Pooled Efficacy and CV Safety Results of Roxadustat in the Treatment of Anemia in Chronic Kidney Disease (CKD) Patients On and Not on Dialysis

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Disclosures

Robert Provenzano:
Vice President of Medical Affairs for DaVita.
Board of Directors for Nephroceuticals and Vasc-Alert

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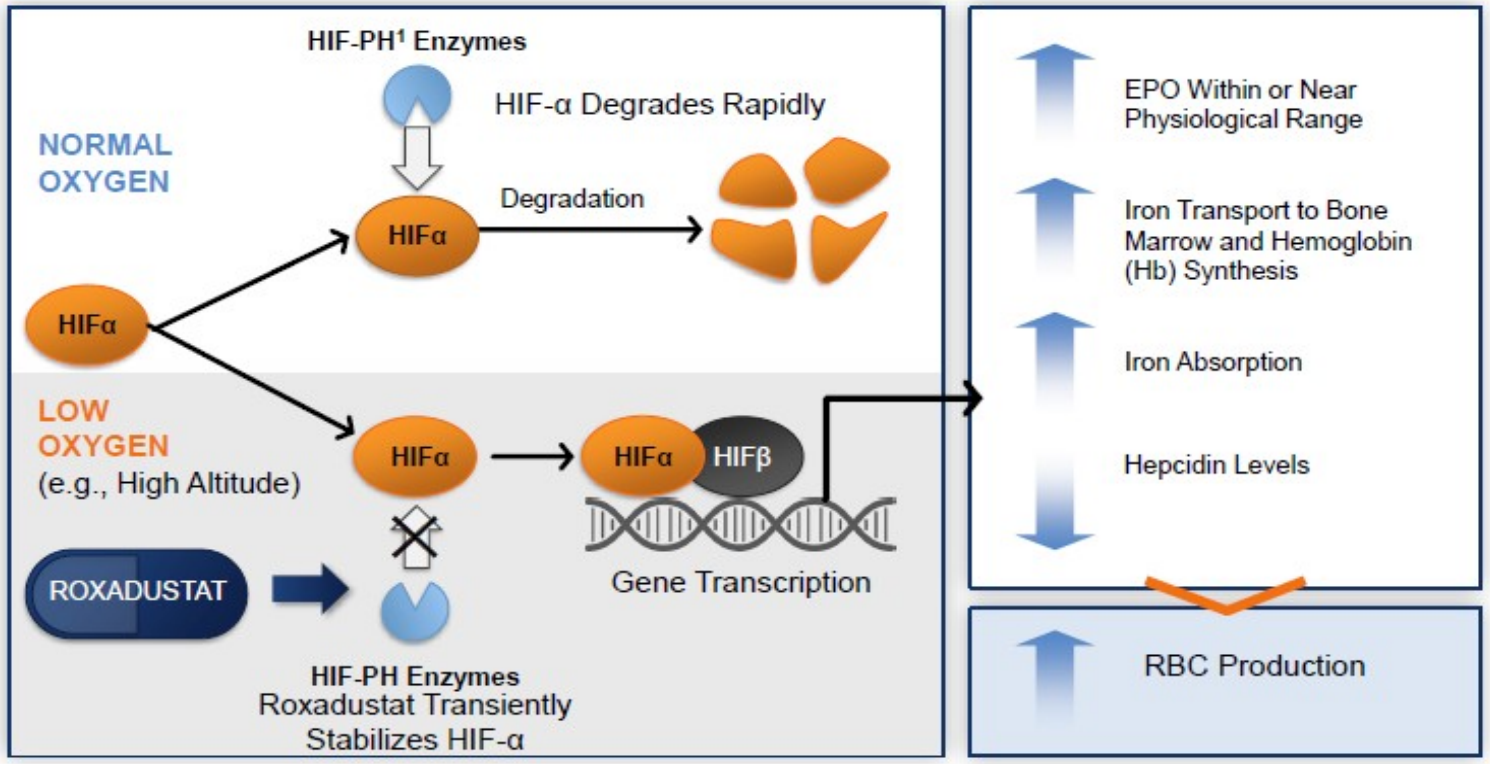
Roxadustat: Novel, First-in-class Treatment for CKD Anemia

- Roxadustat – oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI)
  - 2019 Nobel Prize winning science is the foundation of roxadustat
  - Increases hemoglobin (Hb) by mimicking the body's natural response to low oxygen
  - Studied for treatment of anemia in Stage 3 to 5 CKD patients, both on and not on dialysis
  - Approved in China: (dialysis 12/2018, not on dialysis 8/2019) and Japan: (on dialysis 9/2019)



2019 Nobel Prize In Physiology or Medicine

"for their discoveries of how cells sense and adapt to oxygen availability."

Awarded jointly to:

William G. Kaelin Jr.
Harvard University

Gregg L. Semenza
Johns Hopkins University

Peter J. Ratcliffe
Francis Crick Institute
London

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

Roxadustat Global Phase 3 Studies
Efficacy and Pooled Cardiovascular Safety Endpoints

- **Study populations:** broad range of CKD patients, reflective of intended treatment population
  - **Non-dialysis-dependent (NDD) CKD pool:** placebo comparator
  - **Dialysis dependent (DD) CKD pool:** epoetin alfa comparator
    - **Incident dialysis (ID) pool:** clinically important subgroup of DD pool
- **Efficacy endpoints:**
  - **Primary efficacy endpoint** in individual studies and pooled analyses
  - Pooled efficacy results: potential clinical benefits differentiated from current SOC
- **Safety:**
  - **Cardiovascular (CV) safety endpoints in NDD pool and in DD pool**
  - Other safety findings have been summarized in individual study presentations in other sessions

CKD, chronic kidney disease; SOC, standard of care

Roxadustat NDD and DD Program

Phase 3 CKD non-dialysis-dependent (NDD) Pool				
D5740C00001	FGCL-4592-060	1517-CL-0608	**NDD Pooled**	
OLYMPUS	**ANDES**	**ALPS**		
AstraZeneca	FibroGen	Astellas	**Roxa**	**Placebo**
N=2761	**N=922**	**N=594**	**N=2391**	**N=1886**
R 1:1	R 2:1	R 2:1	**1.62 Avg PEY**	**1.23 Avg PEY**

Number of patients: 4277
Patient exposure years: 6194

Phase 3 CKD dialysis-dependent (DD) Pool				
D5740C00002	FGCL-4592-064	FGCL-4592-063	**DD Pooled**	
ROCKIES	**SIERRAS**	**HIMALAYAS**		
AstraZeneca	FibroGen	FibroGen	**Roxa**	**EPO**
Global	US only	Global		
N=2106	**N=741**	**N=1043**	**N=1943**	**N=1947**
R 1:1	R 1:1	R 1:1		
Correction & maintenance Early & Stable DD	Maintenance Early & Stable DD	Correction DD Vintage<4mos Only (Early)	**1.71 Avg PEY**	**1.92 Avg PEY**

