



WILL WE NEED TO GIVE ANY IRON WHEN WE PRESCRIBE HIF-PHIS?

Jodie L Babitt, M.D.

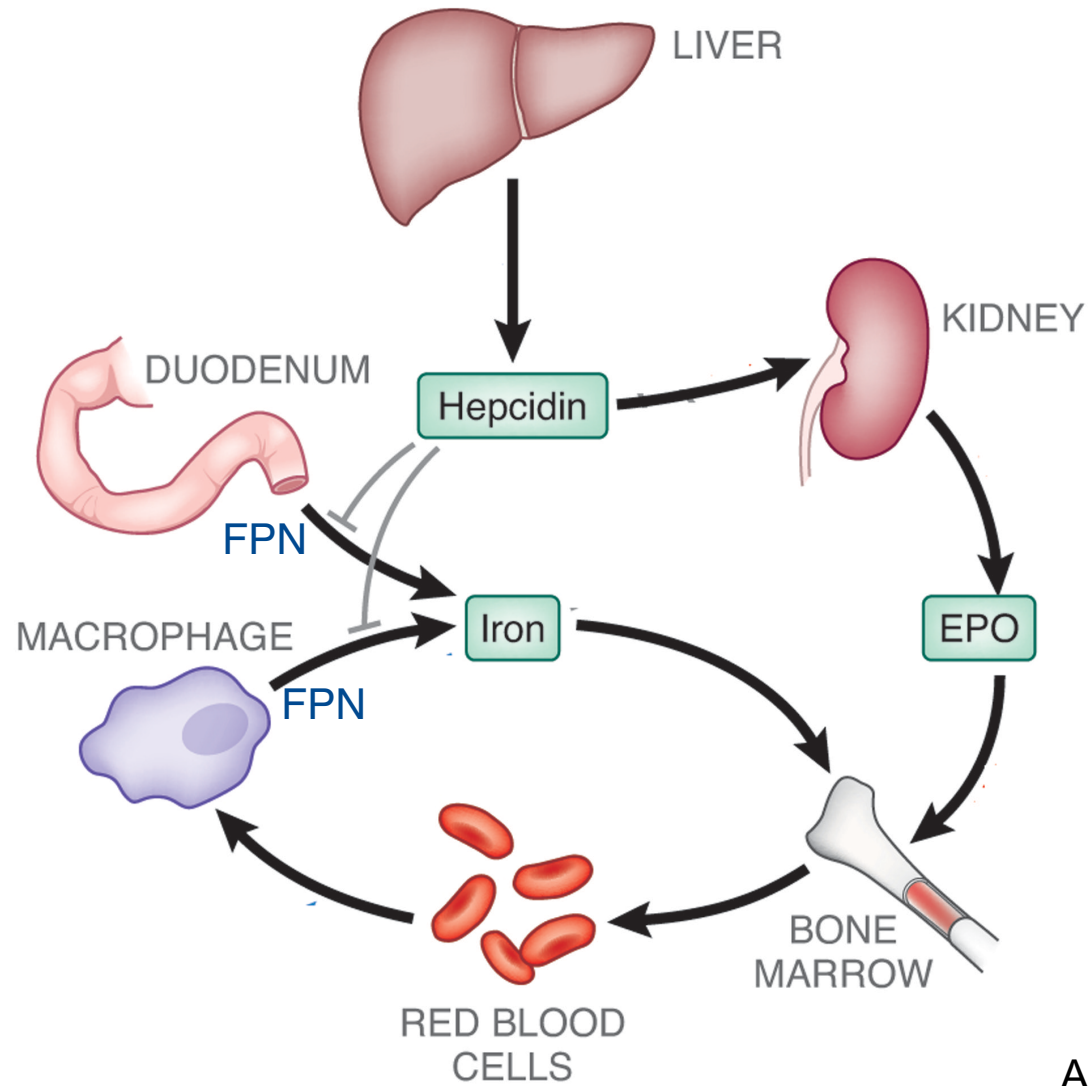
Associate Professor of Medicine

Massachusetts General Hospital, Harvard Medical School

DISCLOSURES

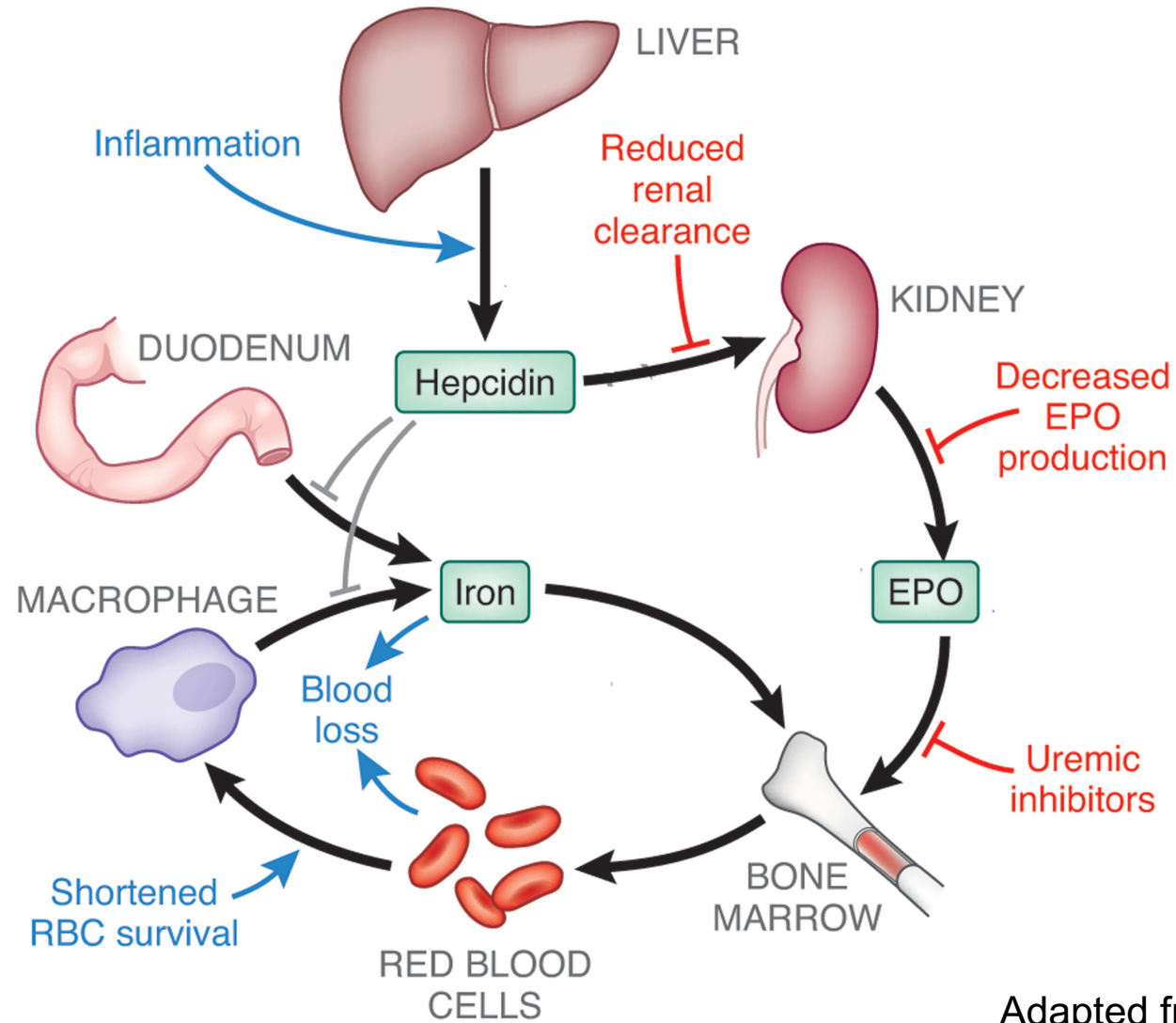
- **Employer:** Massachusetts General Hospital, Harvard Medical School
- **Consultancy agreements:** Incyte Corporation; Alnylam Pharmaceuticals
- **Ownership Interest:** Ferrumax Pharmaceuticals, Inc
- **Patents and inventions:** Massachusetts General Hospital, Ferrumax Pharmaceuticals, Inc.
- **Advisor or membership:** Editorial Board: American Journal of Physiology, Renal Physiology; Board of Directors: International BiIron Society; Co-Chair: KDIGO Anemia Guideline Update

ANEMIA OF CKD



Adapted from: Babitt and Lin.
J Am Soc Nephrol. 2012;23(10):1631.

