



Ο πρώτος αναστολέας HIF-PH. Από το κλινικό πρόγραμμα στην κλινική πράξη

Ιωάννης Γριβέας, MD, PhD

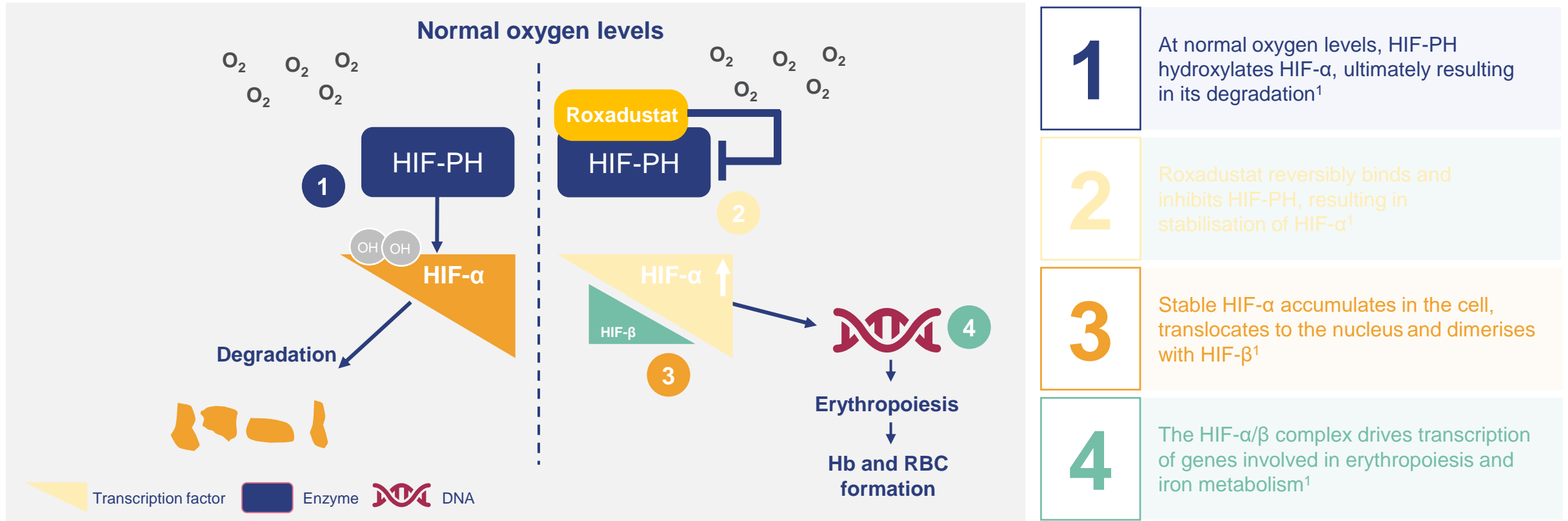
Νεφρολόγος



Conflict of Interest

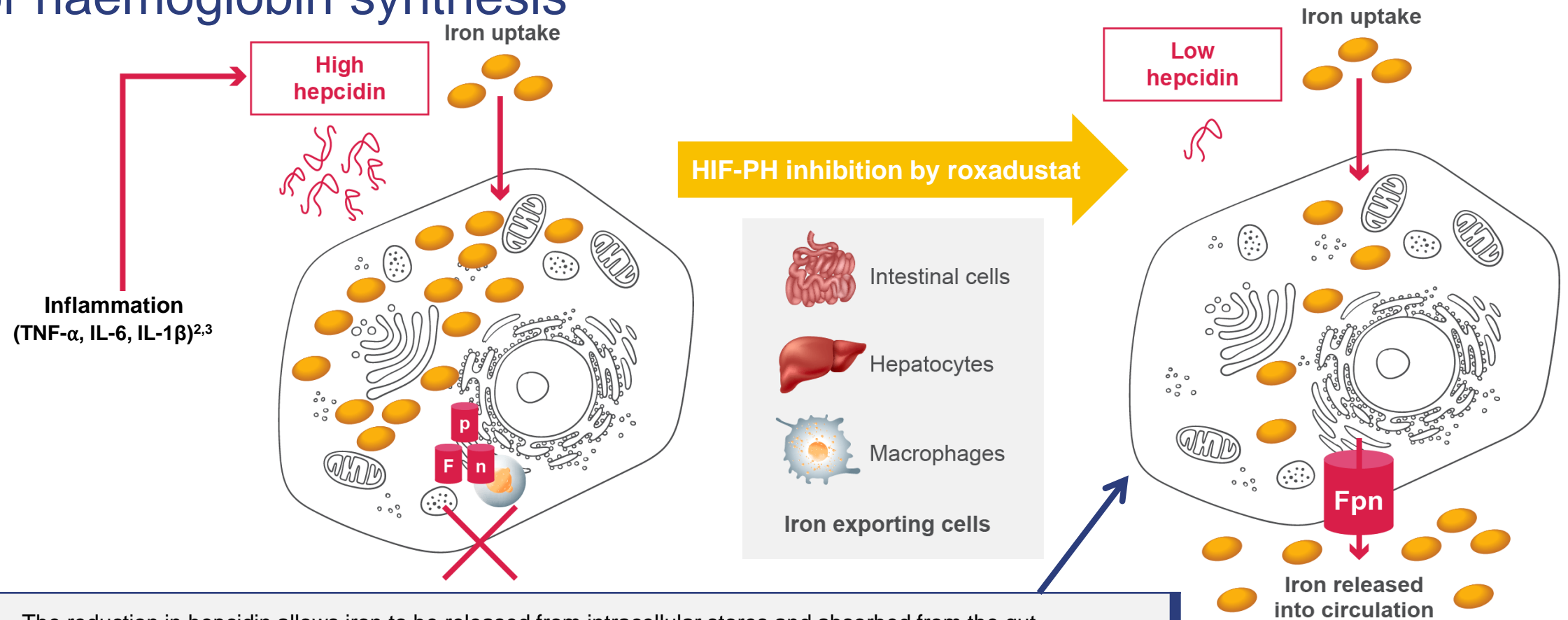
- ASTELLAS
-

Roxadustat prevents degradation of HIF- α to mimic the Body's natural response to hypoxia^{1,2}



Inhibition of HIF-PH by roxadustat prevents degradation of HIF- α , leading to the transcription of genes involved in erythropoiesis and iron absorption/transport²

By reducing hepcidin levels, Roxadustat increases iron availability for haemoglobin synthesis¹⁻⁴



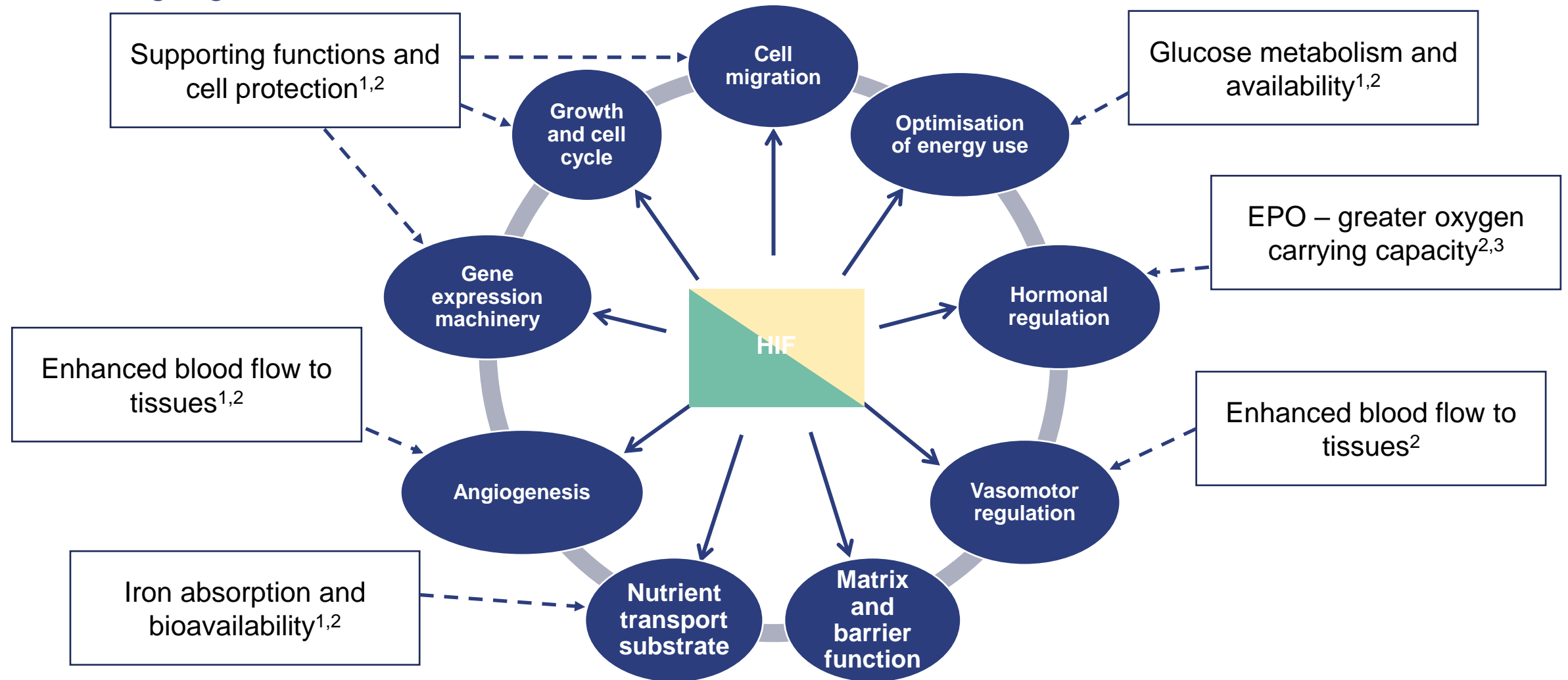
- The reduction in hepcidin allows iron to be released from intracellular stores and absorbed from the gut, increasing iron availability for Hb synthesis
- By regulating hepcidin, HIF-PH inhibition can overcome the suppressive effects of inflammation on erythropoiesis

Fpn, ferroportin; Hb, haemoglobin; HIF-PH, hypoxia-inducible factor-prolyl hydroxylase; IL, interleukin; TNF, tumour necrosis factor.

Adapted from 1. Provenzano R, et al. *Am J Kidney Dis.* 2016;67(6):912–924; 2. Locatelli F, et al. *Am J Nephrol.* 2017;45(3):187–199; 3. Gluba-Brzózka A, et al. *Int J Mol Sci.* 2020;21(3):725;

4. Ganz T and Nemeth E. *Biochim Biophys.* 2012;1823(9):1434–1443.

HIF-PH INHIBITION has the potential to IMPACT many biological processes, WITH >1000 direct target genes OF HIF-1 IDENTIFIED¹



EPO, erythropoietin; HIF, hypoxia-inducible factor; HIF-PH, hypoxia-inducible factor-prolyl hydroxylase.

Adapted from 1. Schödel J and Ratcliffe PJ. *Nat Rev Nephrol.* 2019;15(10):641–659; 2. Schofield CJ and Ratcliffe PJ. *Nat Rev Mol Cell Biol.* 2004;5(5):343–354; 3. Jelkmann W. *J Physiol.* 2011;589(6):1251–1258.

Roxadustat's intermittent dosing regimen Promotes an optimal erythropoietic response

- Continuous HIF stimulation (e.g., severe hypoxia) elicits complete activation of HIF target pathways¹
- Treatment with HIF-PHIs **does not** directly mimic a chronic hypoxia situation²



- HIF-PHIs transiently stimulate HIF activation, improving erythropoiesis while minimising the impact on other HIF-target genes²⁻⁴



Non-clinical and clinical studies with roxadustat utilised an **intermittent dosing regimen** to:⁵

- Induce selective erythropoiesis
- Optimise the Hb dose response

3x
weekly dosing
regimen

Hb, haemoglobin; HIF, hypoxia-inducible factor; HIF-PH, hypoxia-inducible factor-prolyl hydroxylase.

1. Schödel J and Ratcliffe PJ. *Nat Rev Nephrol.* 2019;15(10):641–659; 2. Gupta N and Wish JB. *Am J Kidney Dis.* 2017;69(6):815–826; 3. Locatelli F, et al. *Am J Nephrol.* 2017;45:187–199; 4. Sugahara M, et al. *Kidney Int.* 2017;92:306–312; 5. Li ZN, et al. *Kidney Dis.* 2020;6:65–73.

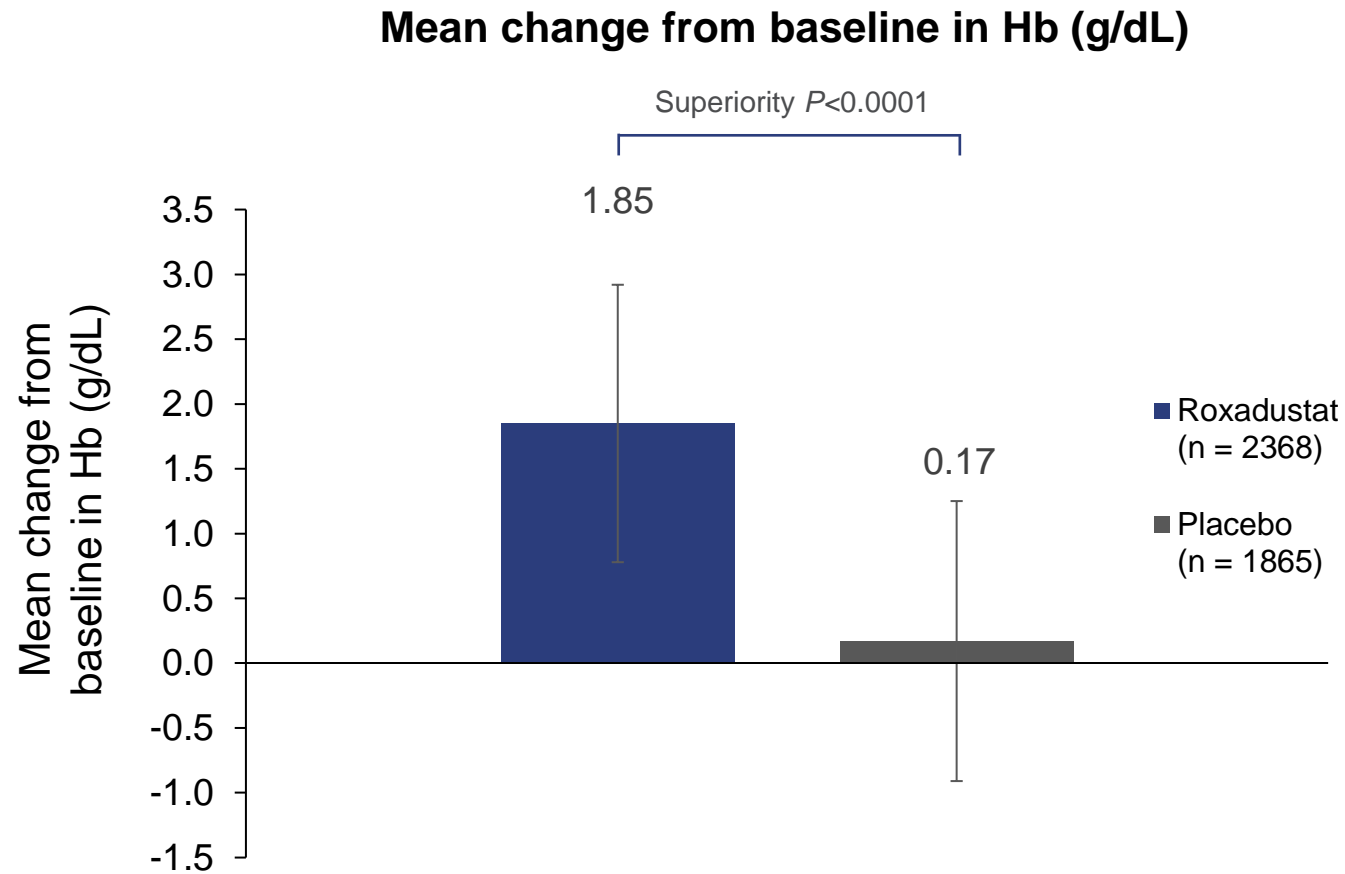
HIF stabilizers and anemia – 5 main questions

- Are HIF stabilizers effective in raising the Hb level in CKD ?
- Do they allow a “fine-tuned”, stable increase in Hb levels ?
- Are there clinically relevant side-effects ?
- Are such side-effects “neutral”, “beneficial” or “harmful” ?
- Does anemia management with HIF-stabilizers impact on patient outcomes ?

→ So far partial answers only available to the first three questions

roxadustat was superior to placebo at maintaining Hb levels in patients with NDD-CKD

NDD pool
vs placebo
ALPS
ANDES
OLYMPUS



Error bars represent standard deviation.

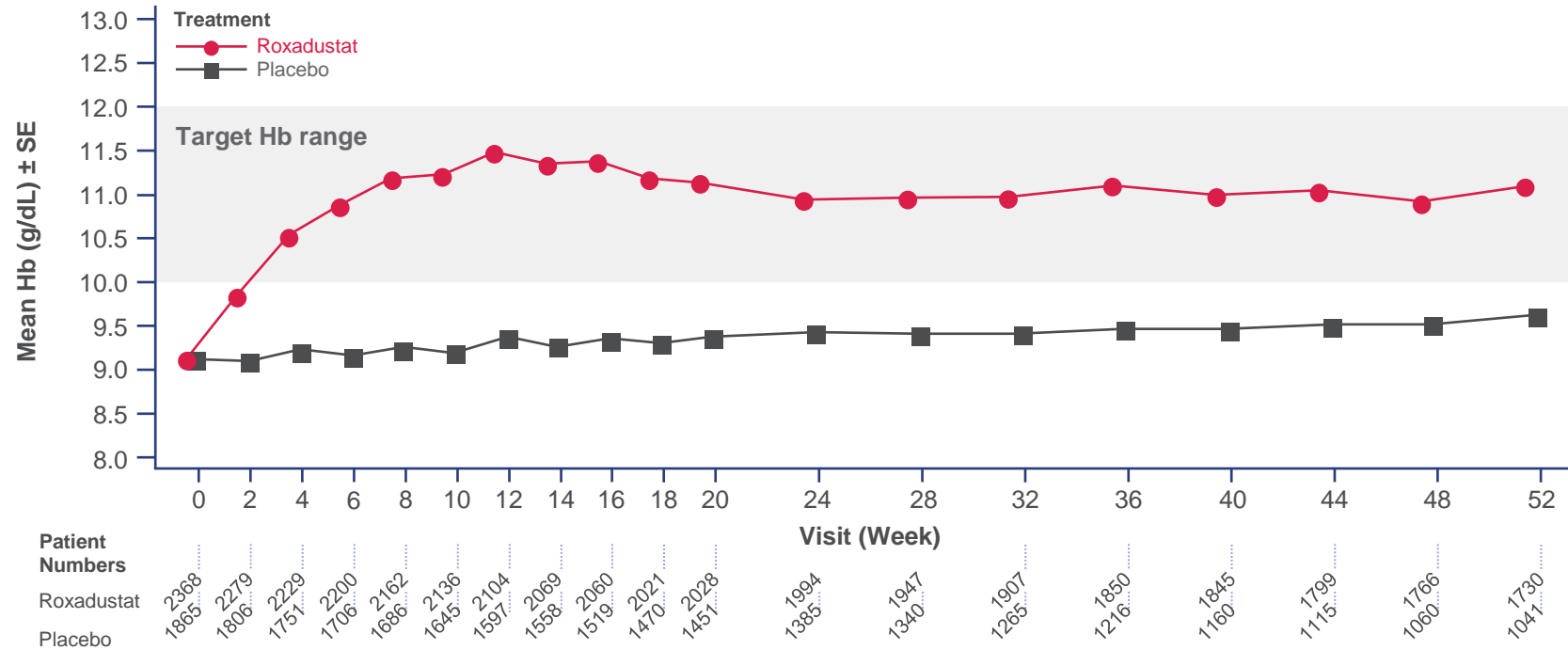
CKD, chronic kidney disease; Hb, haemoglobin; NDD, non-dialysis dependent.

EVRENZO SmPC August 2021.

