HIF PHI Trials in CKD non-dialysis and dialysis: What do the data really show?

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University College London

Korean Society of Nephrology

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Disclosures: Honoraria and/or consultancy fees from Amgen, AstraZeneca (ongoing), Boehringer Ingelheim, Bayer, GlaxoSmithKline, Janssen, Napp, Mundipharma, Merck Sharp and Dohme, Takeda, and Vifor Fresenius.

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Anaemia Management in CKD

- 1950s Transfusions
- 1990s Erythropoiesis Stimulating Agents (ESAs)[1-4]
- 2000s IV and oral Iron[5-8]
- 2020s HIF stabilizers (Prolyl hydroxylase inhibitors)[9-13]

1. Aranesp® Summary of Product Characteristics 2015. 2 Eprex® Summary of Product Characteristics 2014. 3. NeoRecormon® Summary of Product Characteristics 2015. 4.Mircera® Summary of Product Characteristics 2015. 5. CosmoFer® Summary of Product Characteristics 2014. 6. Venofer® Summary of Product Characteristics 2016. 7. Ferrous gluconate Summary of Product Characteristics 2015. 8. Ferinject® Summary of Product Characteristics 2016 9. EVRENZO SmPC, August 2021. 10. Singh AK, et al. N Engl J Med. 2021. 11. Singh AK, et al. N Engl J Med 2021 12. Chertow GM et al, N Engl J Med 2021; 384:1589-1600. 13. Eckardt K-U, et al. N Engl J Med 2021; 384:1601-1612

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The Nobel Prize in Physiology or Medicine 2019

William G. Kaelin Jr
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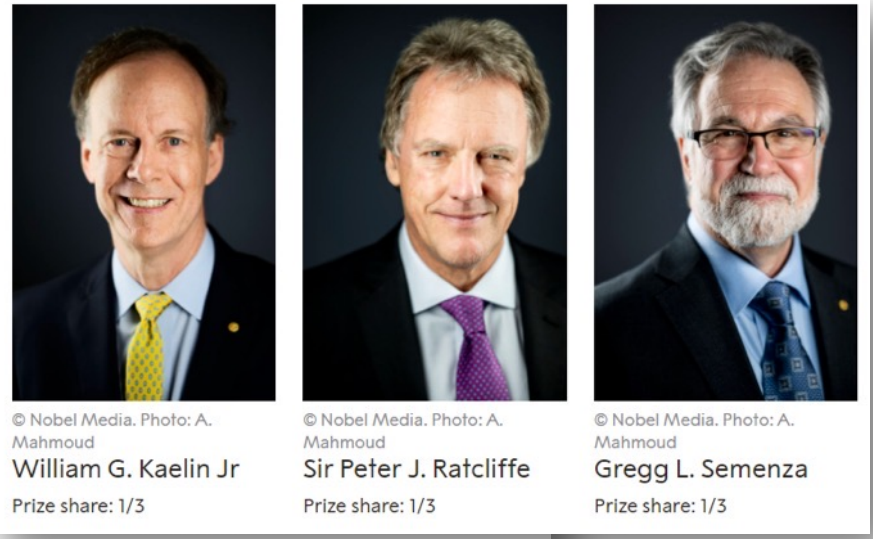
Scientific Background:
How cells sense and adapt to oxygen availability (pdf)

Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

Scientific Background

How cells sense and adapt to oxygen availability



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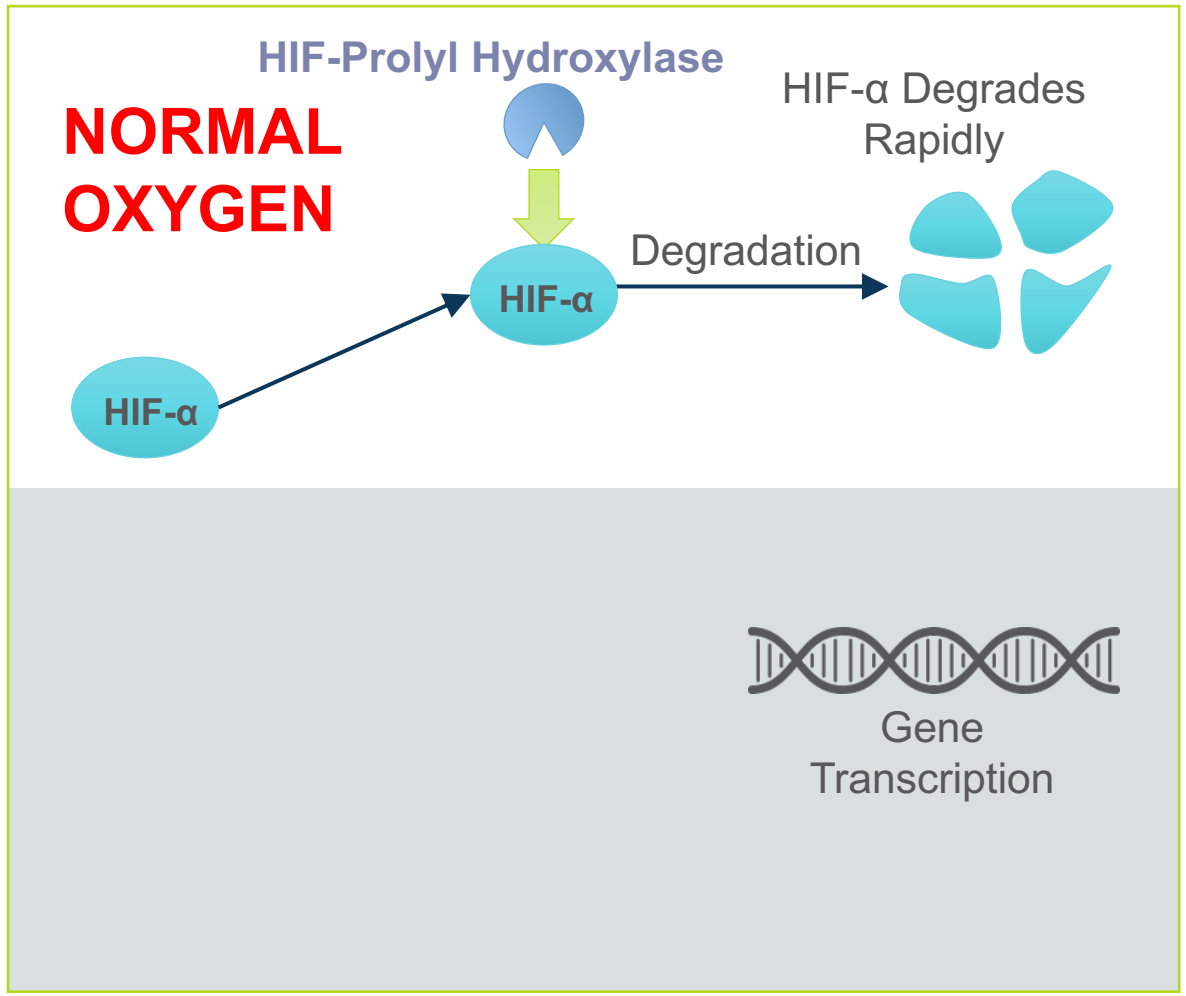
Ref: https://www.nobelprize.org/prizes/medicine/2019/advanced-information/ (accessed April 2022)

Hypoxia mediated gene expression via hypoxia inducible factor (HIF):



Adapted from: Locatelli F et al. Am J Nephrol 2017;45:187-199

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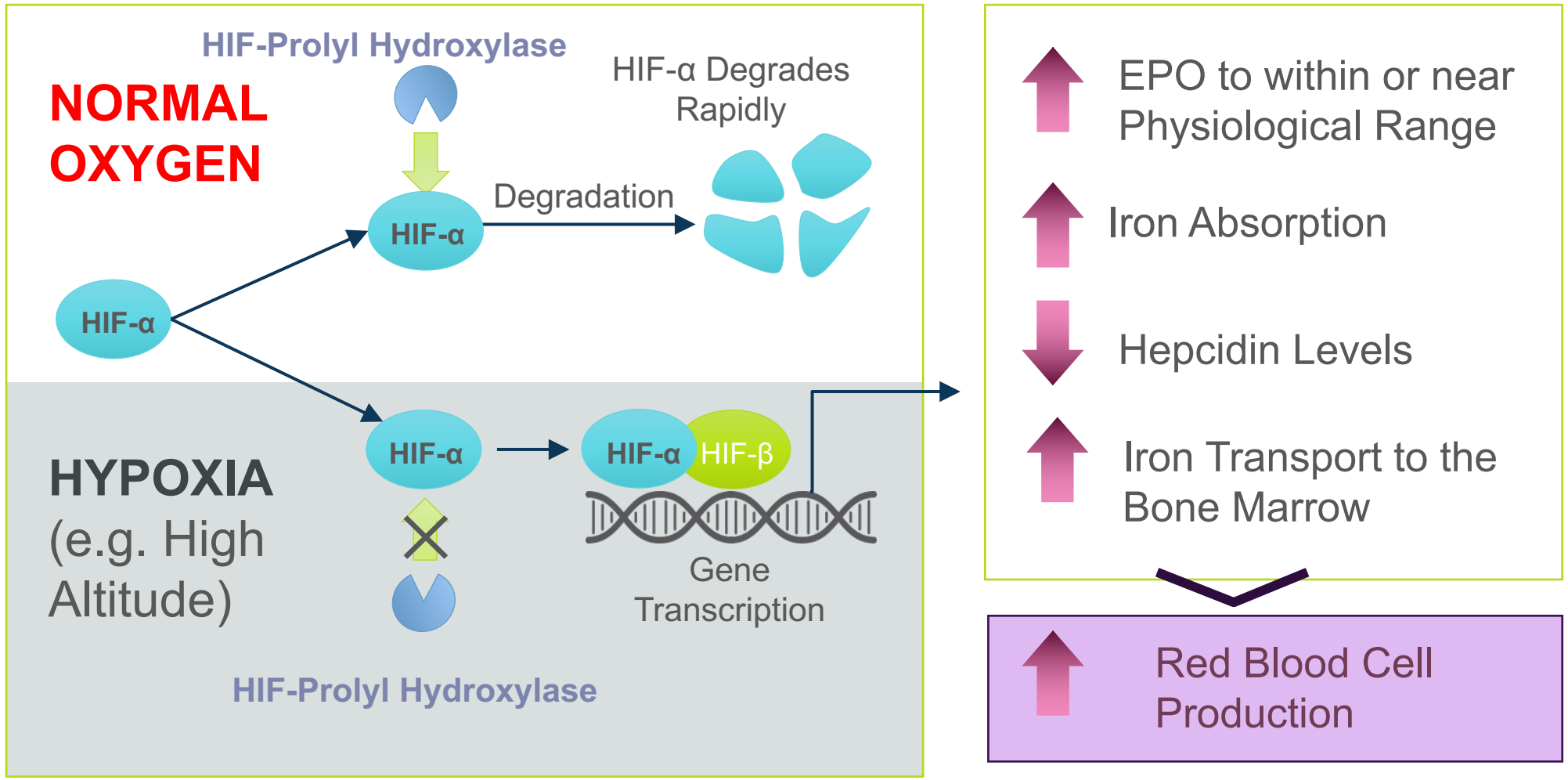
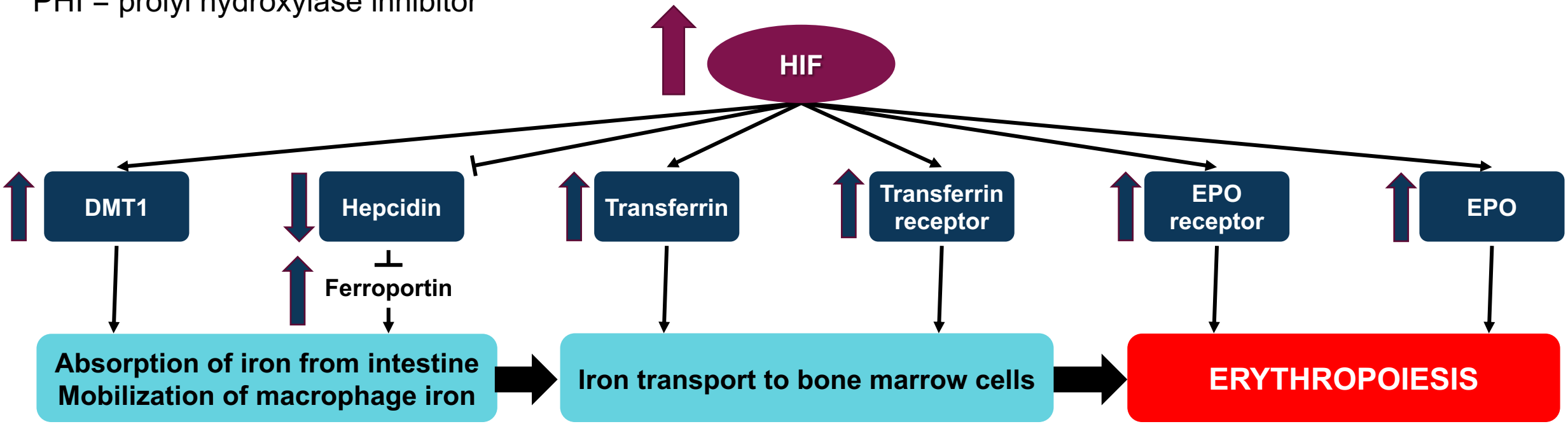