Number of patients: 3880
Patient exposure years: 7059

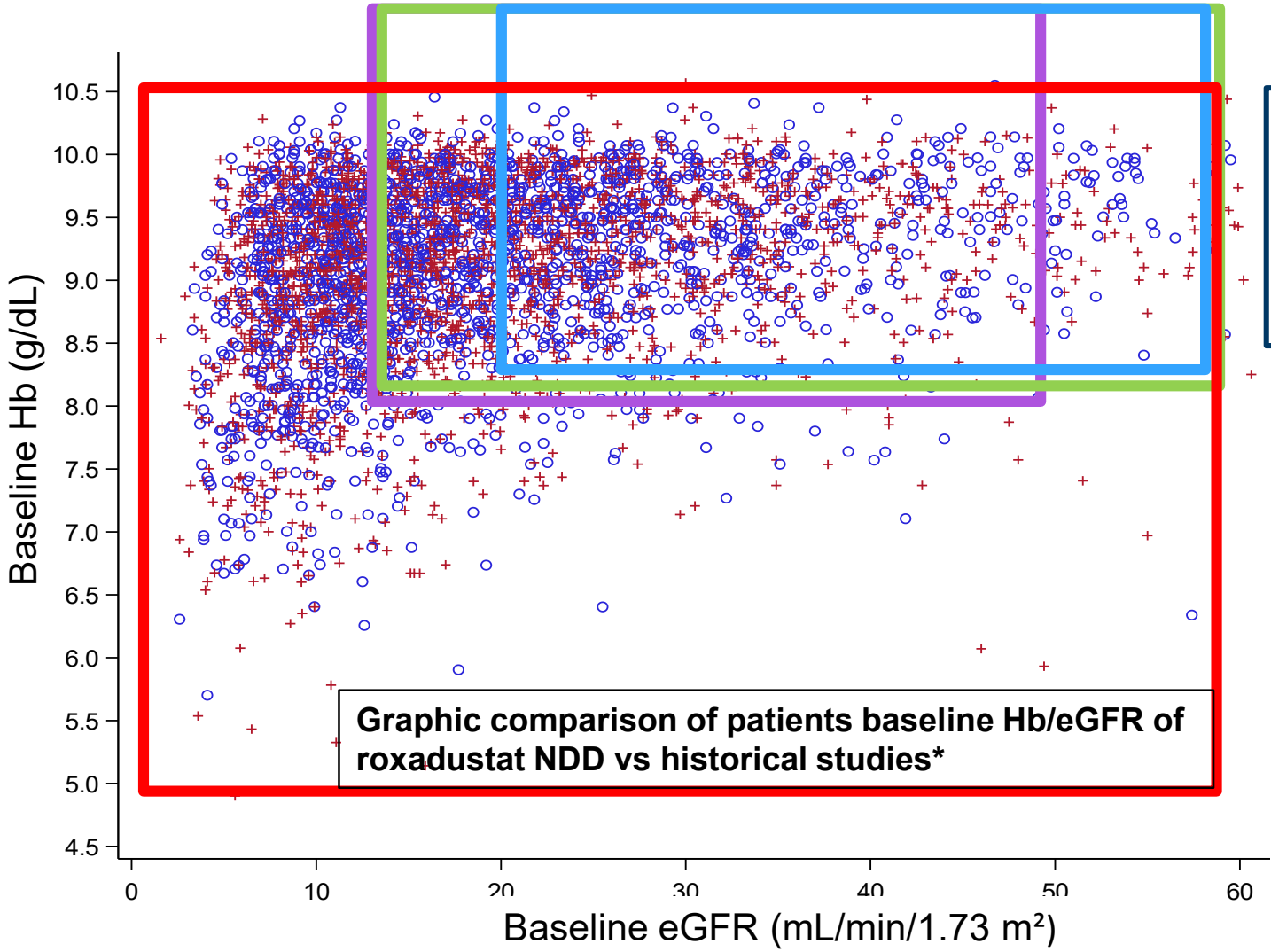
5 EPO, epoetin alfa; Hb, hemoglobin; PEY, patient exposure year; R, Randomization; Roxa, roxadustat

Roxadustat NDD Program: Inclusive of Patients Not Studied in Prior CKD Anemia Trials

NDD Population	Roxadustat (N=2391)	Placebo (N=1886)
Age (years) mean (SD)	61.9 (14.1)	62.7 (14.0)
CKD etiology, n (%)		
Diabetic nephropathy	1082 (45.3)	834 (44.2)
Hypertensive nephropathy	585 (24.5)	381 (20.2)
Other	896 (37.5)	758 (40.2)
Medical history, n (%)		
Cardiac, cerebrovascular, or thromboembolic disease*	886 (37.1)	695 (36.9)
Diabetes, n (%)	1337 (55.9)	1096 (58.1)
Baseline eGFR (ml/min/1.73 m^2)		
Mean (SD)	19.72 (11.56)	20.04 (11.76)
Median (min–max)	16.90 (1.6–68.2)	17.01 (2.6–75.2)
<10, n (%)	481 (20.1)	359 (19.0)
10 – <15, n (%)	526 (22.0)	452 (24.0)
15 – <30, n (%)	954 (39.9)	724 (38.4)
≥30, n (%)	430 (18.0)	351 (18.6)
Baseline Hb (g/dL)		
Mean (SD)	9.10 (0.74)	9.10 (0.73)
Median (Min–Max)	9.23 (4.9–11.6)	9.25 (5.7–10.6)
Iron repletion status at baseline, n (%)		
TSAT <20% or ferritin <100 ng/mL, n (%) non-replete	956 (40.0)	755 (40.0)
TSAT ≥20% and ferritin ≥100 ng/mL, n (%) replete	1433 (59.9)	1127 (59.8)

*History of any of the following: myocardial infarction, percutaneous coronary intervention, coronary artery bypass, congestive cardiac failure, ischemic stroke, hemorrhagic stroke, cerebrovascular incident. eGFR, estimated glomerular filtration rate; SD, standard deviation; TSAT, transferrin saturation

Roxadustat NDD Program: Evaluation of Anemia Therapy In A Broad Range of Patients Not Included In Prior CKD Anemia Trials



Roxadustat NDD Patient Features

Advanced CKD: 42% CKD 5

Low Iron stores: 40% non-iron replete

Low Mean Baseline Hb: 9.1

CHOIR (2006)

ARCTOS Mircera (2008)

TREAT (2009)

Roxadustat NDD

Actual Pooled Treatment 1 for Period
o Placebo + Roxadustat

*Historical study patients baseline Hb & eGFR characteristics in figure is based on approximations from published manuscripts

eGFR, estimated glomerular filtration rate

DD Demographics and Baseline Characteristics

DD Population	Roxadustat (N=1929)	Epoetin Alfa (N=1928)
Age (years)		
Mean (SD)	54.3 (14.88)	55.1 (14.61)
Median (min, max)	56.0 (18, 93)	57.0 (18, 94)
Gender, n (%)		
Male	1113 (57.7)	1136 (58.9)
Female	816 (42.3)	792 (41.1)
Race group, n (%)		
Asian	269 (13.9)	260 (13.5)
Black	348 (18.0)	363 (18.8)
White	1171 (60.7)	1170 (60.7)
Other	141 (7.3)	135 (7.0)
Region, n (%)		
US	874 (45.3)	879 (45.6)
Europe	651 (33.7)	651 (33.8)
Other	404 (20.9)	398 (20.6)

DD Population	Roxadustat (N=1929)	Epoetin Alfa (N=1928)
Medical history, n (%)		
Cardiac, cerebrovascular or thromboembolic disease*	940 (48.7)	923 (47.9)
Diabetes	906 (47.0)	905 (46.9)
Dialysis modality, n (%)		
Hemodialysis	1750 (90.7)	1740 (90.2)
Peritoneal dialysis	177 (9.2)	188 (9.8)
Dialysis Vintage <4months	760 (39.4)	770 (39.9)
Baseline Hb (g/dL)		
Mean (SD)	9.63 (1.30)	9.67 (1.30)
Median (min, max)	9.80 (4.3, 12.0)	9.83 (5.0, 12.2)
<10	1079 (55.9)	1045 (54.2)
≥10	850 (44.1)	883 (45.8)
Baseline ferritin (ng/ml)		
Mean (SD)	608.6 (466.5)	602.2 (469.6)
Baseline TSAT (%)		
Mean (SD)	33.0 (12.74)	32.7 (12.4)
Median (min, max)	31.0 (4.0, 87.0)	30.5 (5.0, 88.0)