Roxadustat was effective at achieving and maintaining target Hb levels over time in patients with NDD-CKD

Mean (SE) Hb (g/dL) over 52 weeks

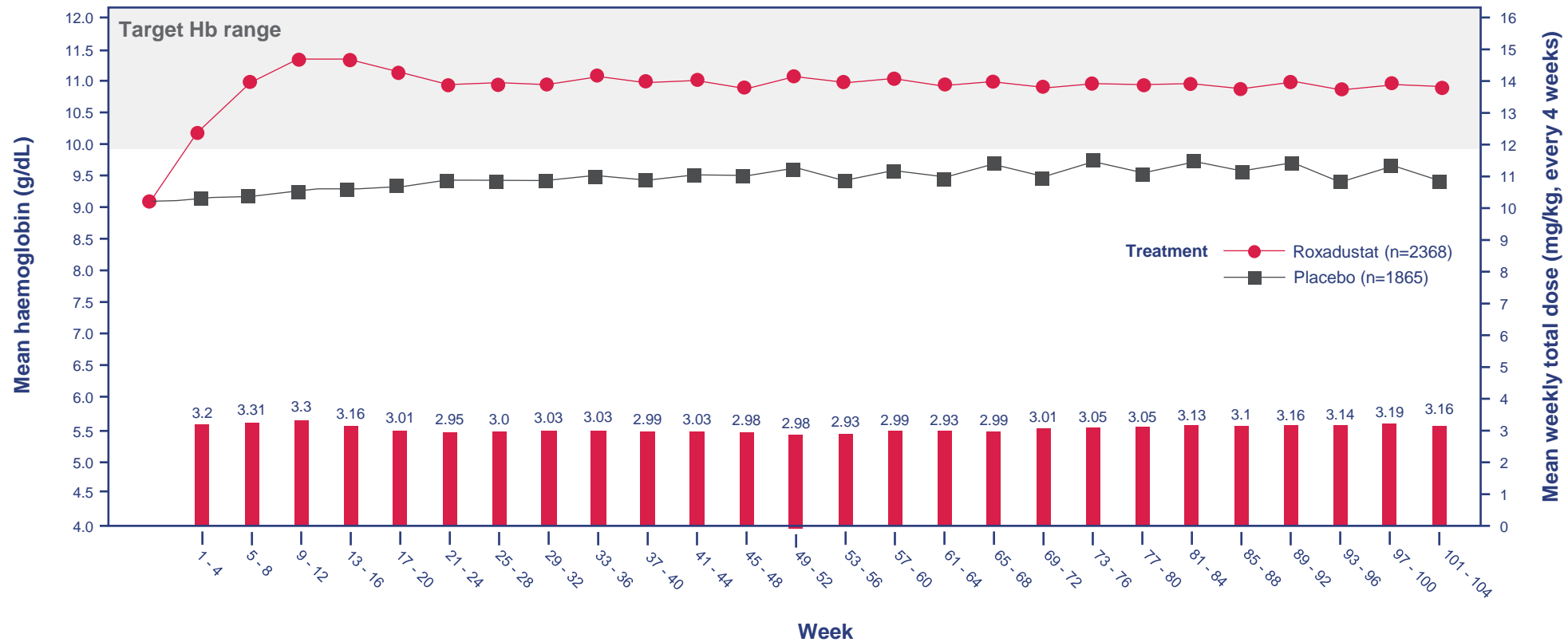
NDD pool
vs placebo
ALPS
ANDES
OLYMPUS



Mean Hb was maintained over time in roxadustat-treated patients vs placebo, following an increase from baseline in NDD-CKD

average Roxadustat dose remained similar over 104 weeks of treatment in patients with NDD-CKD

NDD pool
vs placebo
ALPS
ANDES
OLYMPUS

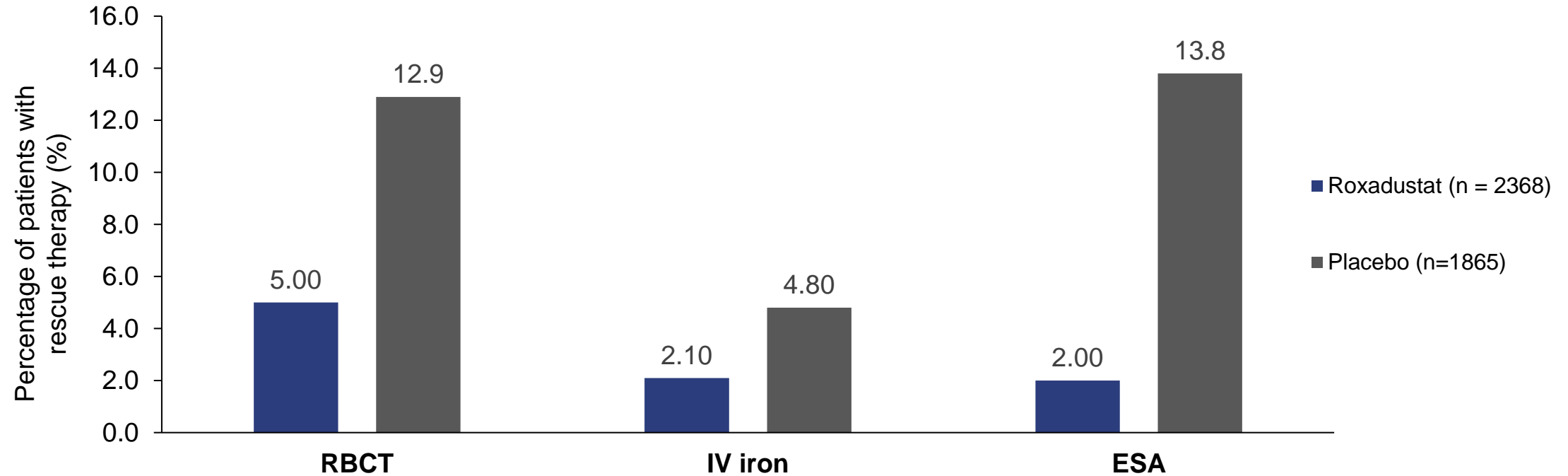


Roxadustat reduced use of all rescue therapies in patients with NDD-CKD vs placebo

NDD pool
vs placebo
ALPS
ANDES
OLYMPUS



Use of rescue therapy in NDD-CKD up to Week 52



P values not yet determined for this data set.

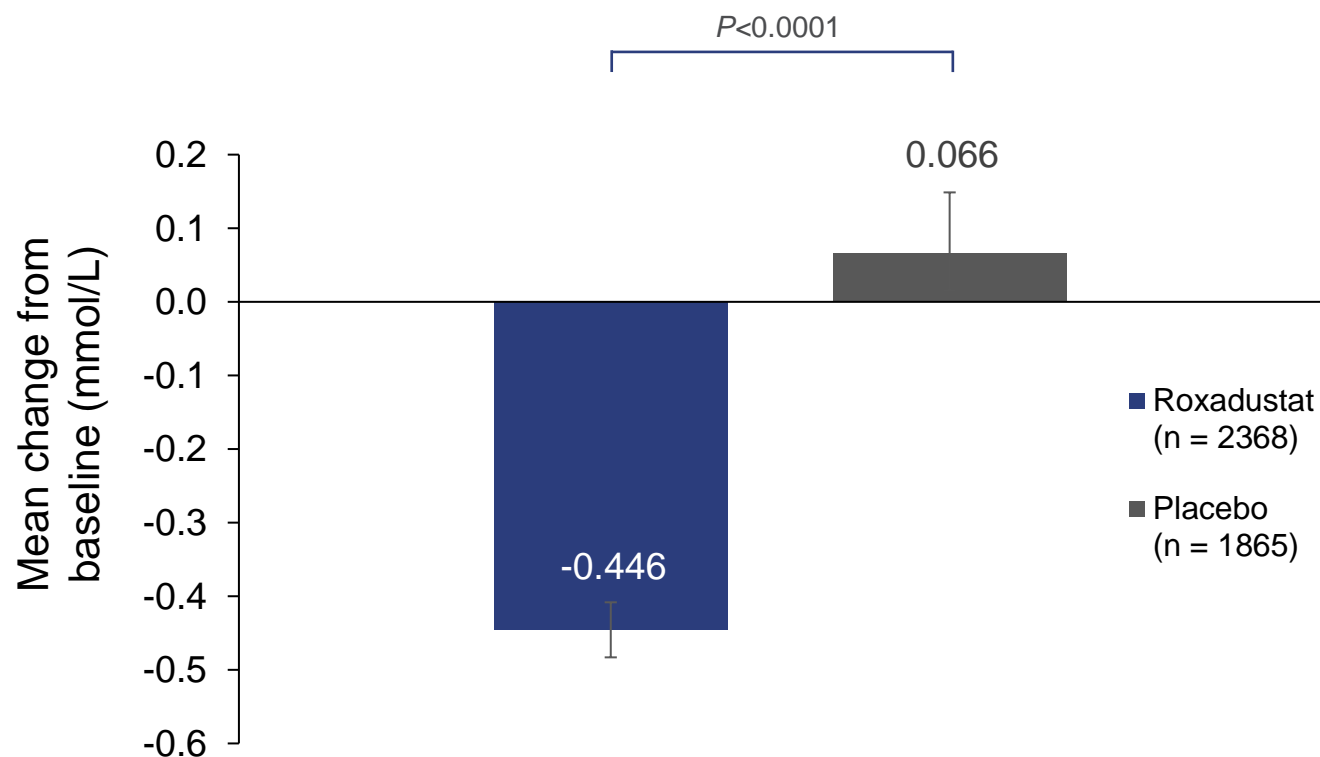
CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; IV, intravenous; NDD, non-dialysis dependent; RBCT, red blood cell transfusion.
EVRENZO draft SmPC. 2021.

Roxadusat significantly reduced LDL cholesterol from baseline VS placebo in patients with NDD-CKD

NDD pool
vs placebo
ALPS
ANDES
OLYMPUS



LS mean change from baseline to Weeks 12–28 in LDL cholesterol*



Error bars represent 95% confidence interval.

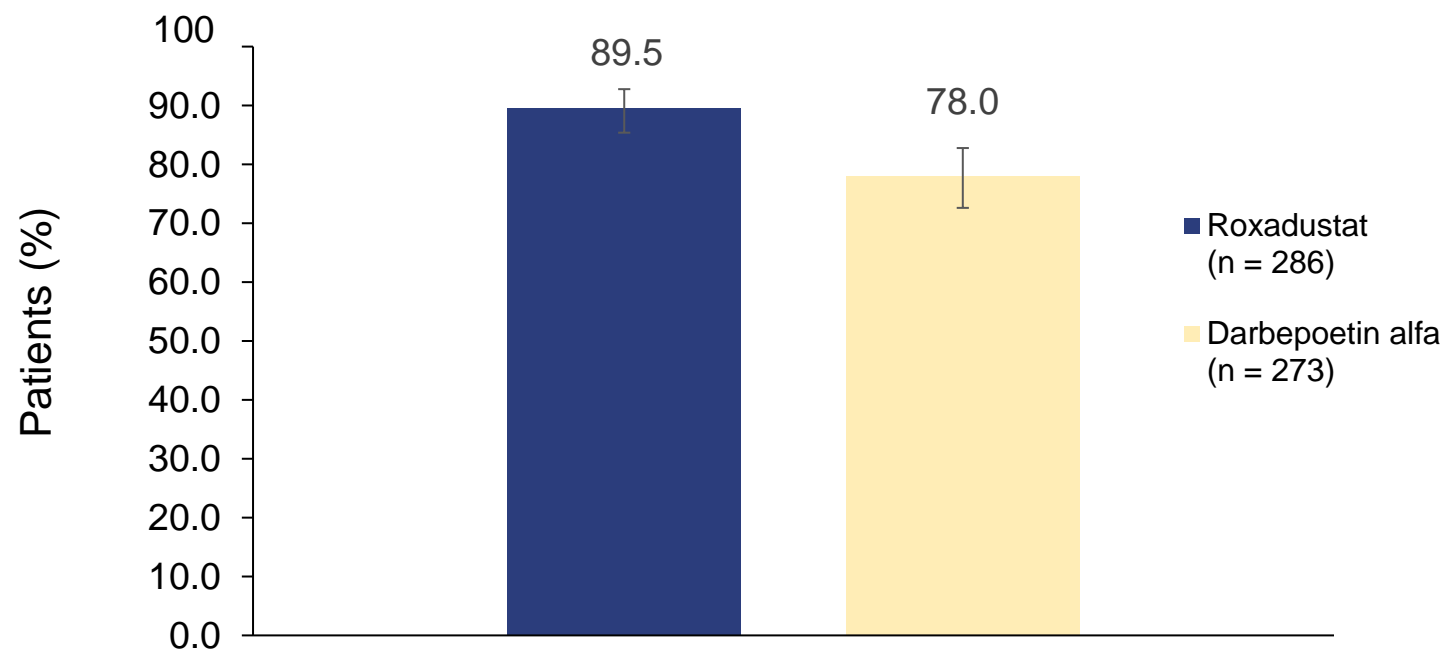
*Change from baseline in LDL cholesterol was assessed only through Week 24 for OLYMPUS.

CKD, chronic kidney disease; LDL, low-density lipoprotein; LS, least squares; NDD, non-dialysis dependent.

EVRENZO SmPC August 2021.

A similar Proportion of patients achieved Hb response with Roxadustat vs darbepoetin alfa in patients with NDD-CKD

**Primary endpoint:
Proportion of patients achieving Hb response (%)**



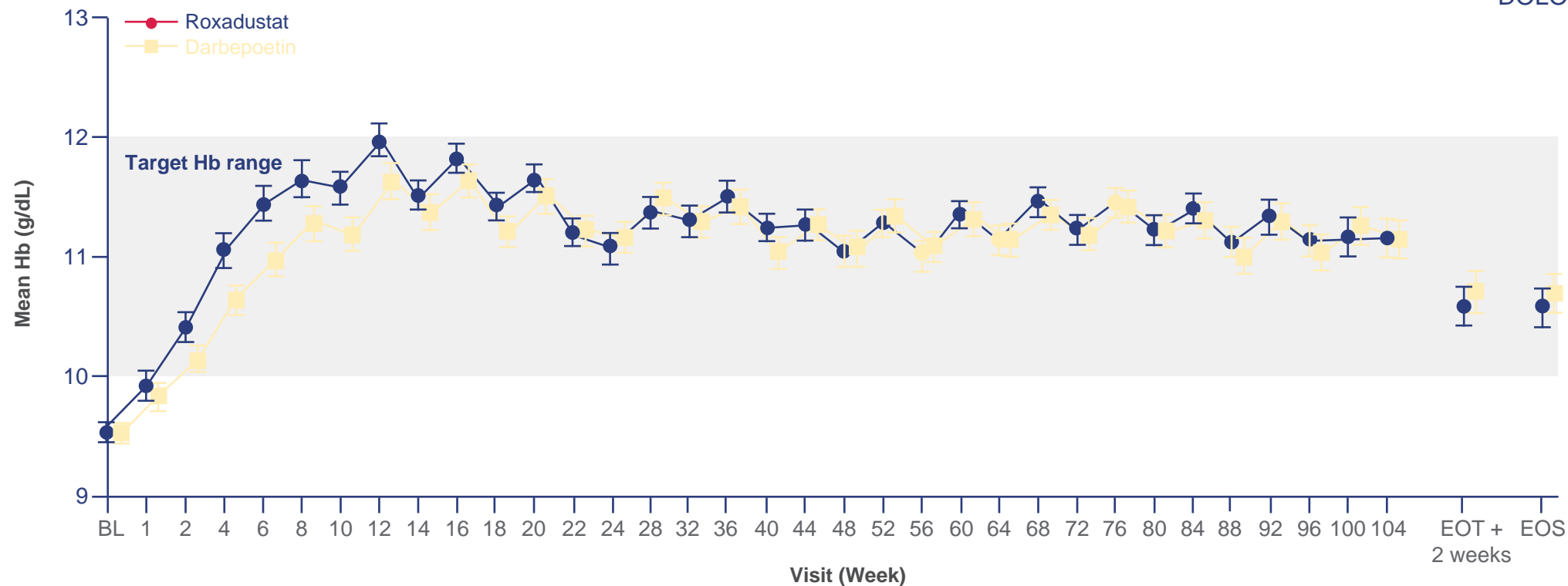
NDD vs active
comparator
DOLOMITES



Roxadustat was effective at achieving and maintaining Hb levels comparable with darbepoetin alfa in patients with NDD-CKD

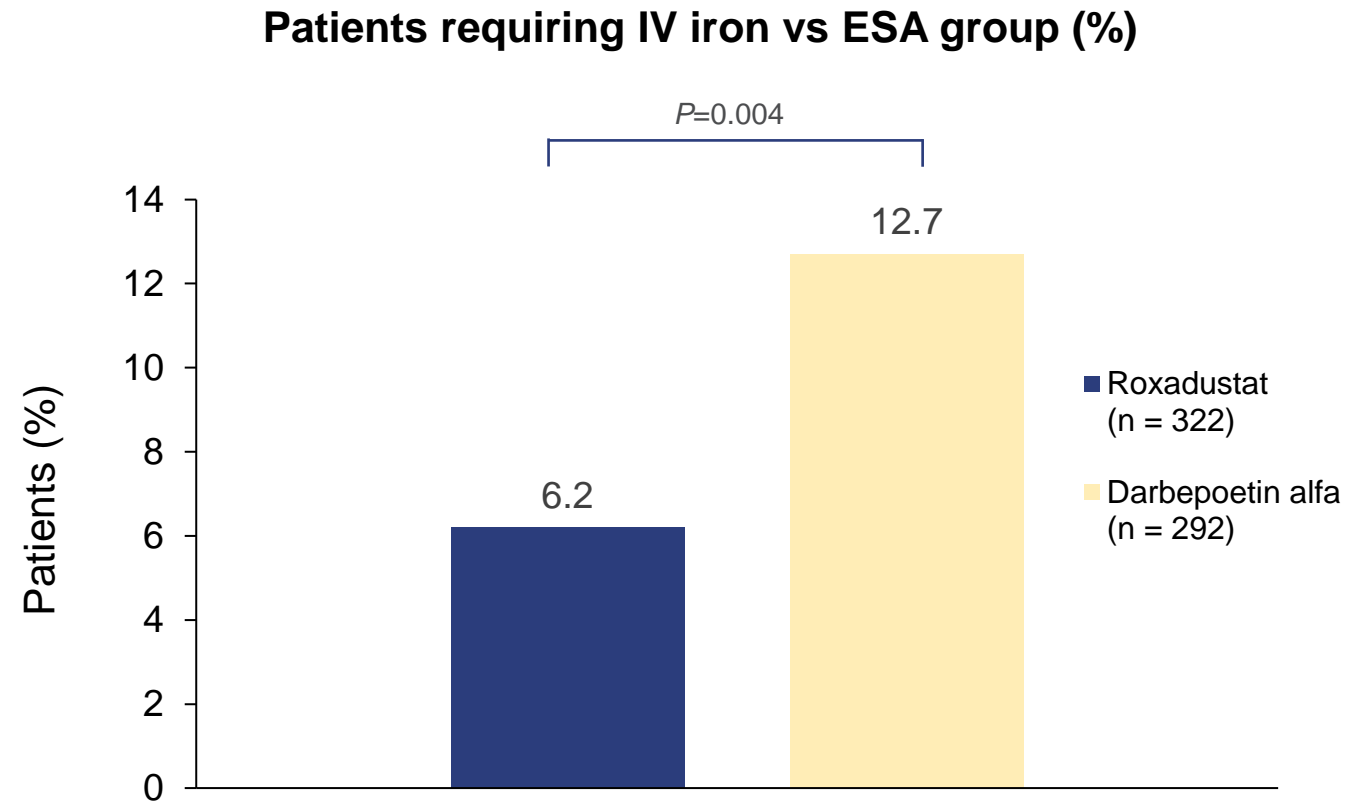
Mean (95% CI) concentrations of Hb (per protocol set)

NDD vs active
comparator
DOLOMITES



Significantly lower incidence of IV iron use was observed with roxadustat vs darbepoetin alfa in patients with NDD-CKD

NDD vs active
comparator
DOLOMITES



KEY Messages



In the NDD pool vs placebo, roxadustat:

- Demonstrated superiority in mean change in Hb from baseline
- Was effective at achieving and maintaining target Hb levels over 52 weeks
- Reduced use of all rescue therapies
- Significantly reduced LDL cholesterol from baseline

In the NDD pool vs active comparator (darbepoetin alfa), roxadustat:

- Demonstrated non-inferiority in mean change in Hb from baseline
- Was effective at achieving and maintaining target Hb levels over 52 weeks
- Significantly reduced LDL cholesterol from baseline
- Was associated with significantly lower IV iron use, reducing the mean number of IV administrations from Weeks 1–52

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ORIGINAL ARTICLE



Factors affecting the doses of roxadustat vs darbepoetin alfa for anemia treatment in hemodialysis patients

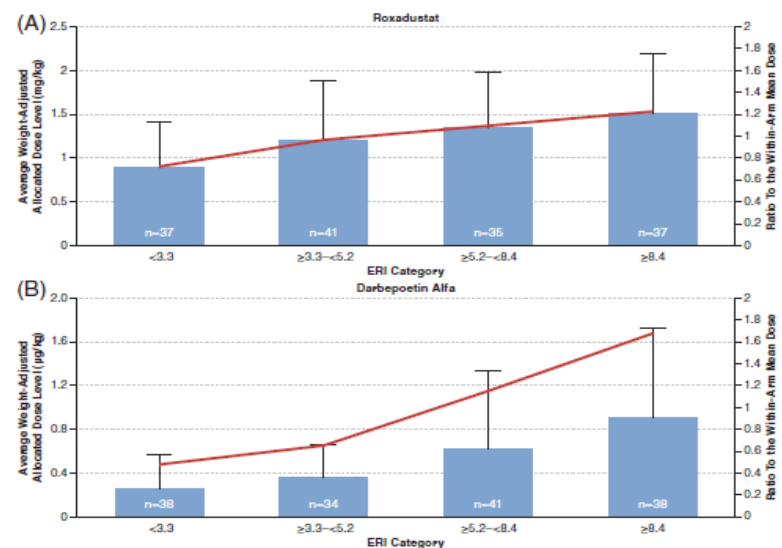
Tadao Akizawa¹ | Yusuke Yamaguchi² | Yoshikatsu Majikawa³ | Michael Reusch⁴

FIGURE 1 Average weight-adjusted allocated dose of study drug per intake in the last 6 weeks stratified by ERI (FAS). DA, darbepoetin alfa; ERI, ESA resistance index; ESA, erythropoiesis-stimulating agent; FAS, full analysis set. Bar plot: mean of average weight-adjusted allocated dose with SD. Line plot: ratio to the within-arm mean dose [Color figure can be viewed at wileyonlinelibrary.com]

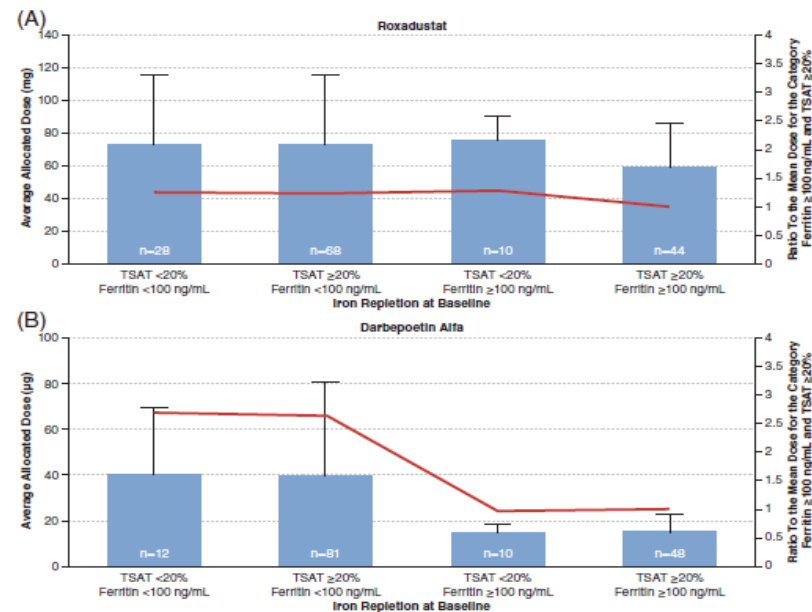


FIGURE 2 Average allocated dose of study drug per intake in the last 6 weeks stratified by baseline levels of ferritin and TSAT (FAS). DA, darbepoetin alfa; FAS, full analysis set; TSAT, transferrin saturation. Bar plot: average allocated dose with SD. Line plot: ratio to the mean dose [Color figure can be viewed at wileyonlinelibrary.com]

Factors affecting the doses of roxadustat vs darbepoetin alfa for anemia treatment in hemodialysis patients

Tadao Akizawa¹ | Yusuke Yamaguchi² | Yoshikatsu Majikawa³ | Michael Reusch⁴

5 | CONCLUSIONS

The results of this post-hoc analysis suggest that the roxadustat doses required to maintain target Hb may not be as heavily impacted by factors contributing to ESA-hyporesponsiveness, including hs-CRP, GNRI, and iron parameters. Moreover, roxadustat doses required to maintain target Hb are affected by ERI to a lesser extent than DA. Overall, these results provide preliminary evidence that roxadustat may be beneficial to ESA hyporesponsive patients.