Adapted from: Locatelli F et al. Am J Nephrol 2017;45:187-199

Inhibiting HIF-PHs stimulates endogenous EPO production, reduces hepcidin, and improves iron metabolism, ultimately increasing Hb levels

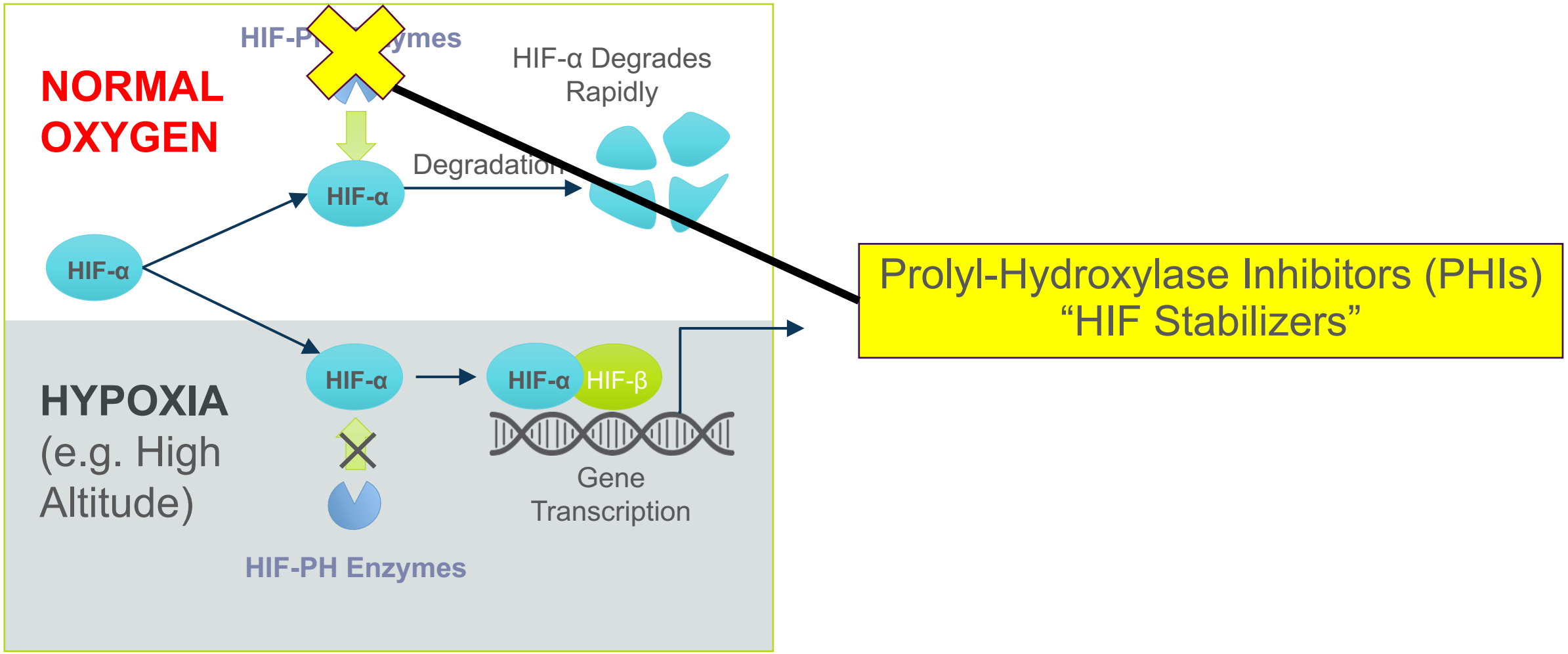
DMT1 = divalent metal transporter 1
HIF = hypoxia-inducible factor;
PHI = prolyl hydroxylase inhibitor



HIF-PHIs activate the HIF pathway and the coordinated response ensures sufficient iron availability for effective erythropoiesis to occur in the presence of physiologic levels of EPO[2]

Adapted from Prabhakar NR, Semenza GL. *Physiol Rev* 2012;92:967–1003;
Besarab A, et al. *J Am Soc Nephrol* 2016;27:1225–1233

Effect of Prolyl-Hydroxylase Inhibitors ("HIF stabilizers") Mimicking Hypoxia:



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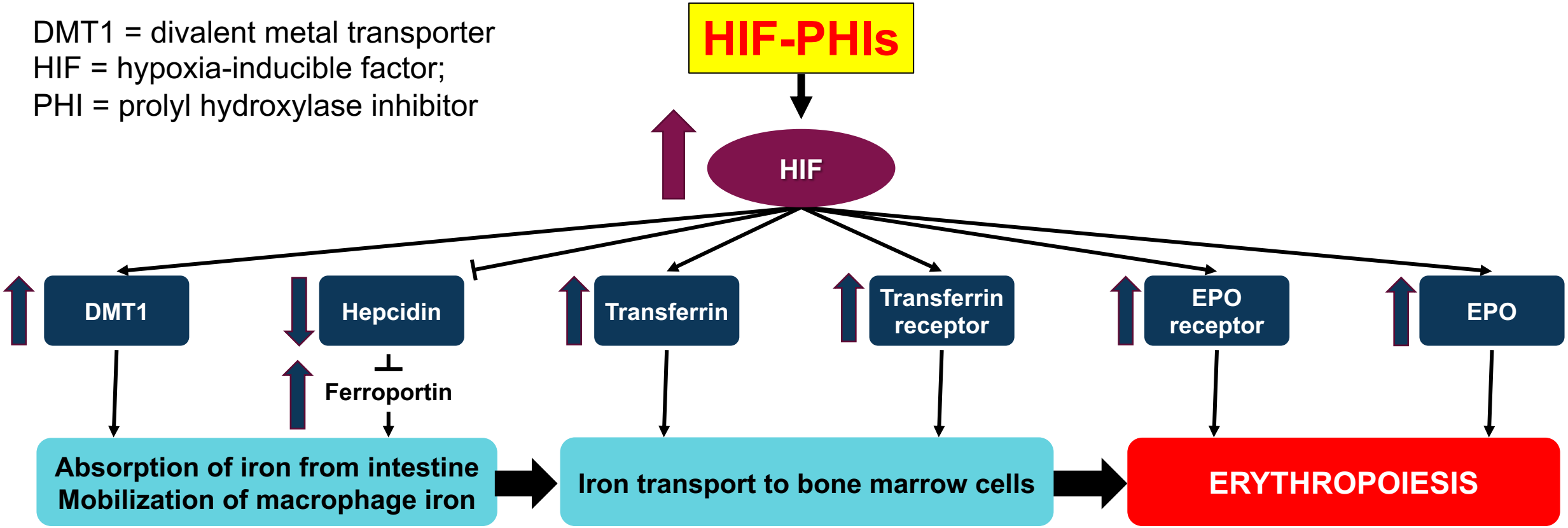