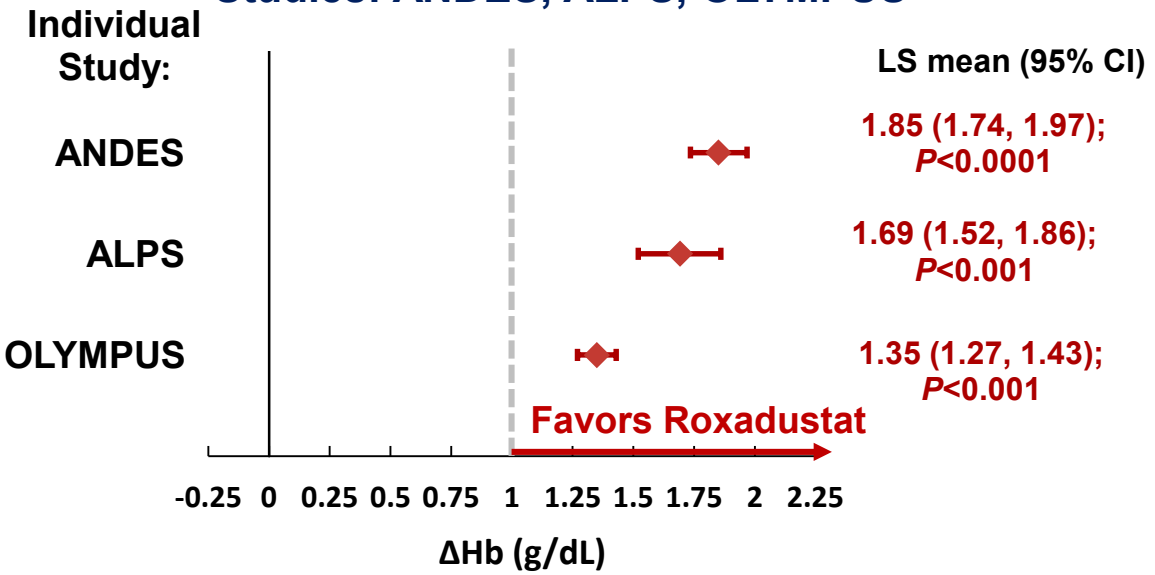
*History of any of the following: myocardial infarction, percutaneous coronary intervention, coronary artery bypass, congestive cardiac failure, ischemic stroke, hemorrhagic stroke, cerebrovascular incident. mo, month

NDD Efficacy: Met Primary Efficacy Endpoint

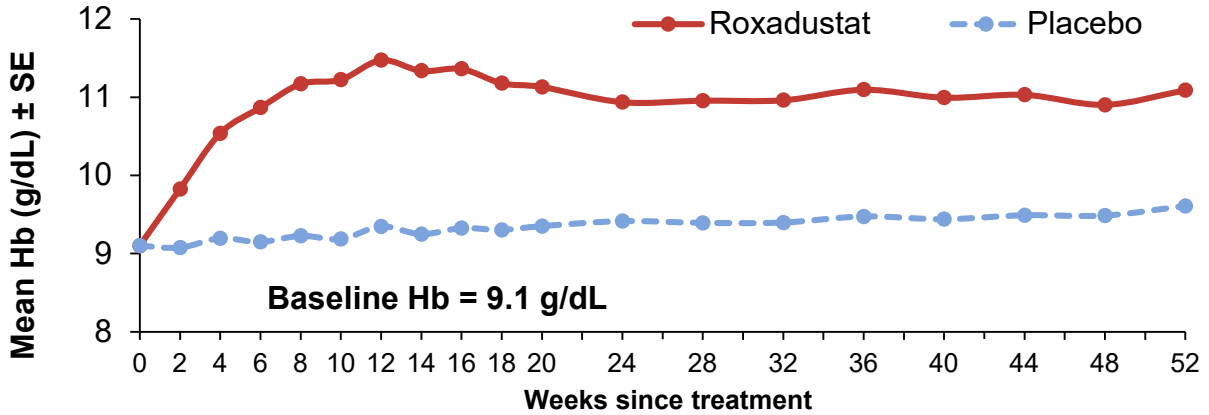
Roxadustat is superior to placebo, regardless of iron-repletion

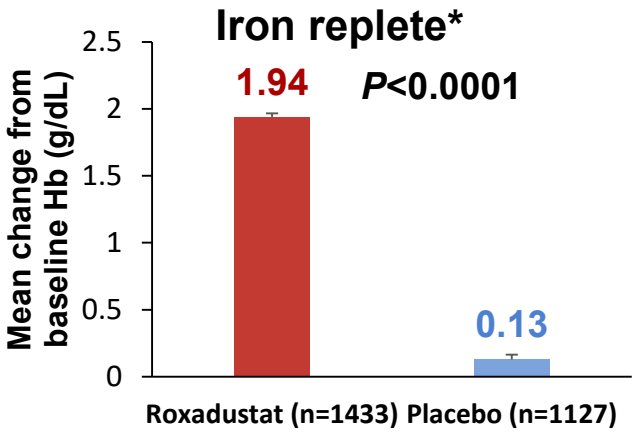
Primary efficacy endpoint (change in Hb from baseline to Hb averaged over Weeks 28–52) was met in individual studies and pooled analyses

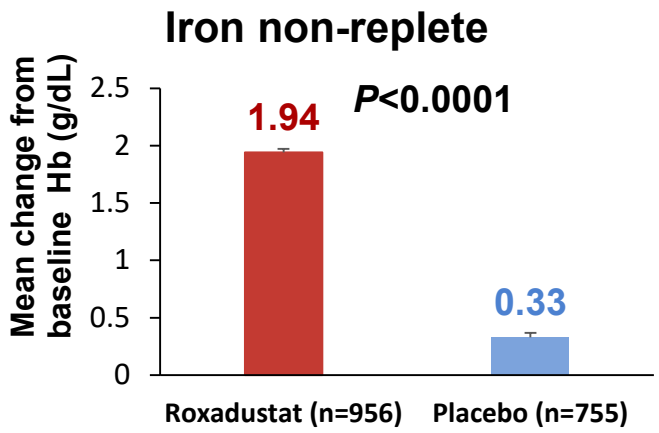
Hb change from baseline to Week 28–52
Studies: ANDES, ALPS, OLYMPUS



NDD (N=4277): Mean Hb over time up to Week 52 (g/dL)
Hb change to Week 28–52: 1.85 (Roxa) vs 0.13 (Placebo) *P<0.001*







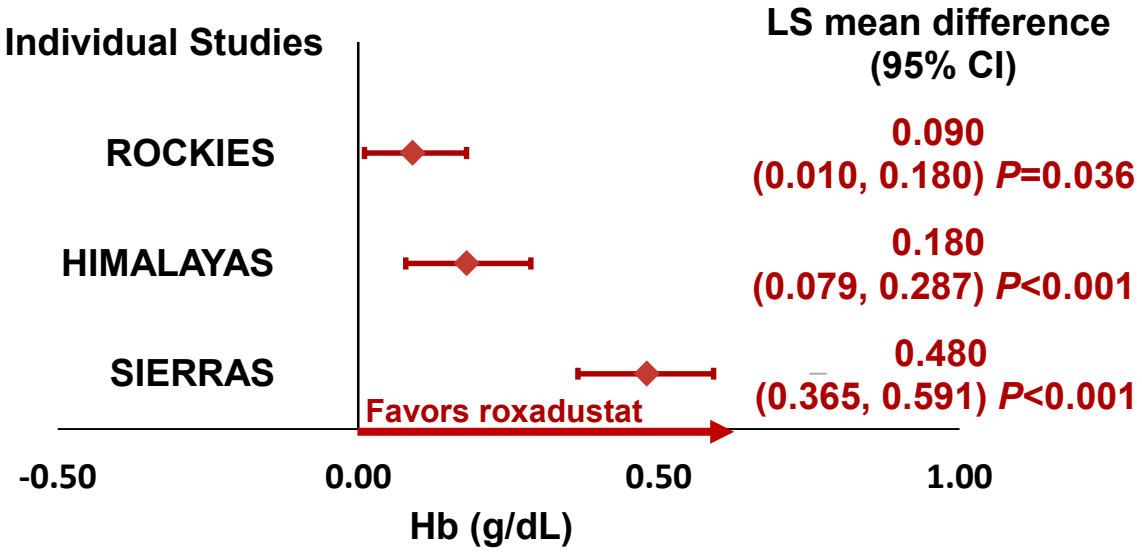
*Iron Replete: TSAT ≥20% and ferritin ≥100 ng/mL