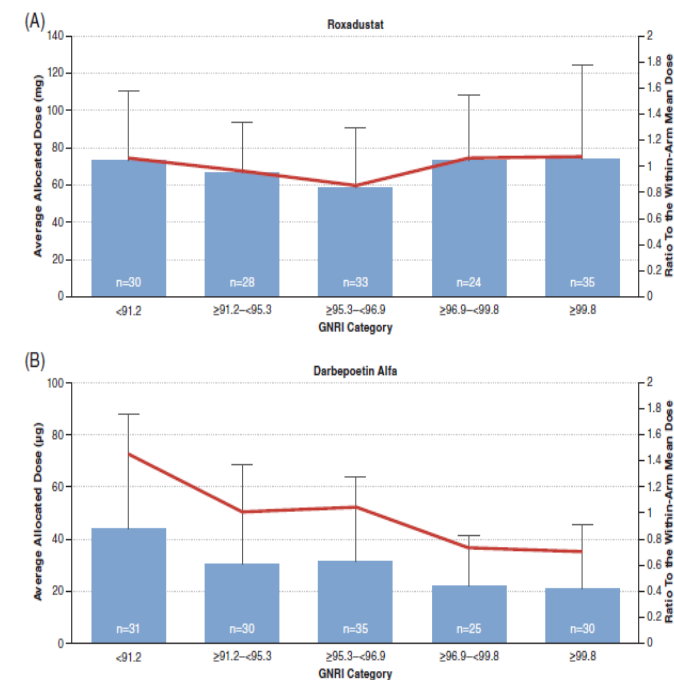
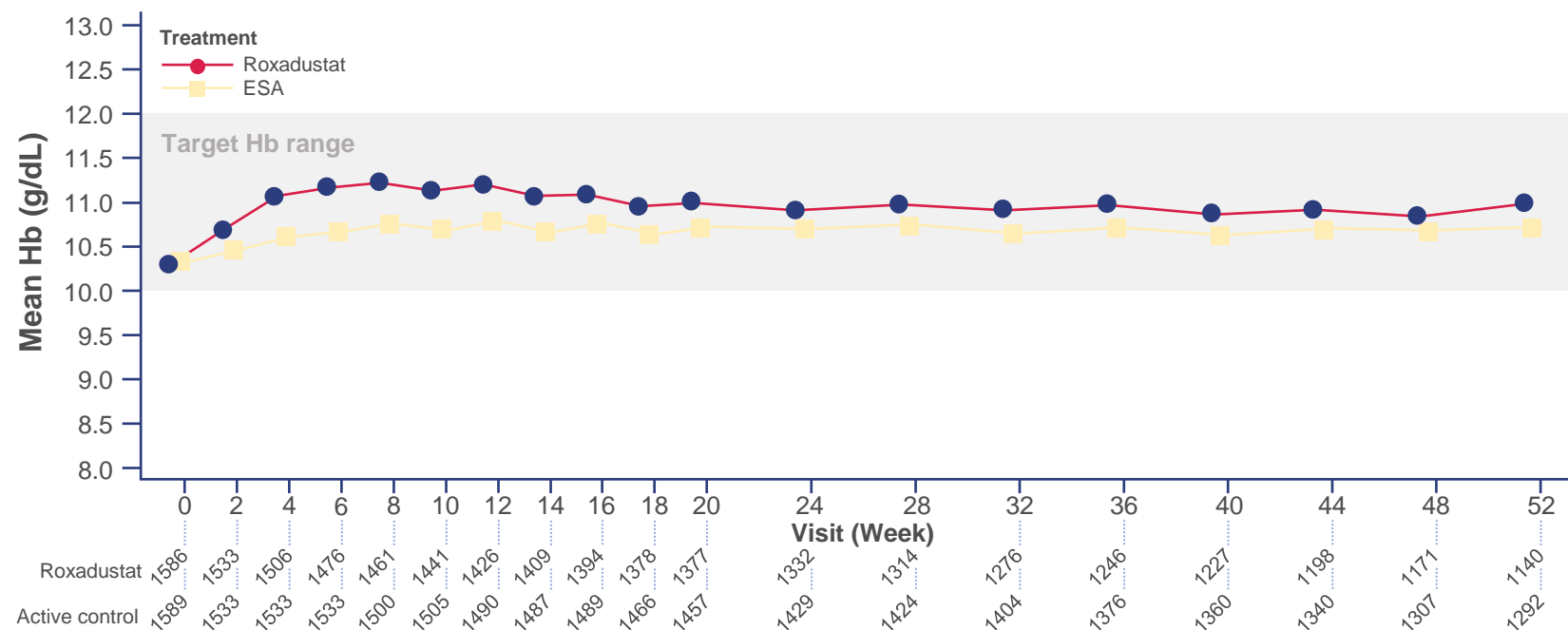


FIGURE 4 Average allocated dose of study drug per intake in the last 6 weeks stratified by GNRI (FAS). DA, darbepoetin alfa; FAS, full analysis set; GNRI, geriatric nutritional risk index. Bar plot: average allocated dose with SD. Line plot: ratio to the mean dose [Color figure can be viewed at wileyonlinelibrary.com]

Roxadustat was effective at achieving and maintaining target Hb levels in patients on stable dialysis

Mean Hb (g/dL) over 52 weeks (FAS)

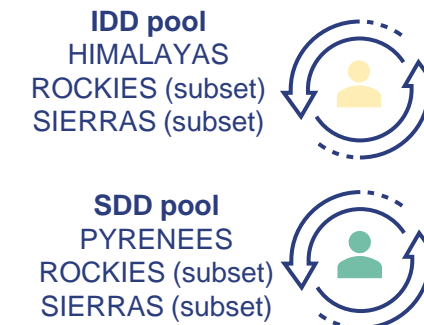
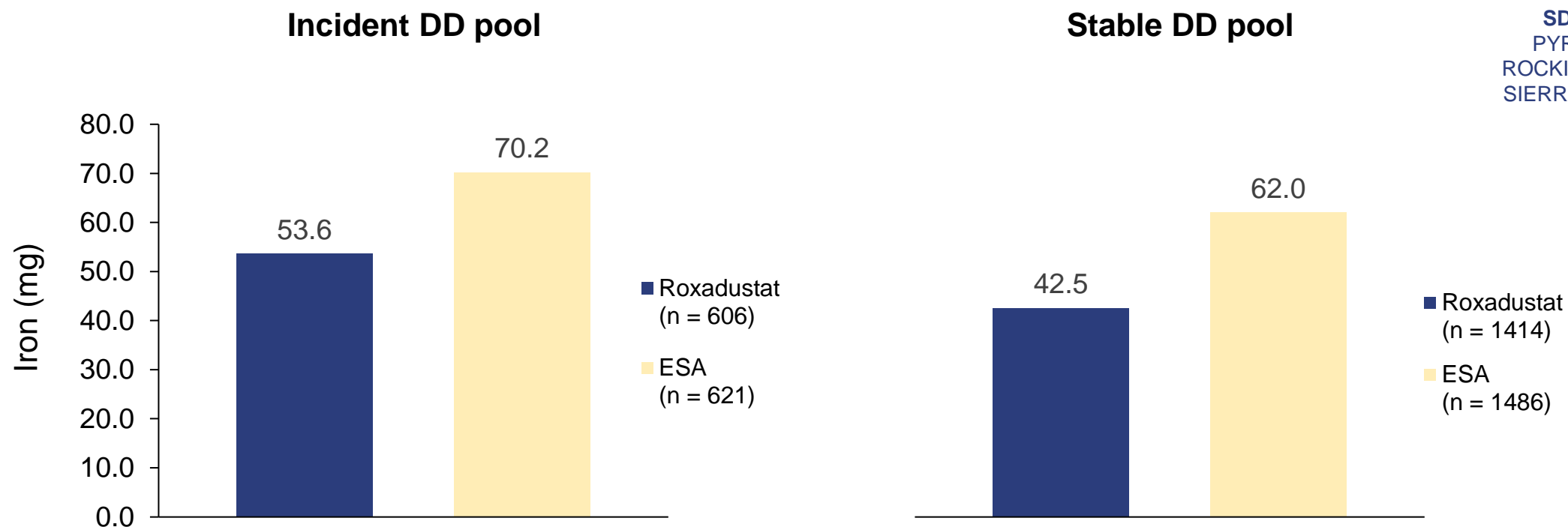
SDD pool
PYRENEES
ROCKIES (subset)
SIERRAS (subset)



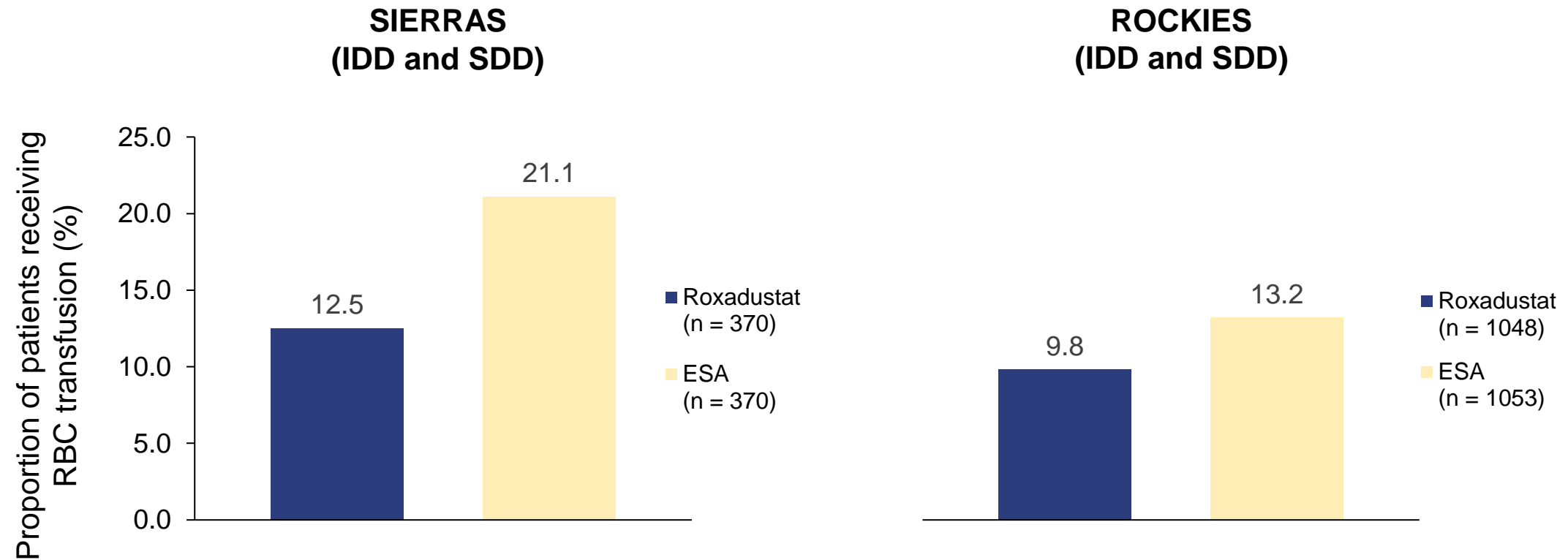
Mean Hb was comparable over time with roxadustat vs ESA treatment in stable DD-CKD patients previously treated with ESA

Roxadustat reduced mean use of IV iron vs ESA in patients on dialysis

- Mean monthly IV iron (mg) over Weeks 28–52



Roxadustat reduced The need for RBC transfusion compared with ESA in patients on dialysis



KEY Messages



Roxadustat demonstrated non-inferiority compared with ESA in patients with IDD- and SDD-CKD, in:¹

- Mean change in Hb from baseline to Weeks 28–36
- Proportion of patients achieving Hb response during Weeks 28–52
- Achieving and maintaining target Hb over 52 weeks

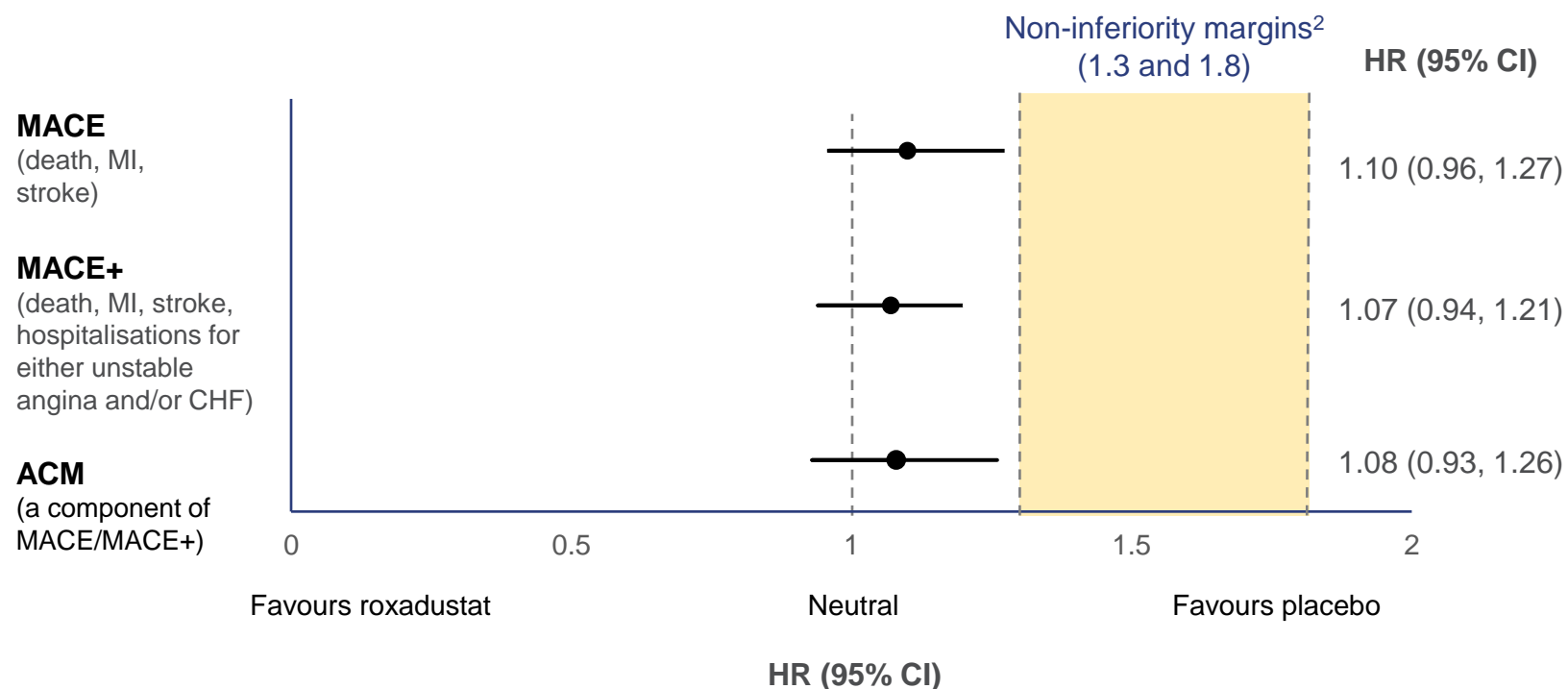
Roxadustat reduced the use of IV iron supplementation in patients with IDD- and SDD-CKD compared with ESA^{1,2}

Roxadustat significantly reduced mean LDL cholesterol in patients with IDD- and SDD-CKD compared with ESA¹

The need for RBC transfusion was reduced in patients treated with roxadustat compared with ESA in IDD- and SDD-CKD¹

Roxadustat treatment did not increase cv or mortality risk VS Placebo in the ITT analysis of NDD-CKD patients¹

NDD pool
vs placebo
OLYMPUS
ANDES
ALPS



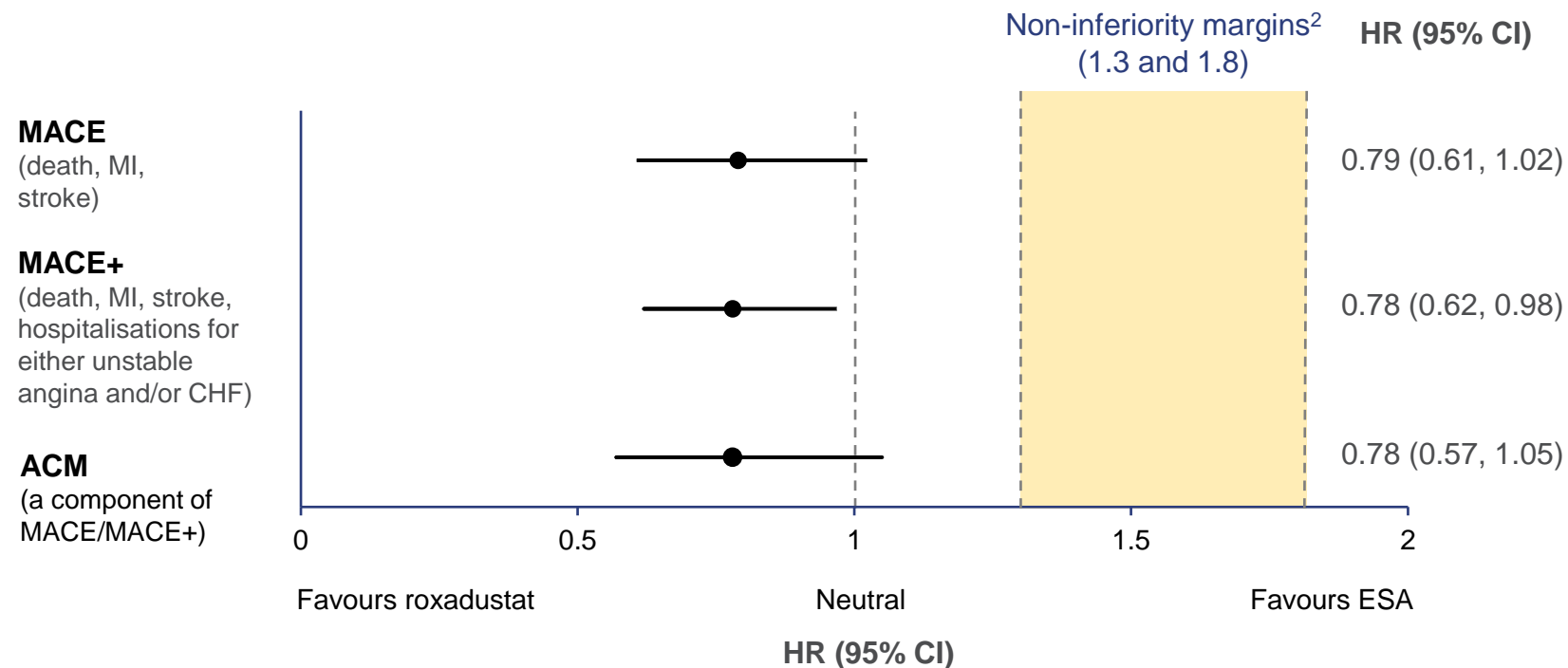
Hazard ratios refer to numbers of patients with events.

ACM, all-cause mortality; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; MACE, major adverse cardiovascular event.

1. EVRENZO SmPC. August 2021;.

Roxadustat was comparable to ESA regarding cv or mortality risk in patients with NDD- and IDD-CKD¹

NDD and IDD pool
vs ESA
DOLOMITES
HIMALAYAS
ROCKIES (subset)
SIERRAS (subset)



Hazard ratios refer to numbers of patients with events.

ACM, all-cause mortality; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; ESA, erythropoietin-stimulating agent; HR, hazard ratio; IDD, incident-dialysis dependent; MACE, major adverse cardiovascular event; NDD, non-dialysis dependent.

