
Unstable angina	**18**	**22**	**0.89** (0.48, 1.67)



OT+7: On-Treatment and within 7 days of last dose of study medication
DD Pool: Studies 002, 063, 064

Study 613: MACE Imbalance Results Are An Outlier

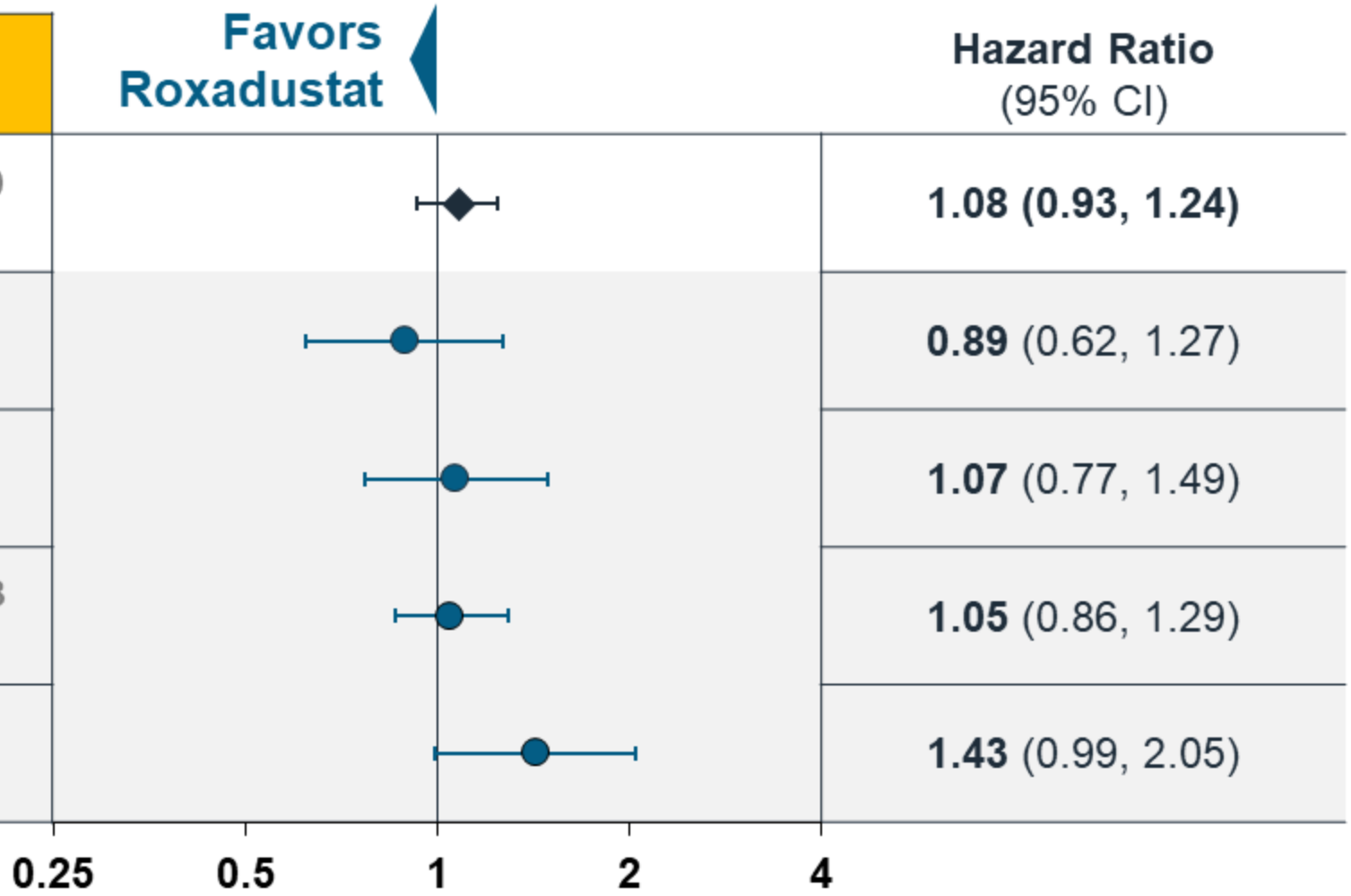
Study 613 only	Roxa N=414	ESA N=420	Hazard Ratio (95% CI)
MACE	65 (15.7%)	59 (14.0%)	**1.43** (0.99, 2.05)
Myocardial Infarction	12 (2.9%)	22 (5.2%)	**0.68** (0.34, 1.40)
Stroke	4 (1.0%)	5 (1.2%)	**0.91** (0.24, 3.41)
All-Cause Mortality	57 (13.8%)	45 (10.7%)	**1.67** (1.12, 2.50)



OT+7: On-Treatment and within 7 days of last dose of study medication

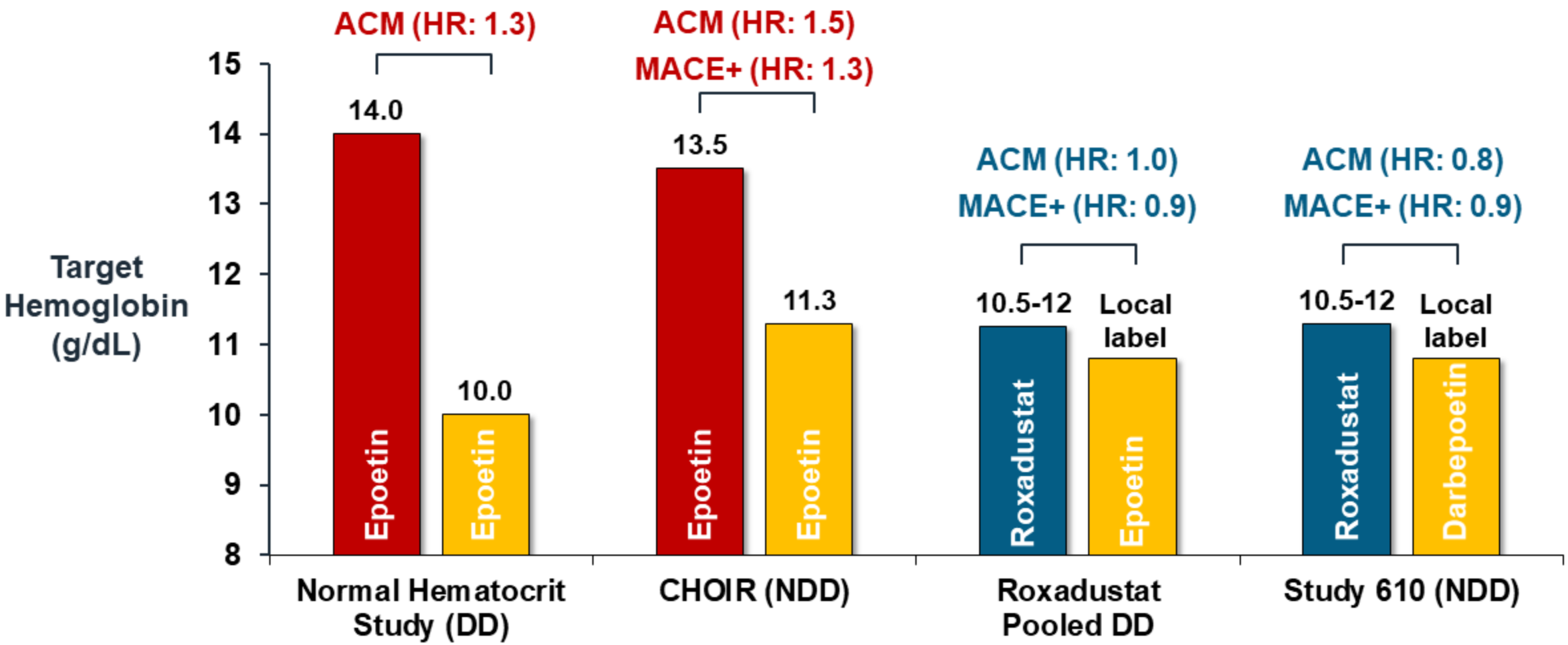
DD: Comparable Risk for Roxadustat and ESA in Pooled Pivotal Trials Plus Study 613

DD+613 by study	Roxa n/N (%)	ESA n/N (%)	Hazard Ratio (95% CI)
Pooled DD	371/2354 (15.8%)	398/2360 (16.9%)	**1.08 (0.93, 1.24)**
Study 063	57/522 (10.9%)	66/517 (12.8%)	**0.89** (0.62, 1.27)
Study 064	68/370 (18.4%)	76/370 (20.5%)	**1.07** (0.77, 1.49)
Study 002	181/1048 (17.3%)	197/1053 (18.7%)	**1.05** (0.86, 1.29)
Study 613	65/414 (15.7%)	59/420 (14.0%)	**1.43** (0.99, 2.05)



OT+7: On-Treatment and within 7 days of last dose of study medication

Roxadustat Studies Used Lower-Risk Hemoglobin Targets



Besarab, 1998; Singh, 2006.

Conclusion: Roxadustat CV Safety Profile Across Continuum of Patients with CKD Anemia

Non-Dialysis-Dependent

- MACE, MACE+, and ACM risk comparable between roxadustat and placebo
- No increased CV risk for roxadustat compared to darbepoetin alfa in 610

Dialysis-Dependent

- MACE, MACE+, and ACM risk comparable between roxadustat and epoetin alfa

Incident Dialysis

Dialysis ≤ 4 months at randomization

- Roxadustat comparable to epoetin alfa

Stable Dialysis

Dialysis > 4 months

- Roxadustat comparable to epoetin alfa

Additional Safety Topics

- Seizures
- Infections
- Thrombosis
  - Deep vein thrombosis (DVT)
  - Vascular access thrombosis (VAT)

NDD and DD: Seizure Events More Frequent in Roxadustat Patients

NDD Pool	Roxadustat N = 2386 n (%)	Placebo N = 1884 n (%)
Convulsions AEs (SMQ)	26 (1.1%)	4 (0.2%)
Seizure in patients *with* reported history of seizure	3 / 31 (9.7%)	0 / 13 (0%)

DD Pool	Roxadustat N = 1940 n (%)	Epoetin alfa N = 1940 n (%)
Convulsions AEs (SMQ)	45 (2.3%)	34 (1.8%)
Seizure in patients *with* reported history of seizure	9 / 38 (23.7%)	5 / 46 (10.9%)

OT+28: On-Treatment and within 28 days of last dose of study medication

Serious and Fatal Infections: Inconsistent Results Across Pools

NDD Pool	Roxadustat N = 2386 n (%)	Placebo N = 1884 n (%)
Infection SAE	452 (18.9%)	243 (12.9%)
Infection death	55 (2.3%)	16 (0.8%)

DD Pool	Roxadustat N = 1940 n (%)	Epoetin alfa N = 1940 n (%)
Infection SAE	473 (24.4%)	478 (24.6%)
Infection death	47 (2.4%)	46 (2.4%)

NDD Pool: Studies 001, 060, 608. DD Pool: Studies 002, 063, 064.
OT+28: On-Treatment and within 28 days of last dose of study medication
AE/SAE data are for the "infections and infestations" system organ class; infection death is as determined by adjudication