CI, confidence interval; LS, least squares; SE, standard error

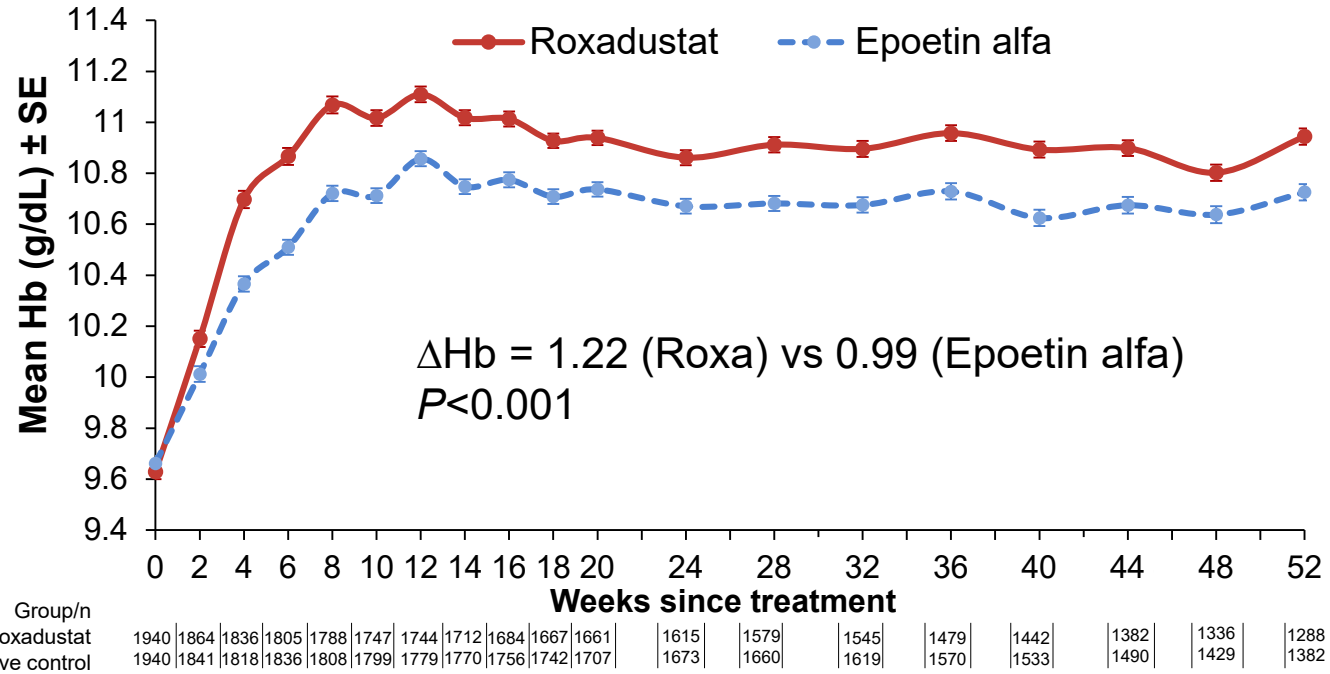
DD: Roxadustat Efficacious, Larger Hb Increase Than EPO in Individual Studies & In Pooled Analysis

Primary efficacy endpoint (change in Hb from baseline to Hb averaged over Weeks 28 to 52): Roxadustat achieved larger Hb increase over epoetin alfa in individual studies & in pooled DD

Hb (g/dL) change from baseline to Week 28–52



DD (N=3857): mean Hb (g/dL) over time

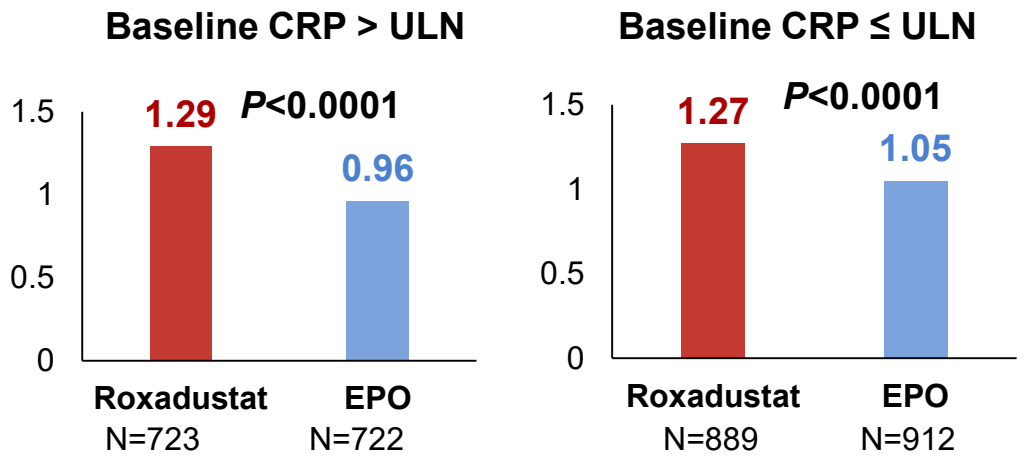


10 CRP, C-reactive protein; EPO, epoetin alfa

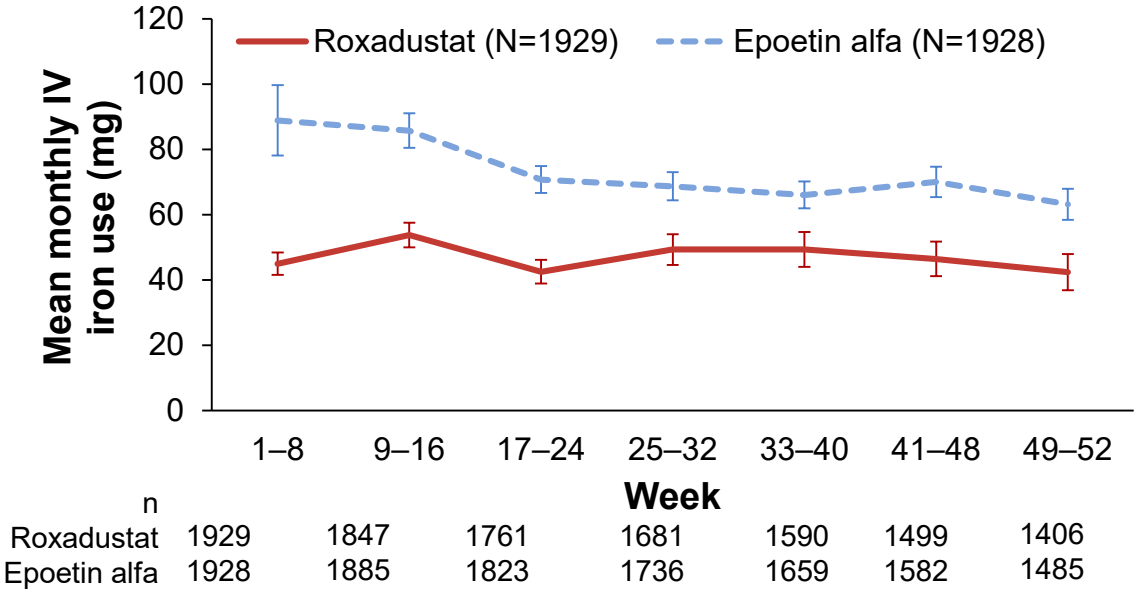
DD: Roxadustat Efficacious Regardless of Inflammation, Less IV iron requirement than Epoetin Alfa