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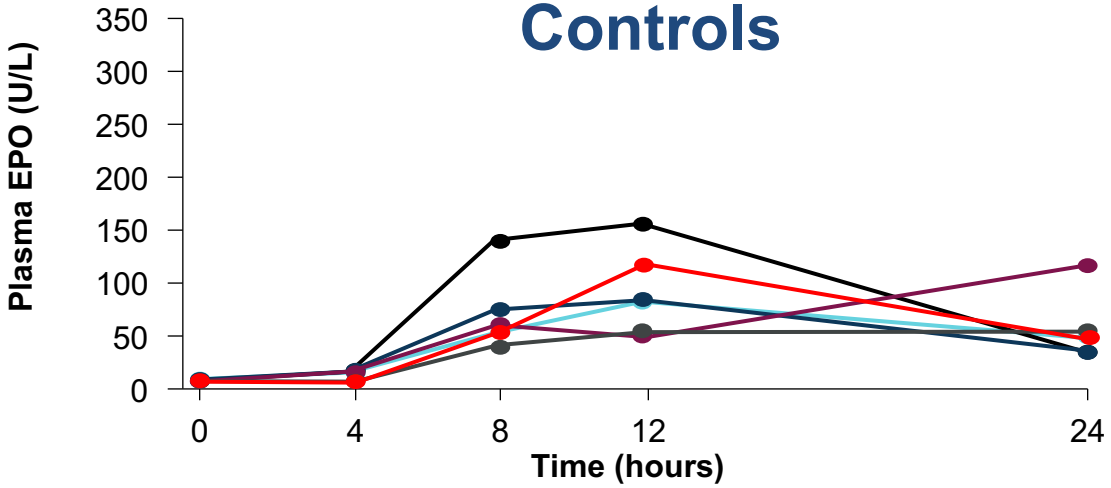
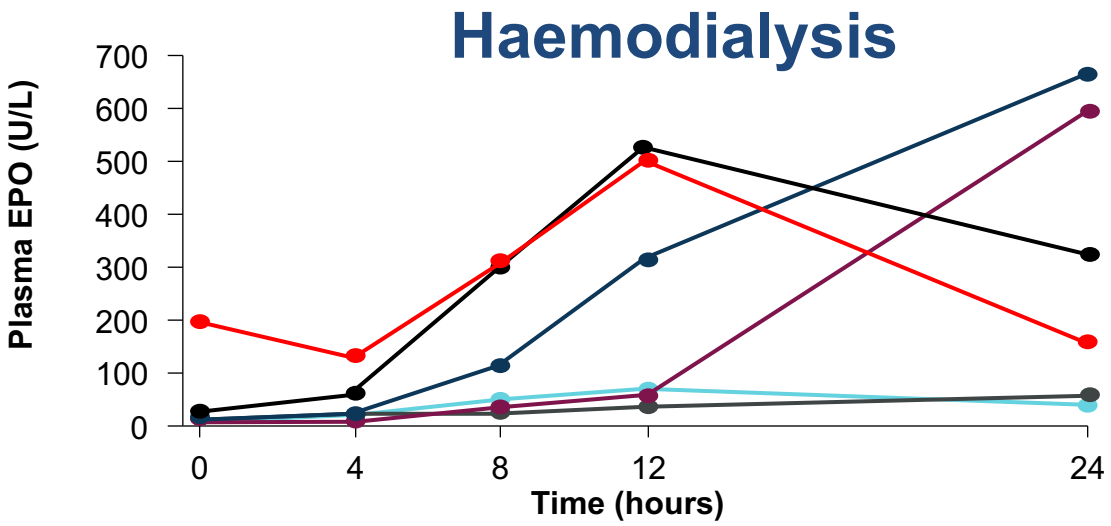
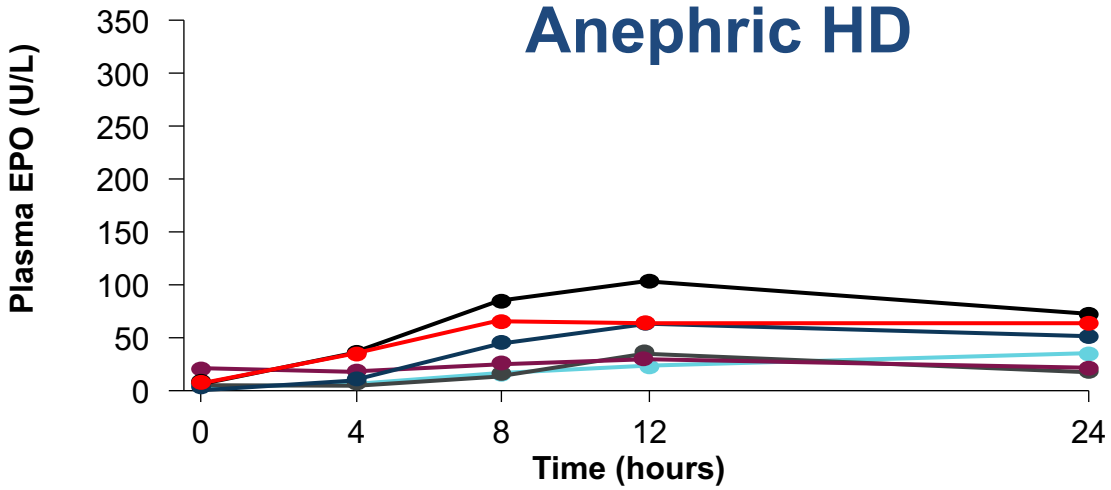
Adapted from Prabhakar NR, Semenza GL. *Physiol Rev* 2012;92:967–1003;
Besarab A, et al. *J Am Soc Nephrol* 2016;27:1225–1233

Increase in plasma EPO after HIF stabilisation

24 hour kinetics of plasma Erythropoietin after a single dose of FG-2216 (individual patient data, n=18)

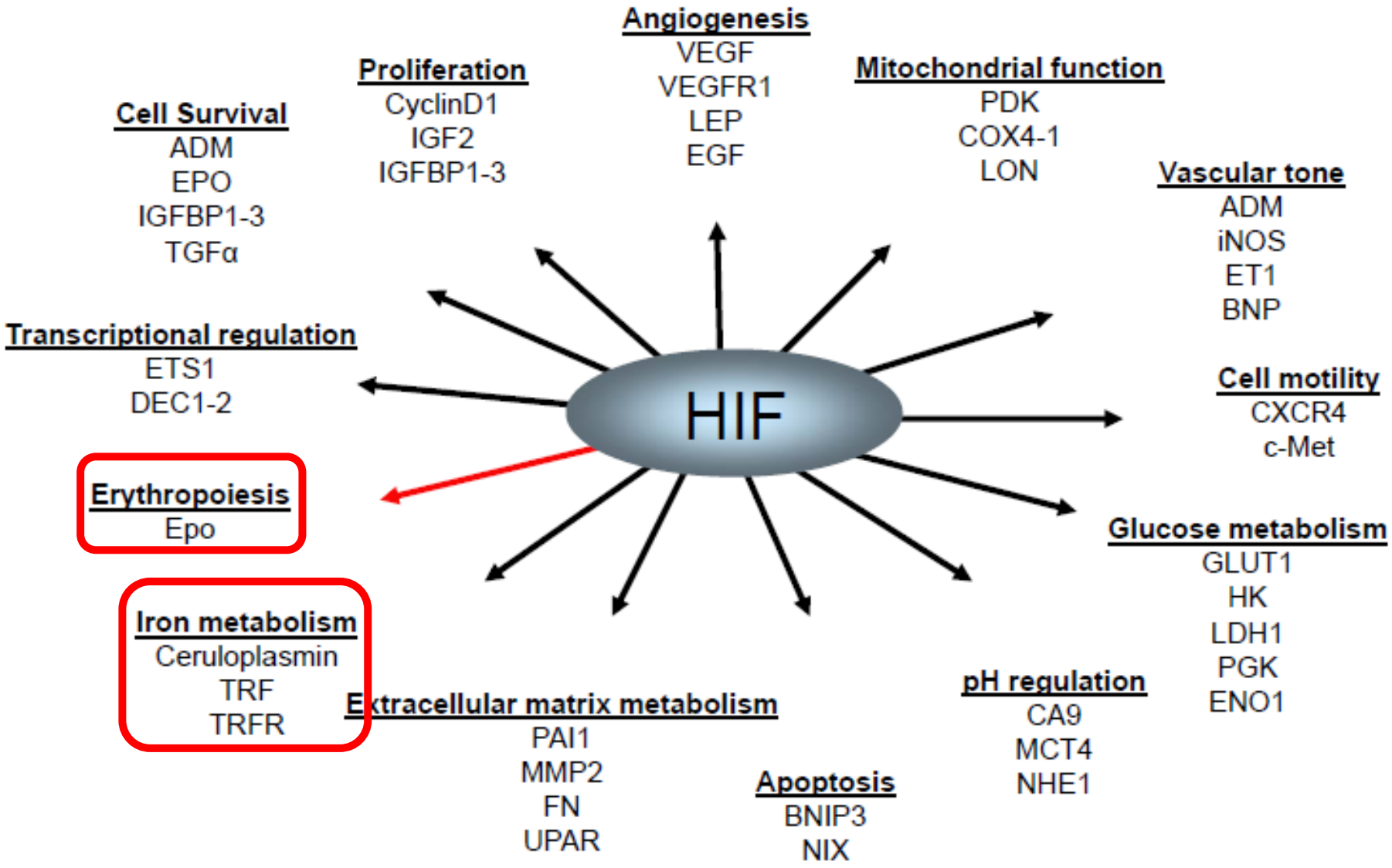






Bernhardt WM, et al. *J Am Soc Nephrol.* 2010;21:2151–6.

HIF target genes



Courtesy Iain Macdougall

Adapted from Schofield & Ratcliffe, *Nat Rev Mol Cell Biol 2004*

Pharmacokinetic properties of HIF-PHIs Daprodustat, Roxadustat, and Vadadustat

Compound	Effective Daily Oral Doses in Phase 2 Trials	Dosing Schedule	Half-Life, h	Plasma EPO, IU/L	Metabolism
Daprodustat (GSK-12278863)	5-25 (also examined 50 and 100 mg)	1×/d	~1-7	24.7[a] and 34.4[b]	CYP2C8 with minor CYP3A4
Roxadustat (FG-4592, ASP1517)	0.7-2.5 mg/kg	3×/wk	12-15	113[c] and 397[d]	CYP2C8
Vadadustat (AKB-6548, MT-6548)	150-600 mg	1×/d (3×/wk)	4.7-9.1	32	NR

Adapted with permission from Sanghani and Haase[11]; original content ©2019 National Kidney Foundation. Abbreviations: CKD, chronic kidney disease; CYP, cytochrome P450; EPO, erythropoietin; HIF, hypoxia-inducible factor; NR not reported/not published.
[a]CKD patients receiving dialysis.
[b]CKD patients not requiring kidney replacement therapy.
[c]For 1 mg/kg dose.
[d]For 2 mg/kg dose.

Wish JB et al.
NKF Scientific Workshop Report on HIF.
Am J Kidney Dis 2021 Nov; 78: 709-718.

HIF stabilisers: Development Programmes

	Roxadustat[1]	Vadadustat[2-3]	Daprodustat[4-5]	Enarodustat[6]	Molidustat[7]	Desidustat[8]
Manufacturer	FibroGen/ AstraZeneca Astellas	Akebia	GlaxoSmithKline	Japan Tobacco	Bayer	Zydus
Area	Global	Global	Global	Japan only	Japan only	Australia, India, China only
Status	Launched Japan/China, Approved EU & launched	Launched Japan, Global Phase 3 published	Launched Japan, Global Phase 3 published	Approved in Japan Phase 3 published	Approved Japan, Phase 3 published	Approved in India Phase 3 published
Half-life	12–13 hours	4.5 hours	4 hours	9 hours[9]	5-10 hours[10]	7-13 hours[11]
Anticipated dosing	Oral; 3x week	Oral; once daily	Oral; once daily	Oral; once daily	Oral; once daily	Oral; 3x week
CVOT data	Yes	Yes	Yes	?	?	?