NDD Pool: Higher Incidence of Serious Infections in Roxadustat Patients

	Roxadustat N = 2386	Placebo N = 1884
	n (%)	n (%)
Infection SAE	452 (18.9%)	243 (12.9%)
Pneumonia*	157 (6.6%)	87 (4.6%)
Sepsis (Narrow SMQ)	100 (4.2%)	27 (1.4%)
Urinary tract infection*	103 (4.3%)	56 (3.0%)
Cellulitis*	40 (1.7%)	16 (0.8%)
Peritonitis*	31 (1.3%)	10 (0.5%)

*FDA Query Terms; SMQ: Standardized MedDRA Query
NDD Pool: Studies 001, 060, 608.
OT+28: On-Treatment and within 28 days of last dose of study medication
Infection SAEs in >1% in Either Treatment Group

DD Pool: Similar Rates of Serious Infections in Roxadustat and Epoetin Alfa Patients

	Roxadustat N = 1940	Epoetin alfa N = 1940
	n (%)	n (%)
Infection SAE	473 (24.4%)	478 (24.6%)
Pneumonia*	150 (7.7%)	163 (8.4%)
Sepsis (Narrow SMQ)	124 (6.4%)	119 (6.1%)
Urinary tract infection*	41 (2.1%)	38 (2.0%)
Cellulitis*	28 (1.4%)	41 (2.1%)
Peritonitis*	39 (2.0%)	43 (2.2%)
Device related infection	22 (1.1%)	19 (1.0%)
Gangrene	19 (1.0%)	25 (1.3%)
Osteomyelitis	17 (0.9%)	26 (1.3%)

*FDA Query Terms; SMQ: Standardized MedDRA Query
DD Pool: Studies 002, 063, 064
OT+28: On-Treatment and within 28 days of last dose of study medication
Infection SAEs in >1% in Either Treatment Group

NDD and DD: Thrombosis More Common in Roxadustat Patients

NDD Pool	Roxadustat N = 2386 n (%)	Placebo N = 1884 n (%)
Thrombosis	224 (9.4%)	96 (5.1%)

DD Pool	Roxadustat N = 1940 n (%)	Epoetin alfa N = 1940 n (%)
Thrombosis	421 (21.7%)	372 (19.2%)

NDD Pool: Studies 001, 060, 608
DD Pool: Studies 002, 063, 064
OT+28: On-Treatment and within 28 days of last dose of study medication
Thrombosis = custom list of AEs provided by FDA

NDD and DD: DVT Events More Common in Roxadustat Patients

NDD Pool	Roxadustat N = 2386 n (%)	Placebo N = 1884 n (%)
DVT and/or PE	35 (1.5%)	9 (0.5%)
Deep vein thrombosis	28 (1.2%)	6 (0.3%)
Pulmonary embolism	10 (0.4%)	3 (0.2%)

DD Pool	Roxadustat N = 1940 n (%)	Epoetin alfa N = 1940 n (%)
DVT and/or PE	41 (2.1%)	36 (1.9%)
Deep vein thrombosis	30 (1.5%)	19 (1.0%)
Pulmonary embolism	13 (0.7%)	17 (0.9%)

OT+28: On-Treatment and within 28 days of last dose of study medication

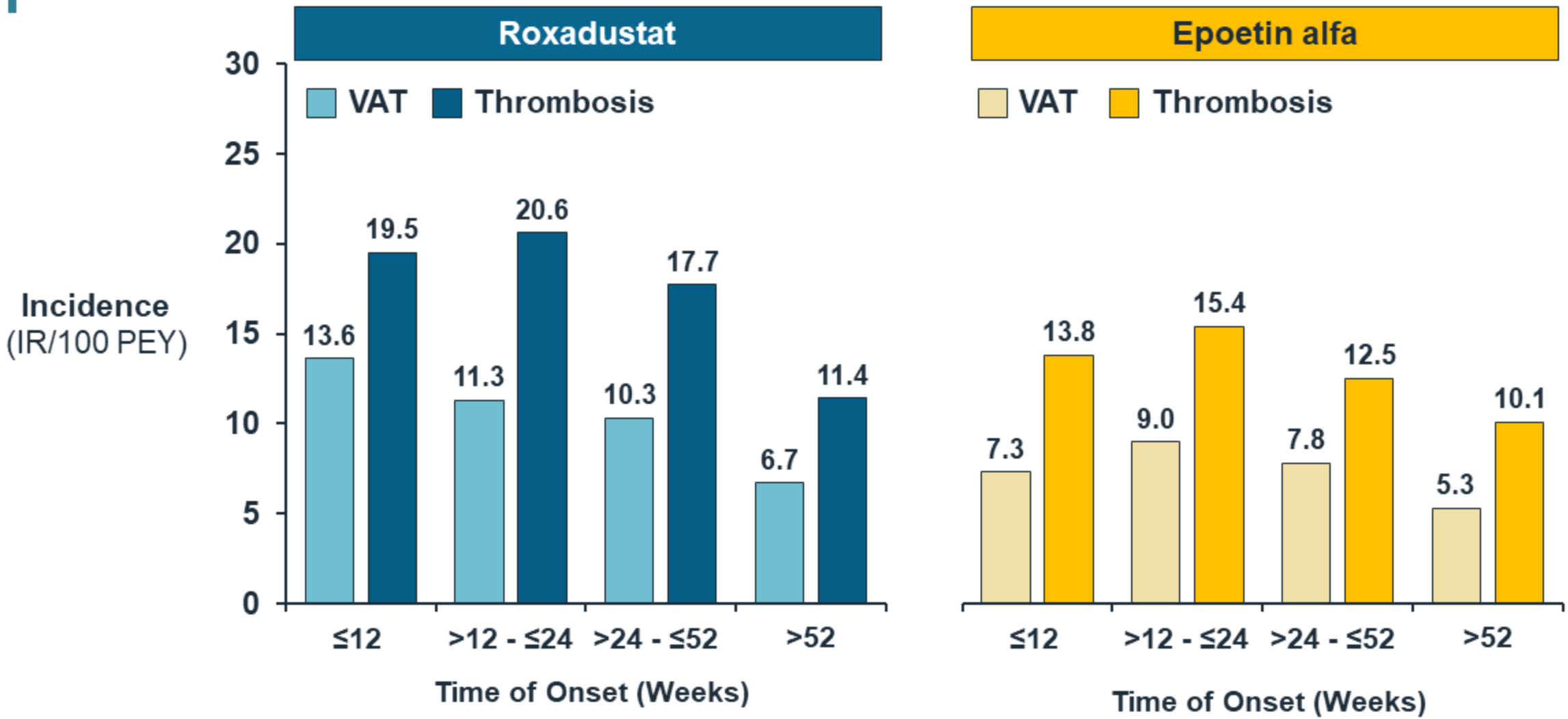
NDD and DD: VAT More Common in Roxadustat Patients

NDD Pool	Roxadustat N = 2386 n (%)	Placebo N = 1884 n (%)
Vascular access thrombosis (VAT)	58 **(2.4%)**	7 **(0.4%)**

DD Pool	Roxadustat N = 1940 n (%)	Epoetin alfa N = 1940 n (%)
VAT	252 **(13.0%)**	204 **(10.5%)**

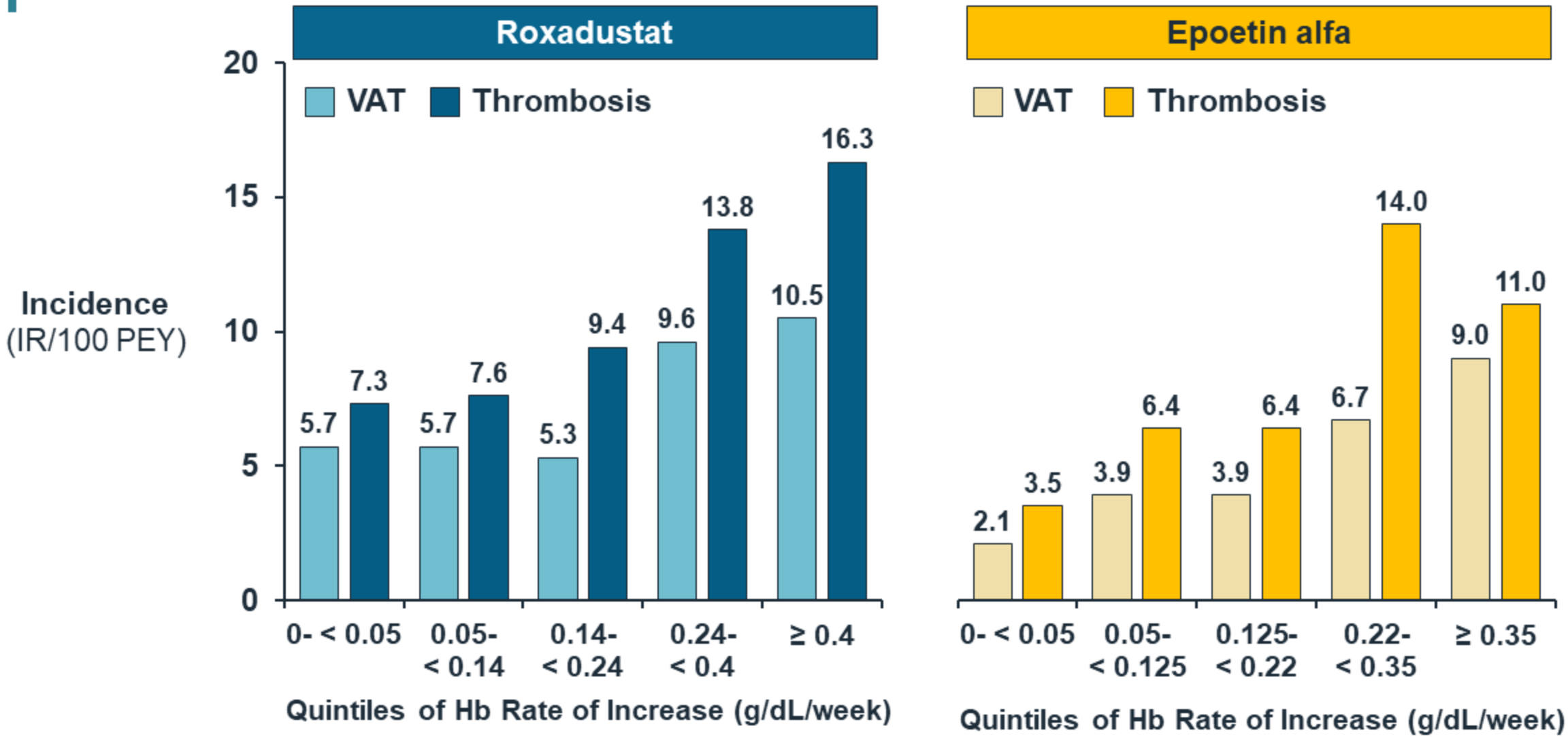
DD Pool: Studies 002, 063, 064
NDD Pool: Studies 001, 060, 608
OT+28: On-Treatment and within 28 days of last dose of study medication