- **Roxadustat achieved higher Hb increase in patients with inflammation (CRP > ULN) and in patients without inflammation (CRP ≤ ULN), compared to epoetin alfa**
- **Less IV iron was required in roxadustat patients than in patients on epoetin alfa**

DD: Hb (g/dL) change from baseline to Weeks 28–52



DD: Less Monthly IV Iron Use in Roxadustat Patients Than in Epoetin Alfa Patients

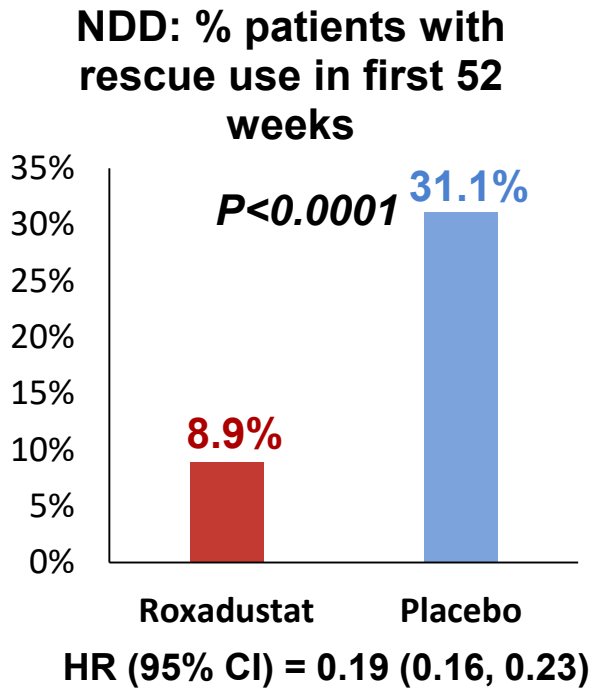


n						
Roxadustat	1929	1847	1761	1681	1590	1499	1406
Epoetin alfa	1928	1885	1823	1736	1659	1582	1485

11 IV, intravenous; ULN, upper limit of normal

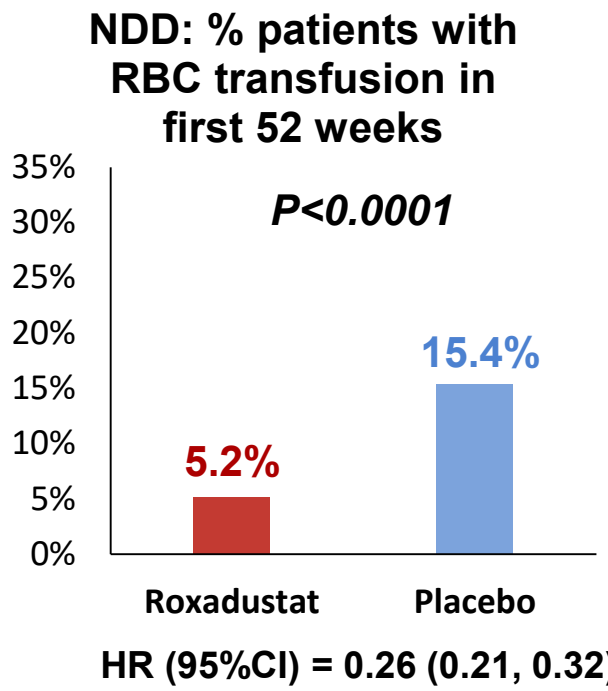
Roxadustat Lowers Use of Rescue* Therapies in NDD; Reduction in RBC Transfusion in NDD (vs Placebo) and in DD (vs Epoetin Alfa)

NDD: Rescue Use



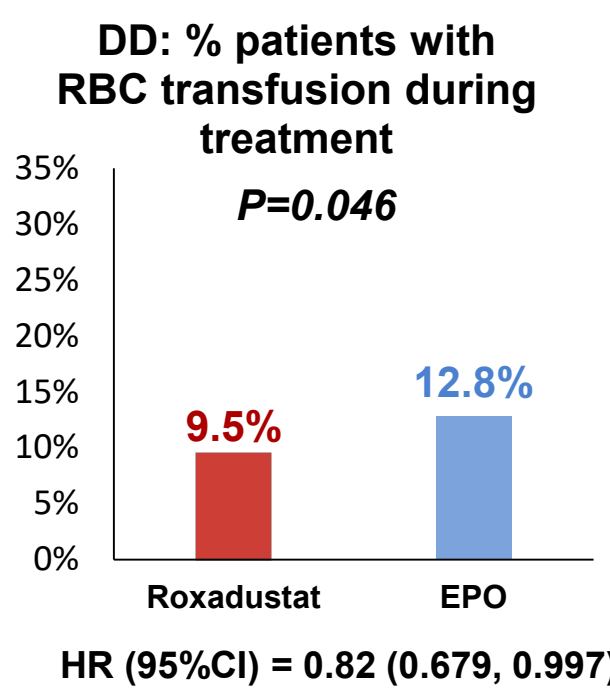
HR (95% CI) = 0.19 (0.16, 0.23)

NDD: RBC Transfusion



HR (95%CI) = 0.26 (0.21, 0.32)

DD: RBC Transfusion



HR (95%CI) = 0.82 (0.679, 0.997)

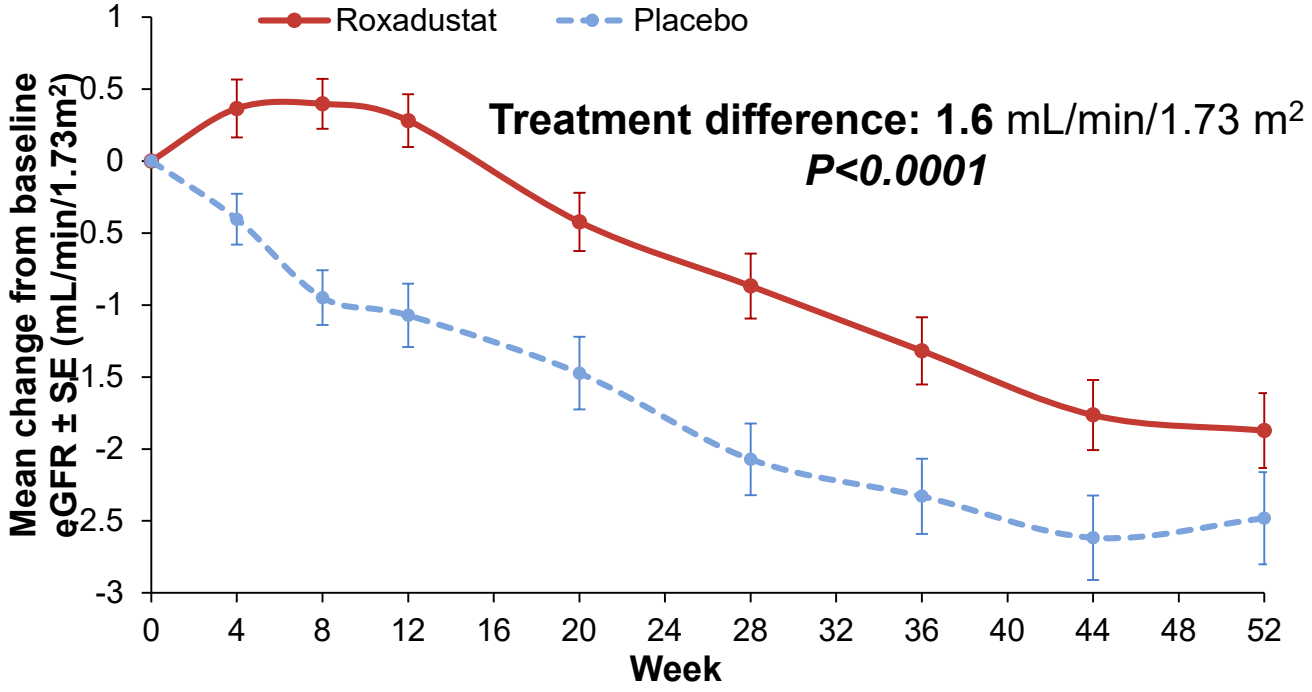
*Rescue = RBC transfusion, ESA, or IV iron