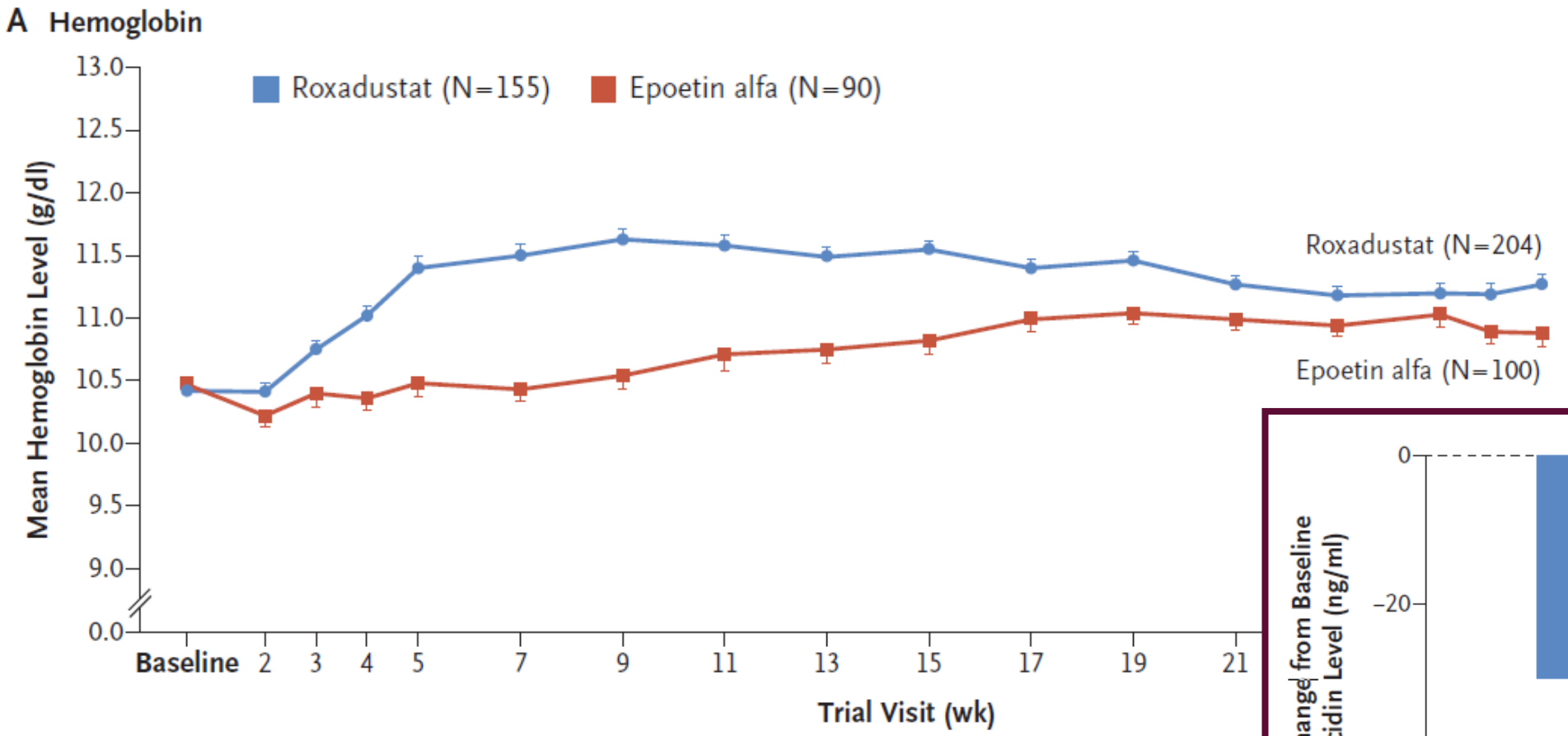
CVOT, Cardiovascular Outcome Trial

1. EVRENZO SmPC, August 2021 2. Chertow GM et al, N Engl J Med 2021; 384:1589-1600. 3. Eckardt K-U, et al. N Engl J Med 2021; 384:1601-1612. 4. Singh AK, et al. N Engl J Med. 2021. 5. Singh AK, et al. N Engl J Med 2021 6. Markham, A. Enarodustat: First Approval. Drugs 81, 169–174 (2021). 7. Akizawa T, Macdougall IC, Berns JS, et al. Am J Nephrol 2019;49:271–280. 8.Agrawal D, et al. Am J Nephrol 2022, doi: 10.1159/000523961. 9. Pai SM, et al. Clin Pharmacol Drug Dev. 020 Aug;9(6):728-741. 10. Böttcher M, et al. Br J Clin Pharmacol. 2018 Jul;84(7):1557-1565.

Phase 3 studies of HIF-PHIs

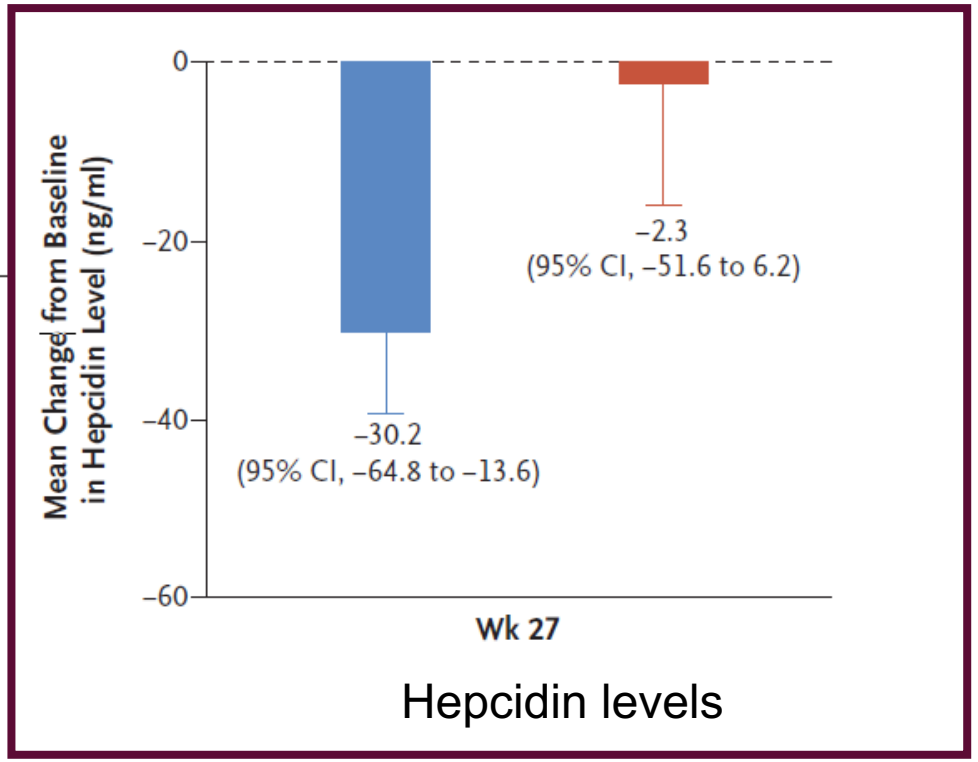
Populations: Non-dialysis CKD, Incident dialysis, Stable dialysis.
Intervention: HIF-PHI
Comparator: No treatment or standard ESA
Outcomes: Haemoglobin target and MACE

Roxadustat phase 3 study



Roxadusatat vs EPO:

- Higher transferrins
- Better maintained serum iron and TSAT
- Lower cholesterol

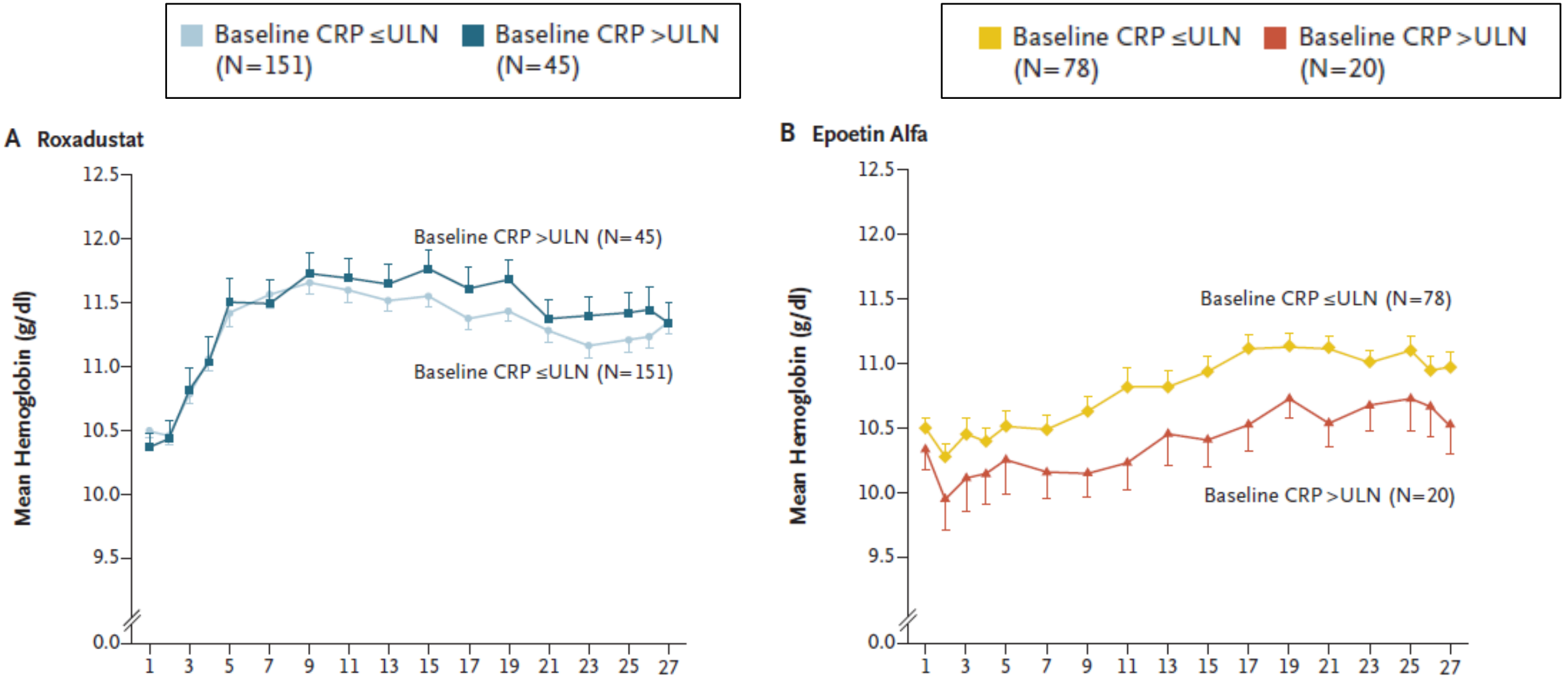


Hepcidin levels

305 dialysis patients on ESAs (China)
Roxadustat vs Epoetin alpha (2:1)
26 weeks. IV iron “rescue”.
Primary endpoint = Hb from baseline to average 23-27 weeks

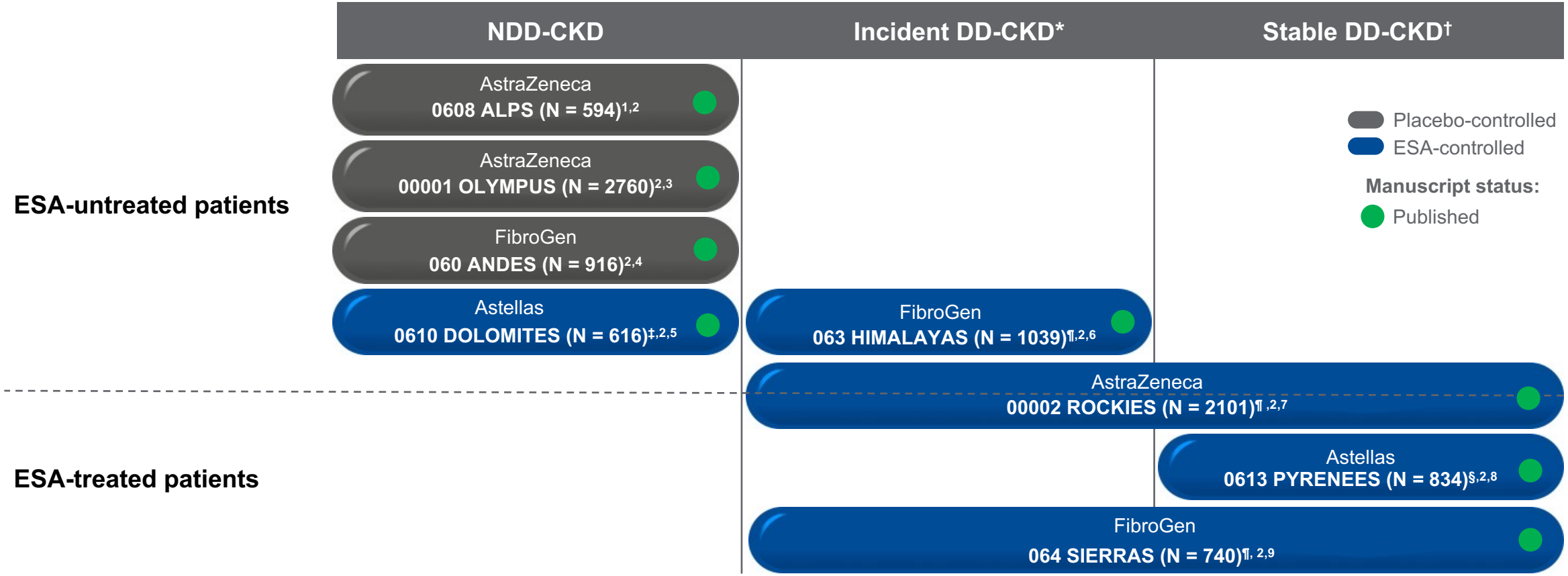
Chen N et al, NEJM 2019;381(11):1011-1022.