DD: Rates of VAT and Thrombosis Decreased Over Time in Roxadustat Patients



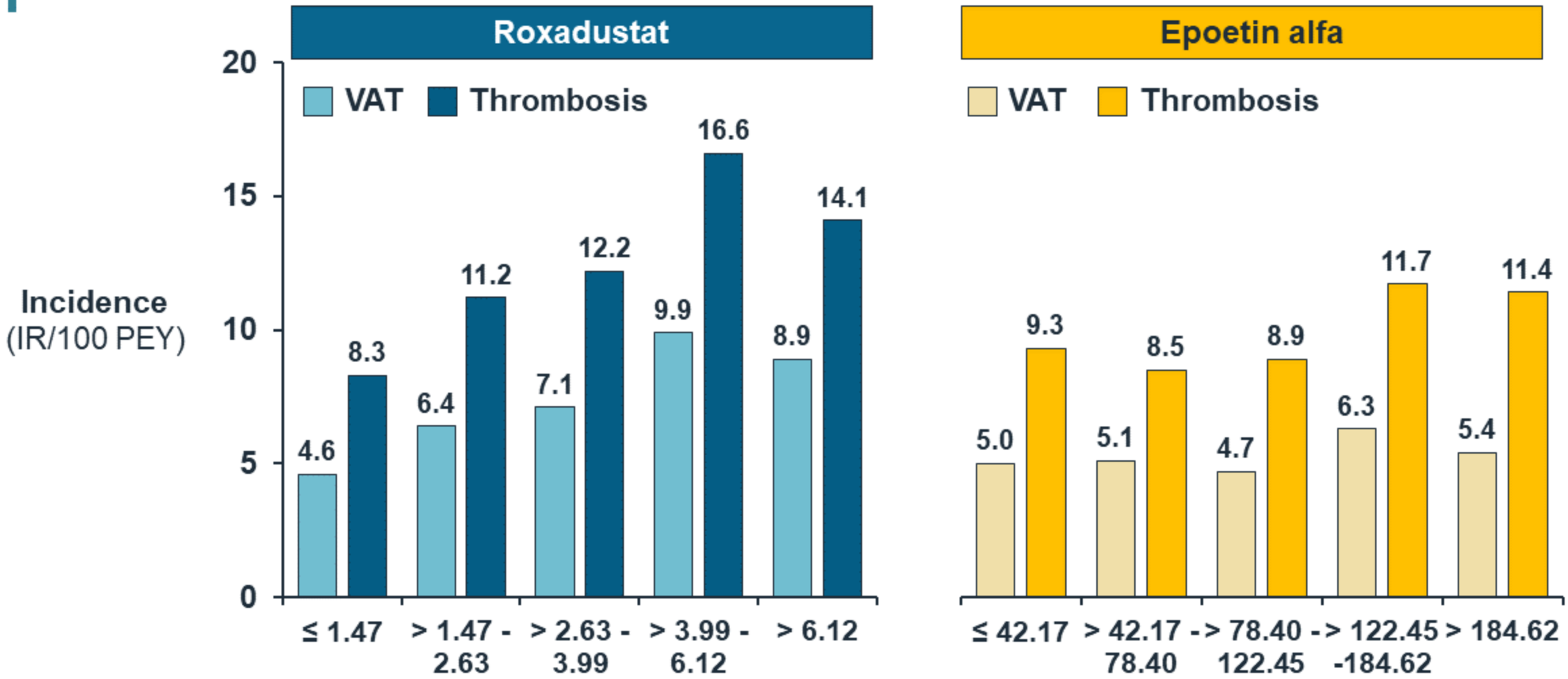
OT+7: On-Treatment and within 7 days of last dose of study medication

DD: Thrombosis and VAT Increased with Increasing Hb Rate of Rise

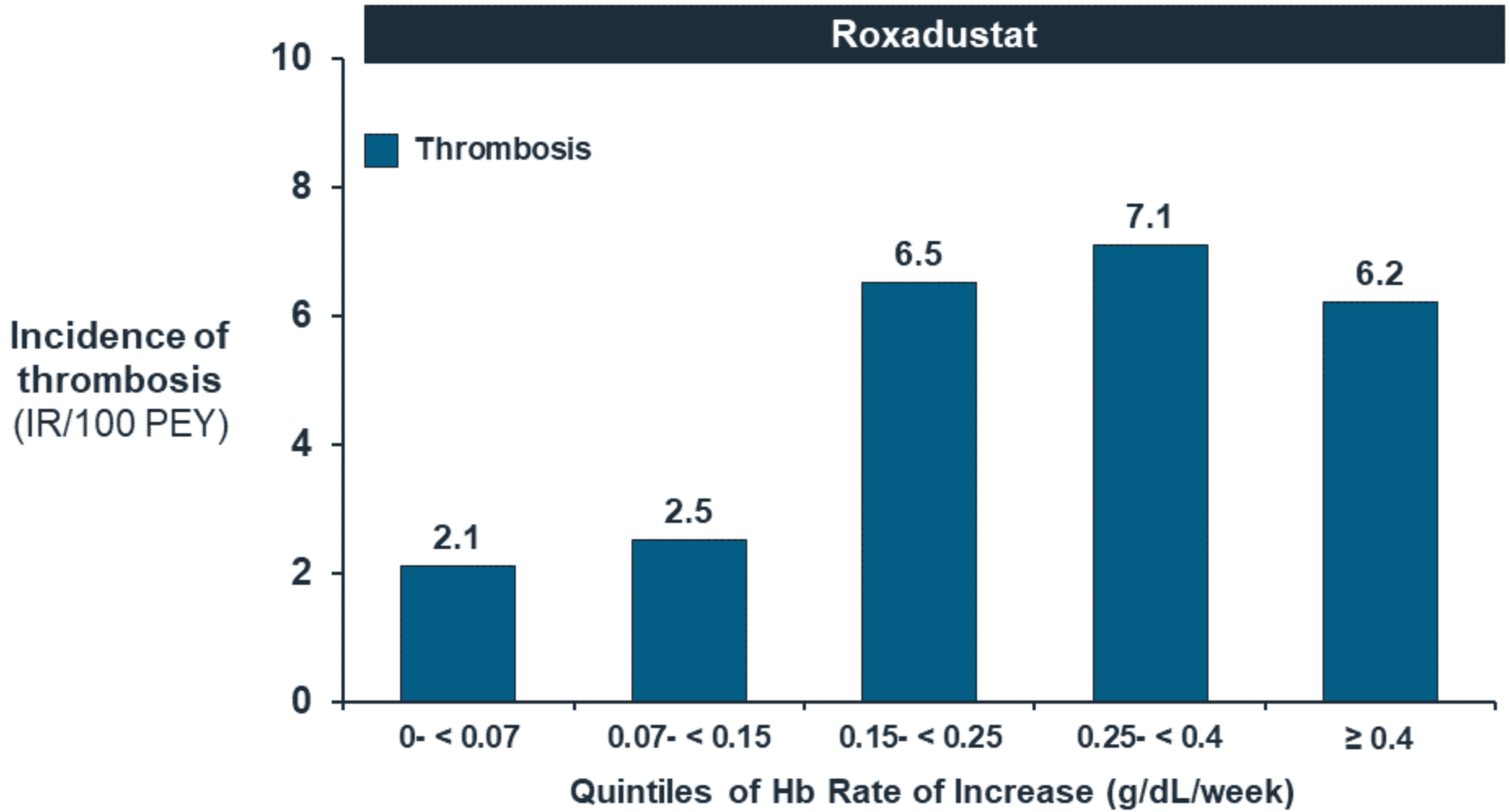


OT+7: On-Treatment and within 7 days of last dose of study medication

DD: Higher Rates of Thrombosis and VAT Observed at Higher Roxadustat Doses

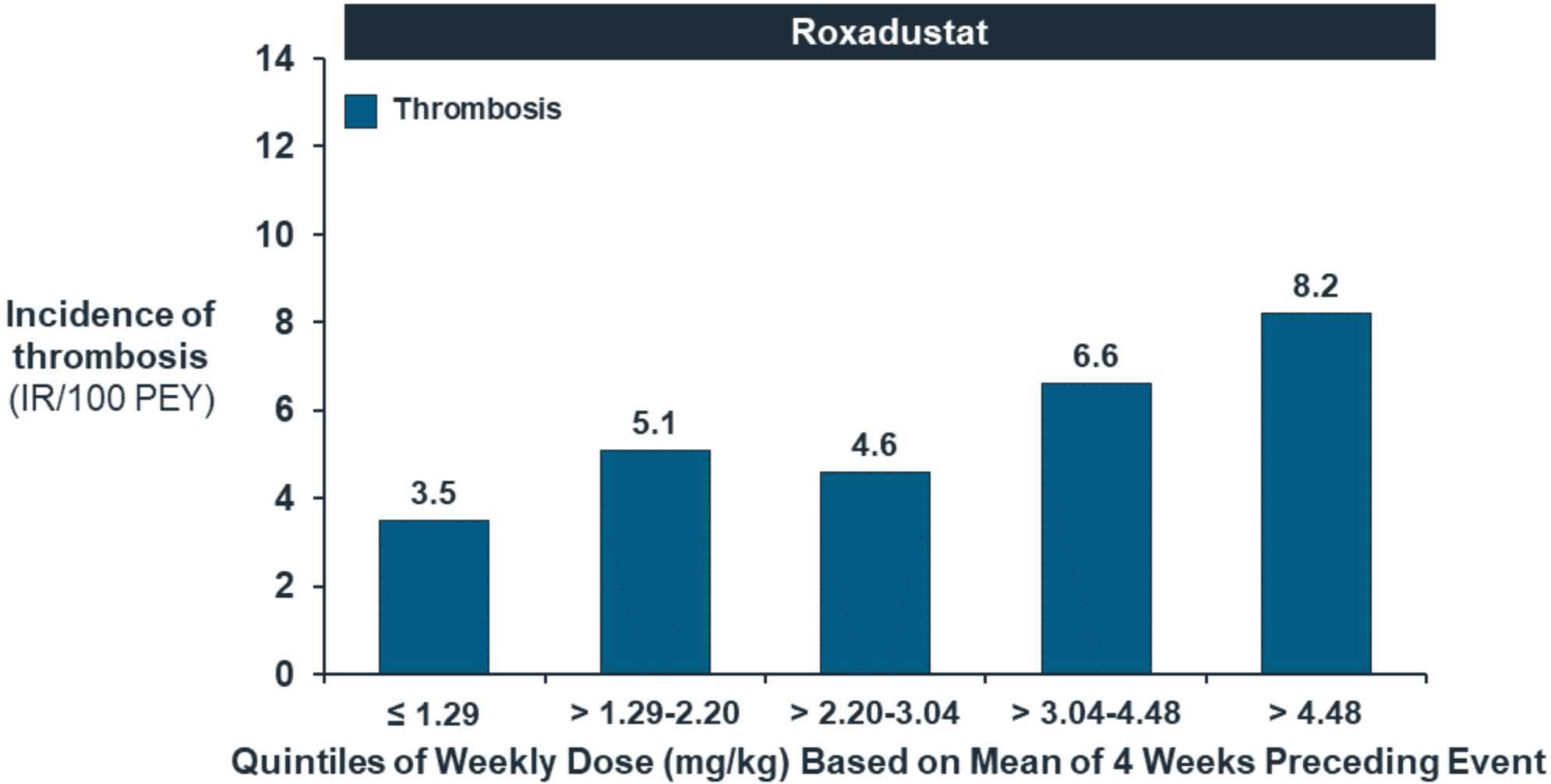


NDD: Thrombosis AEs Increased with Increasing Hb Rate of Rise in Roxadustat Patients