 HR, hazard ratio; RBC, red blood cell

Roxadustat Potential Additional Benefits in NDD

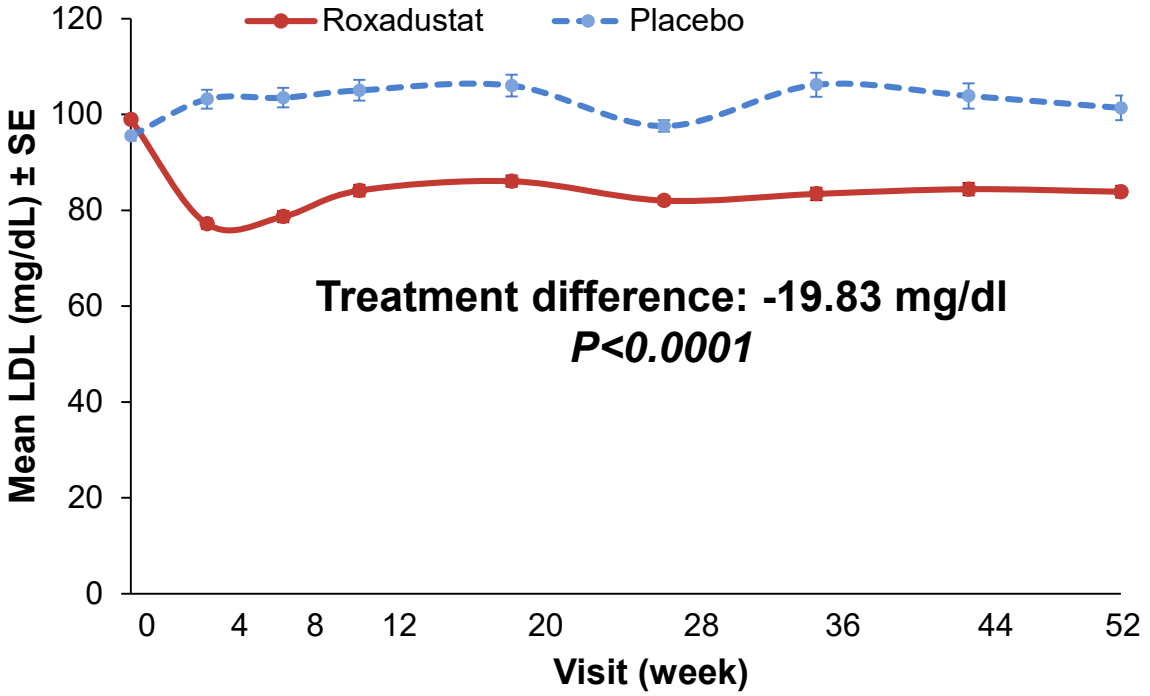
Change in eGFR from Baseline

Patients with baseline eGFR ≥15 mL/min/1.73 m^2 (N=2438)



Group/n									
Roxadustat	1373	1311	1269	1236	1189	1150	1086	1038	990
Placebo	1065	1017	979	936	863	819	760	706	657

Mean LDL (mg/dL) over time up to Week 52



13 LDL, low-density lipoprotein

Cardiovascular Safety Endpoint Pooled Analyses

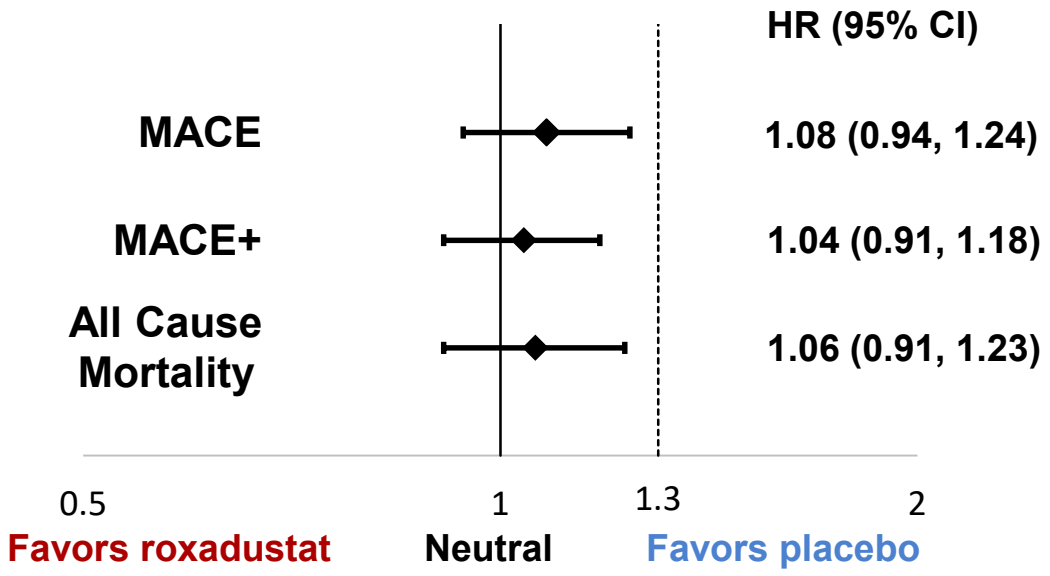
- Cardiovascular (CV) safety endpoints analyzed in **NDD pool** and in **DD pool**
- *Key safety endpoints*:
  - **Time to first MACE**
    - MACE (Major Adverse Cardiovascular Events) include: all-cause mortality, myocardial infarction, and stroke
  - **Time to first MACE+**
    - MACE+ include MACE, unstable angina requiring hospitalization, and congestive heart failure requiring hospitalization
  - **Time to all-cause mortality**
- CV events were **centrally adjudicated** by independent experts blinded to treatment assignment