1. EVRENZO SmPC. August 2021

Adverse drug reactions for roxadustat in patients with NDD-CKD or DD-CKD

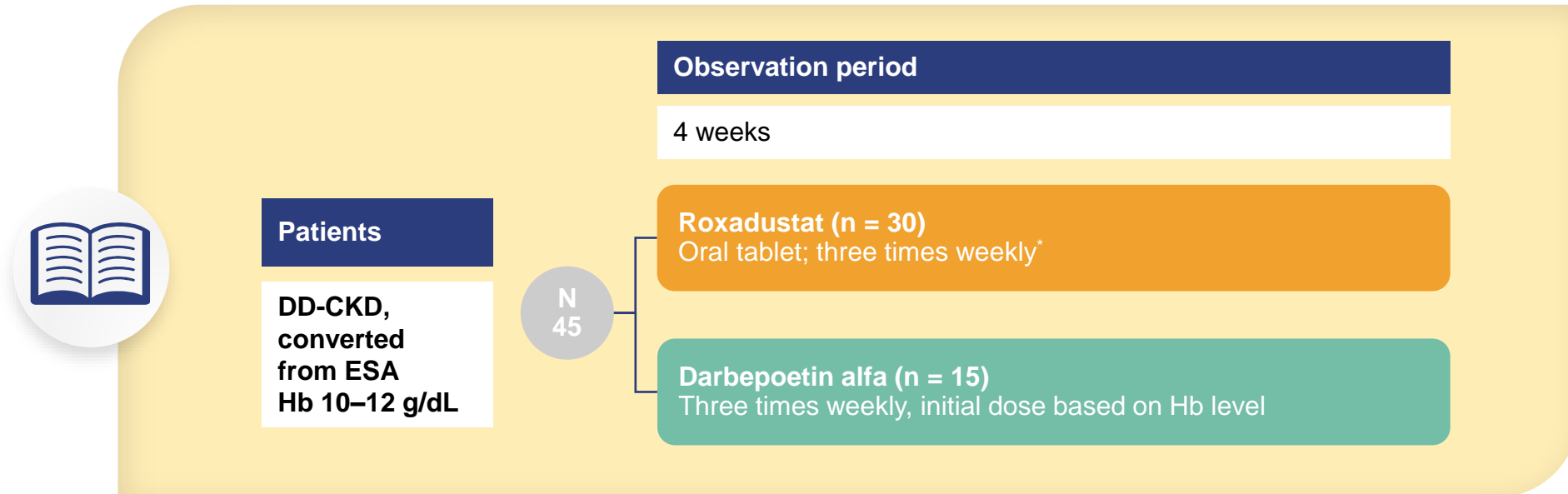
NDD-CKD			DD-CKD			NDD pool vs placebo OLYMPUS ANDES ALPS	
	Roxadustat in NDD-CKD* (n = 3542)	Placebo or ESA in NDD-CKD (n = 1344)		Roxadustat in DD-CKD† (n = 3351)	ESA in DD-CKD (n = 1363)	NDD vs active comparator DOLOMITES	
Sepsis	2.1%	0.4%	Sepsis	3.4%	3.4%	Overall DD pool HIMALAYAS ROCKIES PYRENEES SIERRAS	
DVT	1.0%	0.2%	VAT	12.8%	10.2%		
Seizure	1.1%	0.2%	DVT	1.3%	0.3%		
Pulmonary embolism	0.4%	0.2%	Seizure	2.0%	1.6%		
			Pulmonary embolism	0.6%	0.5%		

For the full listing of adverse events please refer to the EVRENZO draft SmPC.

*Includes those who have received at least one dose of roxadustat, compared with placebo or ESA; †Includes those who have received at least one dose of roxadustat, compared with ESA. CKD, chronic kidney disease; DD, dialysis-dependent; DVT, deep vein thrombosis; ESA, erythropoiesis-stimulating agent; NDD, non-dialysis dependent; VAT, vascular access thrombosis. EVRENZO SmPC. August 2021.

observational study of iron metabolism and haematopoiesis in patients switching from esa to roxadustat

- A single-centre study in patients on haemodialysis, switching from darbepoetin alfa to roxadustat
- Endpoints: Change from baseline in mean Hb (g/dL), s-Fe ($\mu\text{g/dL}$) and TSAT (%) during the treatment period

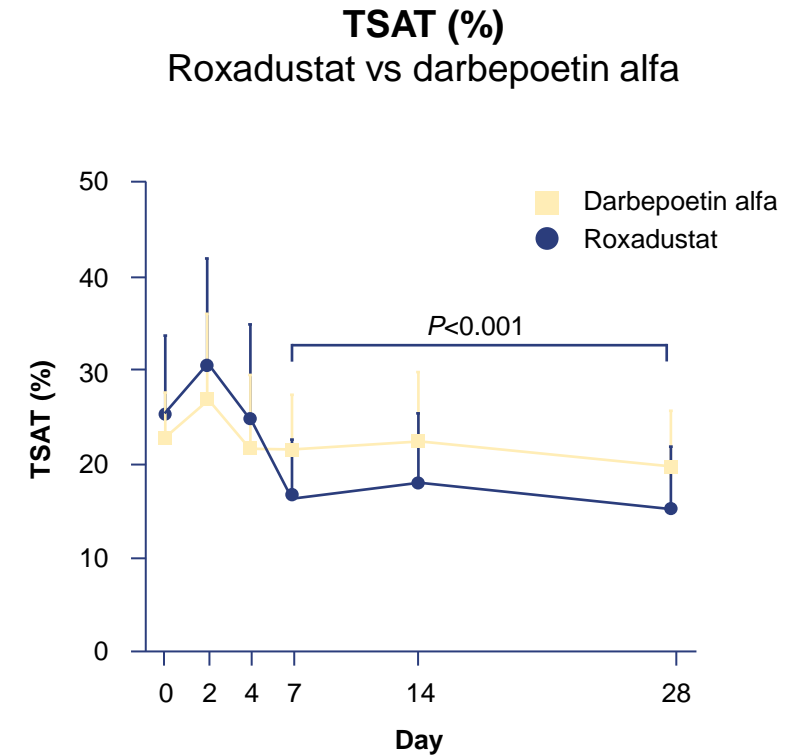
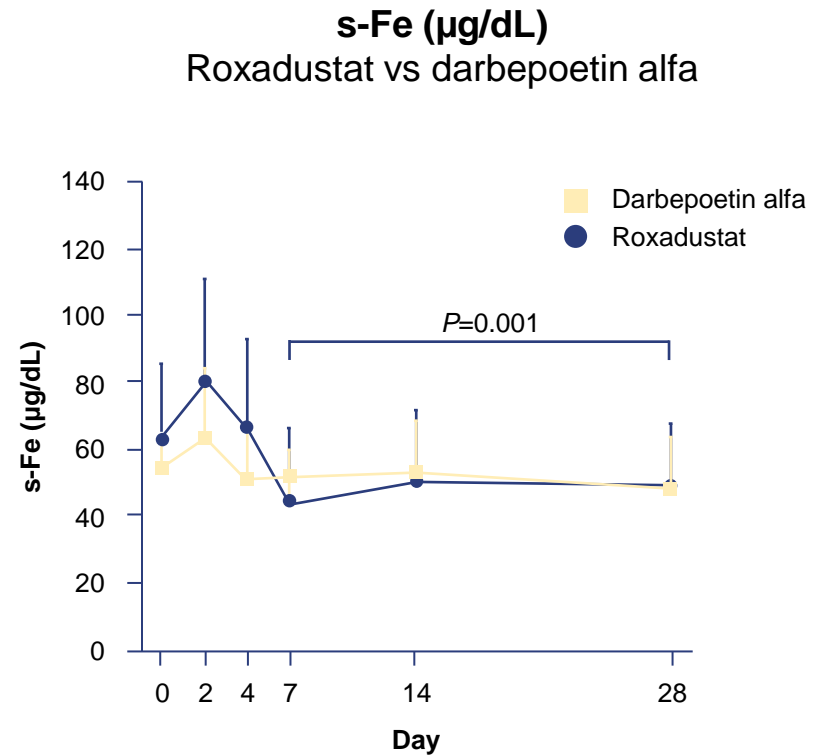
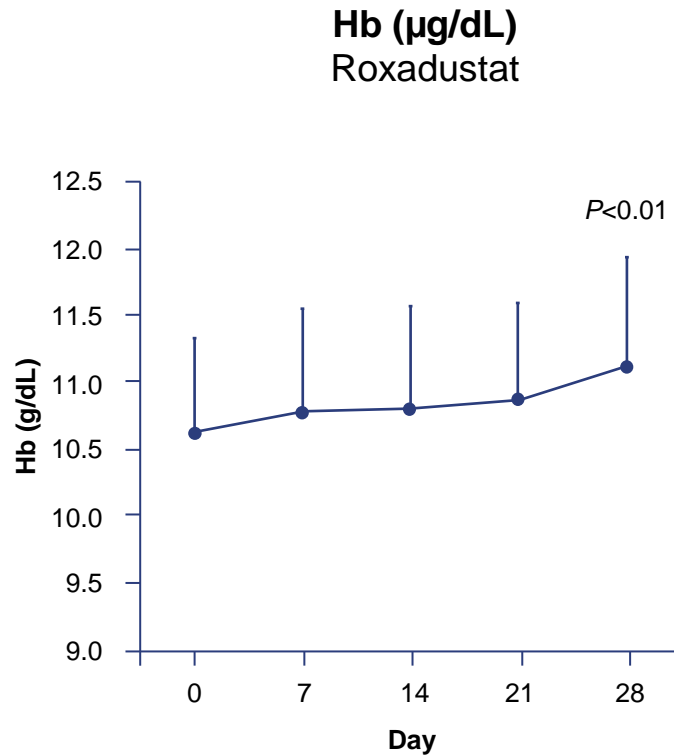


*The starting dose at study entry was either 70 or 100 mg.

CKD, chronic kidney disease; DD, dialysis dependent; ESA, erythropoietin-stimulating agent; Hb, haemoglobin; s-Fe, serum iron; TSAT, transferrin saturation.

Ogawa C, et al. *Int J Mol Sci.* 2020;21(19):7153.

Switching treatment from ESA to Roxadustat improves measures of anaemia, including hb, s-Fe and tsat



Treatment with roxadustat significantly increased Hb levels at day 28 vs day 0, and decreased s-Fe and TSAT to a greater extent vs ESA

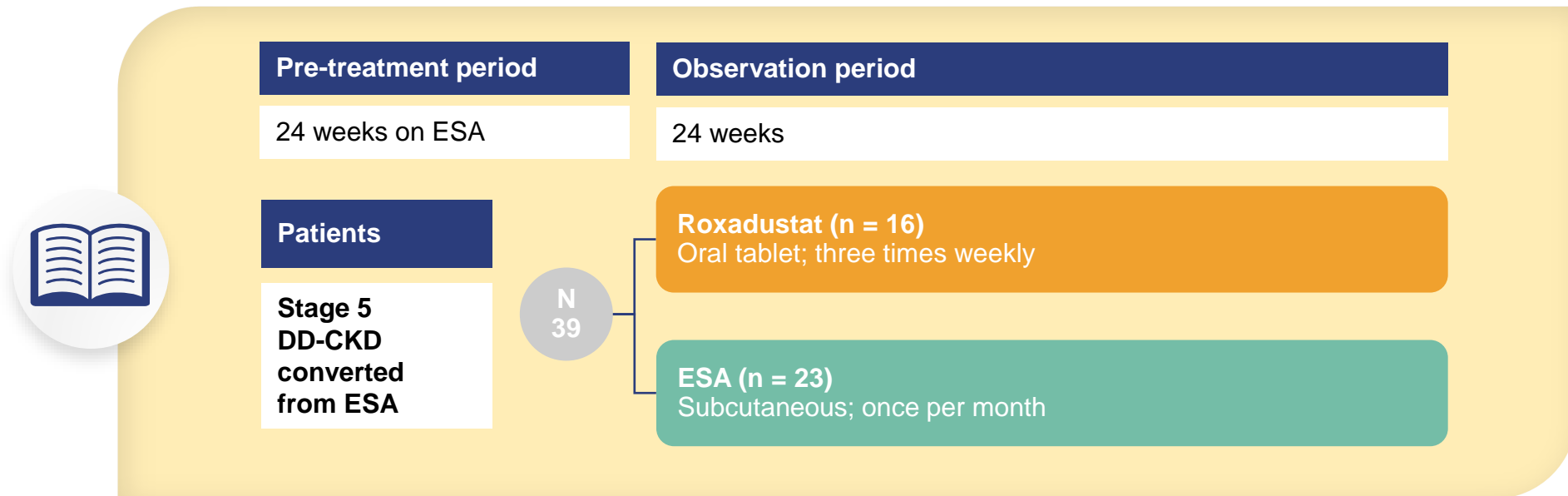
Data are presented as the mean \pm SD.

ESA, erythropoietin-stimulating agent; Hb, haemoglobin; SD, standard deviation; s-Fe, serum iron; TSAT, transferrin saturation.

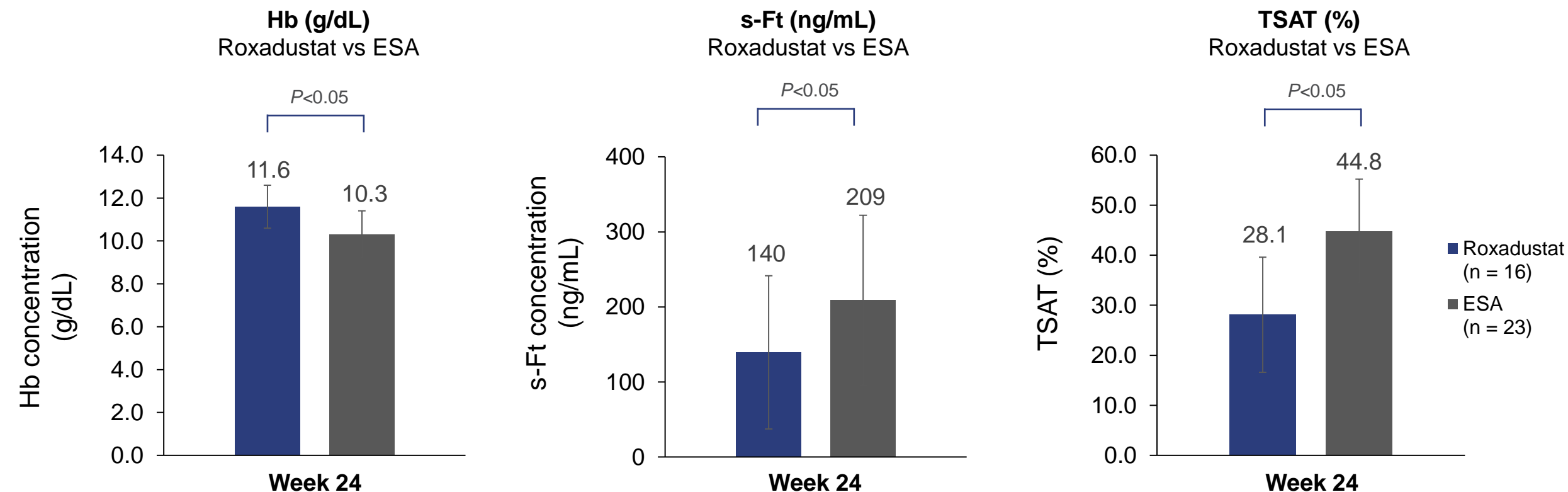
Figures adapted from Ogawa C, et al. *Int J Mol Sci.* 2020;21(19):7153.

observational study of anaemia-related parameters following the change from an ESA to roxadustat

- A single-centre, retrospective, non-interventional study in patients on peritoneal haemodialysis, switching from an ESA to roxadustat
- Endpoints: Mean Hb (g/dL), s-Ft (ng/mL) and TSAT (%) during the treatment period; change in 4-h dialysate/plasma creatinine (peritoneal membrane function) and renal weekly urea clearance (Kt/v, residual renal function) from baseline



Switching treatment from ESA to Roxadustat significantly improved measures of anaemia, including hb, s-ft and tsat



Roxadustat did not affect peritoneal membrane function or residual renal function in peritoneal dialysis patients.
A single adverse event of nausea was reported in one roxadustat-treated patient, resulting in treatment discontinuation.

Error bars represent the standard deviation.

ESA, erythropoietin-stimulating agent; Hb, haemoglobin; s-Ft, serum ferritin; TSAT, transferrin saturation.

Hirai K, et al. *Front Med.* 2021;8:667117.

76 ετών, ΧΝΝ γνωστή από 7 ετίας- e GFR: 38 mils/min

46 ετών, αγγειοπλαστική αρ. στεφανιαίας

56 ετών και 63 ετών , stents

66 ετών, χειρουργηθέν ανεύρυσμα ιγνιακής αρτησίας αρ. κάτω άκρου

70 ετών, χειρουργηθέν ανεύρυσμα κοιλιακής αρτησίας

75 ετών, βηματοδότης

Ιούνιος 2023, 3πλό by pass, GFR 23 mils/min, Hb 9,9, Hct 29,7

Ασθενής 1

«αγγειακός
ασθενής»

Ιούλιος 2023, e GFR: 23 mils/min, Hct29,8, Hb 10,1,
Fer 45,87

16 Αυγούστου 2023: Hct 31,2, Hb 10,2, e GFR: 22 mils/min

31 Αυγούστου 2023, 1 gr Ferric carboxymaltose
start Roxadustat 70 mg, 3/week

18 Σεπτεμβρίου 2023, Hct 35,1, Hb 11,7, e GFR 32 mils/min

Ασθενής 1

«αγγειακός
ασθενής»

64 ετών

Μάρτιος 2022, 3πλό By pass, αντικατάσταση αορτικής βαλβίδας, βηματοδότης

Ασθενής 2

«Καρδιονεφρικό σύνδρομο»

Μάρτιος 2023, triplex καρδιάς, σοβαρή υποκινησία κατώτερου και οπισθίου τοιχώματος, μετρίου/σοβαρού βαθμού ανεπάρκεια τριγλώχινας, πνευμονική υπέρταση, ΚΕ 45%

Χρόνια Νεφρική Νόσος

Μάιος 2023, e GFR: 46 ml/min, Hct 33,8, Hb 10,5, Fer 80,4

Ιούνιος 2023, 1 gr Ferric Carboxymaltose

Ιούλιος 2023, e GFR: 42 mils/min, Hct 36,9, Hb 11,4, Fer 297

Roxadustat 70 mg 3/week

Αύγουστος 2023, Hct 39,8, Hb 12,1, e GFR 58 mils/min

Roxadustat 50 mg 3 /week

Σεπτεμβριος 2023, Hct 42,6, Hb 13,6, e GFR 37 mils/min

προσωρινή διακοπή Roxadustat

Ασθενής 2

«Καρδιονεφρικό
σύνδρομο»

74 ετών, ΣΔ από την ηλικία των 45, καπνιστής, ΧΝΝ από 6 ετίας

59 ετών, 3 πλό by pass- βηματοδότης

69-70 ετών, καρτίδες χει/θήσες

Ιούνιος 2023, e GFR: 25 ml/min, Hct 30,9, Hb 10,2, Ferr 44

triplex καρδιάς, ΚΕ 45 %, μικρή υποκινησία κορυφής μέσου και οπισθοκατώτερου τοιχώματος

Ιούλιος 2023, 1 gr Ferric Carboxymaltose, Roxadustat 70 mg 3/week

Αύγουστος 2023, e GFR: 24 ml/min, Hct 33,8, Hb 11,3

Ασθενής 3

«Διαβητικός»

72 ετών, ΣΦΠΚ από την ηλικία των 70 ετών , καπνιστής, Αρτηριακή Υπέρταση, Αυστραλιανό αντιγόνο θετικό

71 ετών, επεισόδιο περιτονίτιδας

72 ετών, χει/θήσα βουβωνοκήλη, drop out από τη μέθοδο για 6 εβδομάδες

31 Αυγούστου 2023, Hct 29,5, Hb 10,1, Roxadustat 70 mg 3/week

21 Σεπτεμβρίου 2023, Hct 34,4, Hb 11,2

Ασθενής 4

«Περιτοναϊκός
ασθενής»

77 ετών, πολυκυστική νόσος, ΧΝΝ γνωστή από 2 ετίας- e GFR: 44
mils/min, Hct 41,9, Hb 13,8, μέτρια στένωση αορτικής βαλβίδας

Οκτώβριος 2021, Hct 35,8, Hb 12, e GFR: 43 mils/min

Δεκέμβριος 2022, Hct 37,9, Hb 12,4 , e GFR: 43 mils/min

Ιούνιος 2023, Hct 27,6, Hb 9,9 , Fer 17,3, e GFR: 40 mils/min

Γστροσκόπηση, μικρή διαφραγματοκήλη,

Κολονοσκόπηση, χωρίς ιδιαίτερα ευρήματα,

Αιματολογική διερεύνηση χωρίς ευρήματα

Ασθενής 5

«πολυκυστικός

ασθενής»

Ιούνιος 2023, 1 gr Ferric Carboxymaltose,

Roxadustat 70 mg , 3/week

Ιούλιος 2023, Hct 33,3, Hb 10,6, Fer 167,5, e GFR: 40
mils/min

Ασθενής 5

«πολυκυστικός

ασθενής»

Summary

- Dosing Frequency / Ease of Administration
 - ✓ HIF Activators are all oral agents with either daily or three times per week dosing
 - The optimal dose and frequency has yet to be determined
- Efficacy in Raising Hemoglobin
 - ✓ HIF Activators raise hemoglobin comparably to ESAs and to placebo
 - ✓ HIF Activators demonstrate changes in measures of iron metabolism (TSAT, TIBC)
 - They may obviate the need for IV iron
- Other (Beneficial) Effects of HIF Activators
 - ✓ May lower serum cholesterol (both LDL & HDL)
 - ✓ Lower markers of inflammation- Heparin
- Safety
 - ✓ Adverse events reported with HIF Activators appear to be similar to placebo or ESA
 - ± Little available information on downstream effects of modulating the HIF pathway

A dark blue background featuring a network diagram of white lines connecting various nodes. Some nodes are highlighted with yellow circles, while others are smaller white dots. The network is dense and spans the width of the slide.