OT+7: On-Treatment and within 7 days of last dose of study medication

NDD: Higher Rates of Thrombosis Observed at Higher Roxadustat Doses



Phase 3 Dosing vs Proposed Dosing

Phase 3 Dosing

1. Target Hb: **10.5 – 12.0** g/dL
2. Starting doses
   - ESA untreated
     - **70** mg TIW in patients < 70 kg
     - **100** mg TIW in patients 70+ kg
   - ESA conversion

Epoetin Alfa (IU/Week)	Roxadustat Start Dose (mg/dose TIW)
< 5000	**70**
5000 to 7999	**100**
8000 to 16000	**150**
> 16000	**200**

3. No restriction on consecutive dose increases in patients not responding

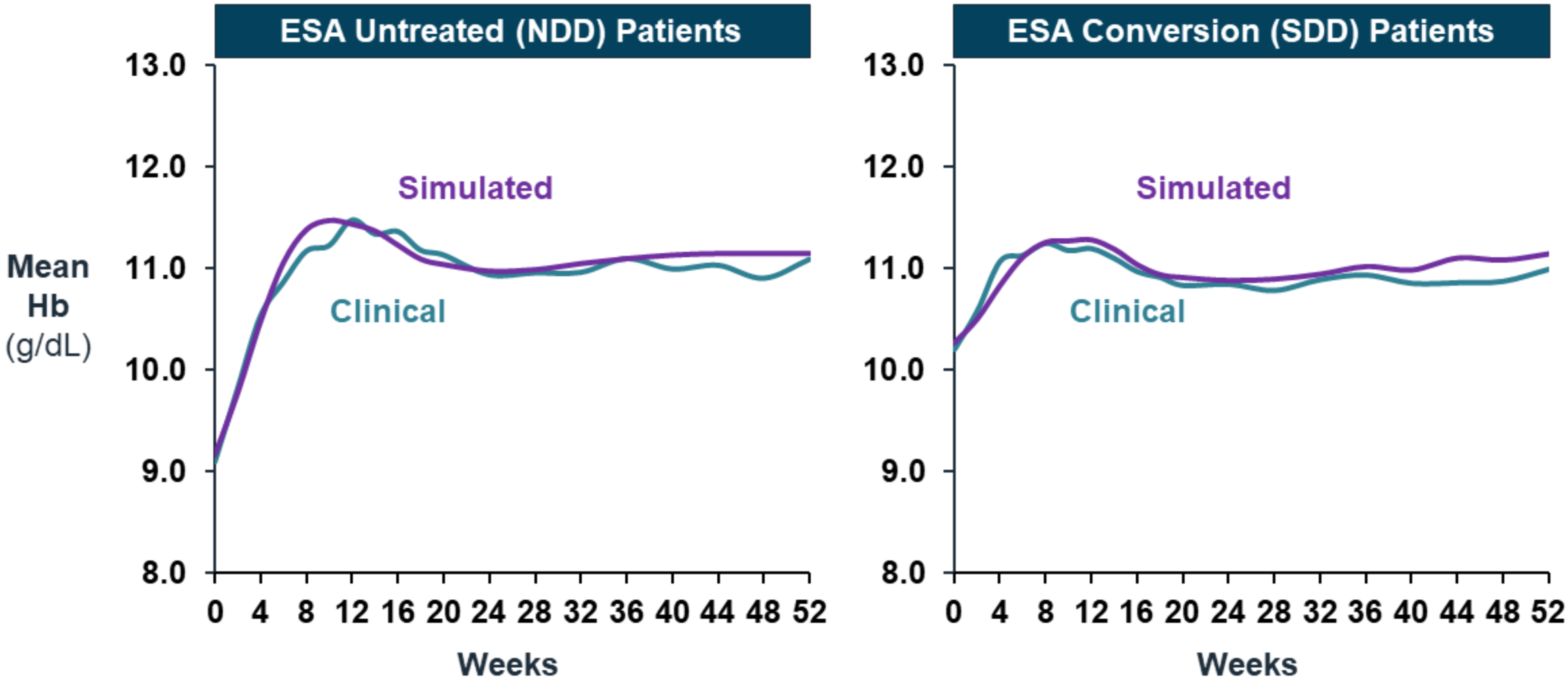
Proposed Dosing

1. Target Hb: **10.0 – 11.0** g/dL
2. Starting doses
   - ESA untreated
     - **40** mg TIW in patients < 70 kg
     - **50** mg TIW in patients 70+ kg
   - ESA conversion

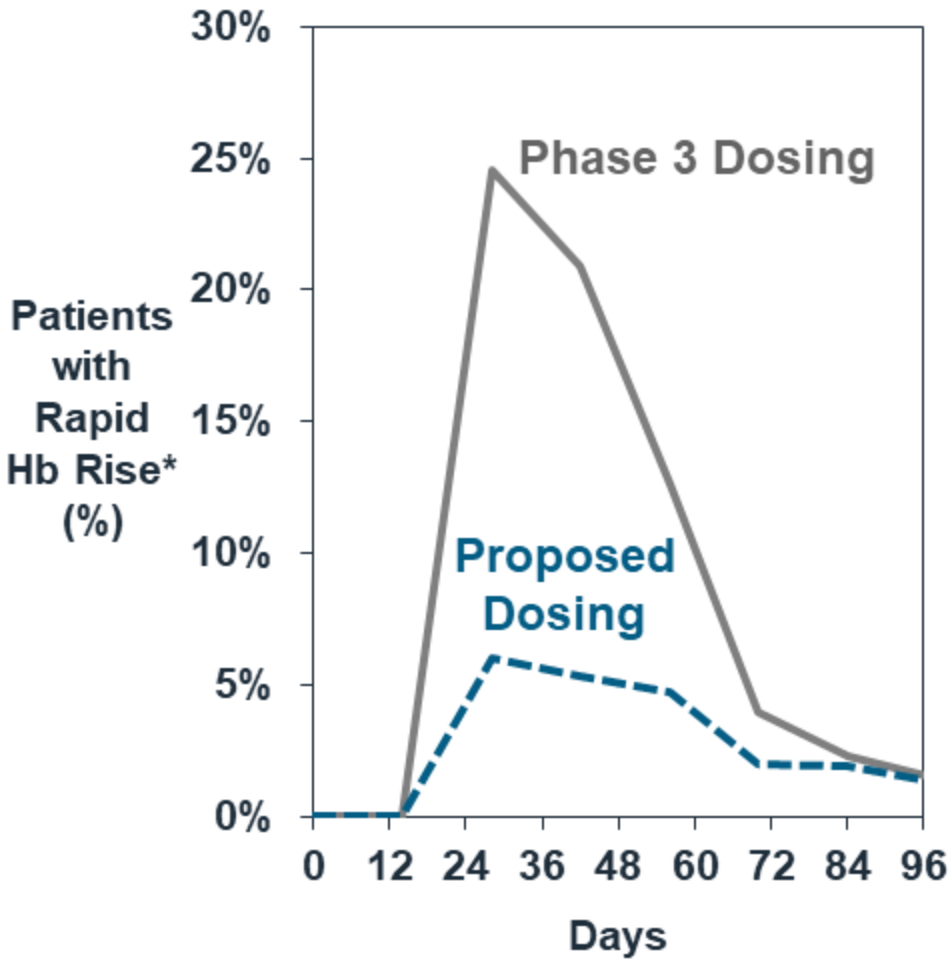
Epoetin Alfa (IU/Week)	Roxadustat Start Dose (mg/dose TIW)
< 5000	**40**
5000 to 7999	**50**
8000 to 16000	**70**
> 16000	**100**

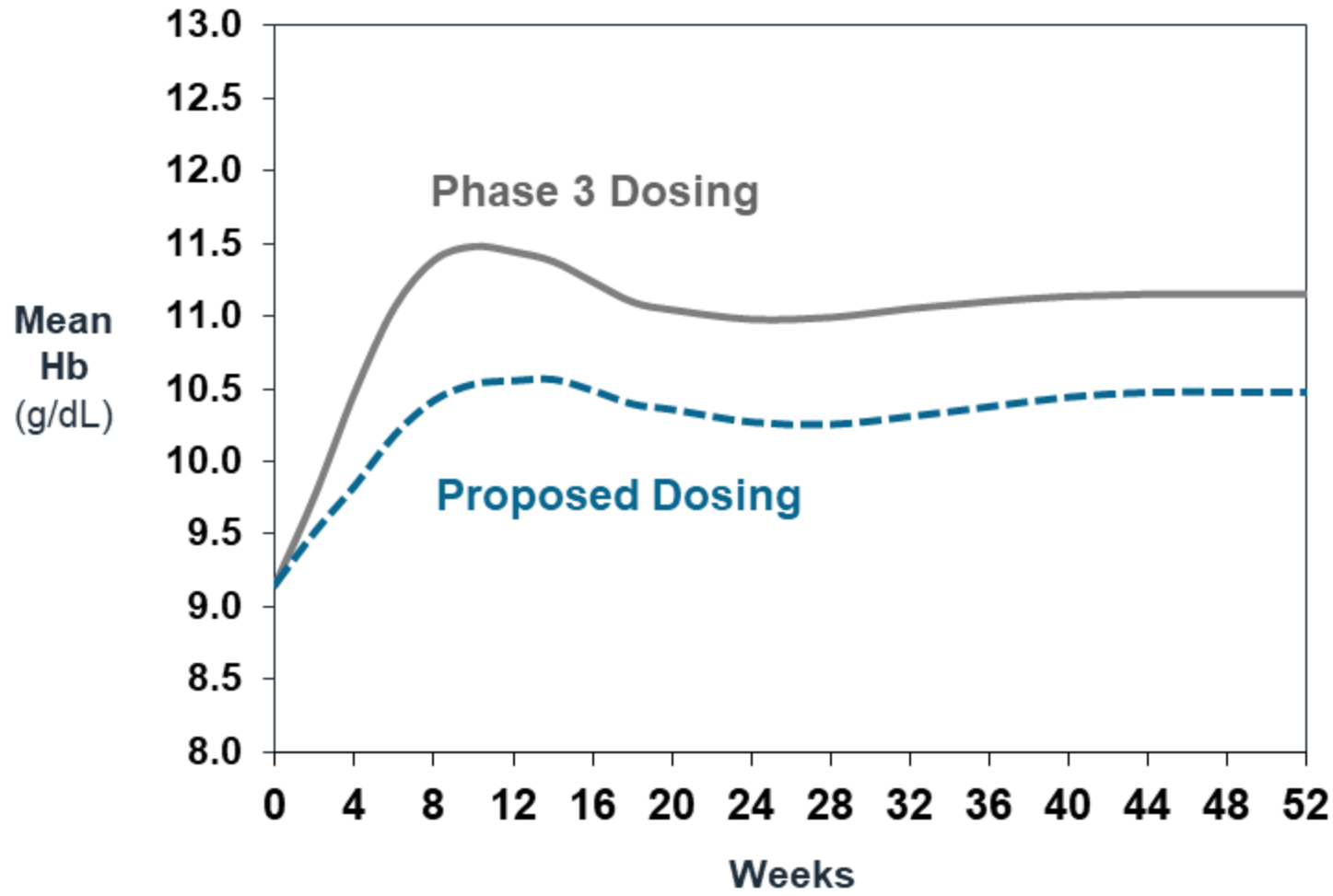
3. No more than 3 consecutive dose increases in patients not responding