CV, cardiovascular

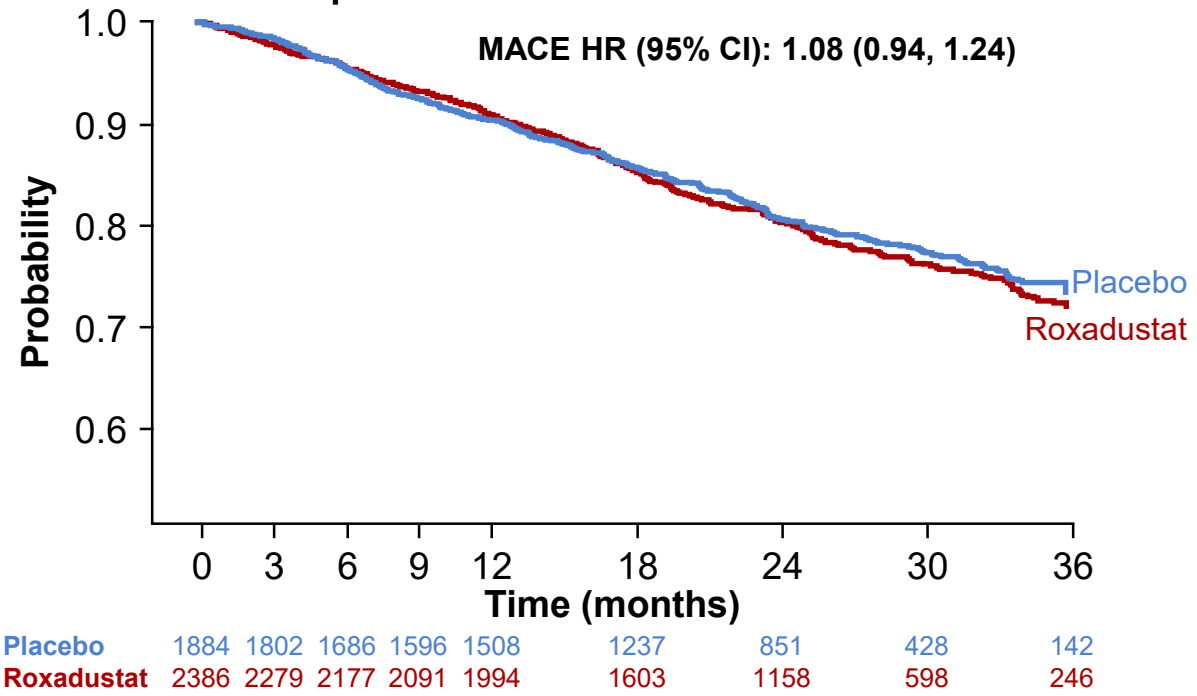
NDD Pool: Cardiovascular Safety Endpoints MACE, MACE+, All-cause Mortality

Risks of MACE, MACE+, or all-cause mortality in roxadustat patients were comparable to placebo in NDD patients*

Time to event endpoints using Cox model, ITT analysis**
NDD (OLYMPUS, ANDES, ALPS), N=4270



Proportion of Patients Without MACE**



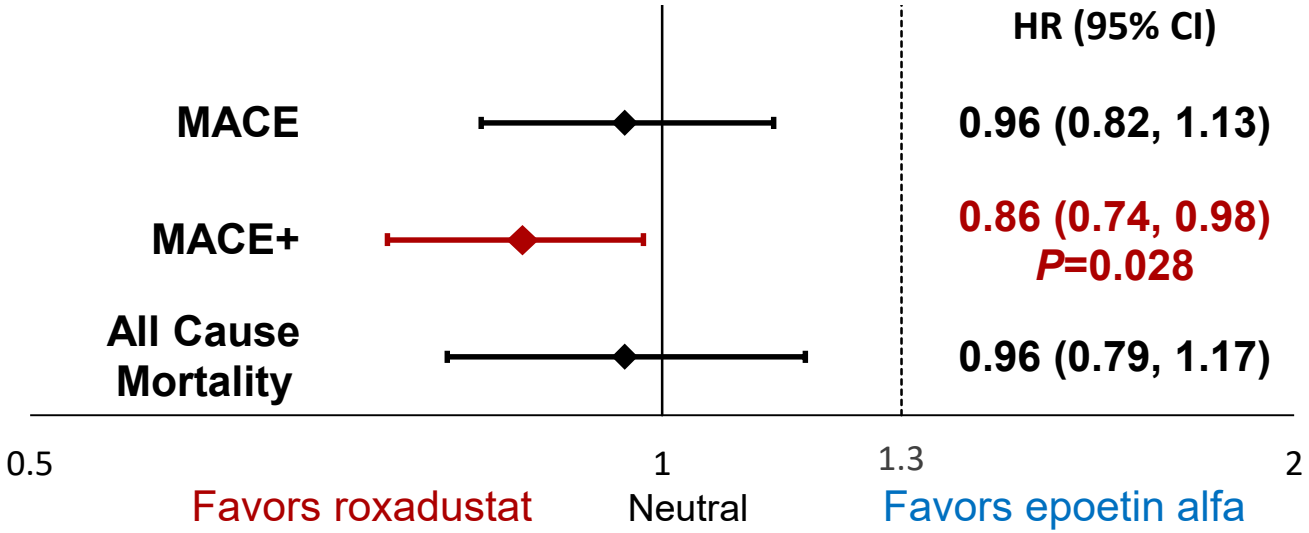
*"comparable" based on hazard ratio (HR) upper bound of 95% confidence interval (95%CI) below reference non-inferiority margin of 1.3

**ITT analysis = Intent to treat analysis evaluation period to include on-treatment and off-treatment long term follow-up, until end of study

DD Pooled: Cardiovascular Safety Endpoints

- **Risk of MACE and all-cause mortality in roxadustat patients were not increased compared to epoetin alfa in DD patients***
- **Roxadustat patients had a lower risk of MACE+ than epoetin alfa patients**

Time to event endpoints using Cox model†
DD (ROCKIES, HIMALAYAS, SIERRAS), N=3880



MACE+ Components Incidence Rates, N (%)		
Events	Roxadustat	Epoetin alfa
n	1940	1940
Death (all-cause mortality)	207 (10.7%)	232 (12.0%)
Myocardial infarction	103 (5.3%)	109 (5.6%)
Stroke	45 (2.3%)	50 (2.6%)
Unstable angina	18 (0.9%)	22 (1.1%)
Congestive heart failure	120 (6.2%)	166 (8.6%)

*"risk not increased" based on hazard ratio (HR) upper bound of 95% confidence interval (95%CI) below reference non-inferiority margin of 1.3.

†On-treatment analysis

Incident Dialysis (ID) Patients: A Large, Clinically Important Subgroup of Dialysis-dependent Patients

- Patients typically **start anemia therapy at start of dialysis**
- A **clinically relevant comparison between roxadustat & EPO**
- Represents the **highest risk** population of patients on dialysis

ID Population	HIMALAYAS All ID	SIERRAS (ID Subgroup)	ROCKIES (ID Subgroup)	ID Pool N=1530	
				Roxa	EPO
Number of subjects	1043	71	416	760	770
Patient exposure years	1842	45	401	1098	1190