BACK UP SLIDES

Γιώργος Κ.

77 ετών, πολυκυστική νόσος, ΧΝΝ γνωστή από 2 ετίας- e GFR: 44
mils/min, Hct 41,9, Hb 13,8, μέτρια στένωση αορτικής βαλβίδας

Οκτώβριος 2021, Hct 35,8, Hb 12, e GFR: 43 mils/min

Δεκέμβριος 2022, Hct 37,9, Hb 12,4 , e GFR: 43 mils/min

Ιούνιος 2023, Hct 27,6, Hb 9,9 , Fer 17,3, e GFR: 40 mils/min

Γαστροσκόπηση, μικρή διαφραγματοκήλη,

Κολonosκόπηση, χωρίς ιδιαίτερα ευρήματα,

Αιματολογική διερεύνηση χωρίς ευρήματα

Γιώργος Κ.

«πολυκυστικός

ασθενής»

Introduction: Oxygen, RBCs, Erythropoiesis, and Kidneys

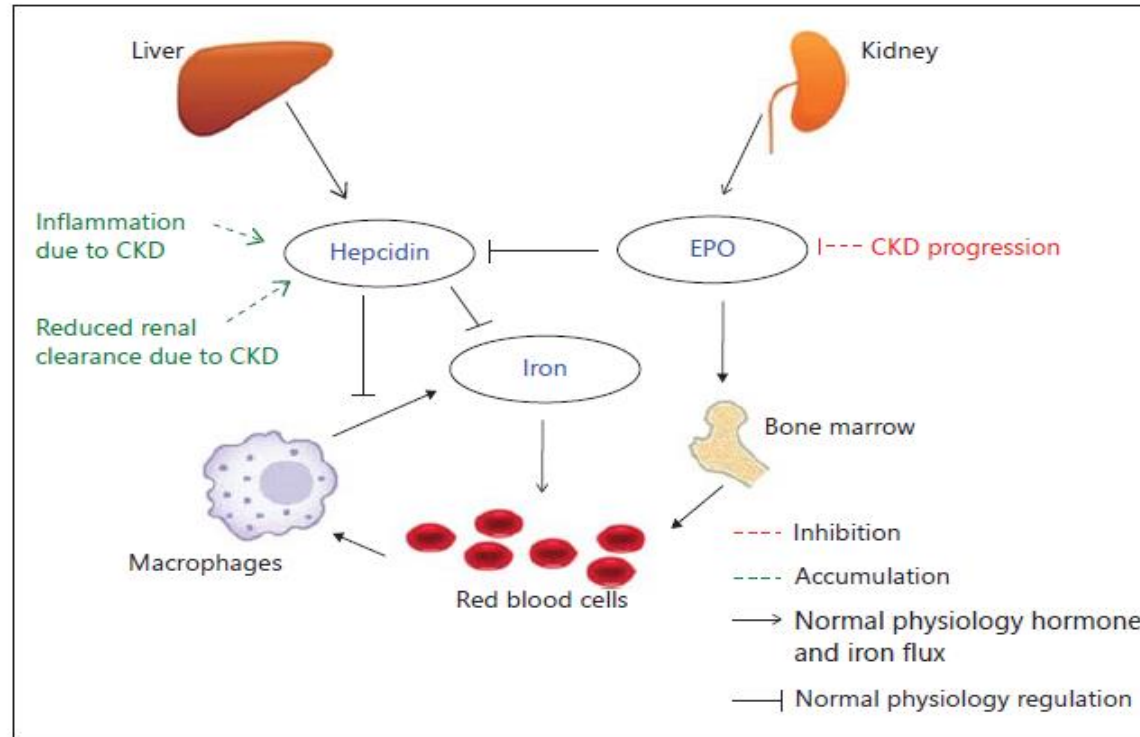
Aerobic respiration requires oxygen. Oxygen is carried by hemoglobin in RBCs from lungs to other organs.

In healthy individuals, RBC numbers and hemoglobin concentrations remain very stable.

The oldest 1% of RBCs are removed from the blood daily and replaced by equal numbers of new RBCs.

Normal RBC production = 2.5×10^{11} /day or 10^{10} /hour

Kidneys sense tissue oxygenation and regulate RBC production via EPO production in response to hypoxia.



Color version available online

Fig. 1. The role of hepcidin, iron, and erythropoietin in erythropoiesis. CKD, chronic kidney disease; EPO, erythropoietin.

Targeting Hypoxia-Inducible Factors for the Treatment of Anemia in Chronic Kidney Disease Patients

Francesco Locatelli^a Steven Fishbane^b Geoffrey A. Block^c Iain C. Macdougall^d

^aDepartment of Nephrology, Alessandro Manzoni Hospital, Lecco, Italy; ^bDepartment of Medicine, Hofstra Northwell School of Medicine, Great Neck, NY; ^cDenver Nephrologists, Denver, CO, USA; ^dDepartment of Renal Medicine, King's College Hospital, London, UK

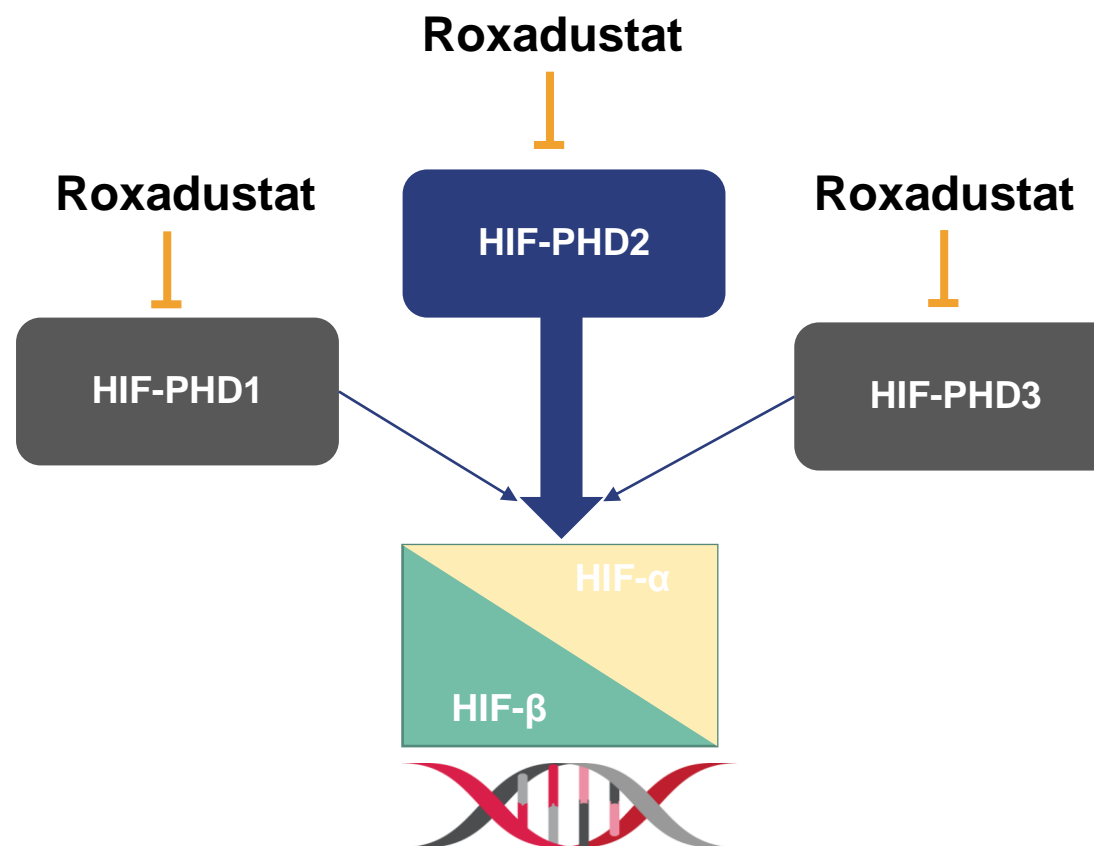
Hypoxia-inducible transcription factors (**HIFs**) bind hypoxia-response sequences of genes related to tissue oxygenation

1. HIFs are transcription factors composed of 2 subunits: HIF- α and HIF- β (ARNT).
2. HIF- β (ARNT) is stable under all levels of oxygenation. HIF- α is continually produced, but undergoes rapid proteasomal degradation during normoxia.
3. Hypoxia stabilizes HIF- α , allowing formation of transcriptionally active HIF- α /HIF- β dimers. The rate limiting step in formation of active HIF- α /HIF- β is stabilization of HIF- α , which is due to decreased prolyl hydroxylation.
4. Genes containing hypoxia responsive elements encode proteins involved in tissue oxygen delivery and utilization:
 - a. Erythropoiesis: *EPO, Transferrin*
 - b. Vascular growth/regulation: *VEGF, VEGF-R/FLT-1, Endothelin1, PAI-1, NOS2*
 - c. Glucose transport + metabolism: *GLUT1, Hexokinase, PFK, G3PD, aldolase, PK, LDH*

Roxadustat reversibly inhibits HIF-PH enzymes^{1,2}

Of the three HIF-PH enzymes in humans that hydroxylate HIF- α and regulate its stability, HIF-PHD2 functions as the main regulator in normoxia^{1,3,4}

Roxadustat reversibly inhibits all three HIF-PH enzymes^{1,2}



HIF- α , hypoxia-inducible factor-alpha; HIF- β , hypoxia-inducible factor-beta; HIF-PH, hypoxia-inducible factor-prolyl hydroxylase; HIF-PHD, hypoxia-inducible factor prolyl-hydroxylase domain.

1. Locatelli F, et al. *Am J Nephrol.* 2017;45(3):187–199; 2. Li ZL, et al. *Kidney Dis* 2020;6(2):65–73; 3. Shih HM, et al. *J Formosan Med Assoc.* 2018;117(11):955e963;

4. Schodel J and Ratcliffe PJ. *Nat Rev Nephrol.* 2019;15(10):641–659.

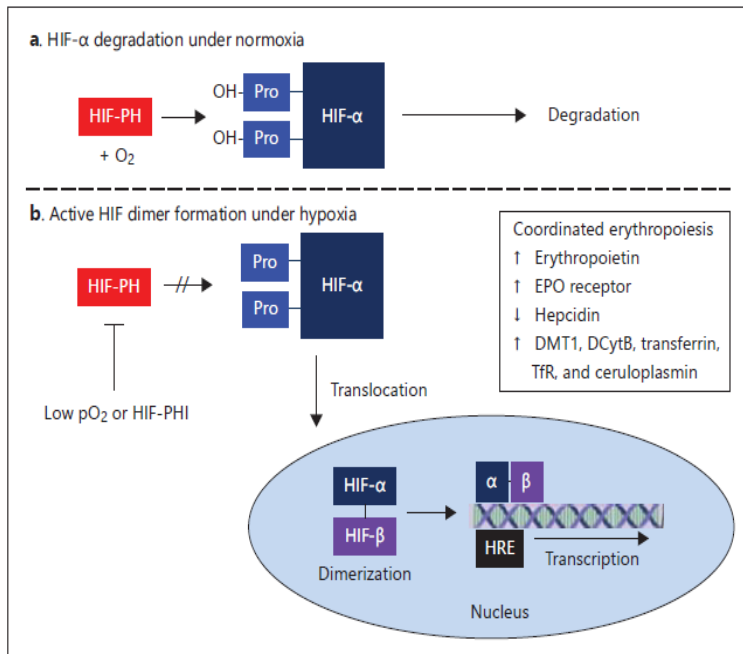


Fig. 2. a, b HIF activity under normoxic/hypoxic conditions and HIF-PHI inhibition, and its effects on erythropoiesis. DCyB, duodenal cytochrome B; DMT1, Divalent metal transporter 1; EPO, erythropoietin; HIF, hypoxia-inducible factor; HIF-PH, hypoxia-inducible factor-prolyl-4-hydroxylase domain; HRE, HIF-responsive element; Pro, proline.

Color version available online

Targeting Hypoxia-Inducible Factors for the Treatment of Anemia in Chronic Kidney Disease Patients

Francesco Locatelli^a Steven Fishbane^b Geoffrey A. Block^c Iain C. Macdougall^d

^aDepartment of Nephrology, Alessandro Manzoni Hospital, Lecco, Italy; ^bDepartment of Medicine, Hofstra Northwell School of Medicine, Great Neck, NY; ^cDenver Nephrologists, Denver, CO, USA; ^dDepartment of Renal Medicine, King's College Hospital, London, UK

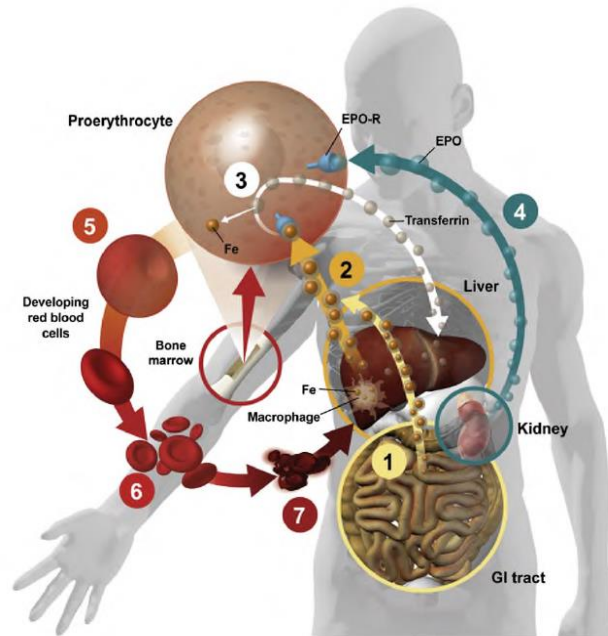


Figure 2. Erythropoietic effects of hypoxia-inducible factor (HIF). (1) HIF upregulates divalent metal transporter 1 (DMT1) and duodenal cytochrome B (DcyfB) to increase intestinal iron (Fe) absorption; (2) transferrin transports Fe to transferrin receptors in the bone marrow; (3) Fe is released from transferrin into the developing erythrocyte; (4) HIF upregulates the erythropoietin (EPO) receptor (EPO-R) and endogenous EPO production; (5) HIF upregulates transferrin receptor, increasing iron uptake by proerythrocytes; (6) HIF promotes the formation of fully functional mature erythrocytes replete with hemoglobin (Hb); (7) after a lifespan averaging approximately 120 days, exhausted erythrocytes are scavenged in the liver and the Fe is returned for reuse. Abbreviation: GI, gastrointestinal.

Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors: A Potential New Treatment for Anemia in Patients With CKD

Nupur Gupta, MD, and Jay B. Wish, MD

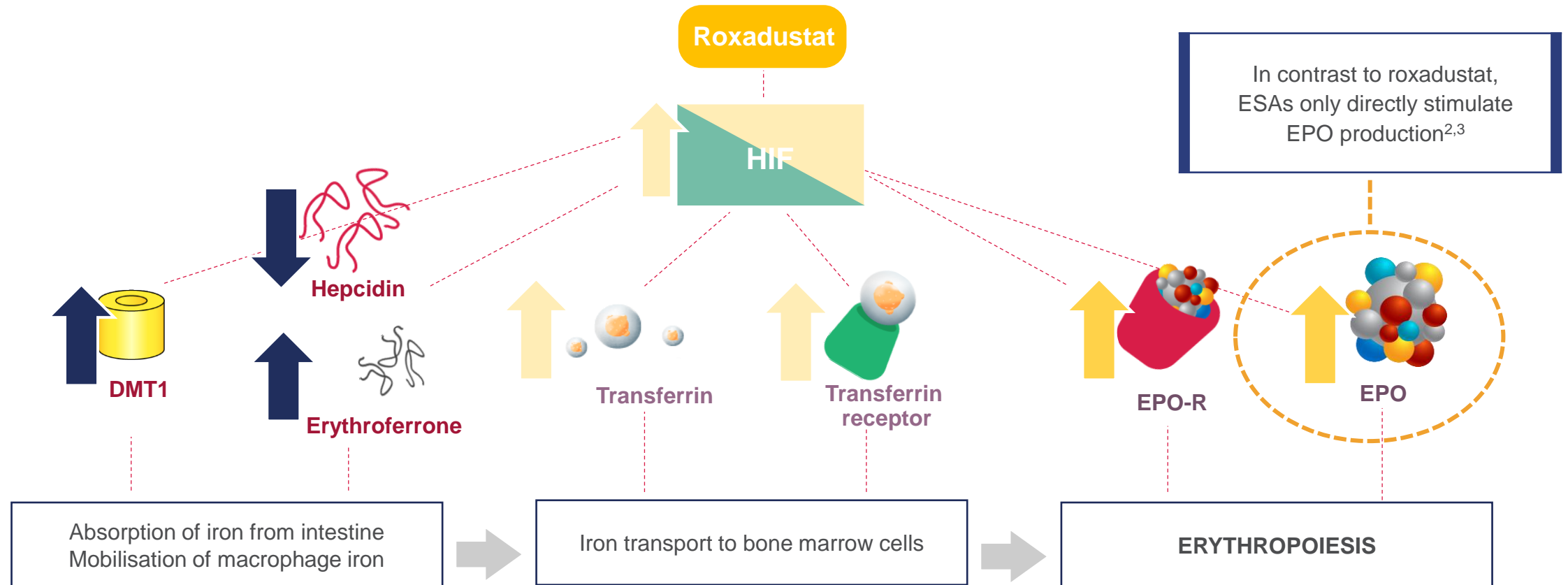


Erythropoiesis-stimulating agents (ESAs) increase hemoglobin levels, reduce transfusion requirements, and have been the standard of treatment for anemia in patients with chronic kidney disease (CKD) since 1989. Many safety concerns have emerged regarding the use of ESAs, including an increased occurrence of cardiovascular events and vascular access thrombosis. Hypoxia-inducible factor (HIF) prolyl hydroxylase (PH) enzyme inhibitors are a new class of agents for the treatment of anemia in CKD. These agents work by stabilizing the HIF complex and stimulating endogenous erythropoietin production even in patients with end-stage kidney disease. HIF-PH inhibitors improve iron mobilization to the bone marrow. They are administered orally, which may be a more favorable route for patients not undergoing hemodialysis. By inducing considerably lower but more consistent blood erythropoietin levels than ESAs, HIF-PH inhibitors may be associated with fewer adverse cardiovascular effects at comparable hemoglobin levels, although this has yet to be proved in long-term clinical trials. One significant concern regarding the long-term use of these agents is their possible effect on tumor growth. There are 4 such agents undergoing phase 2 and 3 clinical trials in the United States; this report provides a focused review of HIF-PH inhibitors and their potential clinical utility in the management of anemia of CKD.

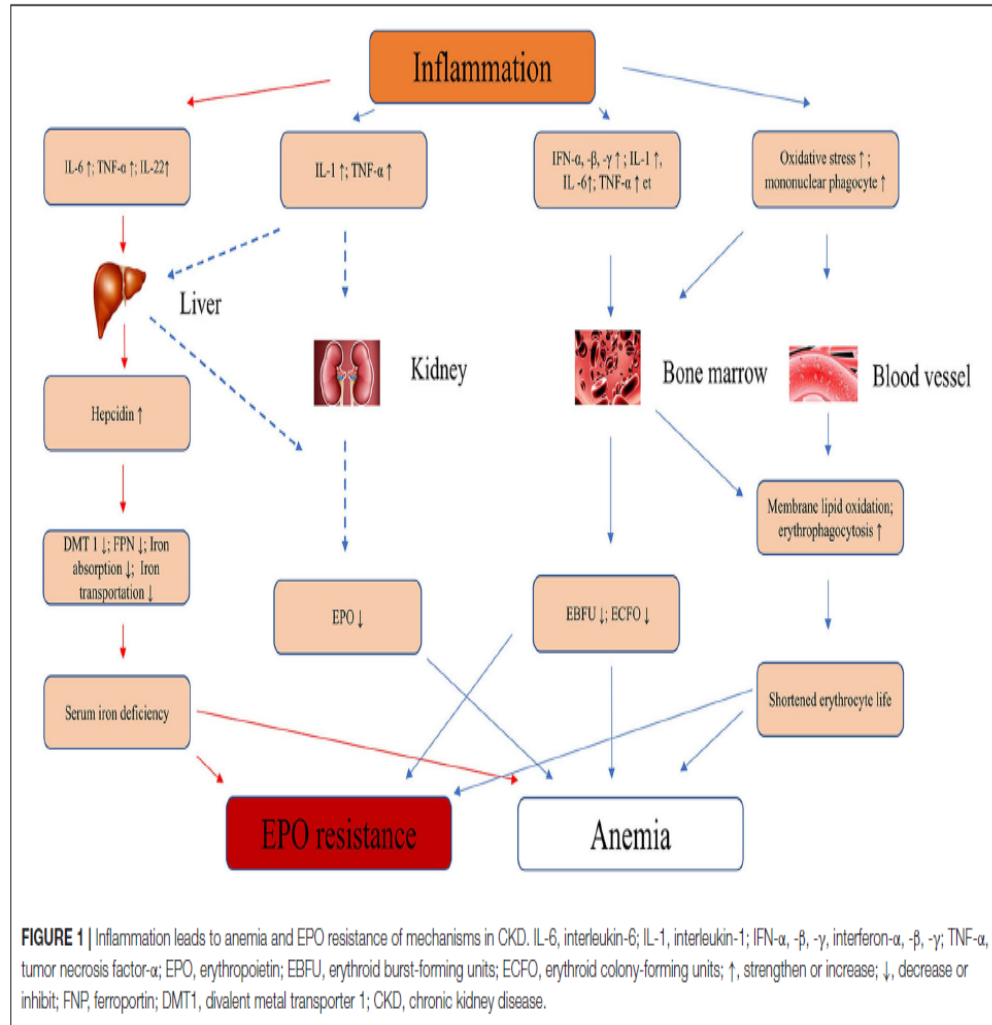
Am J Kidney Dis. 69(6):815-826. © 2017 The Authors. Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

INDEX WORDS: Anemia; chronic kidney disease (CKD); erythropoietin; hypoxia; hypoxia-inducible factor prolyl hydroxylase inhibitor; functional iron deficiency; roxadustat; vadadustat; daprodustat; molidustat; hemoglobin; review.