NDD and SDD: Comparison Between Simulated vs. Actual Hb



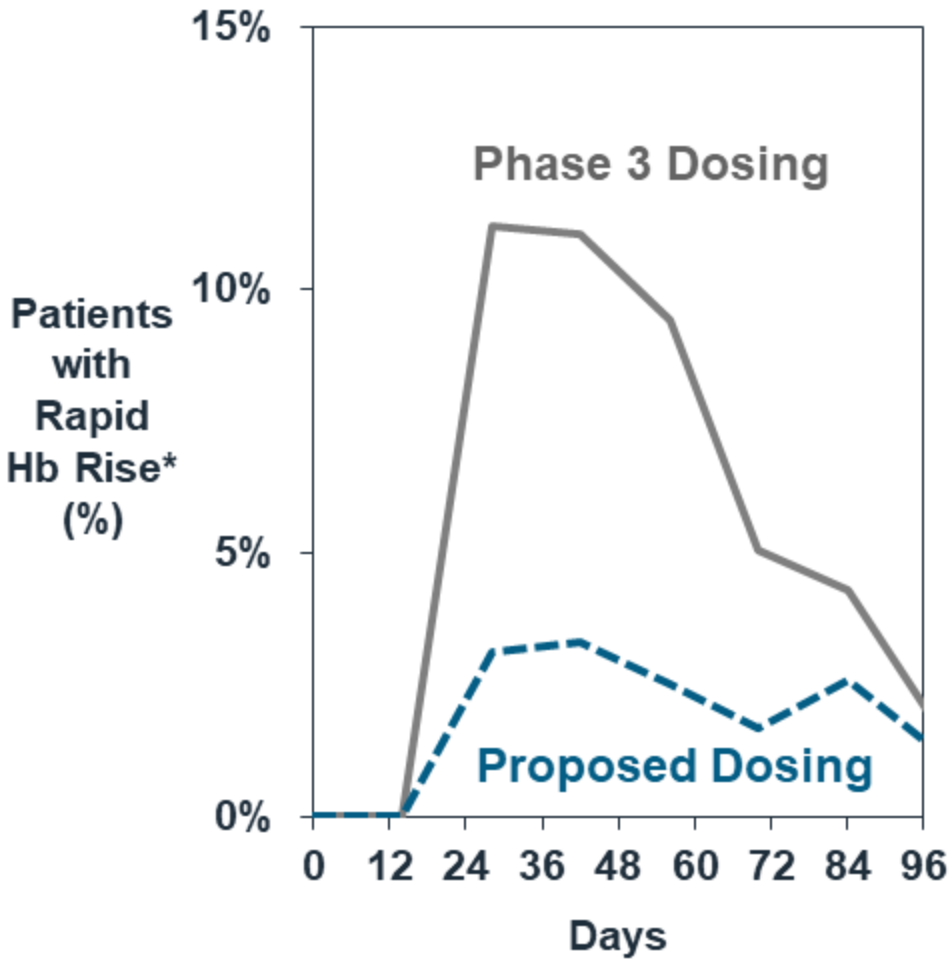
ESA-Untreated Patients: Proposed Dosing Changes Will Lower Incidence of Rapid Hemoglobin Rate of Rise, with Stable Mean Values During Early Treatment (Simulation)

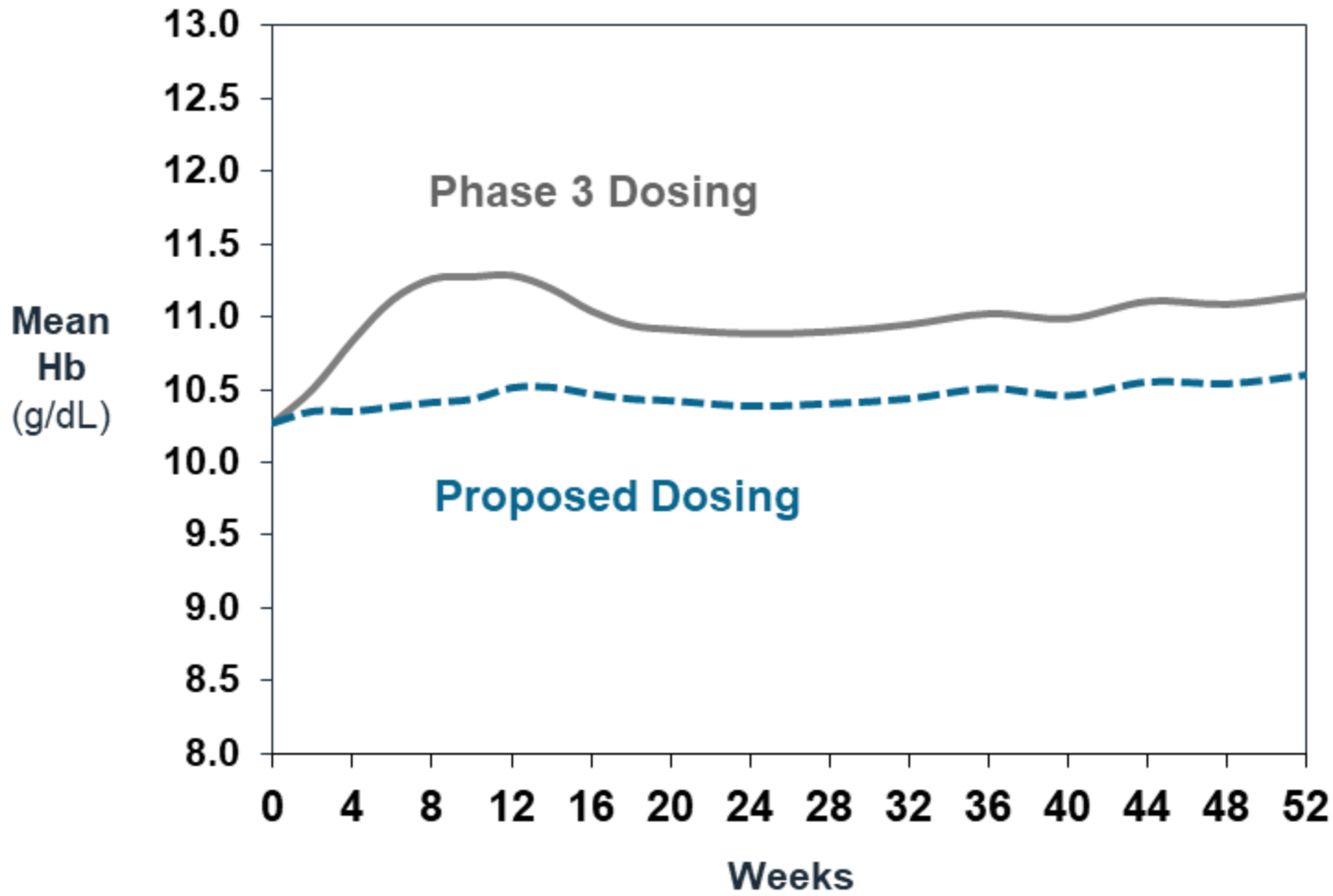




*Rapid rise: 4 week increase >2 g/dL

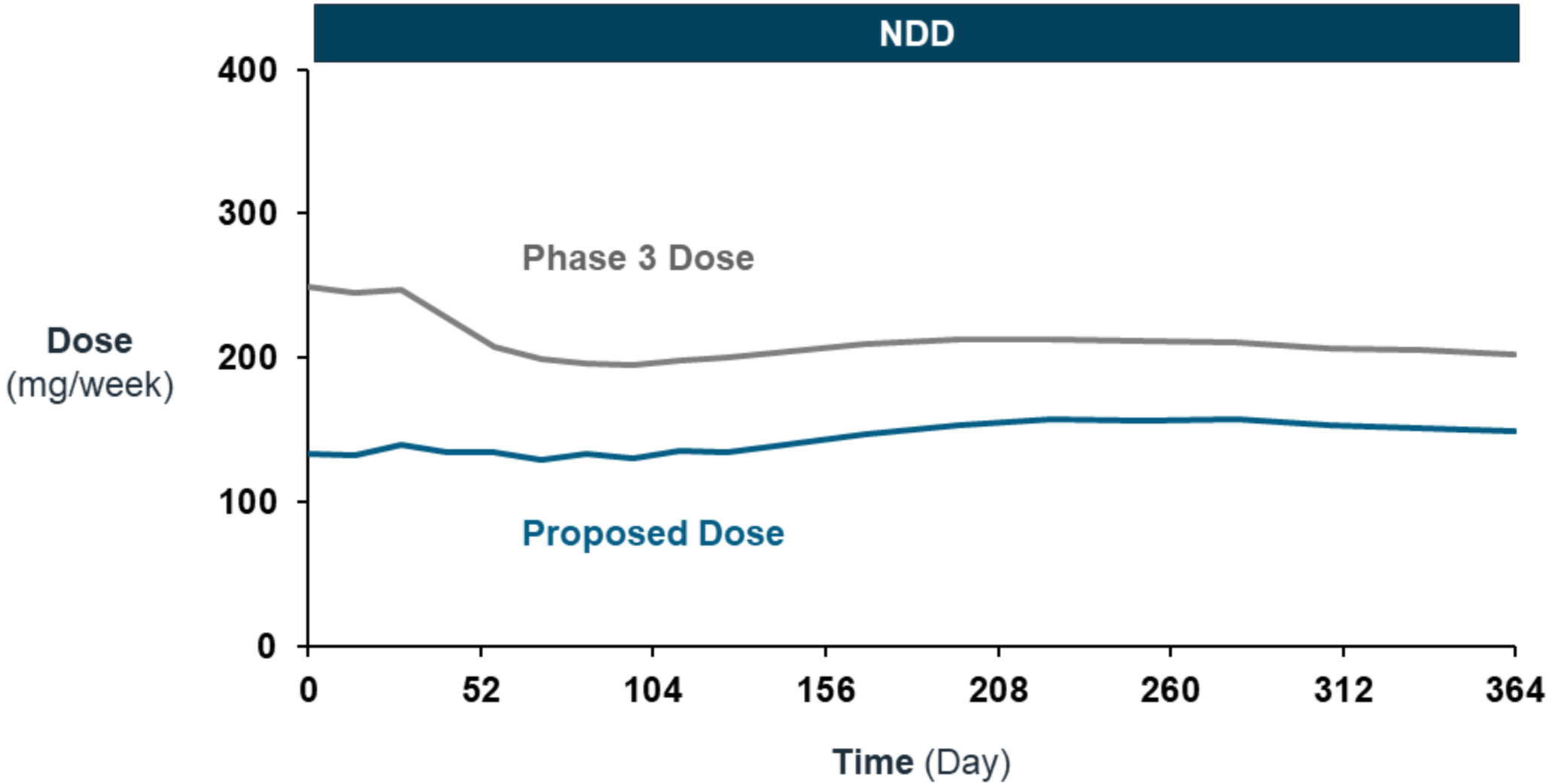
ESA Conversion Patients: Proposed Dosing Changes Will Lower Incidence of Rapid Hemoglobin Rate of Rise, And Lead to Less Fluctuation in Mean Hb Values (Simulation)