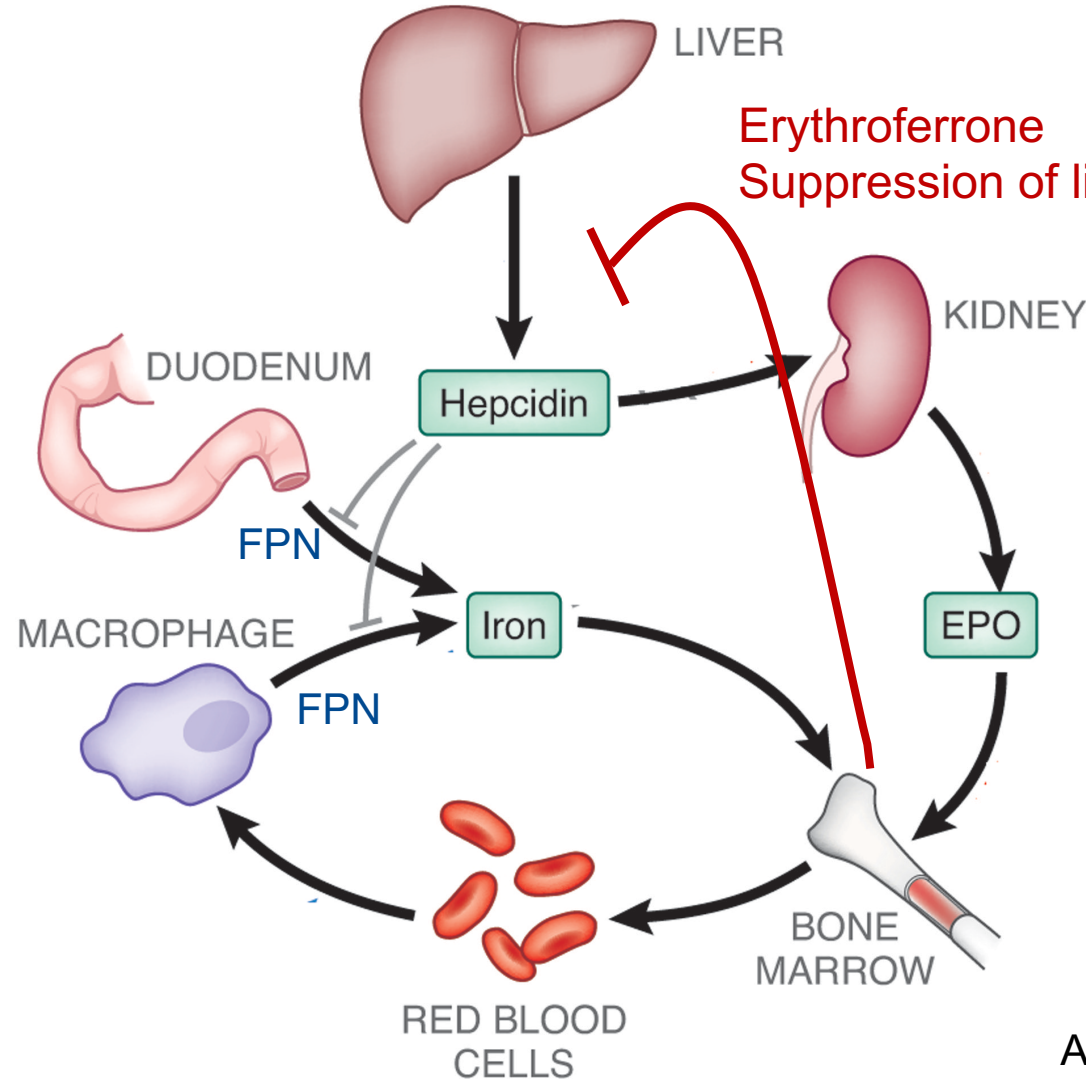
ANEMIA OF CKD



Adapted from: Babitt and Lin.
J Am Soc Nephrol. 2012;23(10):1631.

HOW MIGHT HIF-PHIS IMPACT IRON HOMEOSTASIS AND IRON SUPPLEMENTATION NEEDS?