Demographic and Baseline Characteristics

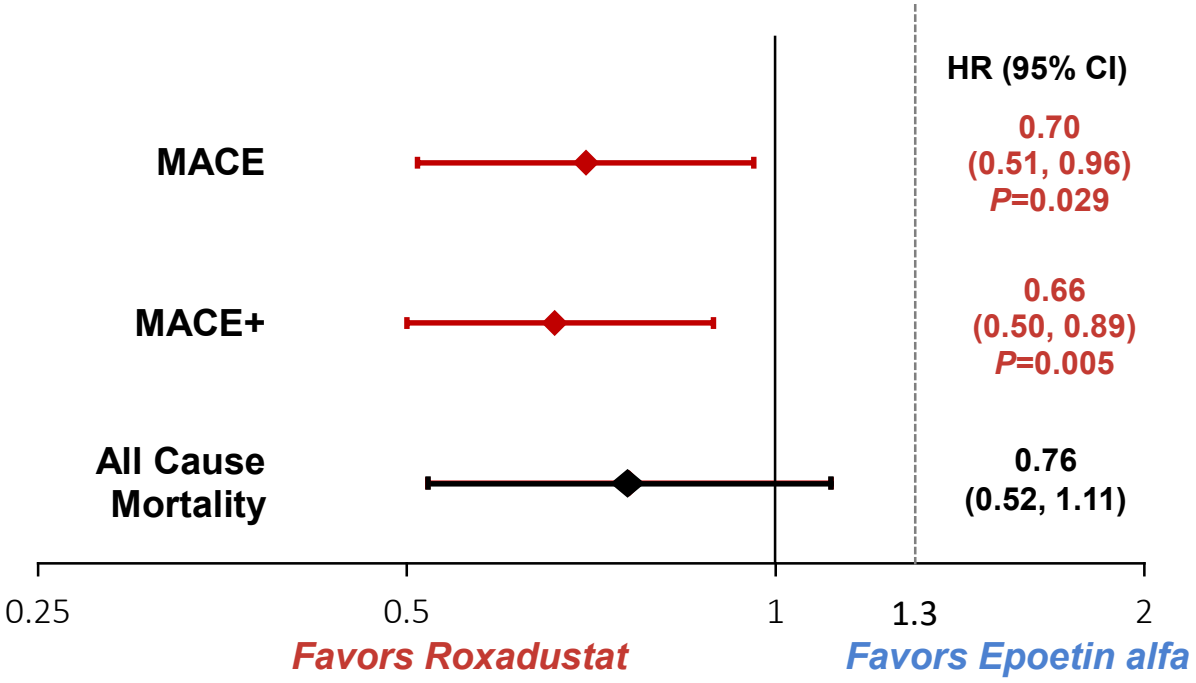
ID Population	Roxadustat (N=760)	Epoetin α (N=770)
Age (years)		
Median (min, max)	**55.0 (18, 87)**	**55.0 (18, 92)**
Race group, n (%)		
Asian	**116 (15.3)**	**127 (16.5)**
Black	**67 (8.8)**	**67 (8.7)**
White	**508 (66.8)**	**505 (65.6)**
Other	**69 (9.1)**	**71 (9.2)**
Baseline Hb (g/dL)		
Mean (SD)	**8.8 (1.2)**	**8.9 (1.2)**
Median (min, max)	**8.9 (5.3, 12.0)**	**8.87 (5.0, 12.0)**
<10 g/dL, n (%)	**647 (85.1)**	**655 (85.1)**
≥10 g/dL, n (%)	**113 (14.9)**	**115 (14.9)**

17 RCT, randomized controlled trial

Incident Dialysis Pool: Cardiovascular Safety Endpoints

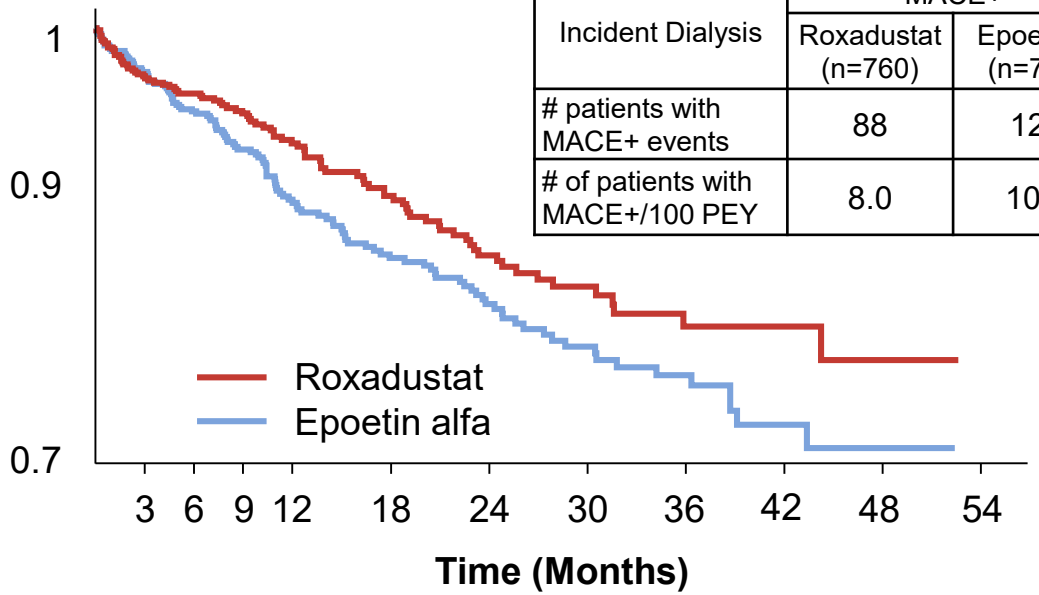
Roxadustat had 30% lower risk of MACE and 34% lower risk of MACE+ than epoetin alfa* and with a trend towards lower all-cause mortality relative to epoetin alfa, in incident dialysis patients

Time to event endpoints using Cox model †
ID (ROCKIES, HIMALAYAS, SIERRAS), N=1526



Proportion of Patients Without MACE+ Over Time

Incident Dialysis	MACE+	
	Roxadustat (n=760)	Epoetin α (n=766)
# patients with MACE+ events	88	121
# of patients with MACE+/100 PEY	8.0	10.2



Epoetin alfa	699	605	511	401	316	246	171	111	50	24	0
Roxadustat	673	594	495	389	304	223	137	87	43	16	0

 *Lower MACE & MACE+ risks – based on the HR upperbound of 95% confidence interval below 1.0. †On-treatment analysis

Conclusions: *Efficacy*

- **Roxadustat efficacy was demonstrated**
  - **Achieved primary efficacy endpoint (change in Hb) in individual studies and pooled analyses**
    - **NDD:** roxadustat was superior to placebo and efficacious regardless of iron-repletion
    - **DD:** roxadustat achieved larger mean Hb increase than epoetin alfa, especially in inflamed patients, and less IV iron was required in roxadustat arm than in epoetin alfa.
  - **Lower RBC transfusion risk**
    - **NDD:** In roxadustat patients compared with placebo
    - **DD:** In roxadustat patients compared with epoetin alfa
  - **Other potential benefits in NDD**
    - Reduced LDL cholesterol
    - Less decline in eGFR

Conclusions: *Roxadustat CV Safety*

- **CV safety was demonstrated in all study populations**
  - **Non-dialysis:** Risk of MACE, MACE+, and all-cause mortality in roxadustat patients were comparable to placebo in NDD patients
  - **Incident dialysis:** Roxadustat had 30% lower risk of MACE and 34% lower risk of MACE+ than epoetin alfa, and with a trend towards lower all-cause mortality relative to epoetin alfa
  - **Dialysis-dependent:**
    - Roxadustat patients had a lower risk of MACE+ than epoetin alfa patients
    - Risk of MACE and all-cause mortality in roxadustat patients were not increased compared to epoetin alfa in DD patients

In Memory Of Thomas B. Neff

- Founder, CEO and Chairman of the Board of FibroGen, Inc. (1995– Aug 25, 2019)
- Inventor and champion for selection of CKD anemia as first clinical application of HIF science (oxygen sensing and biology of adaption to hypoxia)
- Leader for development of roxadustat (HIF-PHI) for the treatment of CKD anemia

Thomas B. Neff

(6/18/1954 - 8/25/2019)

Thank You

To the many contributors who made Roxadustat clinical studies possible

- Study patients & family
- Investigators & research staff
- Expert Advisors
- DSMB members
- CV safety endpoint adjudication team
- Reviewers at health authorities around the world
- IRB Members
- Clinical research organizations
- Academic research collaborators
- Funders of Roxadustat R&D
- FibroGen, AstraZeneca, & Astellas employees & family
- Supporters of the Roxadustat Project