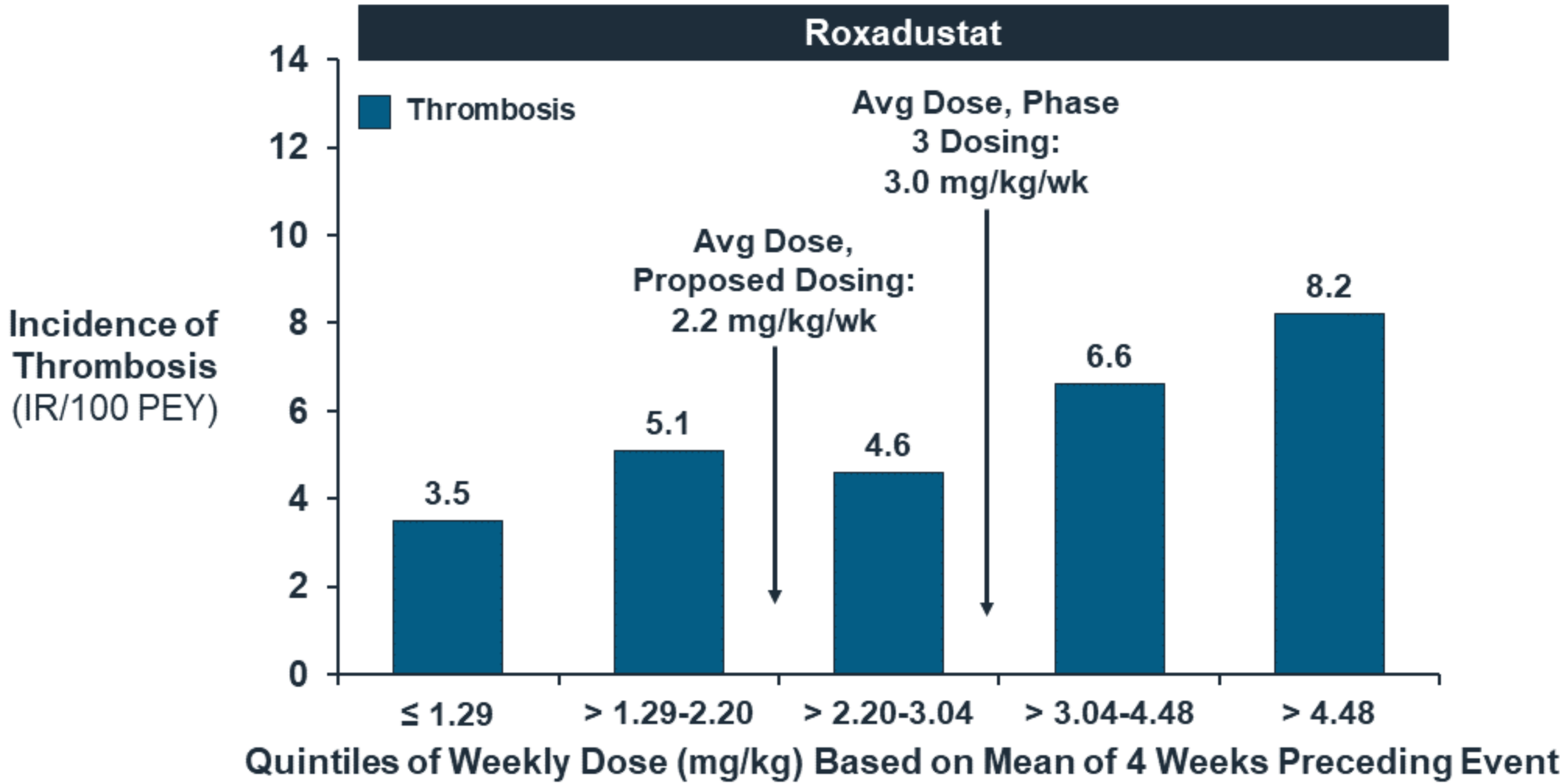


*Rapid rise: 4 week increase >2 g/dL

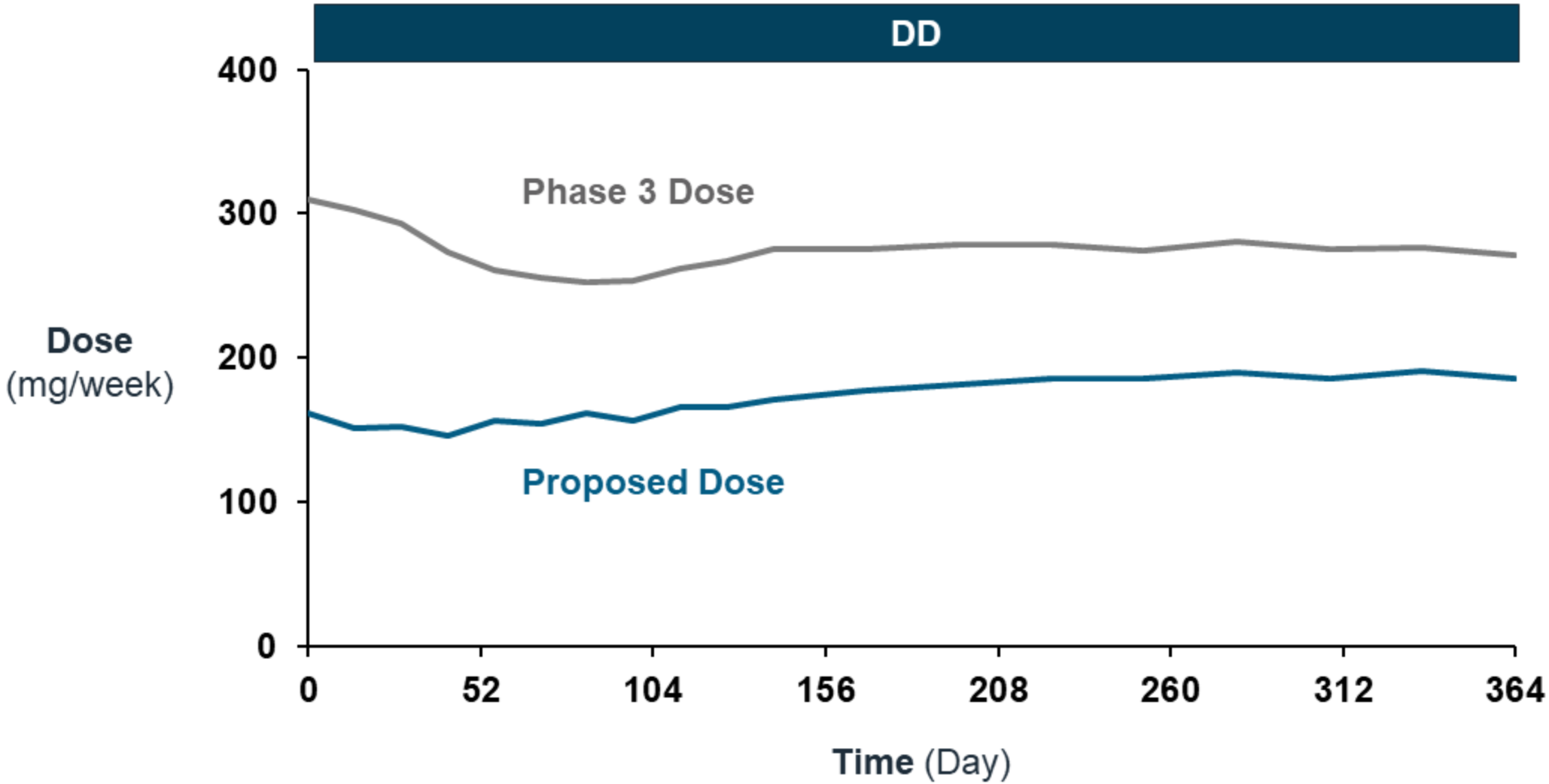
NDD: > 25% Reduction in Overall Mean Doses (Simulation)



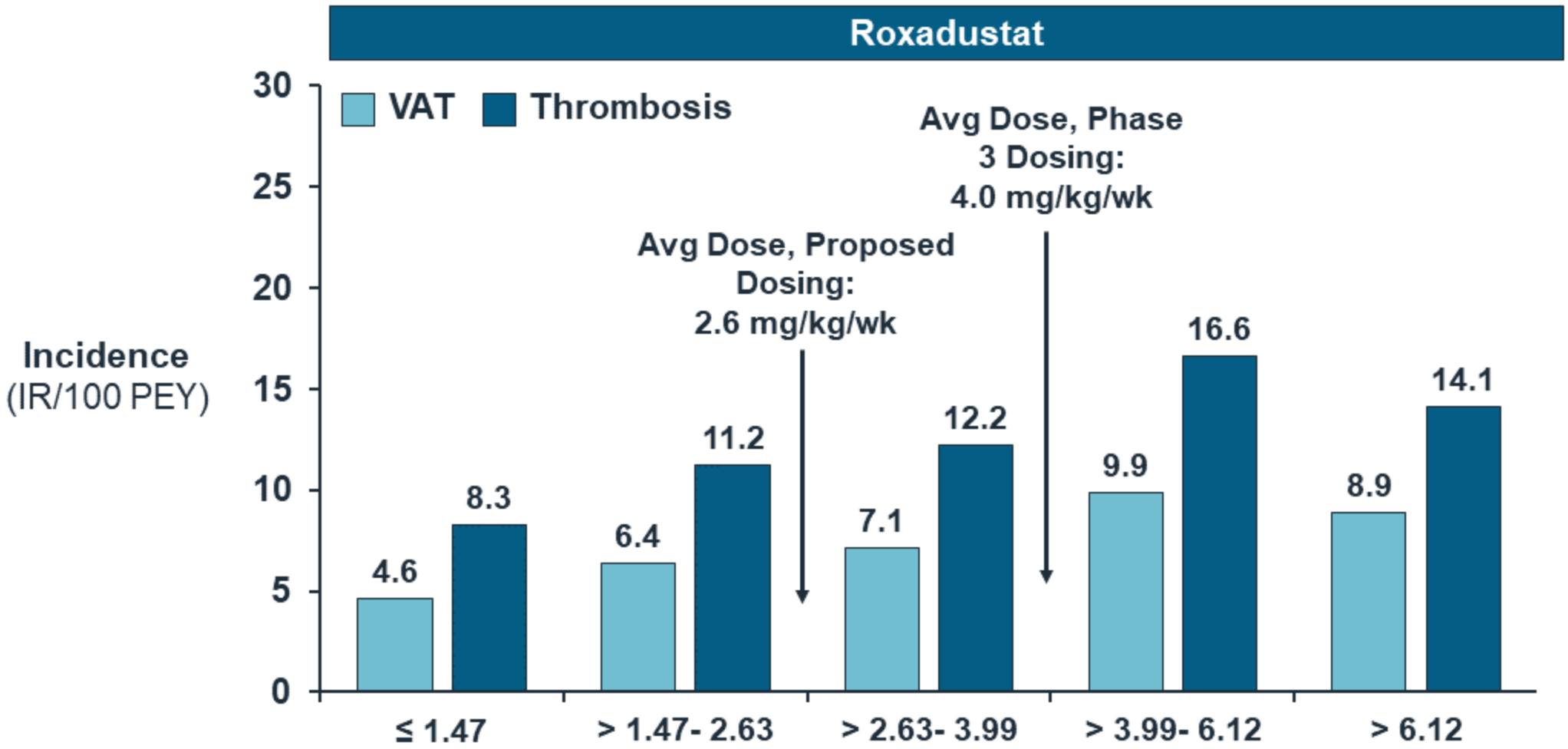
NDD: Proposed Dosing Changes Lead to Reduction in Mean Doses, to Doses Associated with Lower Thrombosis Risk