Roxadustat phase 3 study



Chen N et al, NEJM 2019;381(11):1011-1022.

Roxadustat clinical trial overview including 9600 patients

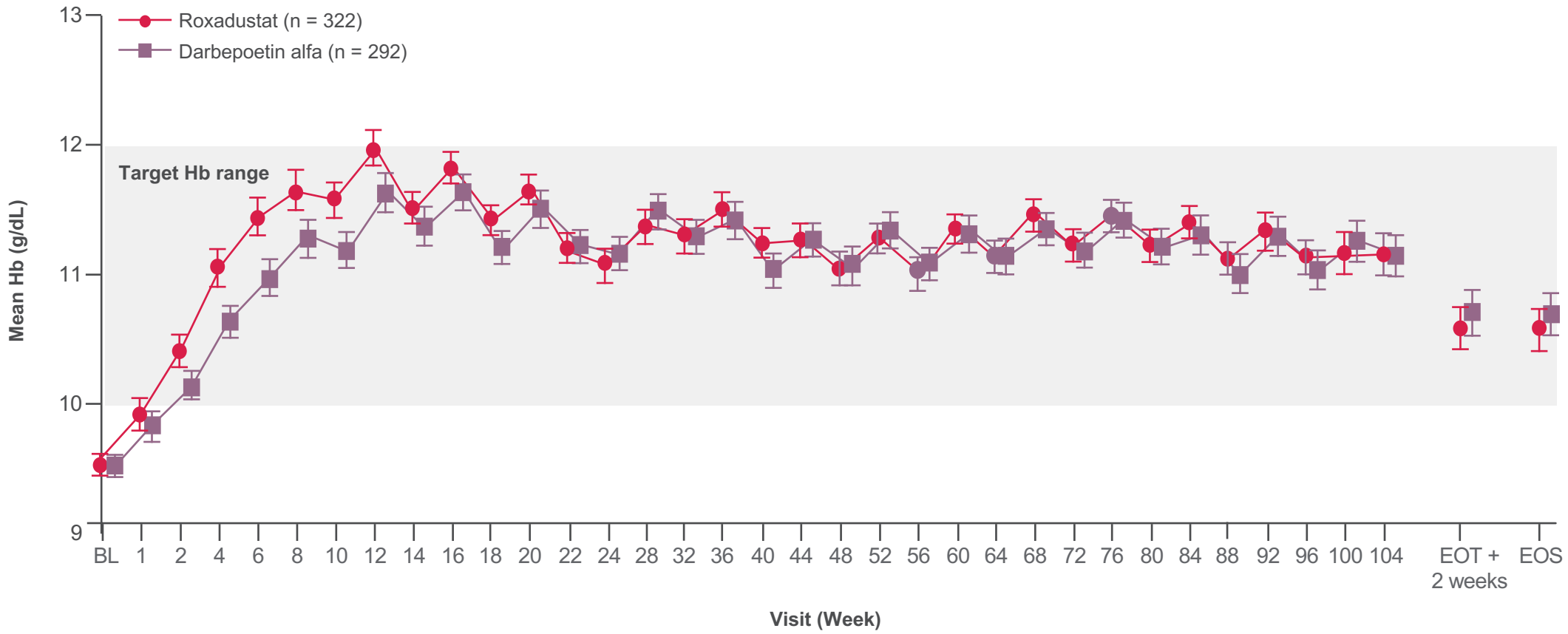


The NDD studies are pooled, as are the DD studies.
*Subset of patients with ≥ 2 weeks and ≤ 4 months of dialysis at the time of randomisation; †Subset of patients with > 4 months of dialysis at the time of randomisation; ‡Darbepoetin alfa active comparator; ¶Epoetin alfa active comparator;
§Darbepoetin alfa and epoetin alfa active comparator.
CKD, chronic kidney disease; DD, dialysis-dependent; ESA, erythropoiesis-stimulating agent; NDD, non-dialysis-dependent; SmPC, Summary of Product Characteristics.
1. Shutov E, et al. Nephrol Dial Transplant. 2021;36:1629–39; 2. EVRENZO SmPC, August 2021; 3. Fishbane S, et al. J Am Soc Nephrol. 2021;32(3):737–55; 4. Coyne DW, et al. Kidney Int Rep. 2020;6(3):624–35; 5. Barratt J, et al. Nephrol Dial Transplant. 2021;36(9):1616–28; 6. Provenzano R, et al. Nephrol Dial Transplant. 2021;36(9):1717–30; 7. Barratt J, et al. Adv Ther. 2021;38:5345–60; 8. Csiky B, et al. Adv Ther. 2021;38:5361–80; 9. Charytan C, et al. Kidney Int Rep. 2021;6(7):1829–39.

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

NDD vs active comparator
DOLOMITES

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



BL, baseline; CI, confidence interval; DA, darbepoetin alfa; EOS, end of study; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; NDD, non-dialysis-dependent.

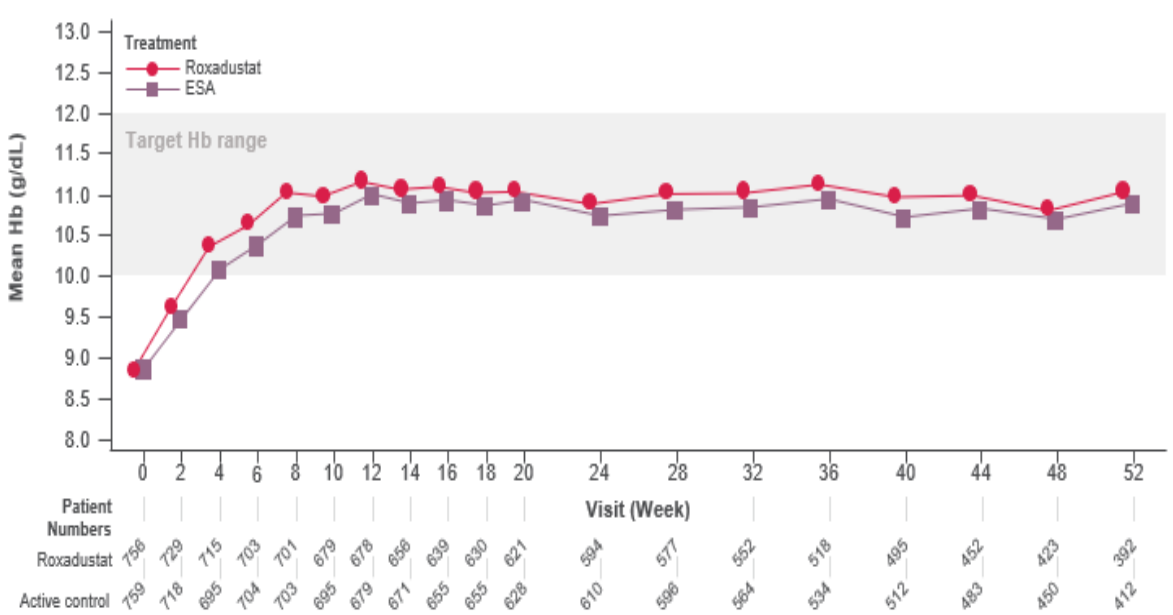
Barratt J, et al. Nephrol Dial Transplant. 2021;36(9):1616–28.

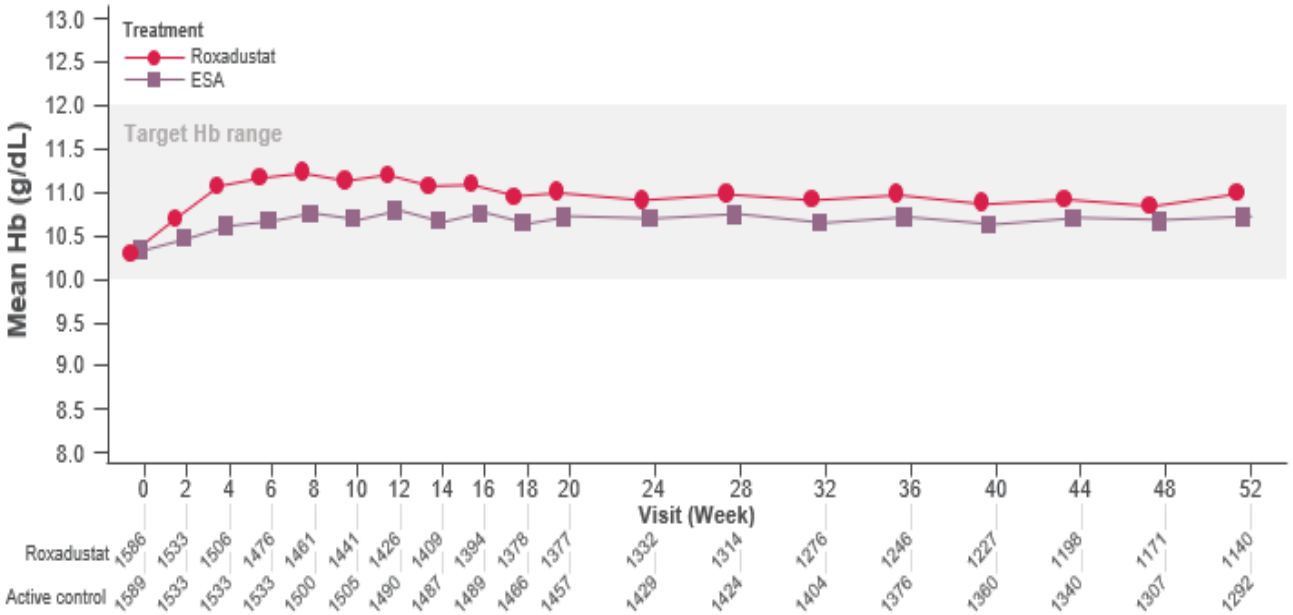
Roxadustat was effective at achieving and maintaining target Hb levels comparable with ESA in patients on dialysis

Mean (SE) Hb over 52 weeks (FAS)

IDD pool*
HIMALAYAS,
ROCKIES,
SIERRAS

SDD pool†
ROCKIES,
PYRENEES,
SIERRAS





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

Incident dialysis was defined as ≥2 weeks and ≤4 months, and stable dialysis as >4 months.
*Subset of patients from ROCKIES and SIERRAS with ≤ 4 months of dialysis at the time of randomisation; †Subset of patients from ROCKIES and SIERRAS with > 4 months of dialysis at the time of randomisation.
CKD, chronic kidney disease; DD, dialysis-dependent; ESA, erythropoiesis-stimulating agent; FAS, full analysis set; Hb, haemoglobin; IDD, incident dialysis-dependent; SDD, stable dialysis-dependent; SE, standard error.
EVRENZO SmPC, August 2021.