Activation of the HIF pathway by Roxadustat drives a coordinated erythropoietic response¹



DMT1, divalent metal transporter 1; EPO, erythropoietin; EPO-R, EPO receptor; ESA, erythropoietin-stimulating agent; HIF, hypoxia-inducible factor; HIF-PH, hypoxia-inducible factor-prolyl hydroxylase. Adapted from 1. Prabhakar NR and Semenza GL. *Physiol Rev.* 2012;92(3):967–1003; 2. Locatelli F, et al. *Am J Nephrol.* 2017;45(3):187–199; 3. Eggold JT and Rankin E. *Bone.* 2019;119:36–41.



A Novel Choice to Correct Inflammation-Induced Anemia in CKD: Oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor Roxadustat

Zhipeng Yan and Gaosi Xu*

Department of Nephrology, The Second Affiliated Hospital of Nanchang University, Nanchang, China

Roxadustat pharmacodynamics and pharmacokinetics

Pharmacodynamics^{1,2}

- Roxadustat **inhibits** HIF-PH enzymes and stabilises HIF under **normal oxygen conditions** i.e., roxadustat imitates the body's natural hypoxic response to sensing oxygen. It is *not* the same as hypoxia

Pharmacokinetics²

- C_{\max} and AUC are dose-proportional within the recommended therapeutic range
- The mean effective half-life ($t_{1/2}$) of roxadustat is approx. 15 hours in patients with CKD
- Roxadustat is excreted in both urine and faeces (~50% via each route)
- Food has no clinically relevant effect on roxadustat plasma exposure
- Age, sex or race/ethnicity have no clinically relevant impact on roxadustat exposure
- The pharmacokinetics of roxadustat do not change over time

AUC, area under the plasma drug concentration over time curve; CKD, chronic kidney disease; C_{\max} , maximum plasma concentration; HIF, hypoxia-inducible factor; HIF-PH, hypoxia-inducible factor-prolyl-hydroxylase.
1. Locatelli F, et al. *Am J Nephrol.* 2017;45(3):187–199; 2. EVRENZO SmPC August 2021.

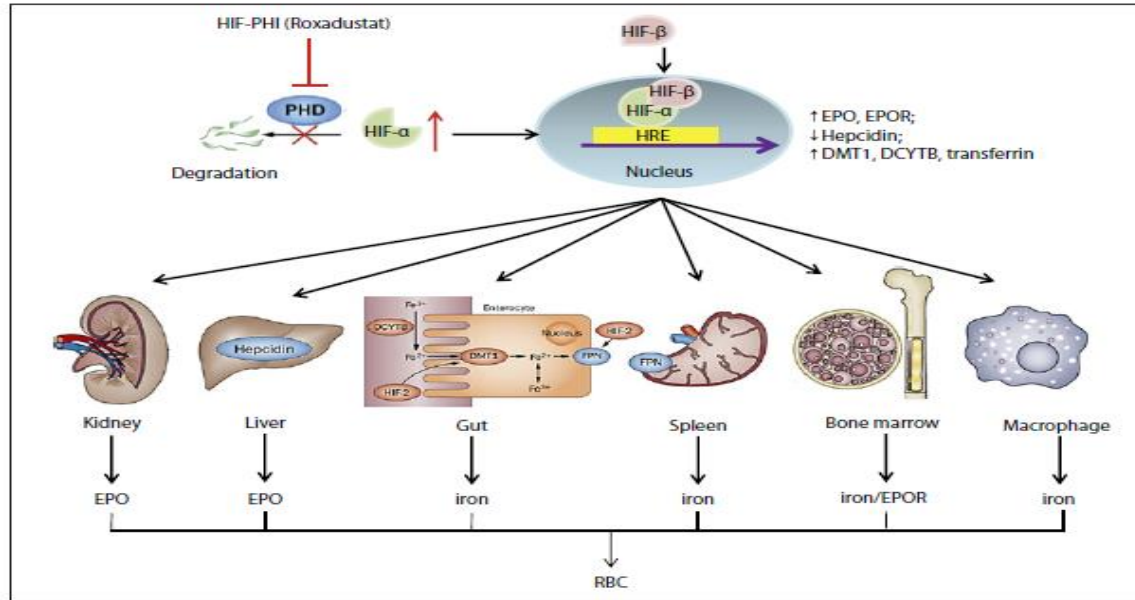


Fig. 1. HIF coordinates erythropoietin production with iron metabolism. The oxygen-dependent PHDs as key regulators of HIF-dependent erythropoiesis became the direct therapeutic target for anemia correction. HIF-PHIs stabilize HIF via suppressing the function of PHDs directly. EPO synthesis could be stimulated by HIF (induced by pharmacologic PHD inhibition) in kidney and liver, which plays a central role in stimulating erythropoiesis in the bone marrow. In the duodenum, it is well recognized that DCYTb, DMT1, and FPN are regulated by HIF-2. DCYTb reduces Fe^{3+} to Fe^{2+} , which then enters enterocytes via DMT1. Iron is then re-

leased into the circulation via FPN. The increasing evidence demonstrated that HIF activation could suppress hepcidin expression, which increases FPN expression on enterocytes, hepatocytes, and macrophages, resulting in increased iron absorption and mobilization from internal stores. HRE, hypoxia response element; DCYTb, duodenal cytochrome b reductase 1; DMT1, divalent metal transporter-1; EPO, erythropoietin; EPOR, erythropoietin receptor; RBC, red blood cell; HIF, hypoxia-inducible factor; FPN, ferroportin; Fe^{2+} , ferrous iron; Fe^{3+} , ferric iron.

Review Article

**Kidney
Diseases**

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Published online: January 10, 2020

Treatment of Renal Anemia with Roxadustat: Advantages and Achievement

Zuo-Lin Li Yan Tu Bi-Cheng Liu

Institute of Nephrology, Zhong Da Hospital, Southeast University School of Medicine, Nanjing, China

Οι στρατηγικές αντιμετώπισης της αναιμίας στη ΧΝΝ



ΠΑΡΕΛΘΟΝ

Η μόνη επιλογή ήταν η μετάγγιση RBC

(ερυθρά αιμοσφαίρια)

- Η μετάγγιση αποτελούσε τη μόνη επιλογή όταν δεν επαρκούσε ο σίδηρος μόνο

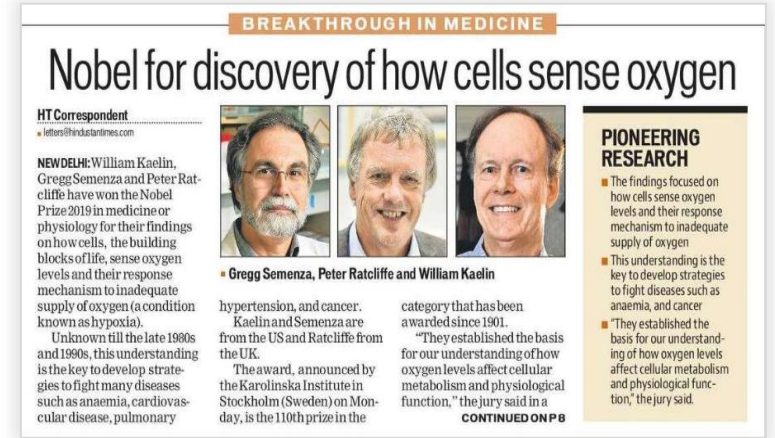


ΠΑΡΟΝ

Αντιμέτωση ως ανεπάρκεια EPO¹

(ερυθροποιητίνη)

- Συμπληρωματική ερυθροποιητίνη (EPO) σε συνδυασμό με συμπληρώματα σιδήρου για την παραγωγή ερυθρών αιμοσφαιρίων



ΜΕΛΛΟΝ

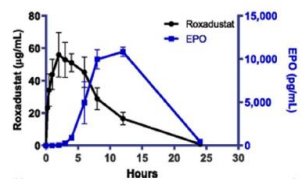
Αντιμέτωση της αναιμίας σχετιζόμενη με ΧΝΝ δίνοντας στον οργανισμό τη δυνατότητα να διεγείρει συντονισμένη ερυθροποίηση

- Το roxadustat είναι ο πρώτος στην κατηγορία του από στόματος λαμβανόμενος HIF-PHI που προσφέρει μια εντελώς διαφορετική προσέγγιση στην αντιμετώπιση της αναιμίας σχετιζόμενης με ΧΝΝ,
- Το roxadustat αξιοποιεί τη φυσική ικανότητα του οργανισμού (ανίχνευση του O₂ ή μονοπάτι του HIF) να προωθεί μια συντονισμένη ερυθροποίηση, ενεργοποιώντας ορισμένα γονίδια τα οποία διεγείρουν την παραγωγή ερυθροποιητίνης και τη ρύθμιση του Fe και υπερνικούν την αρνητική επίδραση της φλεγμονής μέσω της μείωσης των επιπέδων της εψιδίνης.

Το roxadustat είναι ένας HIF-PHI με καινοτόμο μηχανισμό δράσης, ο οποίος βασίζεται σε βραβευμένη με Νόμπελ έρευνα στο μονοπάτι του HIF

Pharmacokinetics

$t_{max} = 2.5$ h
 $C_{max} = 59$ μ g/mL
 $AUC = 660$ h \cdot μ g/mL



Pharmacodynamics

$t_{onset} = 12$ h
 $E_{max} = 11,000$ pU/mL
 $AUEC = 130,500$ h \cdot pU/mL

[del Balzo 2020]

Fig. 2 Reversible effect–concentration correlation between roxadustat and EPO. When roxadustat concentrations rise, EPO levels start increasing, with a 5 h delay. When roxadustat concentrations decrease, the EPO levels decline faster here in animals than in

humans [16]. EPO erythropoietin, t_{max} time to reach maximum concentration, C_{max} maximum concentration, AUC area under the concentration–time curve, t_{onset} time to peak concentration, $AUEC$ area under the effect–time curve

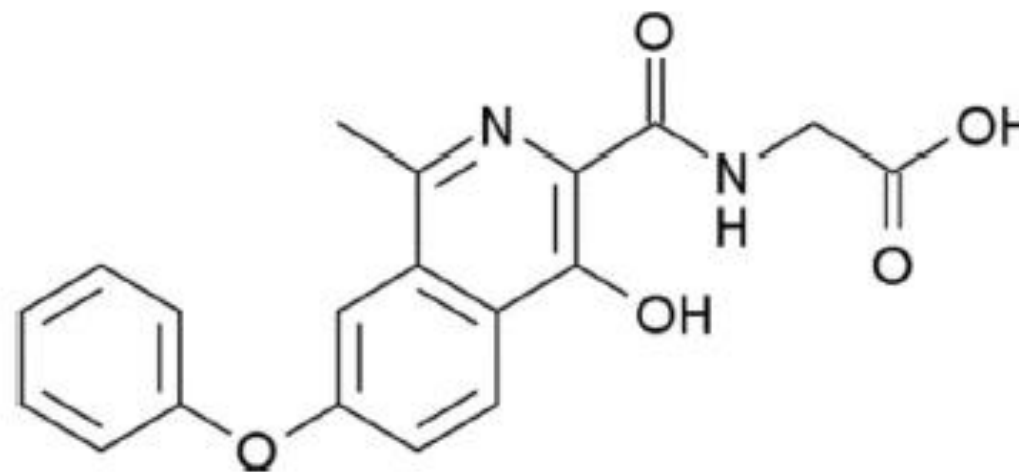


Fig. 1 Chemical structure of roxadustat

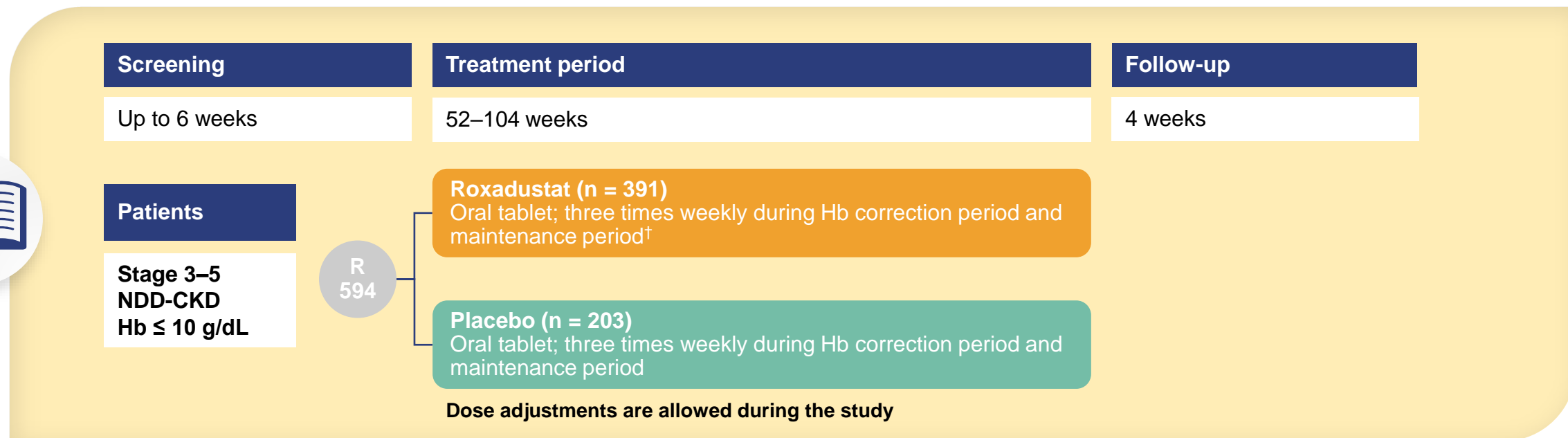


Clinical Pharmacokinetics and Pharmacodynamics of Roxadustat

David Czock¹ · Frieder Keller²

ALPS (Study 0608): study design^{1,2}

- ALPS was a randomised, double-blind, placebo-controlled study with patients not on dialysis
- Primary endpoint: Hb response* without rescue therapy, during the first 24 weeks of treatment



*Hb response was defined as Hb ≥ 11.0 g/dL that increased from baseline by ≥ 1.0 g/dL in patients with Hb > 8.0 g/dL or ≥ 2.0 g/dL in patients with baseline Hb ≤ 8.0 g/dL

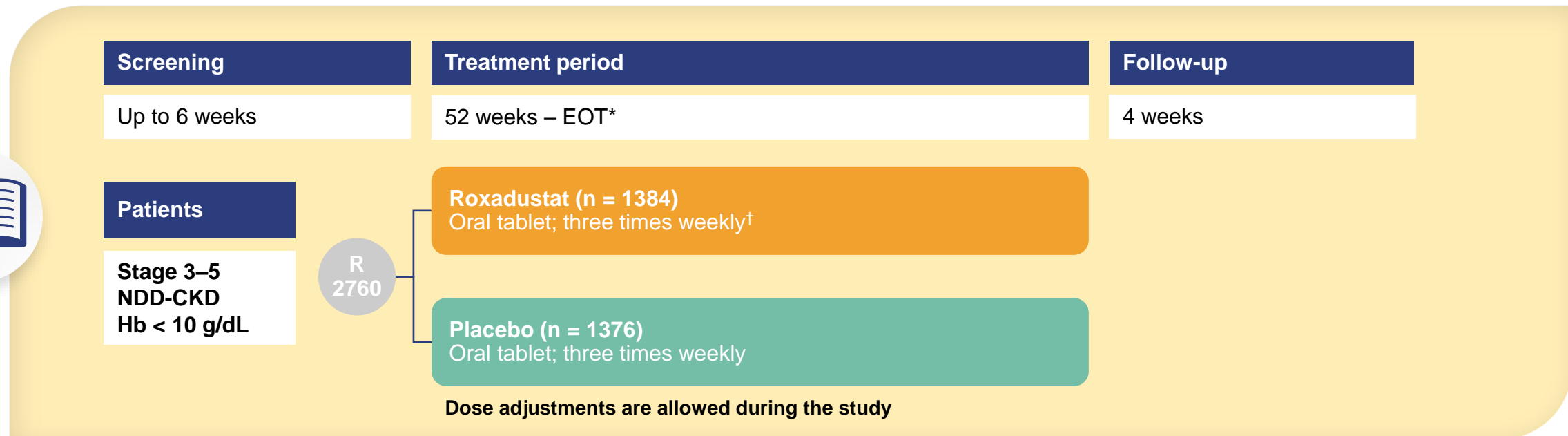
[†]Starting dose was weight-based: 70 mg for patients ≥ 45.0 kg and ≤ 70.0 kg; 100 mg for patients > 70.0 kg to ≤ 160.0 kg.

CKD, chronic kidney disease; Hb, haemoglobin; NDD, non-dialysis dependent; R, randomisation.

1. Shutov E, et al. *Nephrol Dial Transplant*. 2021; ; 2. EVRENZO SmPC August 2021.

OLYMPUS (d5740C00001): study design^{1,2}

- OLYMPUS was a randomised, double-blind, placebo-controlled study with patients not on dialysis
- Primary endpoint: mean change in Hb (g/dL) from baseline to Weeks 28–52



*EOT visit occurred as soon as possible after the target number of cardiovascular events was accrued; treatment duration was variable for individual patients (estimated duration up to 4 years)

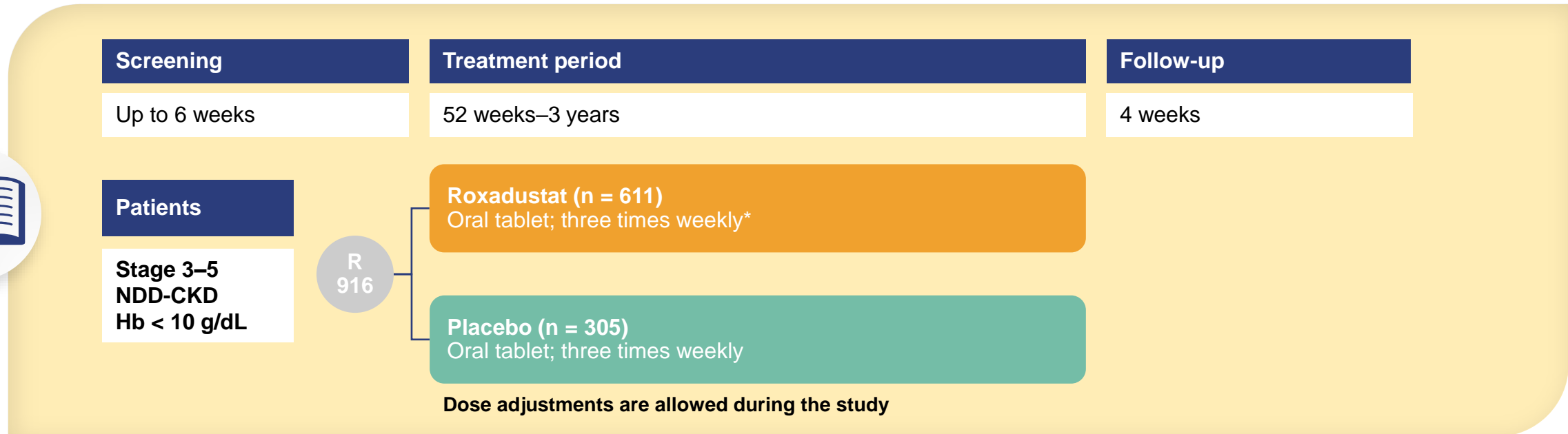
[†]The starting dose was 70 mg.

CKD, chronic kidney disease; Hb, haemoglobin; NDD, non-dialysis dependent; R, randomisation.

1. Fishbane S, et al. *J Am Soc Nephrol.* 2021;32(3):737–755; 2. EVRENZO SmPC August 2021.

ANDES (Study 060): study design^{1,2}

- ANDES was a multi-centre, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of roxadustat in patients not on dialysis
- Primary endpoint: proportion of patients achieving a Hb response at two consecutive visits ≥ 5 days apart during the first 24 weeks, without rescue therapy



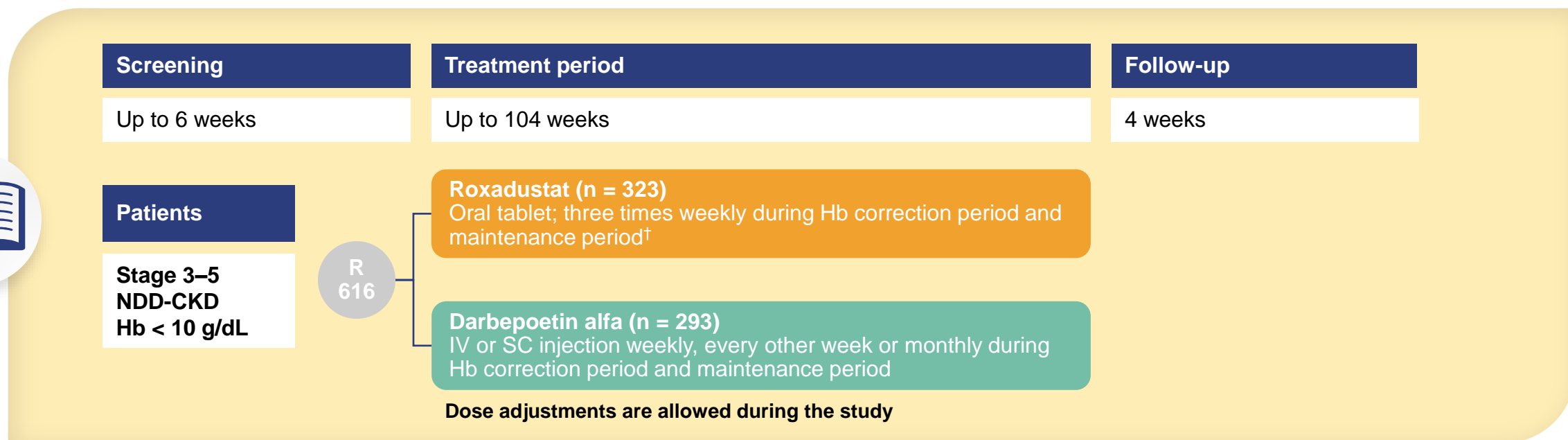
*Starting dose was weight-based: 70 mg for patients ≥ 45.0 kg and ≤ 70.0 kg; 100 mg for patients >70.0 kg to ≤ 160.0 kg.