DD: > 30% Reduction in Overall Mean Doses (Simulation)



DD: Proposed Dosing Changes Lead to Reduction in Mean Doses, to Doses Associated with Lower Thrombosis Risk



Risk Management

- Sponsor plans to communicate all important safety information
  - US Prescribing Information for HCPs
  - Medication Guide for patients
  - Educational materials for HCPs

Risk Mitigation in Proposed Product Labeling

- **Thrombotic events**
  - Dosing changes (lower starting doses, Hb 10-11 g/dL, maximum 3 consecutive dose increases in non-responsive patients)
  - Monitor Hb during treatment (i.e., when initiating or adjusting therapy, monitor Hb levels at least every two weeks until stable, then monitor every 4 weeks)
  - Consider withholding treatment for severe or life-threatening thrombosis and manage all thromboses promptly
- **Seizures**
  - Advise patients to promptly report new onset seizures, premonitory symptoms, or increase in seizure frequency or severity to their healthcare provider
  - Use caution in patients with a history of seizure
- **Serious infections**
  - Avoid starting roxadustat in patients with an active severe or serious infection
  - Monitor patients for signs and symptoms of infection and promptly treat

Practice Model for US Dialysis Patients Uniquely Suited for Prospective Assessment of VAT Risk Using Real-World Evidence in the Postmarketing Setting

- Large pool of dialysis patients allows study of well-matched cohorts
  - > 100K US patients starting dialysis/year
  - > 500K prevalent US dialysis patients
- Anemia treatment data collected systematically
  - Hemoglobin assessed monthly
  - Dosing information frequently collected for anemia treatments
- VAT assessed as part of clinical practice
  - Patients assessed for VAT 3x/week
  - Outcomes of VAT (e.g. requirement for new access) captured
- Overall benefits of real-world evidence
  - Broader, more generalizable patient profile compared to RCTs
  - Real-world evidence directly translates to clinical practice

Effectiveness of Risk Minimization Measures Will be Confirmed with Real-World Evidence from Post-Marketing Study

- **Study Design**
  - Prospective, matched cohort study of US dialysis patients treated with roxadustat vs. ESA in a real-world setting, according to approved labels
    - Matched based on pre-defined criteria; ESA-untreated and conversion patients included
- **Main Objectives**
  1. Assess risk of VAT with roxadustat compared to ESA
  2. Assess risk factors for VAT with roxadustat and ESA
- **Study Size**
  - 5000 roxadustat-treated patients, matched to 5000 ESA patients; observed for one year; expected total ~1000 events
  - Expected to estimate the incidence rate of VAT with roxadustat and ESA with precision of ± 1.0 event/100 PY

Roxadustat Safety and Risk Management Summary

Safety Summary

- Large safety database allowed for comprehensive safety evaluation
- Comparable risk for CV events vs placebo and darbepoetin in NDD patients and vs epoetin alfa in DD patients
- Increased incidence of thrombosis (driven by VAT and DVT) and seizure
- Higher incidence of serious and fatal infections observed versus placebo in NDD patients but not vs ESA in DD patients

Risk Management

- Product Labeling
  - Safety risks are manageable through adequate warnings and precautions
  - Changes to roxadustat dosing to lower risk while preserving benefit of reduction in transfusion risk
- Medication Guide: communicate risks to patients
- Educational Material: inform HCPs of risks
- Postmarketing / Real-World Evidence will confirm effectiveness of risk mitigation measures

- Sponsor will continuously evaluate, communicate, and mitigate known and potential risks
- Sponsor committed to working with FDA in further characterizing the safety profile in post-approval setting

Clinical Perspective

Steven Fishbane, MD

Professor of Medicine

Chief, Division of Nephrology

Donald and Barbara Zucker School of Medicine

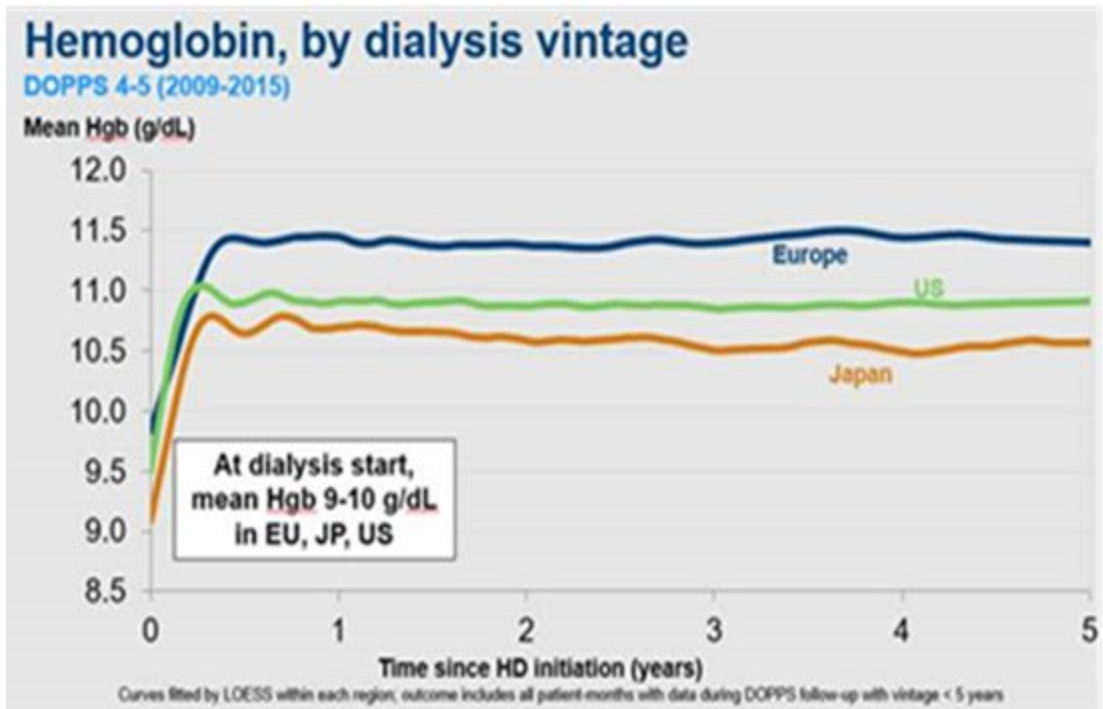
Anemia Treatment Historical Perspective

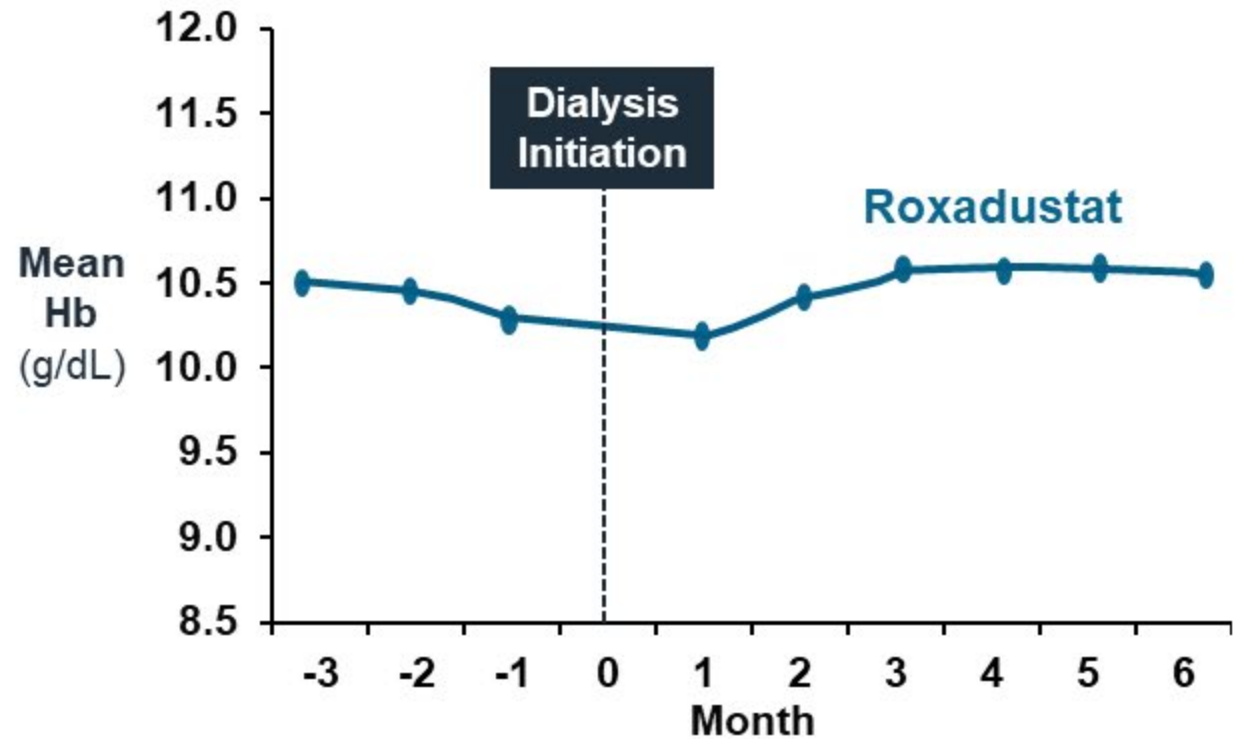
- 1980s – Blood Transfusions
  - Dismal quality of life
  - Alloantibodies and Iron Overload
- 1989 – ESA approval – Major advance in treatment

Roxadustat Addresses Current Dialysis Anemia Challenges

Dialysis Anemia

- Transition to dialysis burdensome





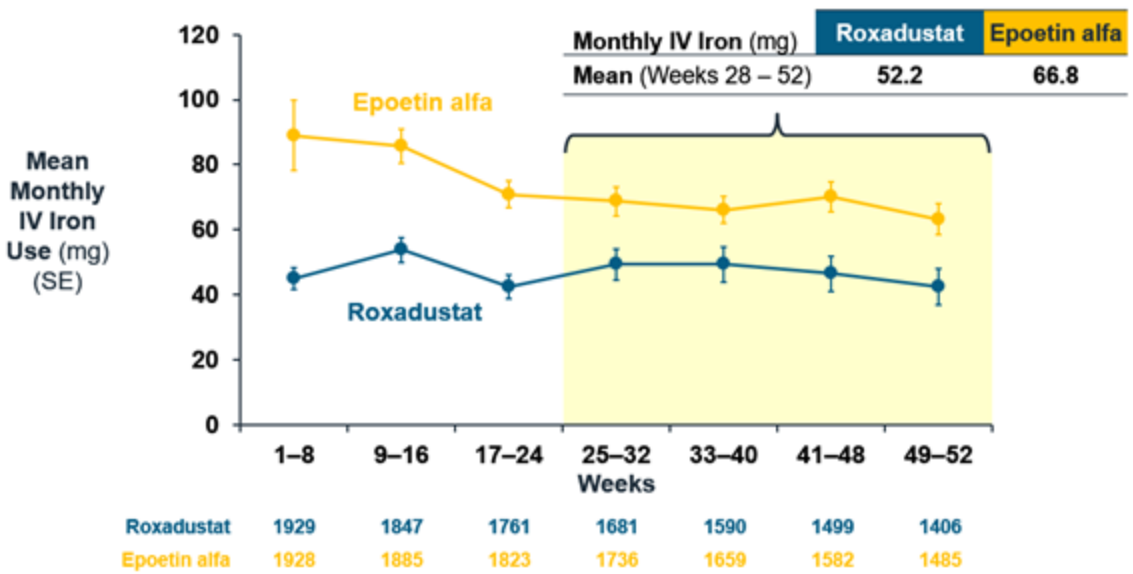
Adapted from DOPPS 4-5 (2009-2015)