Global Phase 3 PRO$_2$TECT Program

Studies of Vadadustat for Treatment of Anemia due to Chronic Kidney Disease (CKD) in Adult Patients Not on Dialysis

PRO$_2$TECT Consists of Two Randomized, Open-Label, Active-Controlled, Non-Inferiority Phase 3 Cardiovascular Outcomes Studies

PRO$_2$TECT CORRECTION

Not ESA Treated
N=1,751

Vadadustat vs
Darbepoetin Alfa

N =3, 476

PRO$_2$TECT CONVERSION

ESA Treated
N=1,725

Vadadustat vs
Darbepoetin Alfa

PRIMARY EFFICACY ENDPOINTS:

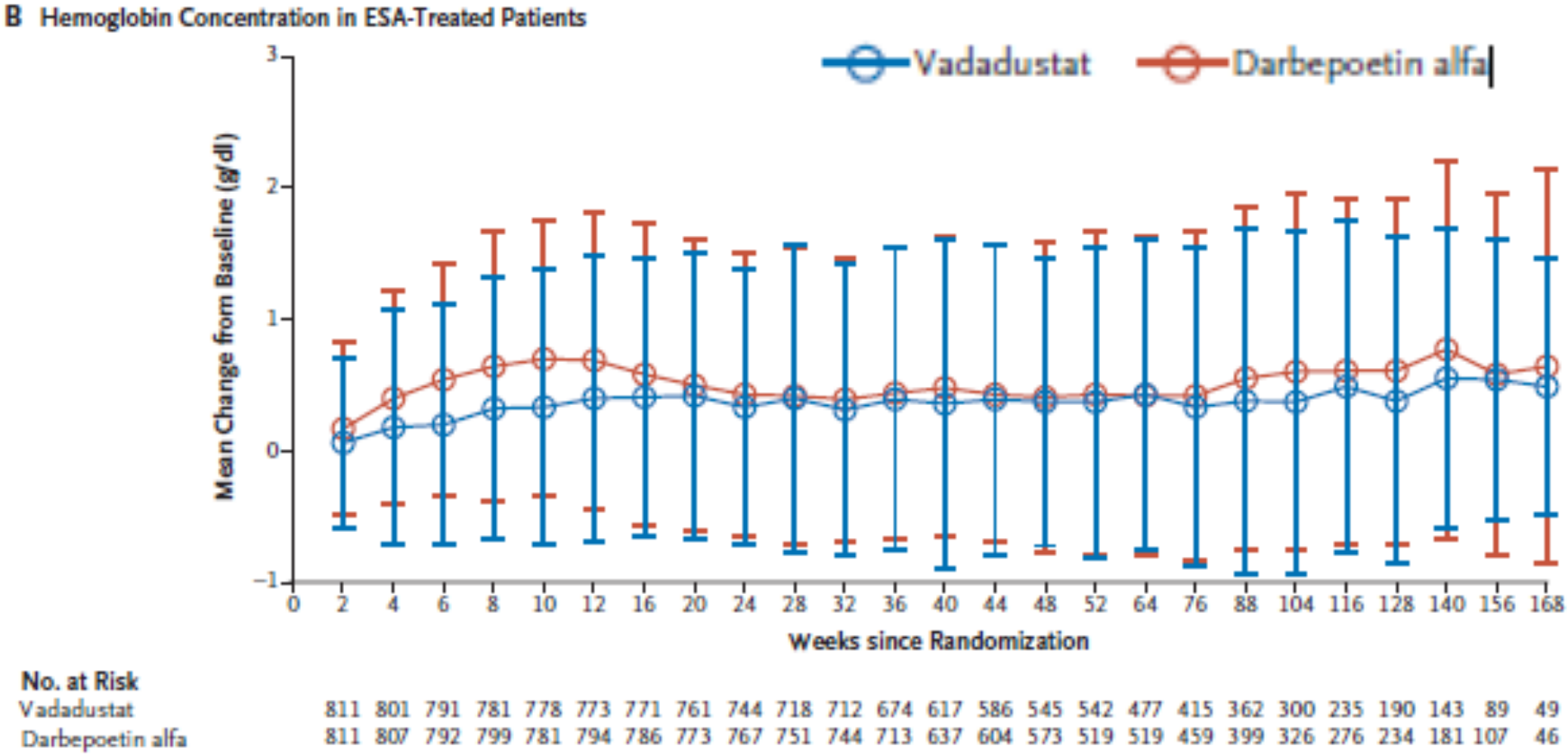
- Mean change in hemoglobin (Hb) between baseline and the primary evaluation period (weeks 24 to 36)
- Non-inferiority margin of -0.75 g/dL

PRIMARY SAFETY ENDPOINT:

- Time to first occurrence of major adverse cardiovascular events (MACE) which is the composite of all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke
- Non-inferiority margin for hazard ratio 1.25

Darbepoetin alfa is an erythropoiesis-stimulating agent (ESA).
Non-inferiority margins referenced are regulatory agency-approved non-inferiority margins.

Effect of Vadadustat in patients with anaemia and CKD (NDD)



Chertow et al. N Engl J Med 2021;384:1589-600.

Global Phase 3 INNO$_2$VATE Program

Studies of Vadadustat for Treatment of Anemia due to Chronic Kidney Disease (CKD) in Adult Patients on Dialysis

INNO$_2$VATE Consists of Two Randomized, Open-Label, Active-Controlled, Non-Inferiority Phase 3 Cardiovascular Outcomes Studies

INNO$_2$VATE
CORRECTION
CONVERSION

Incident Dialysis

N = 369

Vadadustat vs
Darbepoetin Alfa

N= 3,923

INNO$_2$VATE
CONVERSION

ESA Treated

N = 3,554

Vadadustat vs
Darbepoetin Alfa

PRIMARY EFFICACY ENDPOINTS:

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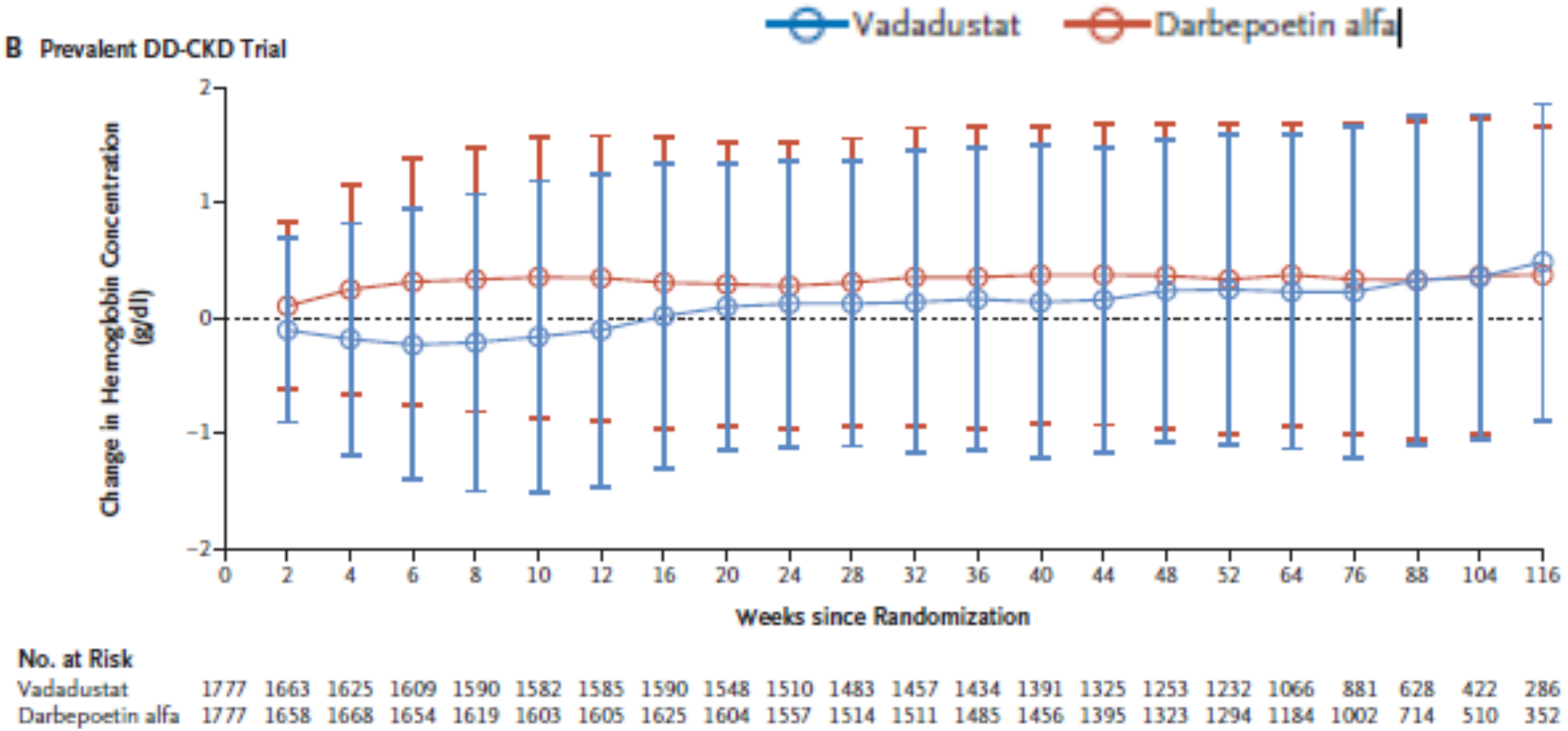
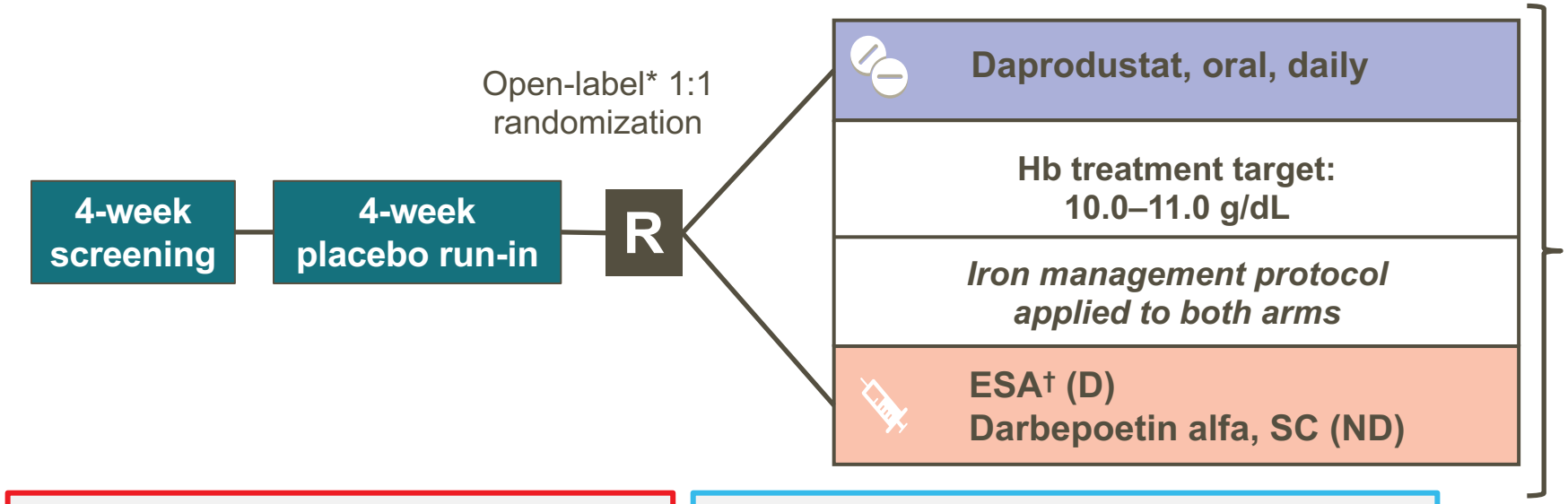


Eckardt K-U et al. N Engl J Med 2021;384:1601-12.