HIF-PHIS AND ESAs INDIRECTLY SUPPRESS HEPCIDIN, WHICH MAY INCREASE IRON AVAILABILITY

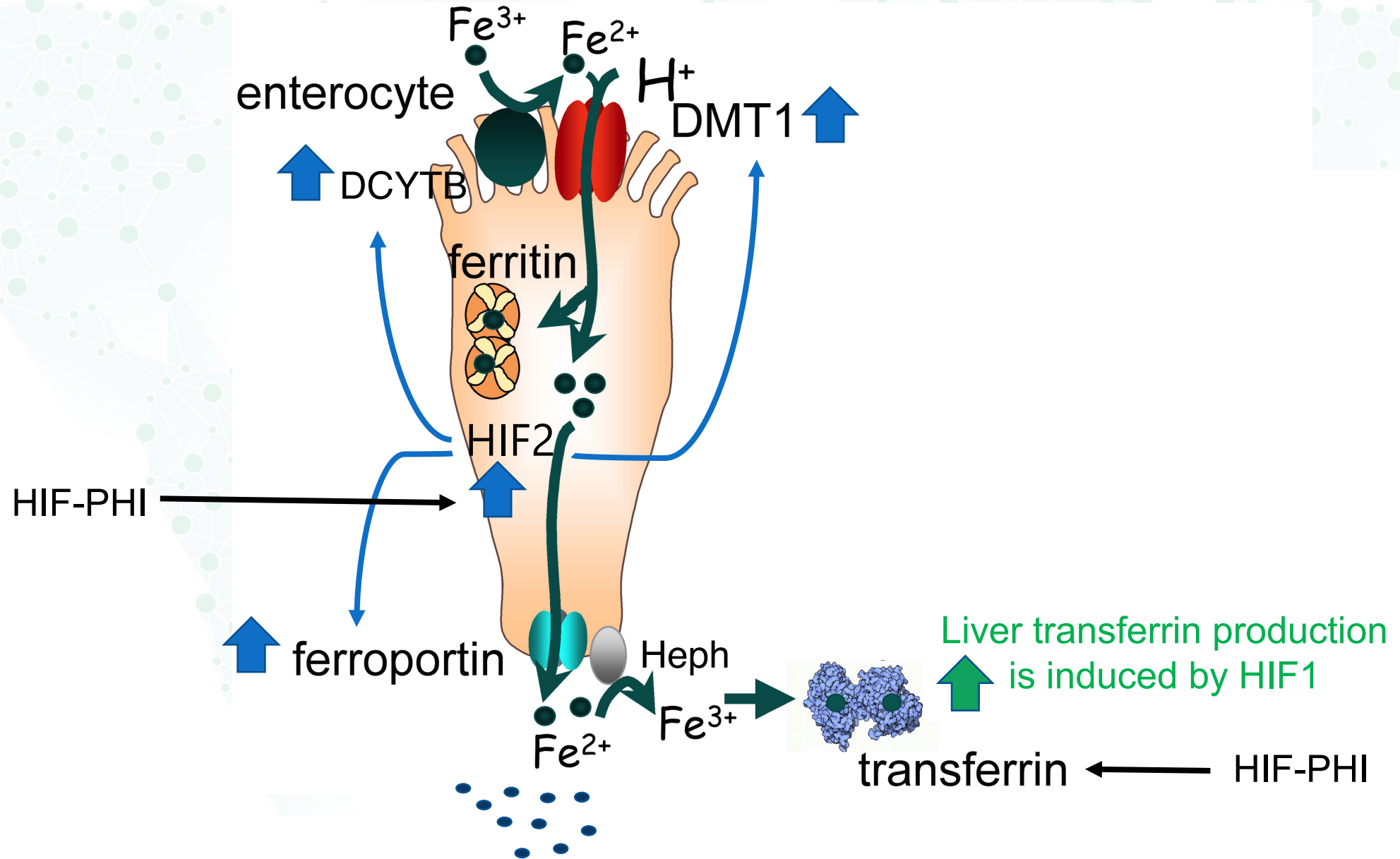


Adapted from: Babitt and Lin.
J Am Soc Nephrol. 2012;23(10):1631.

HIFs DIRECTLY REGULATE NUMEROUS IRON HOMEOSTASIS PROTEINS

- Transferrin
- Divalent Metal Transporter 1 (DMT1)
- Ferroportin (FPN)
- Duodenal cytochrome reductase B (DCYTB)
- Transferrin receptor 1 (TFR1)
- Ceruloplasmin (CP)
- Heme oxygenase 1 (HO1)

HIF-PHIs MAY INCREASE INTESTINAL IRON ABSORPTION



IMPACT OF HIF-PHI-MEDIATED INDUCTION OF TRANSFERRIN

- $TSAT = \text{Iron} / \text{TIBC}$; TIBC is reflective of transferrin levels
- \uparrow transferrin \rightarrow \downarrow TSAT (& may change proportion of diferric vs different monoferric transferrin species vs apotransferrin)
- \downarrow TSAT will suppress hepcidin via liver iron sensing pathway
 - This may help to increase iron absorption from the diet and iron release from body stores
- \downarrow TSAT may also make iron uptake in erythrocytes less efficient
- \downarrow TSAT may destabilize EPO receptors in erythrocytes

WHAT IS THE IMPACT OF HIF-PHIS ON IRON PARAMETERS AND IRON SUPPLEMENTATION NEEDS IN CLINICAL TRIALS?

LIMITATIONS AND INTERPRETATION OF HIF-PHI CLINICAL TRIALS FOR IRON OUTCOMES

1) Iron utilization and iron parameters were not primary outcomes

- At best, secondary outcomes or other endpoints of interest
- Many trials do not report statistical comparison between groups
 - Some report no statistical comparison or show only 95% confidence intervals
 - Some only report statistical comparison relative to baseline for both groups, not between treatment arms

LIMITATIONS AND INTERPRETATION OF HIF-PHI CLINICAL TRIALS FOR IRON OUTCOMES

- 2) Most trials had open label design. This can lead to biases in how iron supplementation was utilized.
- 3) What is protocol for iron supplementation in the study?
 - Notable differences in how iron was handled across trials
 - Many aspects of iron supplementation were left up to the treating physician
 - For some trials, there were prescribed iron treatment differences between the arms that may bias results (e.g. roxadustat DD and NDD trials PYRENEES and DOLOMITES)
 - Often, this info is only provided in supplementary materials

LIMITATIONS AND INTERPRETATION OF HIF-PHI CLINICAL TRIALS FOR IRON OUTCOMES

- Example of Iron supplementation protocol: PYRENEES
 - Mean monthly IV iron use weeks 1-36 was a secondary endpoint
 - *“For patients receiving roxadustat, concomitant oral iron was permitted during the study, whereas IV iron was allowed only if the patient’s Hb level had not responded adequately to roxadustat after two consecutive dose increases or if the maximum dose limit had been reached, and if the patient had either ferritin <100 ng/mL or TSAT <20% or was intolerant to oral iron. For patients treated with ESA, IV iron supplementation was given according to local standard of care”*

LIMITATIONS AND INTERPRETATION OF HIF-PHI CLINICAL TRIALS FOR IRON OUTCOMES

4) What is comparator?

- HIF-PHIs do NOT have direct effect to lower hepcidin
- Both HIF-PHIs and ESAs will lower hepcidin via indirect mechanisms:
 - induction of erythropoiesis, which will increase erythroferrone and increase iron utilization
- The key comparison will be HIF-PHI vs ESA
- Most of the roxadustat NDD (ANDES, OLYMPUS, ALPS) trials were placebo/no comparator

LIMITATIONS AND INTERPRETATION OF HIF-PHI CLINICAL TRIALS FOR IRON OUTCOMES

5) What is HIF-PHI?

- HIF-PHIs may have different effects on iron parameters
- Different pharmacokinetic and pharmacodynamic properties
- Differences in relative activity vs 3 PHD isoforms

LIMITATIONS AND INTERPRETATION OF HIF-PHI CLINICAL TRIALS FOR IRON OUTCOMES

6) What is Hgb achieved?