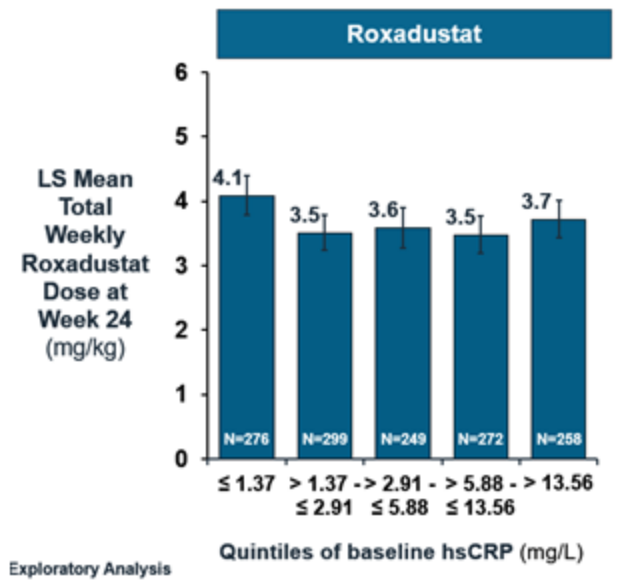
Roxadustat Addresses Current Dialysis Anemia Challenges

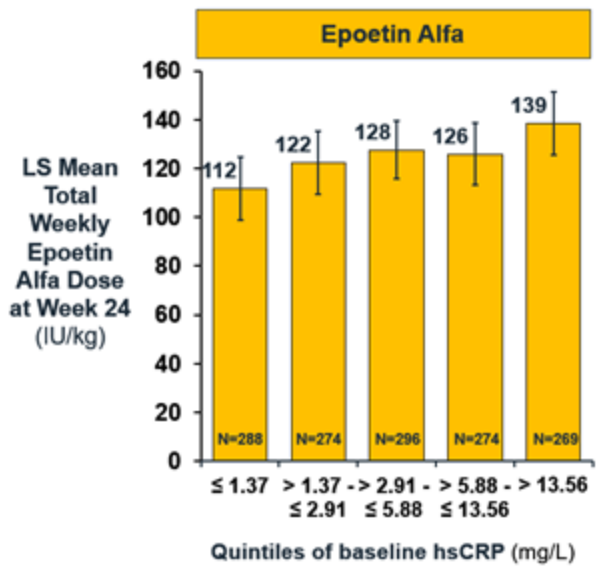
Dialysis Anemia

- Transition to dialysis burdensome
- Hyporesponsiveness common with ESAs

Roxadustat Improved Iron and Inflammation Response







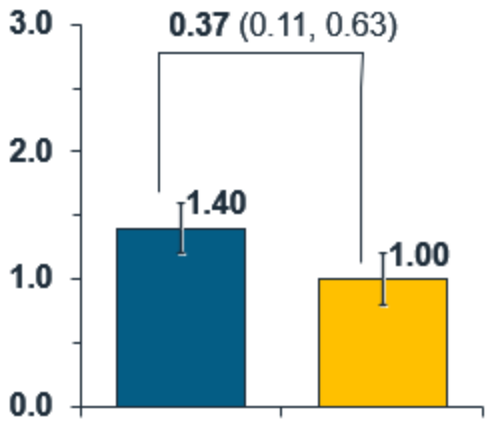
Exploratory Analysis

Roxadustat Addresses Current Dialysis Anemia Challenges

Dialysis Anemia

- Transition to dialysis burdensome
- Hyporesponsiveness common with ESAs
- Home Dialysis - difficult to manage anemia

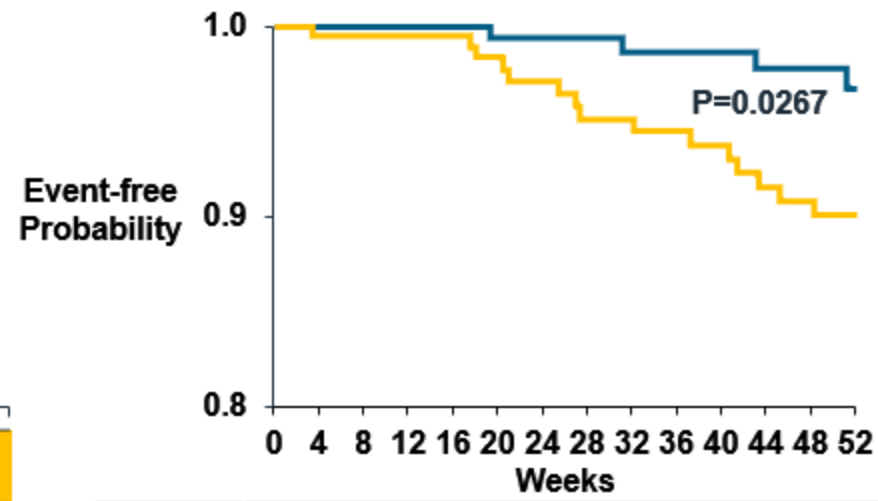
Hb Change



Mean Hb (g/dL)	Roxadustat N = 180	Epoetin alfa N = 192
Baseline	9.58	9.56
Week 28 – 52 (averaged)	11.00	10.64

Peritoneal Dialysis (N = 372) – 9.6% of enrolled DD population

Time to First RBC Transfusion*



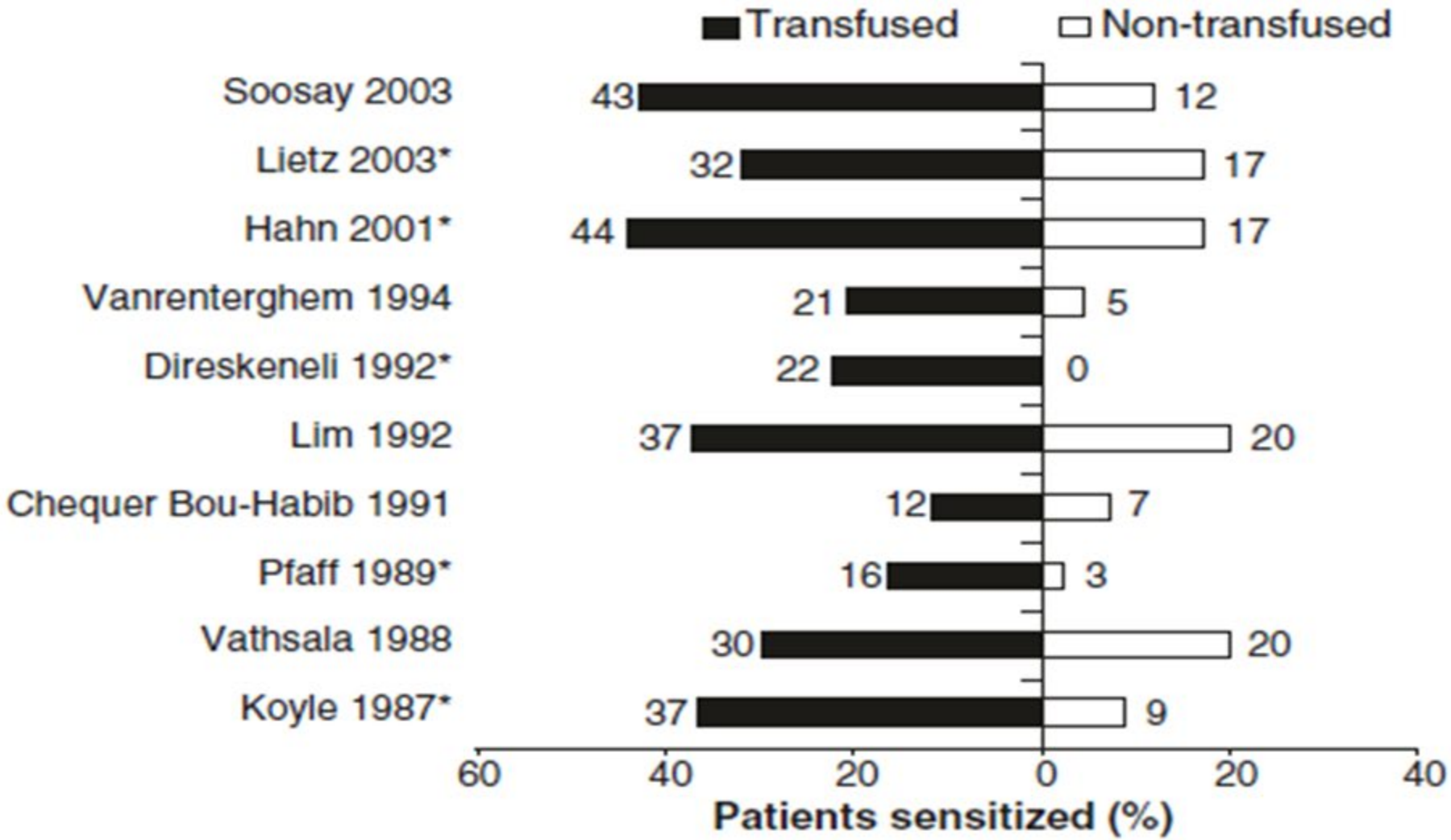
Roxadustat	177	169	163	160	158	151	143	137	129	121	116	109	101	95
Epoetin alfa	188	182	177	174	168	160	151	146	139	133	130	126	116	105

* Not controlled for multiplicity

Missed Opportunities in Nondialysis Anemia

- But in 2021, nondialysis CKD remains grossly undertreated
  - 50% anemia – most untreated
    - 15% nondialysis patients receive ESA
    - 67% iron deficient – Few patients receive treatment
  - More transfusions than ESA or Iron
  - 40% blood transfusions in two years before starting dialysis

Risk of Allosensitization Due to RBC Transfusion



Scornik, 2013

Anemia of CKD Treatment in Nondialysis and Dialysis Widely Supported by World Guideline Groups and Regulatory Approvals

- Anemia Guidelines
  - KDIGO
  - Canada Society of Nephrology
  - European Renal Best Practice (ERBP) for Anaemia in CKD
  - Kidney Disease Outcomes Quality Initiative (KDOQI)
  - The National Institute for Health and Care Excellence (NICE) guidelines (ng8)
  - England- Renal association clinical practice guideline on Anaemia of Chronic Kidney Disease
  - Anaemia management in patients with chronic kidney disease: Taiwan practice guidelines
  - Clinical Practice Guidelines for the Diagnosis and Treatment of Renal Anemia in China
- Regulatory
  - FDA, EMA, Japan Ministry of Health, Worldwide

Clinical Perspective Summary

- Novel oral therapy
- Addresses anemia needs across spectrum of patients with CKD
- Clinical program data support positive roxadustat benefit / risk
- Roxadustat provides an important seamless choice for patients across their entire clinical course

Moderator for Q&A

Mark Eisner, MD

Chief Medical Officer

FibroGen

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

July 15, 2021

FibroGen

Cardiovascular and Renal Drugs Advisory Committee