ASCEND-D and -ND: Trial Design

Event-driven, open-label, randomized, active-controlled, parallel-group, multicenter, Phase 3 trials

ASCEND-D and ASCEND-ND accepted for publication



Co-primary Endpoints

Mean change in Hb from baseline to the average during the primary evaluation period (Week 28 through Week 52)

Time to first MACE‡ (target 664 adjudicated first events)

ASCEND-D: Key Entry Criteria

- ≥18 years of age
- Randomization Hb criteria:
  - Hb 8.0–11.5 g/dL
- ESA users
- Dialysis (HD/PD) >90 days prior to screening
- Iron replete: Ferritin >100 ng/mL; TSAT >20%

ASCEND-ND: Key Entry Criteria

- ≥18 years of age
- CKD Stage 3–5
- Randomization Hb criteria:
  - Hb 8.0–10.0 g/dL, if not using ESAs
  - Hb 8.0–11.0 g/dL, if using ESAs
- Not on dialysis and no plans to start within 90 days
- Iron replete: Ferritin >100 ng/mL; TSAT >20%

*The sponsor, steering committee and endpoint adjudication committee remained blind to aggregate treatment assignment throughout the trial.

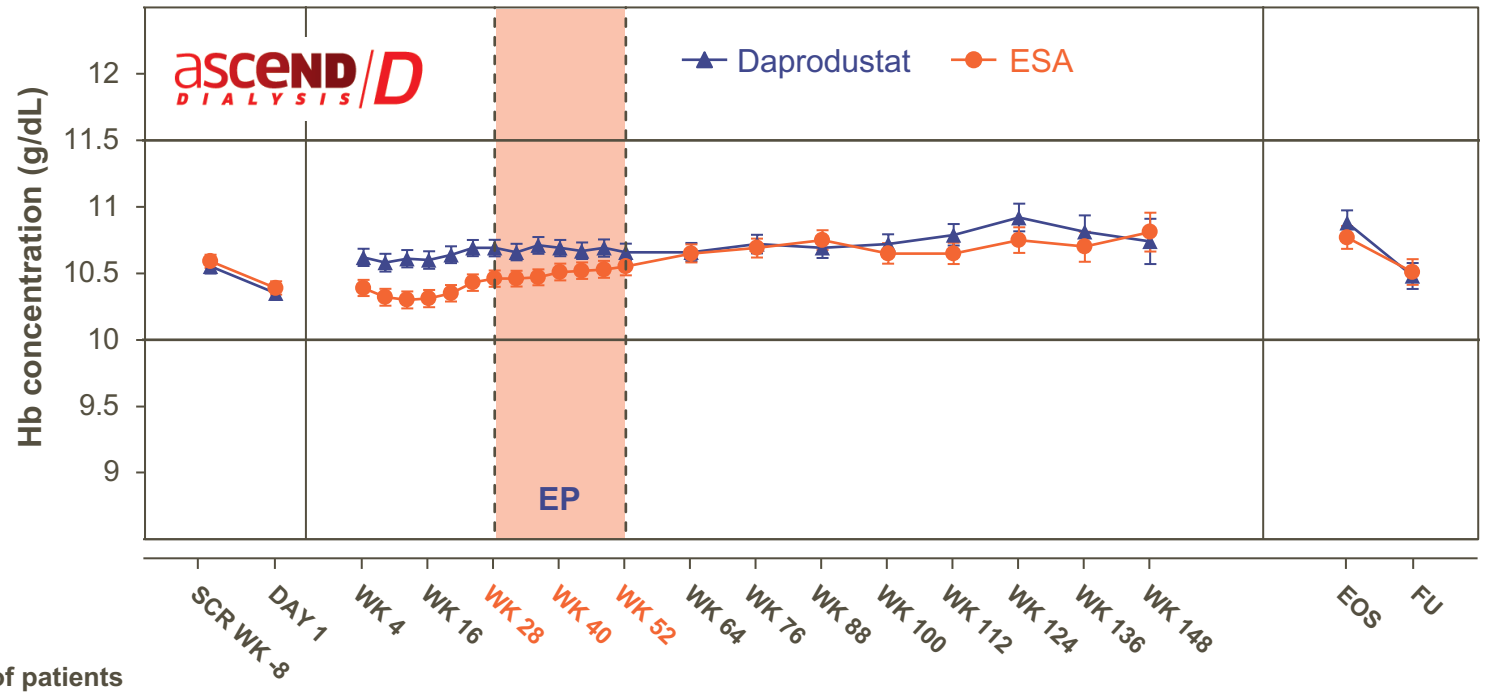
†Epoetin alfa (IV; HD patients) or darbepoetin alfa (SC; PD patients). ‡MACE: composite of all-cause mortality, a non-fatal myocardial infarction, or a non-fatal stroke.

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HD, hemodialysis; IV, intravenous; MACE, major adverse cardiovascular event; PD, peritoneal dialysis; R, randomization; SC, subcutaneous; TSAT, transferrin saturation.

Co-primary Efficacy Endpoint: ASCEND-D

Mean Hb change from baseline to the evaluation period (Weeks 28–52) – ITT Population

Daprodustat was noninferior to ESA for mean change in Hb from baseline to the evaluation period (Weeks 28–52)



No. of patients	SCR WK -8	DAY 1	WK 4	WK 16	WK 28	WK 40	WK 52	WK 64	WK 76	WK 88	WK 100	WK 112	WK 124	WK 136	WK 148	EOS	FU
Daprodustat	1487	1485	1453	1403	1336	1274	1241	1191	1138	1092	1039	863	612	432	248	862	639
ESA	1477	1475	1449	1381	1323	1270	1225	1175	1125	1059	998	838	601	419	230	839	628

Prespecified NI margin:
-0.75 g/dL

Adjusted Mean Treatment Difference (95% CI)*
0.18 (0.12, 0.24)

Noninferiority was achieved because the lower limit of the 95% CI of the treatment difference was greater than the prespecified noninferiority margin of **−0.75 g/dL**

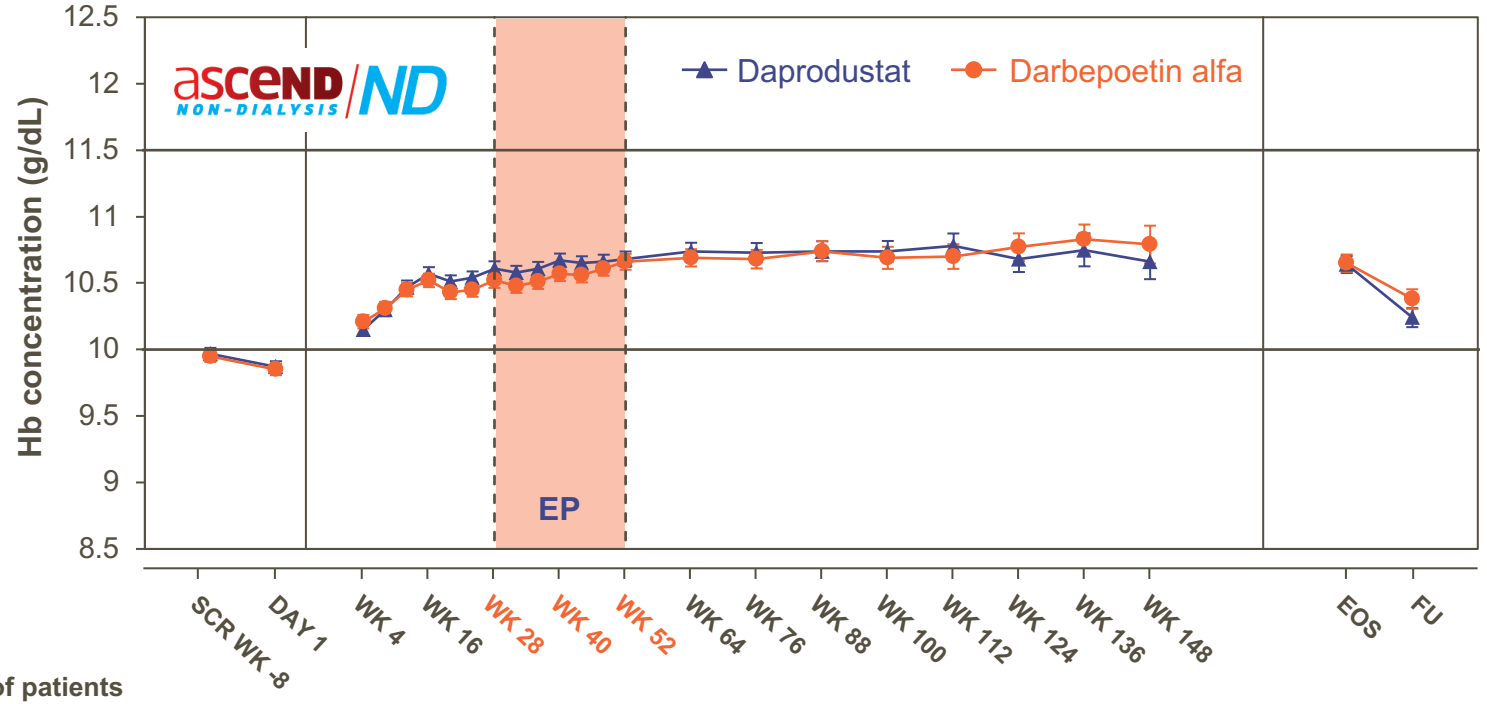
*Based on an ANCOVA model using observed and imputed data with terms for treatment, baseline hemoglobin, dialysis type and region. Error bars indicate 95% CI. Post-randomization values include on- and off-treatment values. Visits on or before Day 1 include only pre-treatment values. Horizontal reference lines represent the Hb analysis range (10–11.5g/dL). The Hb target range for dose changes is 10–11g/dL. Vertical dotted lines represent the EP.

CI, confidence interval; EP, evaluation period; EOS, end of study; ESA, erythropoiesis-stimulating agent; FU, follow up; Hb, hemoglobin; ITT, intent-to-treat; NI noninferiority; SCR screening; Wk, week.