CKD, chronic kidney disease; Hb, haemoglobin; NDD, non-dialysis dependent; R, randomisation.

1. Coyne DW, et al. *Kidney Int Rep.* 2020;6(3):624–635; 2. EVRENZO SmPC August 2021.

Dolomites (Study 0610): study design^{1,2}

- DOLOMITES was a randomised, open-label, active-controlled study with patients not on dialysis
- Primary endpoint: Hb response* at two consecutive visits ≥ 5 days apart, during the first 24 weeks and without having received rescue therapy



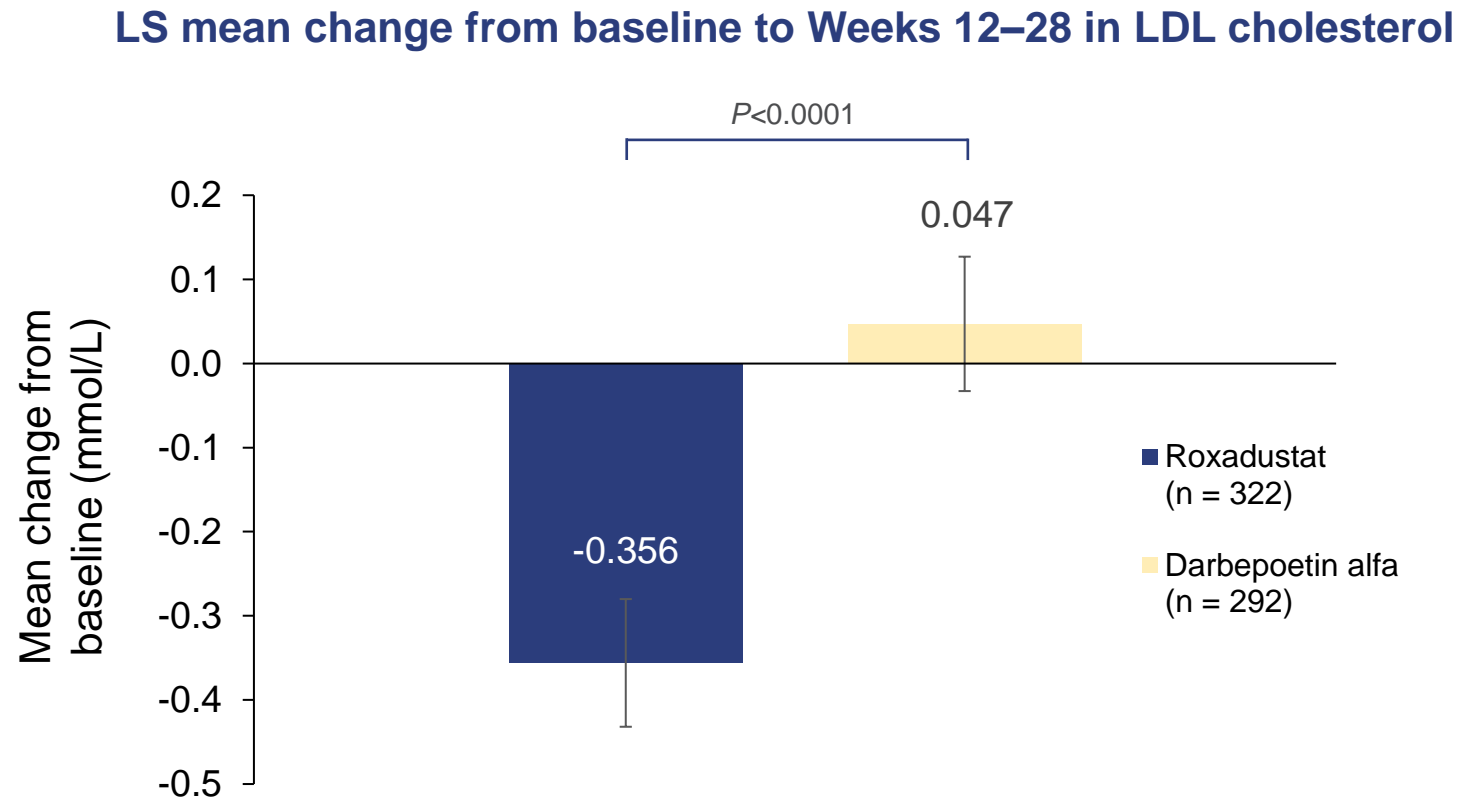
*Hb response was defined as Hb ≥ 11.0 g/dL that increased from baseline by ≥ 1.0 g/dL in patients with Hb > 8.0 g/dL or ≥ 2.0 g/dL in patients with baseline Hb ≤ 8.0 g/dL

[†]Starting dose was weight-based: 70 mg for patients ≥ 45.0 kg and ≤ 70.0 kg; 100 mg for patients > 70.0 kg to ≤ 160.0 kg.

CKD, chronic kidney disease; Hb, haemoglobin; IV, intravenous; NDD, non-dialysis dependent; R, randomisation; SC, subcutaneous.

1. Barratt J, et al. *Nephrol Dial Transplant*. 2021;gfab191; 2. EVRENZO SmPC August 2021.

Roxadusat significantly reduced ldl cholesterol from baseline VS darbepoetin alfa in patients with NDD-CKD



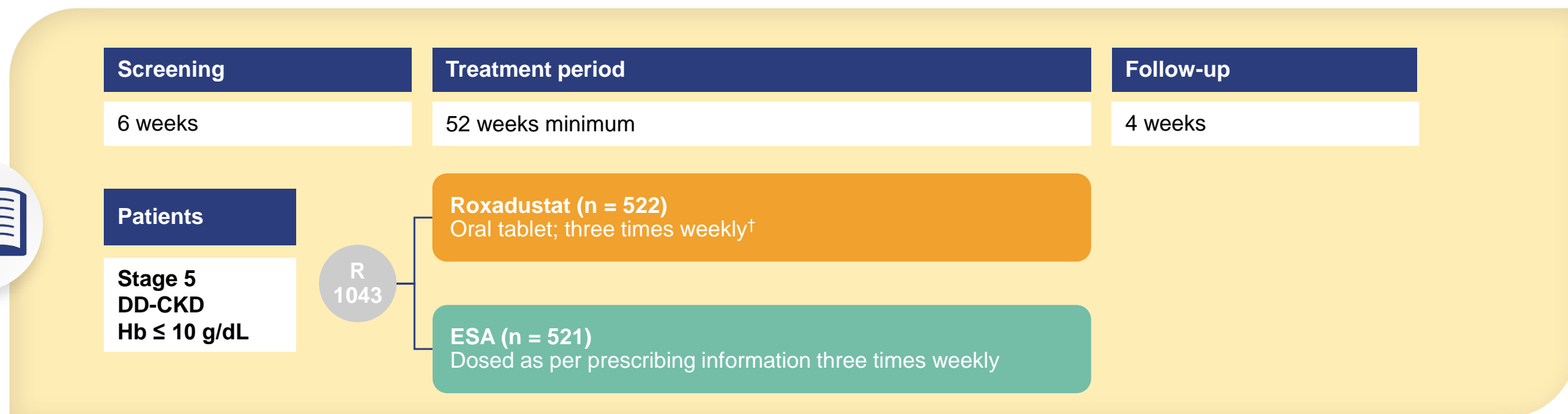
NDD vs active
comparator
DOLOMITES



Error bars represent 95% confidence interval.
CKD, chronic kidney disease; LDL, low-density lipoprotein; NDD, non-dialysis dependent.
EVRENZO SmPC. August 2021.

HIMALAYAS (study 063): study design^{1,2}

- HIMALAYAS was a randomised, open-label, active-controlled study investigating the efficacy and safety of roxadustat vs epoetin alfa in incident dialysis patients
- Primary endpoint: Proportion of patients achieving a Hb response* at two consecutive visits ≥ 5 days apart during the first 24 weeks



*Hb response was defined as Hb ≥ 11.0 g/dL that increased from baseline by ≥ 1.0 g/dL in patients with Hb > 8.0 g/dL or ≥ 2.0 g/dL in patients with baseline Hb ≤ 8.0 g/dL

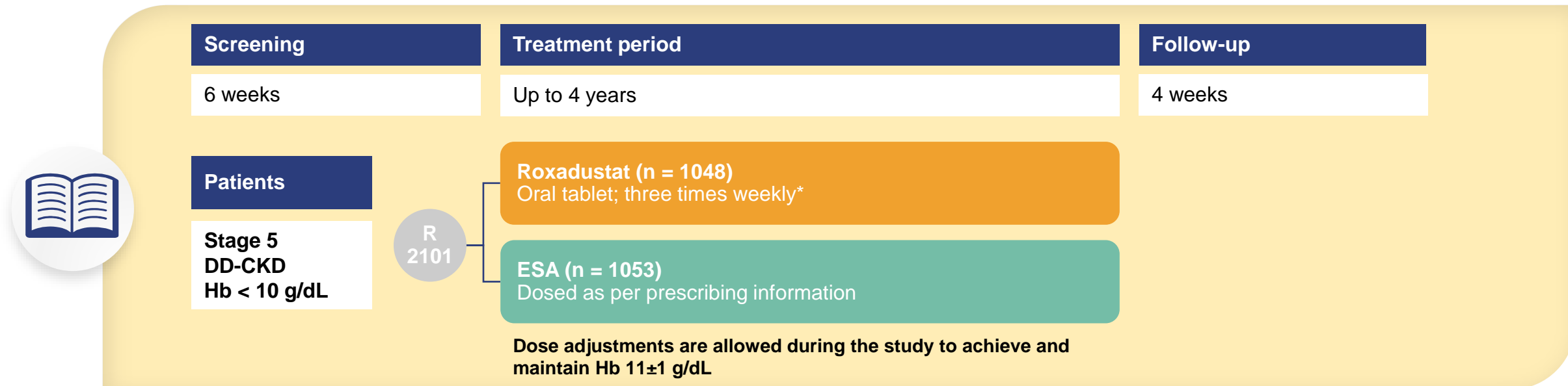
[†]Starting dose was weight-based: 70 mg for patients ≥ 45.0 kg and ≤ 70.0 kg; 100 mg for patients > 70.0 kg to ≤ 160.0 kg.

CKD, chronic kidney disease; DD, dialysis dependent; ESA, erythropoietin-stimulating agent; Hb, haemoglobin; R, randomisation.

1. Provenzano R, et al. *Nephrol Dial Transplant*. 2021;gfab051; 2. EVRENZO draft SmPC. August 2021.

ROCKIES (d5740C00002): study design^{1,2}

- ROCKIES was a randomised, open-label, active-controlled study investigating the efficacy and safety of roxadustat vs epoetin alfa in DD-CKD patients
- Primary endpoint: Hb (g/dL) change from baseline to the average Hb of Weeks 28–52



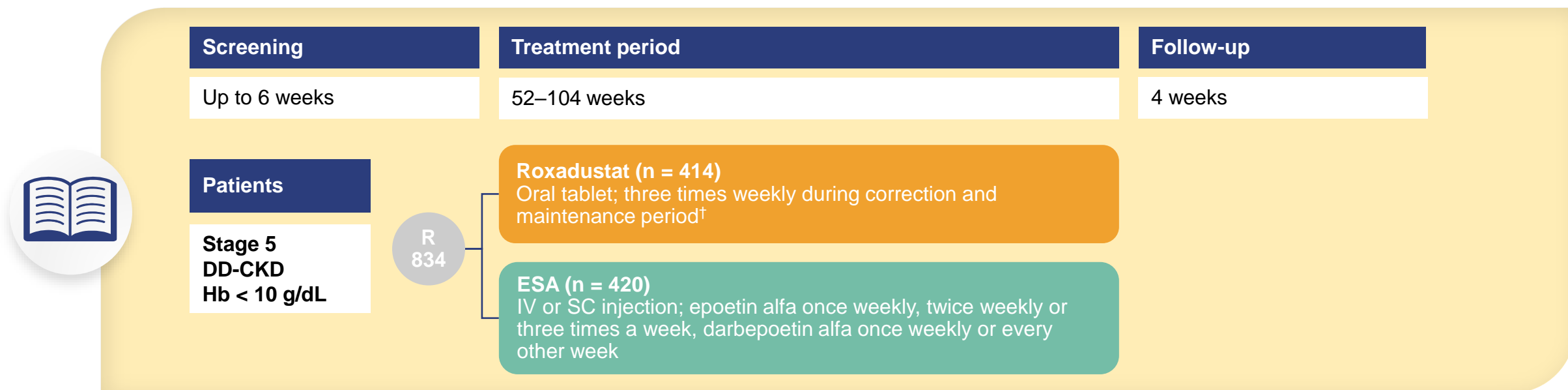
*The starting dose at study entry was either 70, 100, 150 or 200 mg depending on baseline ESA dose.

CKD, chronic kidney disease; DD, dialysis dependent; ESA, erythropoietin-stimulating agent; Hb, haemoglobin; R, randomisation.

1. Fishbane S, et al. Presented at American Society of Nephrology Kidney Week 2019. November 5–10, 2019. Washington, DC. Abstract #TH-OR022; 2. EVRENZO SmPC. August 2021.

PYRENEES (Study 0613): study design^{1,2}

- PYRENEES was a randomised, open-label, active-controlled study designed to investigate the efficacy and safety of roxadustat in the maintenance treatment of anaemia in patients on stable dialysis
- Primary endpoint: Hb response during the first 24 weeks without having received rescue therapy*



*The dose conversion algorithm was adjusted for subsequent trials so that patients on lower doses of ESA were converted to 70mg of roxadustat (rather than the 100 mg starting conversion dose in PYRENEES)

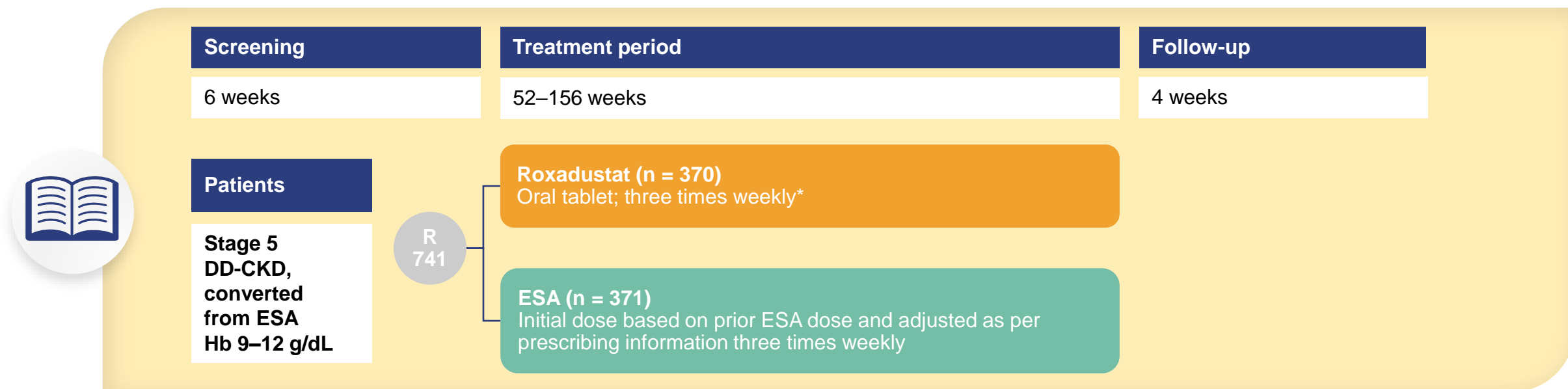
[†]The starting dose at study entry was either 100, 150 or 200 mg depending on baseline ESA dose prior to randomisation.

CKD, chronic kidney disease; DD, dialysis dependent; ESA, erythropoietin-stimulating agent; Hb, haemoglobin; IV, intravenous; R, randomisation; SC, subcutaneous.

1. ClinicalTrials.gov NCT02278341. (Accessed: July 2021); 2. EVRENZO SmPC. August 2021.

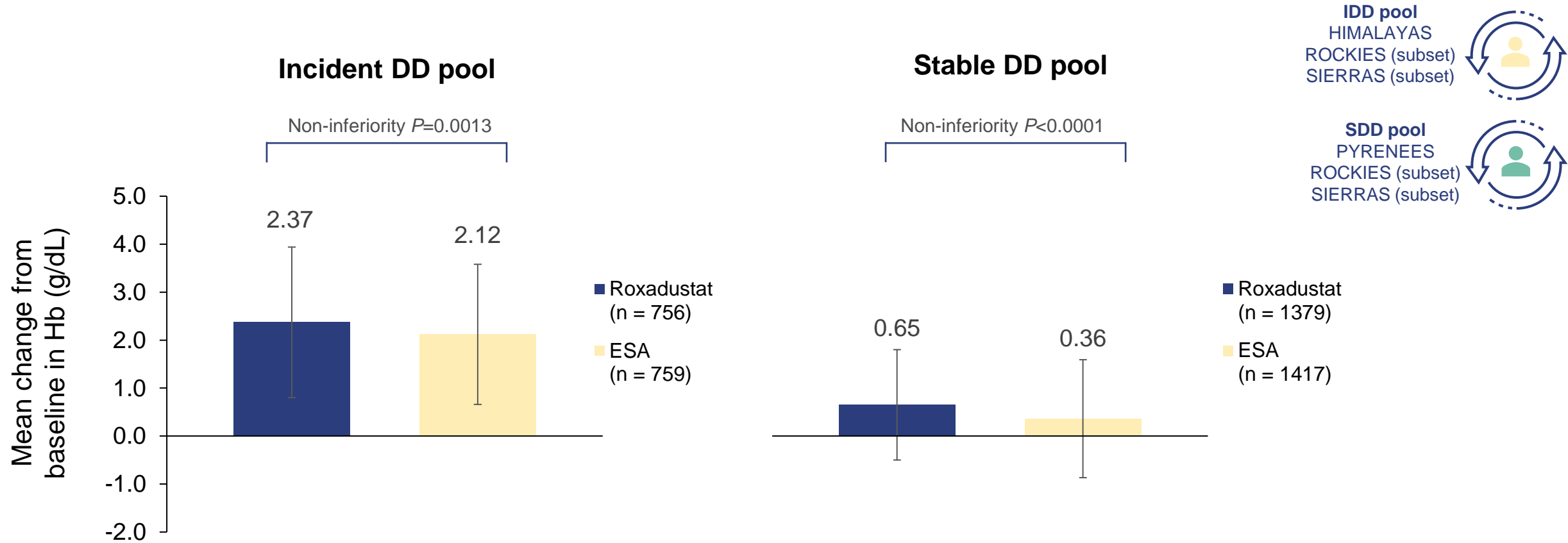
SIERRAS (Study 064): study design^{1,2}

- SIERRAS was a randomised, open-label, active-controlled study in patients on newly-initiated or stable dialysis
- Primary endpoint: Hb (g/dL) change from baseline to the average Hb of Weeks 28–52, without having received rescue therapy



*The starting dose at study entry was either 70, 100, 150 or 200 mg depending on baseline ESA dose.
CKD, chronic kidney disease; DD, dialysis dependent; ESA, erythropoietin-stimulating agent; Hb, haemoglobin; R, randomisation.
1. Charytan C, et al. *Kidney Int Rep.* 2021;6(7):1829–1839; 2. EVRENZO SmPC. August 2021.