- Many trials had imbalances in Hgb achieved in HIF-PHI vs ESA arm, typically more robust Hgb increase in HIF-PHI arm
- By inducing more erythropoiesis, targeting a higher Hgb may have a stronger effect to lower hepcidin and may impact other iron parameters/utilization
- Ideally want to compare HIF-PHI vs ESA that achieve equivalent Hgb levels to better compare iron parameters and iron supplementation needs.

LIMITATIONS AND INTERPRETATION OF HIF-PHI CLINICAL TRIALS FOR IRON OUTCOMES

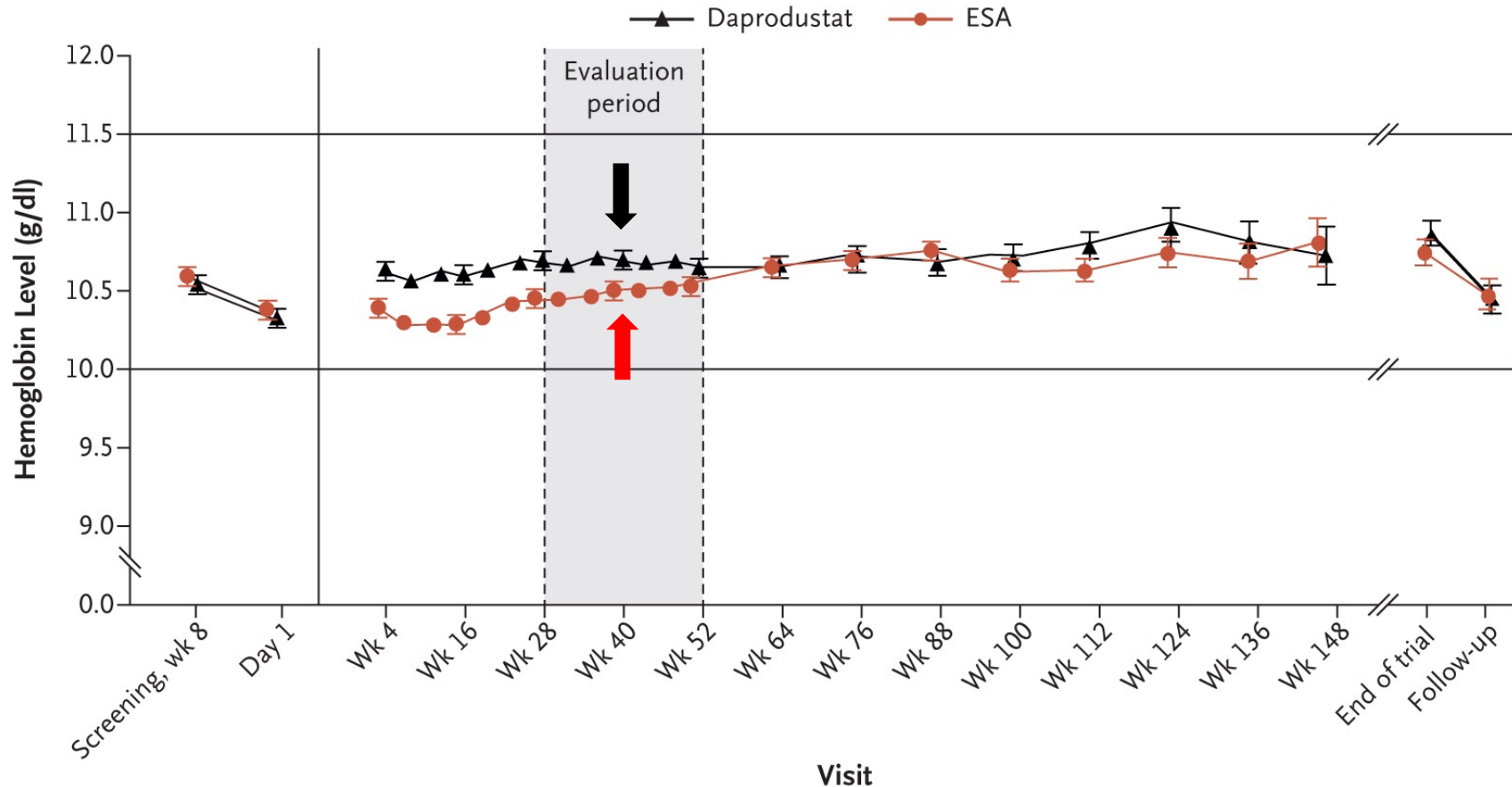
- 7) What is baseline iron/hepcidin status and other co-morbidities?
- Some trials do not use exclude iron deficient patients (e.g. roxadustat NDD trials ANDES, OLYMPUS, ALPS, DOLOMITES enrolled ~40-50% iron deficient patients)
 - Some trials have imbalances in baseline status which complicates with data interpretation:
 - Chen NEJM 2019: baseline hepcidin higher in Roxa group, but ending value same in both groups
 - PYRENEES: More DM and other co-morbidities in ESA group; baseline ferritin and hepcidin higher in ESA group

HIF-PHI PHASE 3 TRIALS: DAPRODUSTAT (DD PATIENTS)