Co-primary Efficacy Endpoint: ASCEND-ND

Mean Hb change from baseline to the evaluation period (Weeks 28–52) – ITT Population

Daprodustat was noninferior to darbepoetin alfa for mean change in Hb from baseline to the evaluation period (Weeks 28–52)



No. of patients	SCR	WK -8	DAY 1	WK 4	WK 16	WK 28	WK 40	WK 52	WK 64	WK 76	WK 88	WK 100	WK 112	WK 124	WK 136	WK 148	EOS	FU
Daprodustat	1936	1932	1866	1705	1511	1364	1254	1100	961	832	725	587	453	349	243		1276	1056
Darbepoetin alfa	1935	1933	1867	1697	1506	1398	1243	1100	952	835	727	602	482	378	272		1278	1043

Prespecified NI margin:
-0.75 g/dL

Adjusted Mean Treatment Difference (95% CI)*
0.08 (0.03, 0.13)

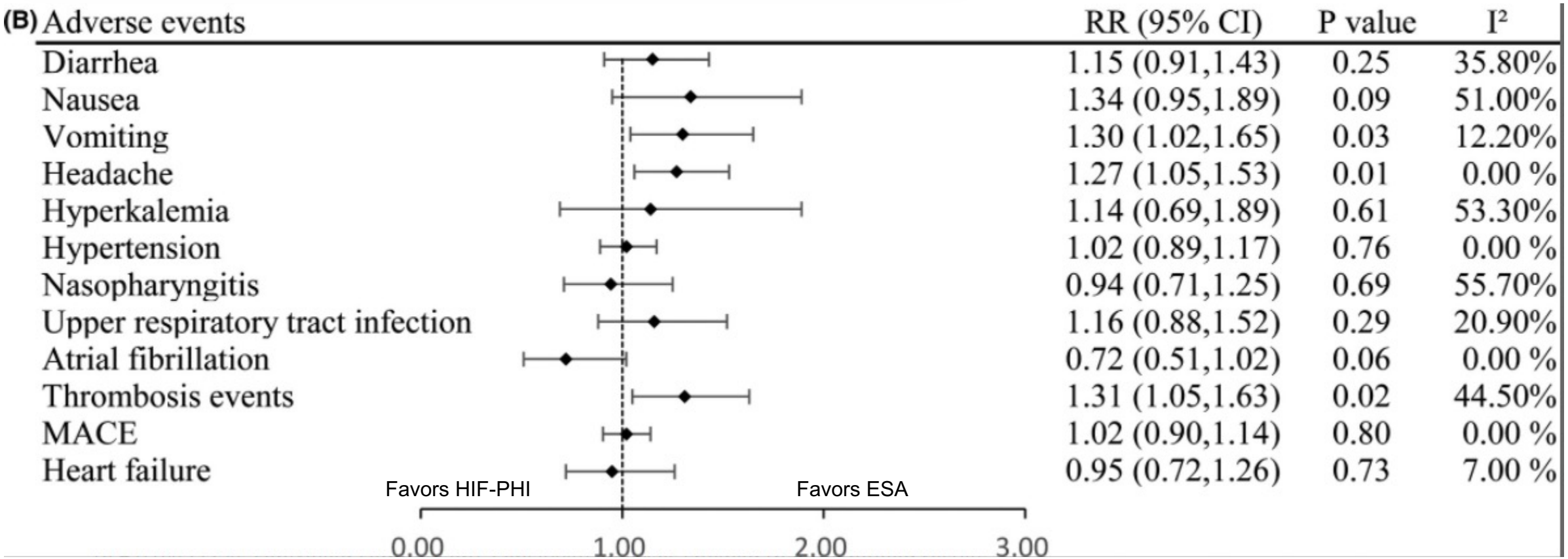
Noninferiority was achieved because the lower limit of the 95% CI of the treatment difference was greater than the prespecified noninferiority margin of **−0.75 g/dL**

*Based on an ANCOVA model using observed and imputed data with terms for treatment, baseline hemoglobin, current ESA use and region. Error bars indicate 95% CI. Post-randomization values include on- and off-treatment values. Visits on or before Day 1 include only pre-treatment values. Horizontal reference lines represent the Hb analysis range (10–11.5g/dL). The Hb target range for dose changes is 10–11g/dL. Vertical dotted lines represent the EP.

CI, confidence interval; EP, evaluation period; EOS, end of study; ESA, erythropoiesis-stimulating agent; FU, follow up; Hb, hemoglobin; ITT, intent-to-treat; NI noninferiority; SCR screening; Wk, week.

Long-term efficacy and safety of hypoxia-inducible factor prolyl hydroxylase inhibitors in anaemia of chronic kidney disease: A meta-analysis including 13,146 patients

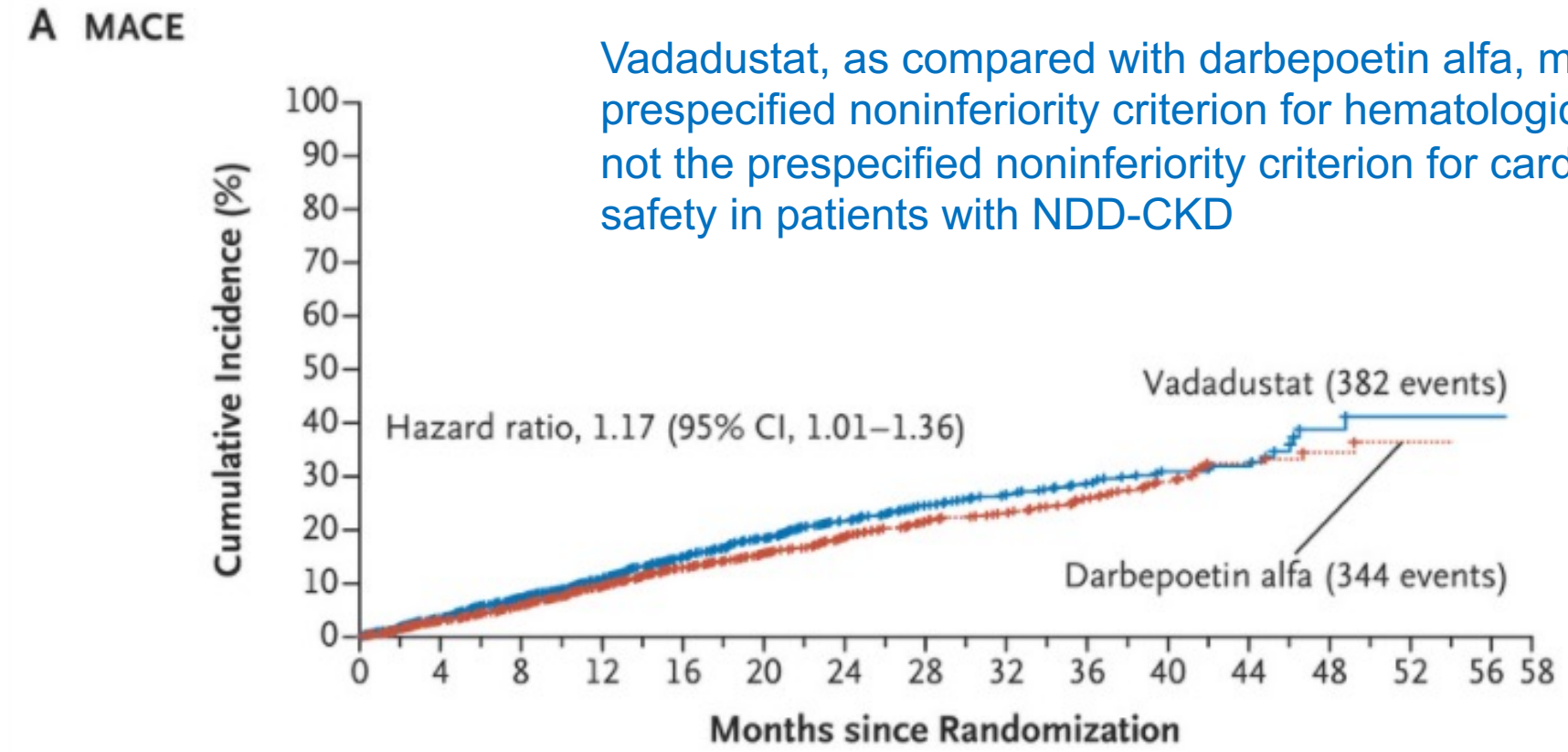
Huanhuan Chen [1,2], Qingfeng Cheng [3], Jiuxiang Wang [1], Xiaofang Zhao [1], Shenyin Zhu [1]



J Clin Pharm Ther. 2021;46:999–1009.

VADADUSTAT AND MACE IN GLOBAL PHASE 3 STUDIES: NDD

Vadadustat, as compared with darbepoetin alfa, met the prespecified noninferiority criterion for hematologic efficacy but not the prespecified noninferiority criterion for cardiovascular safety in patients with NDD-CKD



No. at Risk

Vadadustat	1739	1668	1587	1301	1108	931	759	588	459	311	185	97	30	4	1 0
Darbepoetin alfa	1732	1674	1618	1329	1129	961	774	621	505	346	213	103	43	6	0

N Engl J Med 2021; 384:1589-1600

MACE OUTCOME SUMMARY

	Population	Primary analysis HR (95% CI)
Daprodustat[1]	NDD	1.03 (0.89, 1,19) OS
Daprodustat[2]	DD	0.93 (0.81, 1.07) OS
Vadadustat[3]	NDD	1.17 (1.01, 1.36) OS
Vadadustat[4]	DD	0.96 (0.83, 1.11) OS
Roxadustat[6]	NDD	0.81 (0.52, 1.25) OT+28
Roxadustat[7]	DD	1.09 (0.95, 1.26) OT+7

OT, On-treatment; OS, On-study; NDD, Non-dialysis dependent; DD, Dialysis dependent, HR, Hazard ratio; CI, Confidence interval

1. Singh AK, et al. N Engl J Med. 2021. 2. Singh AK, et al. N Engl J Med 2021. 3. Chertow GM et al, N Engl J Med 2021; 384:1589-1600. 4. Eckardt K-U, et al. N Engl J Med 2021; 384:1601-1612. 5. Robert Provenzano, et al. CJASN August 2021, 16 (8) 1190-1200 6. Barratt J, et al. Nephrol Dial Transplant. 2021;36(9):1616–28 7. Barratt, J. et al Advances in Therapy volume 38, pages 5345–5360 (2021).

What we do know and what are the remaining questions?

Certainties

Efficacy – correct and maintain Hb

Physiological, endogenous EPO doses

Uncertainties

Safety / secondary effects of HIF-PHIs – MACE?, cancer?

Long-term consequences of HIF-PH inhibition

My view on current status of HIF-PHIs May 2022

- Do HIF-PHIs correct anaemia in patients with CKD as effectively as ESAs? Yes, when used in an appropriate dose.
- Do HIF-PHIs maintain haemoglobin levels in patients with CKD as effectively as ESAs? Yes, when used in an appropriate dose.
- Do HIF-PHIs have therapeutic advantages over ESAs?

  Not sure, possibly less iron required (oral iron instead of IV iron) and may be more effective in inflamed patients.

  But… and the MoA is physiological
- Do HIF-PHIs have better safety profiles than ESAs? No.
- Are we sure that HIF-PHIs do not have “off target” effects? No.