Roxadustat was non-inferior to ESA in mean change from baseline in Hb during weeks 28–36 in DD-CKD



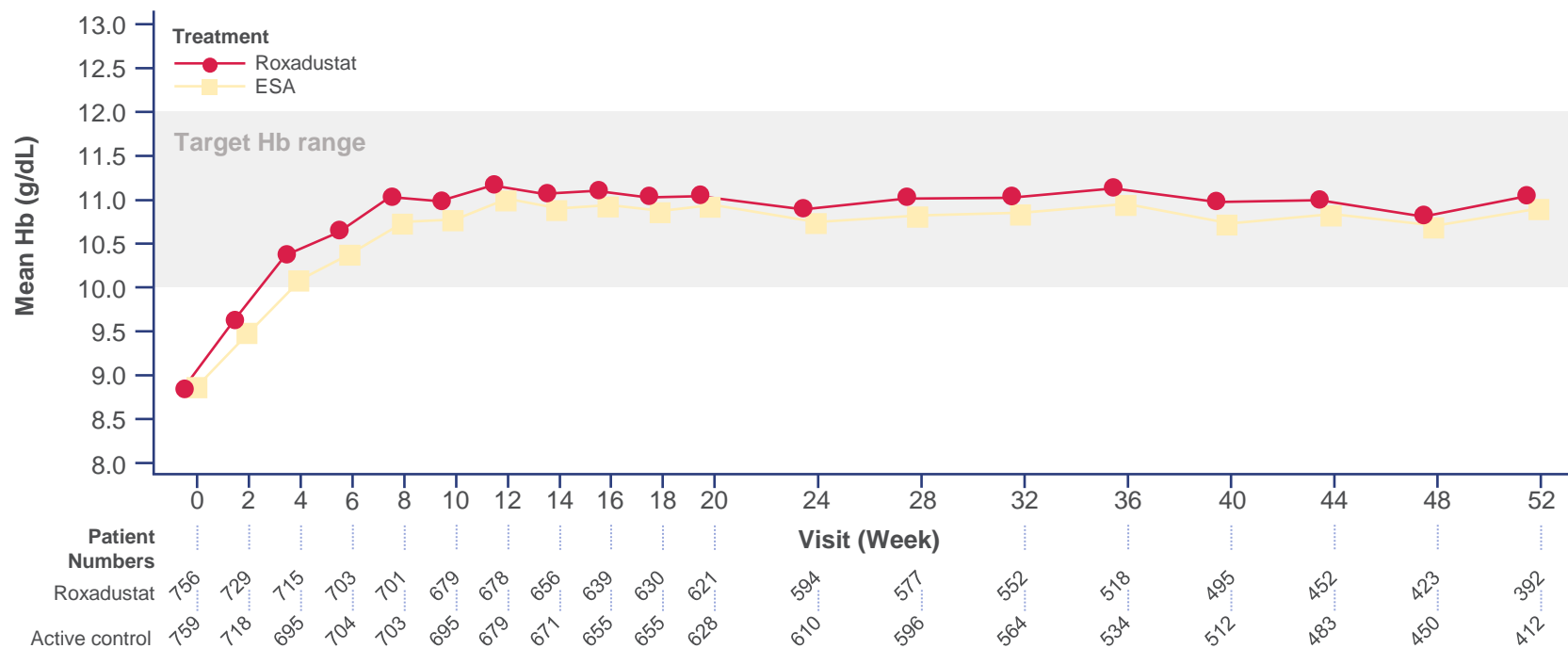
Error bars represent standard deviation.

CI, confidence interval; CKD, chronic kidney disease; DD, dialysis dependent; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IDD, incident-dialysis dependent; SDD, stable-dialysis dependent. EVRENZO SmPC. August 2021.

Roxadustat was effective at achieving and maintaining target Hb levels in patients on incident dialysis

Mean Hb (g/dL) over 52 weeks (FAS)

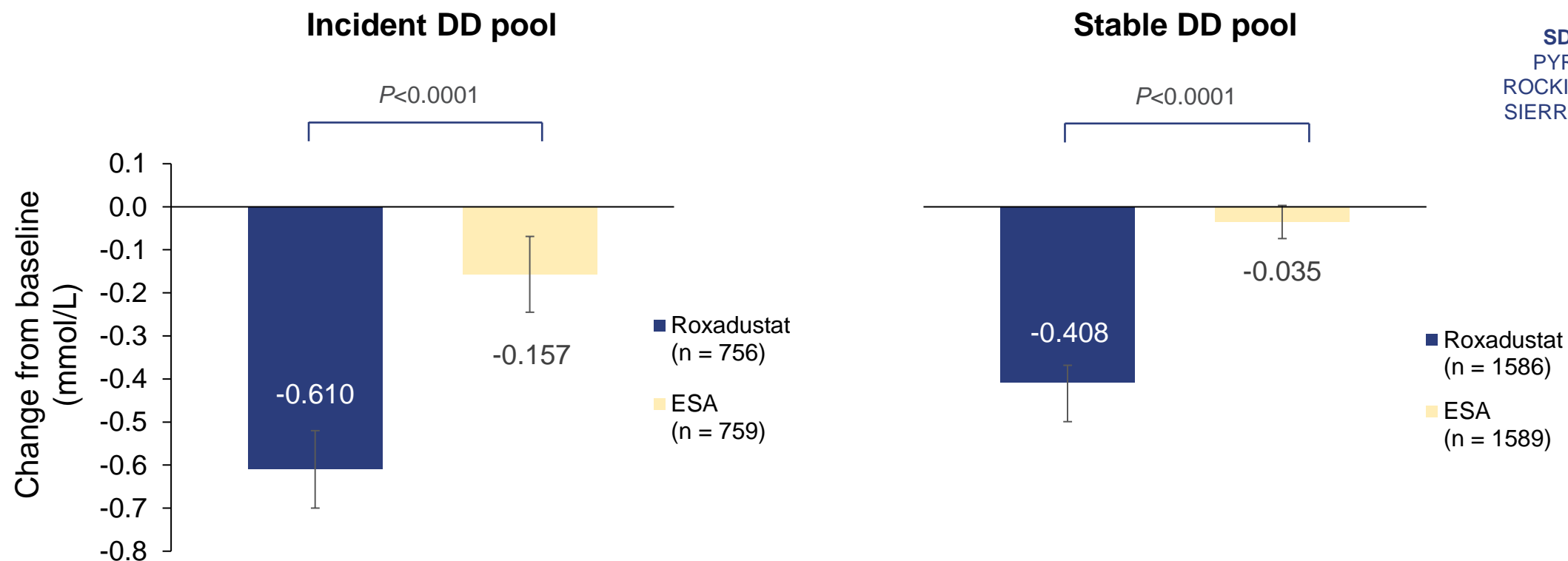
IDD pool
HIMALAYAS
ROCKIES (subset)
SIERRAS (subset)



Mean Hb was comparable over time with roxadustat vs ESA treatment in incident DD-CKD patients

Significant reduction in mean LDL cholesterol in patients on dialysis treated with roxadustat vs ESA^{1,*}

- LS mean change from baseline to Weeks 12–28 in LDL cholesterol



IDD pool
HIMALAYAS
ROCKIES (subset)
SIERRAS (subset)



SDD pool
PYRENEES
ROCKIES (subset)
SIERRAS (subset)



Error bars represent 95% confidence interval.

*Controlling LDL cholesterol in patients on dialysis has not been shown to improve outcomes^{2,3}

DD, dialysis dependent; ESA, erythropoiesis-stimulating agent; IDD, incident-dialysis dependent; LDL, low-density lipoprotein; LS, least squares; SDD, stable-dialysis dependent.

1. EVRENZO SmPC. August 2021; 2. Baigent C, et al. *Lancet*. 2011;377(9784):2181–2192; 3. Fellstrom BC, et al. *N Engl J Med*. 2009;360(14):1395–1407.

SDD pool in an esa conversion setting (On-Treatment analysis)

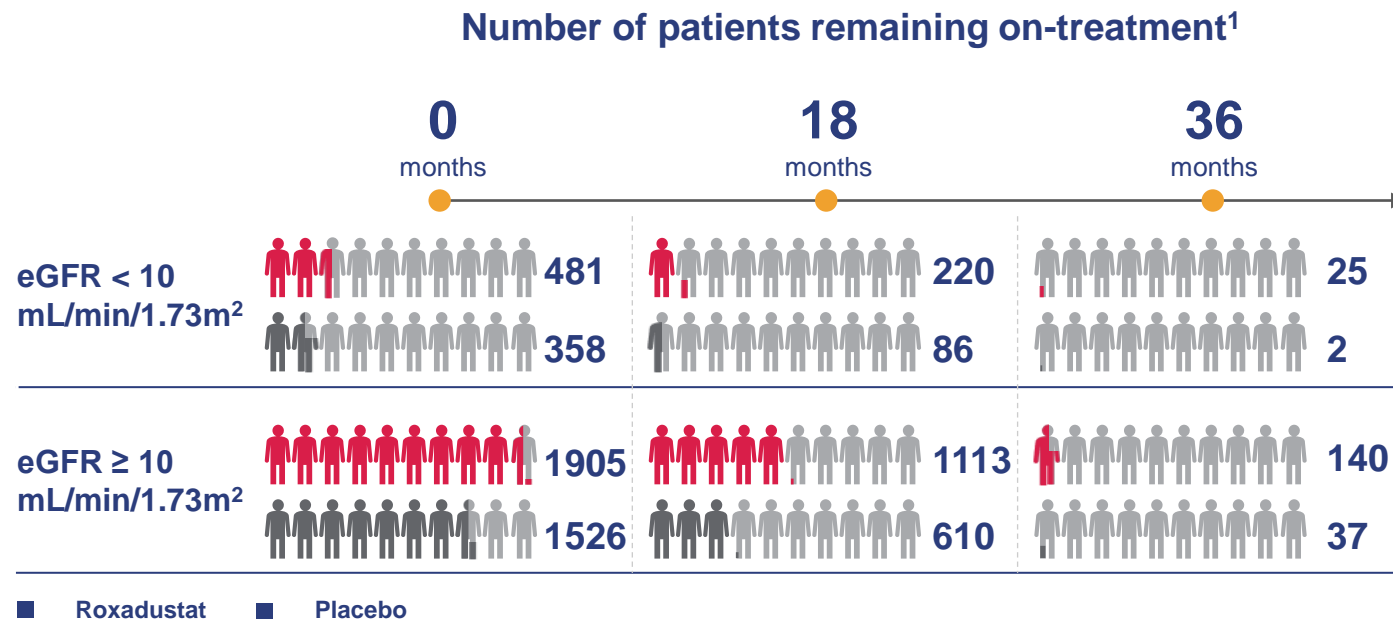
Patients allocated to roxadustat were switched from an ESA at the start of the study and the inherent risk in switching to any new treatment versus remaining on a treatment with a stabilised Hb may confound the observed results. Therefore, any comparison of treatment effect estimates cannot be reliably established.

SDD pool vs ESA
PYRENEES
ROCKIES (subset)
SIERRAS (subset)



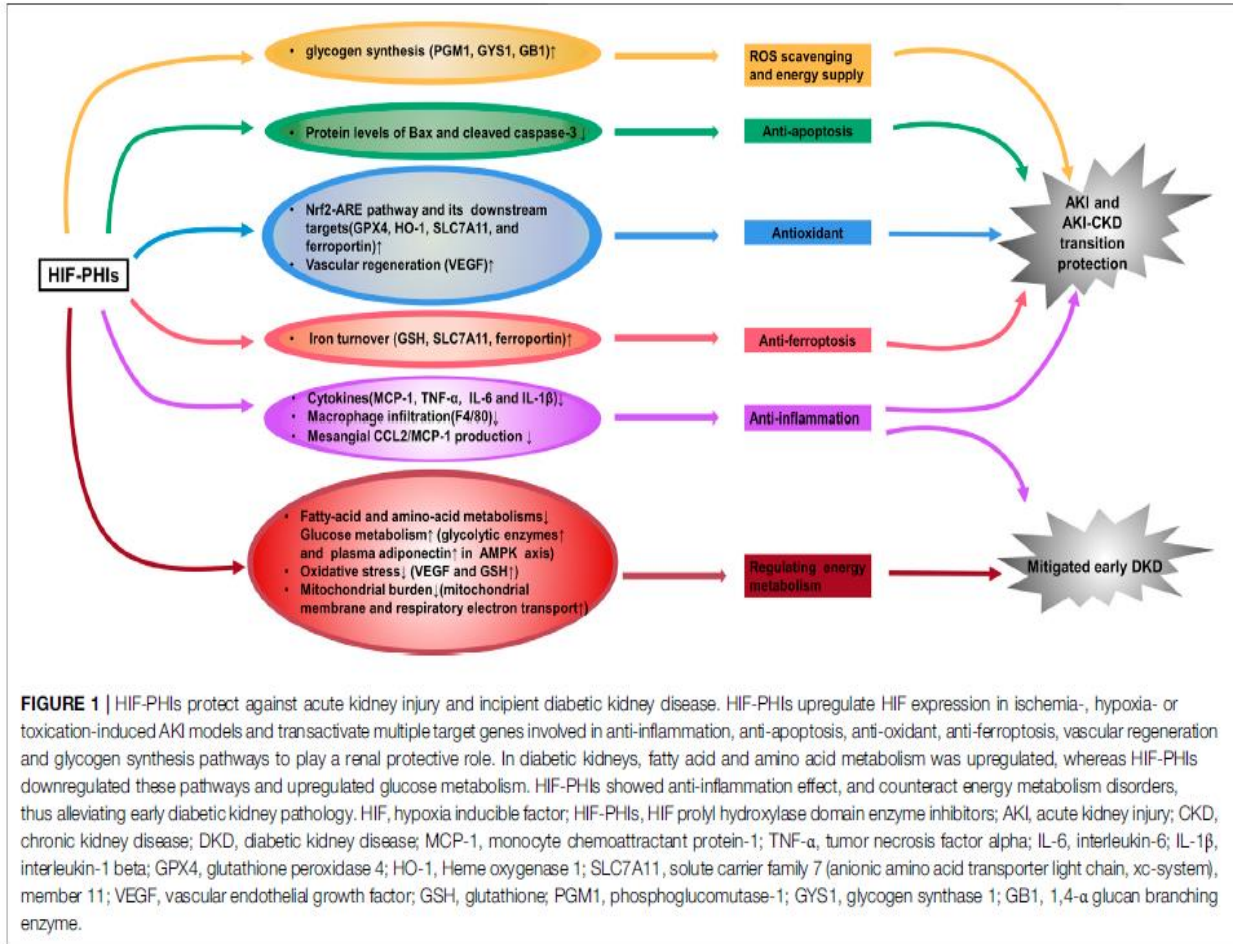
OT population	MACE		MACE+		ACM	
	Roxadustat N = 1594	ESA N = 1594	Roxadustat N = 1594	ESA N = 1594	Roxadustat N = 1594	ESA N = 1594
Number of patients with events, n (%)	297 (18.6)	301 (18.9)	357 (22.4)	403 (25.3)	212 (13.3)	207 (13.0)
IR	10.4	9.2	12.5	12.3	7.4	6.3
HR (95% CI)	1.18 (1.00, 1.38)		1.03 (0.90, 1.19)		1.23 (1.02, 1.49)	

General safety analysis is by definition on-treatment, so suffers from the same bias as the placebo-controlled NDD-CKD



In NDD-CKD studies, a **substantially greater proportion of patients in the placebo arm discontinued treatment compared to the roxadustat arm**, especially those with lower baseline eGFRs who were **most susceptible to CV events**¹

- CKD is associated with CV morbidity and mortality; potent predictors of mortality are greater age and lower eGFR^{2,3}
- A larger proportion of susceptible patients in the roxadustat arm remained on-study to contribute to CV events¹
- **This produces bias by informative censoring**

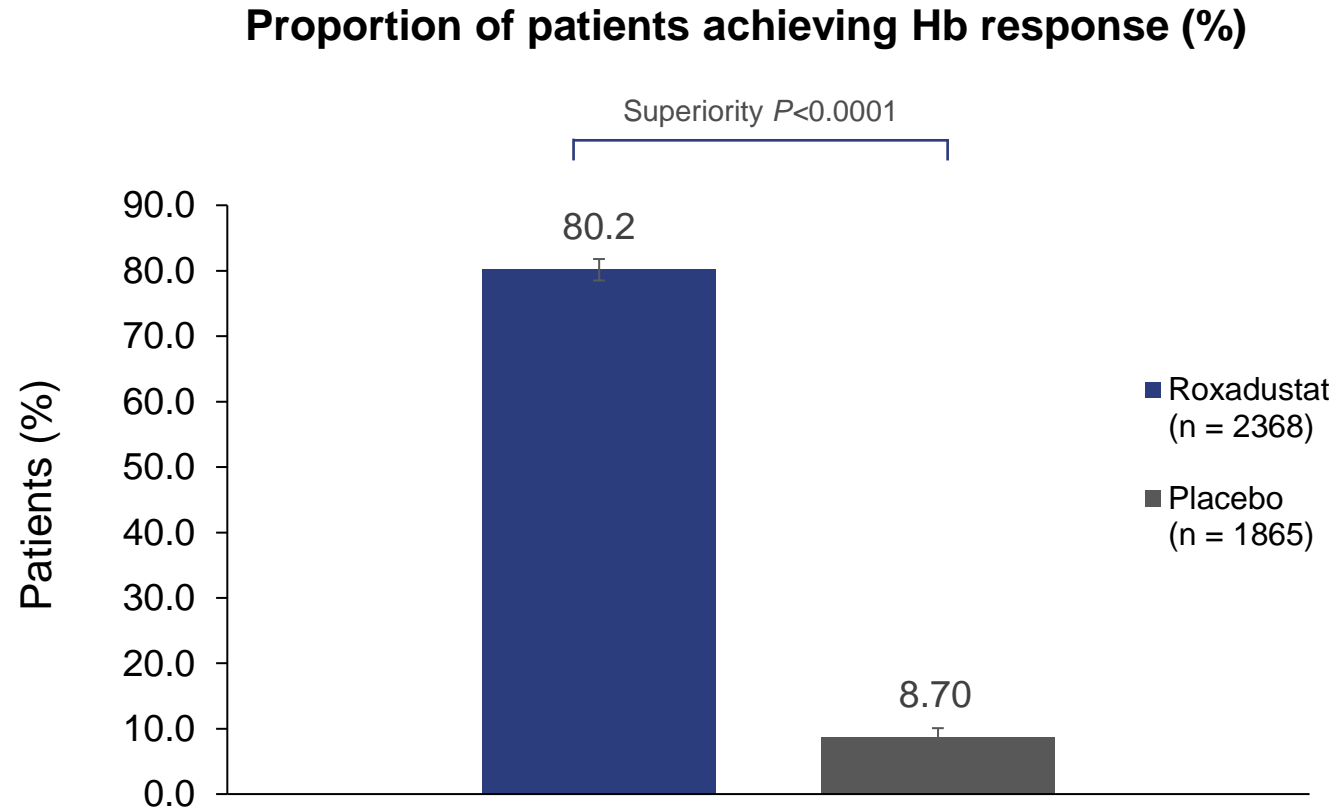


Clinical Potential of Hypoxia Inducible Factors Prolyl Hydroxylase Inhibitors in Treating Nonanemic Diseases

Mengqiu Miao^{1,2,3†}, Mengqiu Wu^{1,2,3†}, Yuting Li^{1,2,3}, Lingge Zhang^{1,2,3}, Qianqian Jin^{1,2,3}, Jiaojiao Fan^{1,2,3,4}, Xinyue Xu^{1,2,3,4}, Ran Gu^{1,2,3}, Haiping Hao^{5*}, Aihua Zhang^{1,2,3*} and Zhanjun Jia^{1,2,3*}

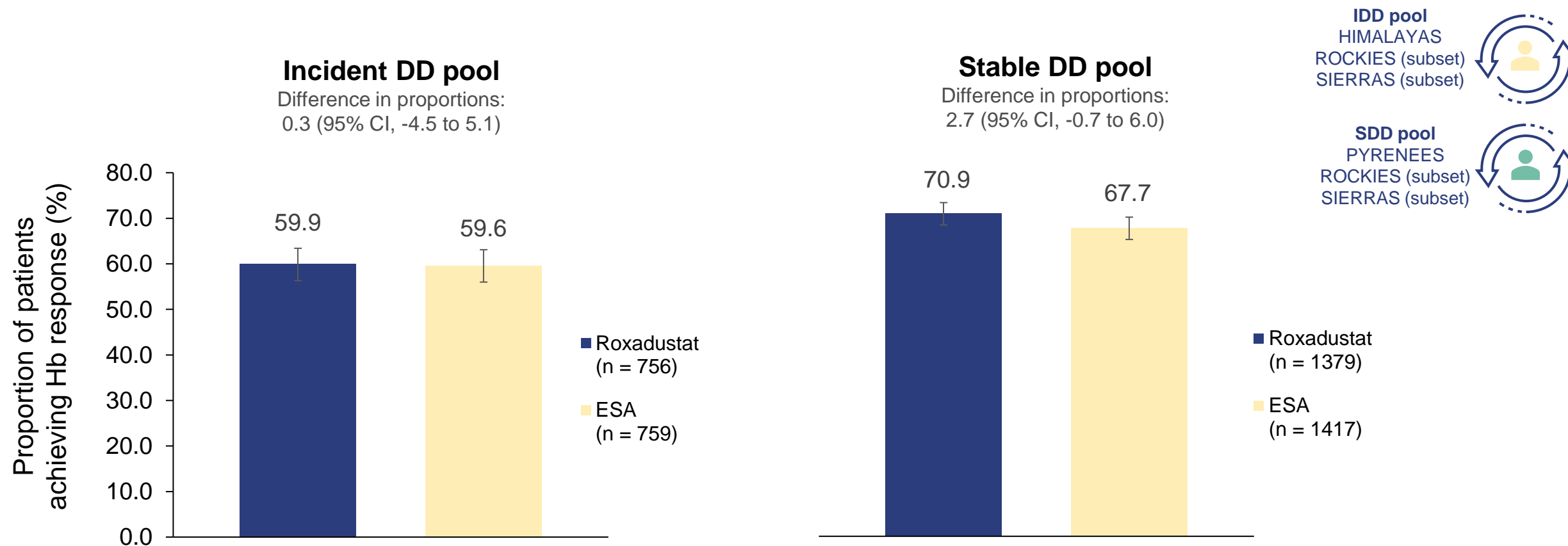
A significantly higher Proportion of patients achieved HB response with roxadustat vs placebo in NDD-CKD

NDD pool
vs placebo
ALPS
ANDES
OLYMPUS



Error bars represent 95% confidence interval.
CKD, chronic kidney disease; Hb, haemoglobin; NDD, non-dialysis dependent.
EVRENZO SmPC August 2021.

Roxadustat was non-inferior to esa in Patients achieving HB response during weeks 28–52* in DD-CKD



Error bars represent 95% CI.

*Hb within the target range of 10.0 to 12.0 g/dL during weeks 28 to 36 without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.

Data in the IDD pool were only analysed for weeks 28 to 52.

CI, confidence interval; CKD, chronic kidney disease; DD, dialysis dependent; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IDD, incident-dialysis dependent; SDD, stable-dialysis dependent.
EVRENZO SmPC. August 2021.