ASCEND-D

- Prospective, open label, RCT of daprodustat vs epoetin alfa (HD patients) or darbepoetin alfa (PD patients)
- N=2964, duration 52 weeks, target Hgb 10-11
- For both arms, treat with iron if ferritin <100 and/or TSAT <20% with dose/route chosen by local investigator. Iron stopped if ferritin >800 and TSAT >20% or TSAT >40%
- Primary outcomes: mean change in Hgb from baseline to weeks 28-52; first occurrence of MACE (non-inferiority)
- Principal secondary outcome: average monthly dose IV iron baseline-52 weeks

HIF-PHI PHASE 3 TRIALS: DAPRODUSTAT (ASCEND-D)



No. of Patients

ESA	1477	1475	1449	1381	1323	1270	1225	1175	1125	1059	998	838	601	419	230	839	628
Daprodustat	1487	1485	1453	1403	1336	1274	1241	1191	1138	1092	1039	863	612	432	248	862	639

Singh *et al.* *N Engl J Med.* 2021 Nov 5. epub ahead of print

HIF-PHI PHASE 3 TRIALS: DAPRODUSTAT (ASCEND-D)

- Mean monthly IV iron dose not different between daprodustat and ESA

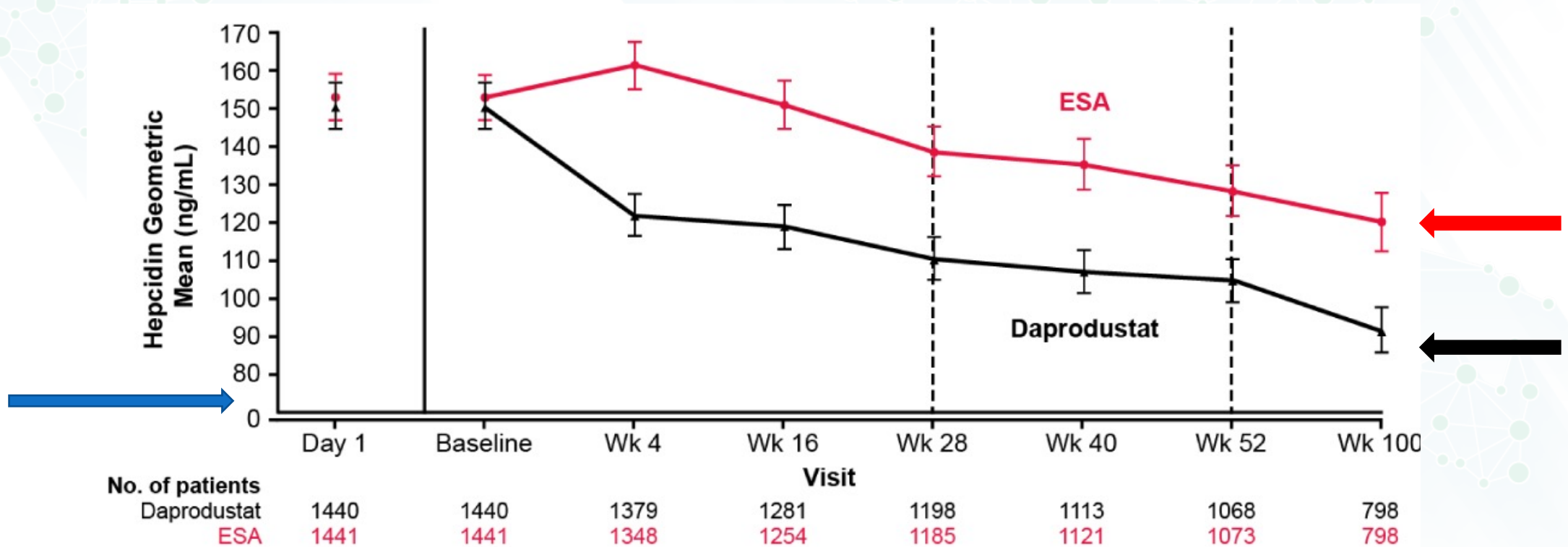
Table 2. Primary and Principal Secondary Outcomes (Intention-to-Treat Population).*

Outcome	Daprodustat (N=1487)		ESA (N=1477)		Treatment Effect (95% CI)	P Value†
	Value	No. of Events	Value	No. of Events		
Principal secondary efficacy outcome¶						
Adjusted mean monthly intravenous iron dose from baseline to wk 52 — mg	90.8±3.3	—	99.9±3.3	—	Mean difference, -9.1 (-18.4 to 0.2)	—



HIF-PHI PHASE 3 TRIALS: DAPRODUSTAT (ASCEND-D)

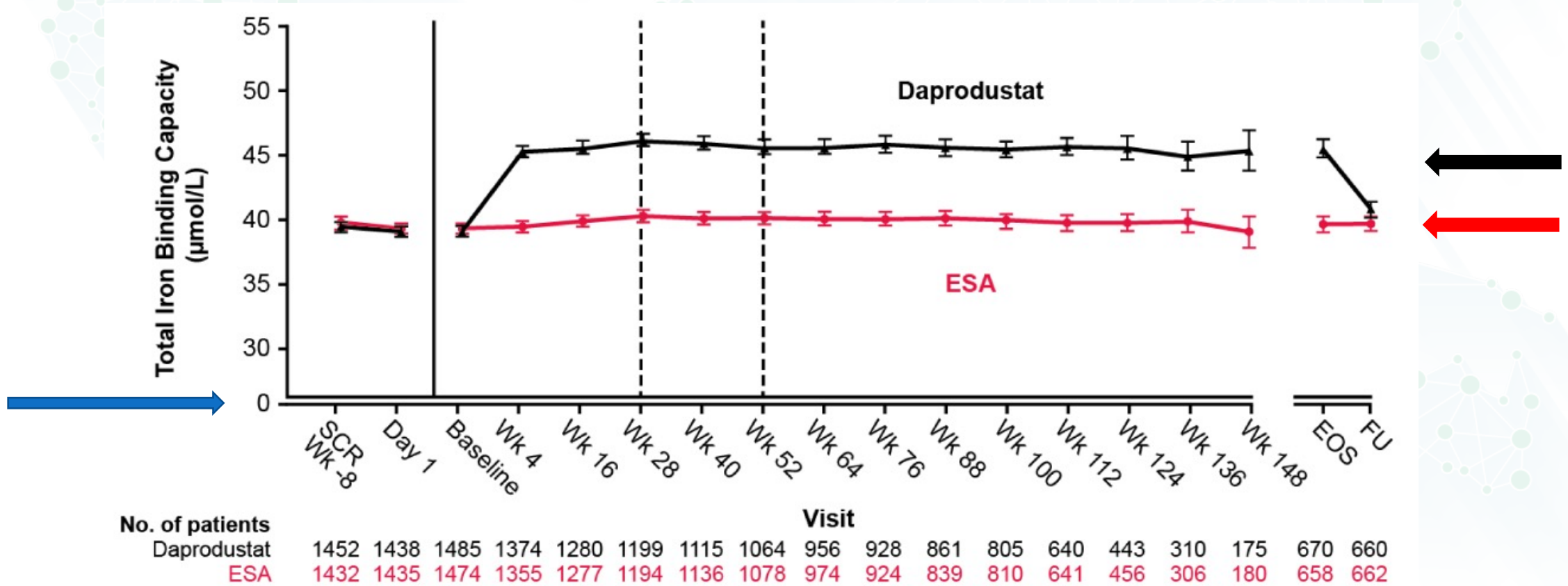
- Hepcidin reduced in daprodustat arm vs ESA (*P* value not provided)



Singh *et al.* *N Engl J Med.* 2021 Nov 5. epub ahead of print

HIF-PHI PHASE 3 TRIALS: DAPRODUSTAT (ASCEND-D)

- TIBC increased in daprodustat arm vs ESA (*P* value not provided)

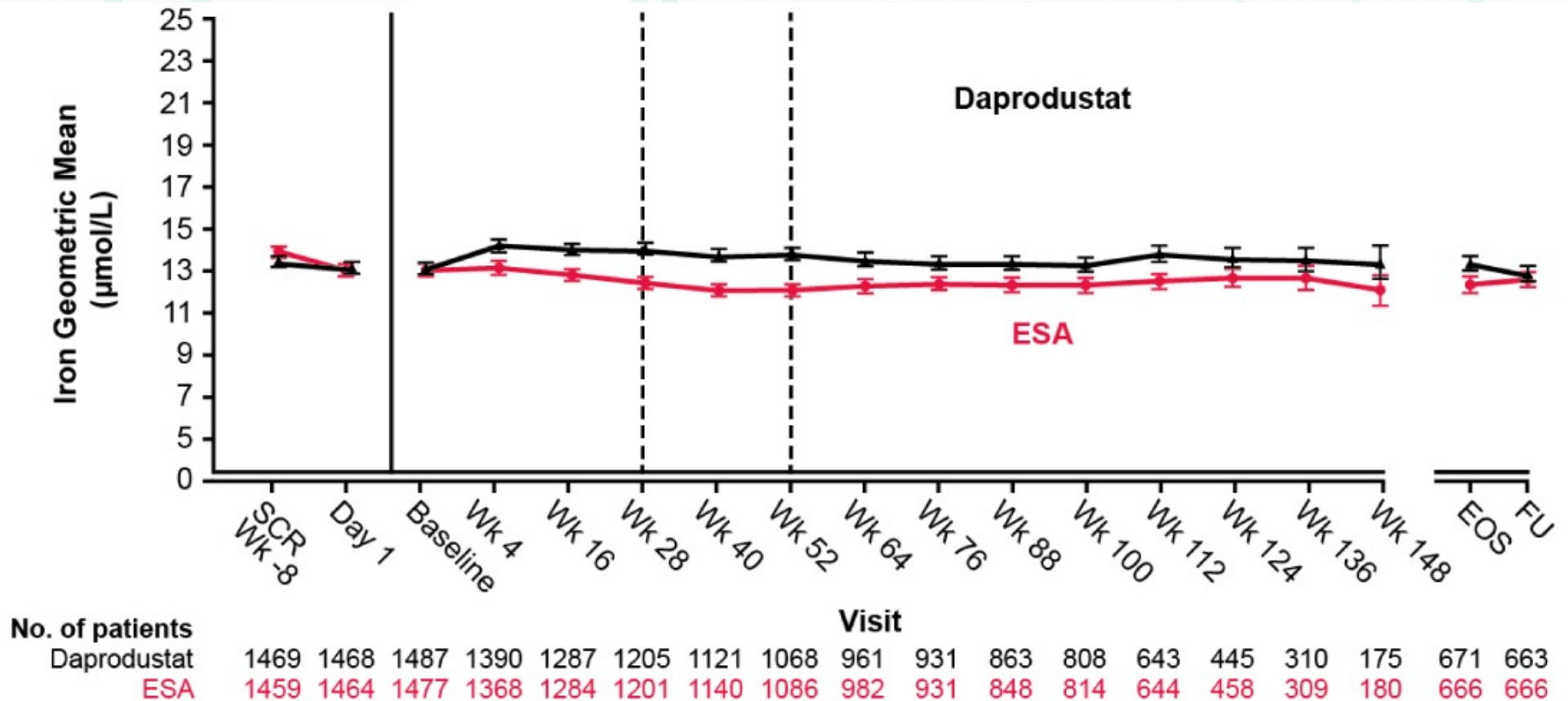


Singh *et al.* *N Engl J Med.* 2021 Nov 5. epub ahead of print



HIF-PHI PHASE 3 TRIALS: DAPRODUSTAT (ASCEND-D)

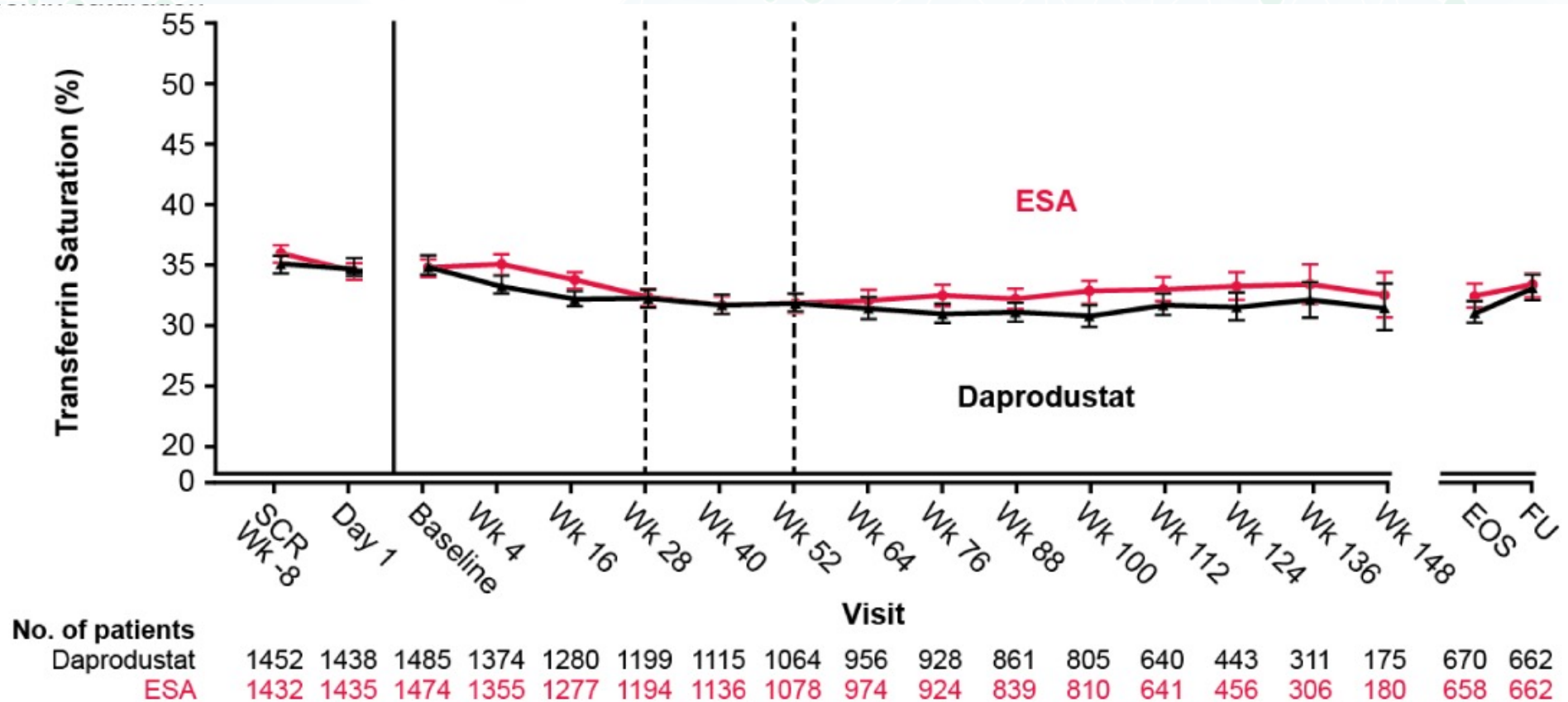
- Serum iron levels increased slightly with daprodustat, but not ESA (P value not provided)



Singh *et al.* *N Engl J Med.* 2021 Nov 5. epub ahead of print

HIF-PHI PHASE 3 TRIALS: DAPRODUSTAT (ASCEND-D)

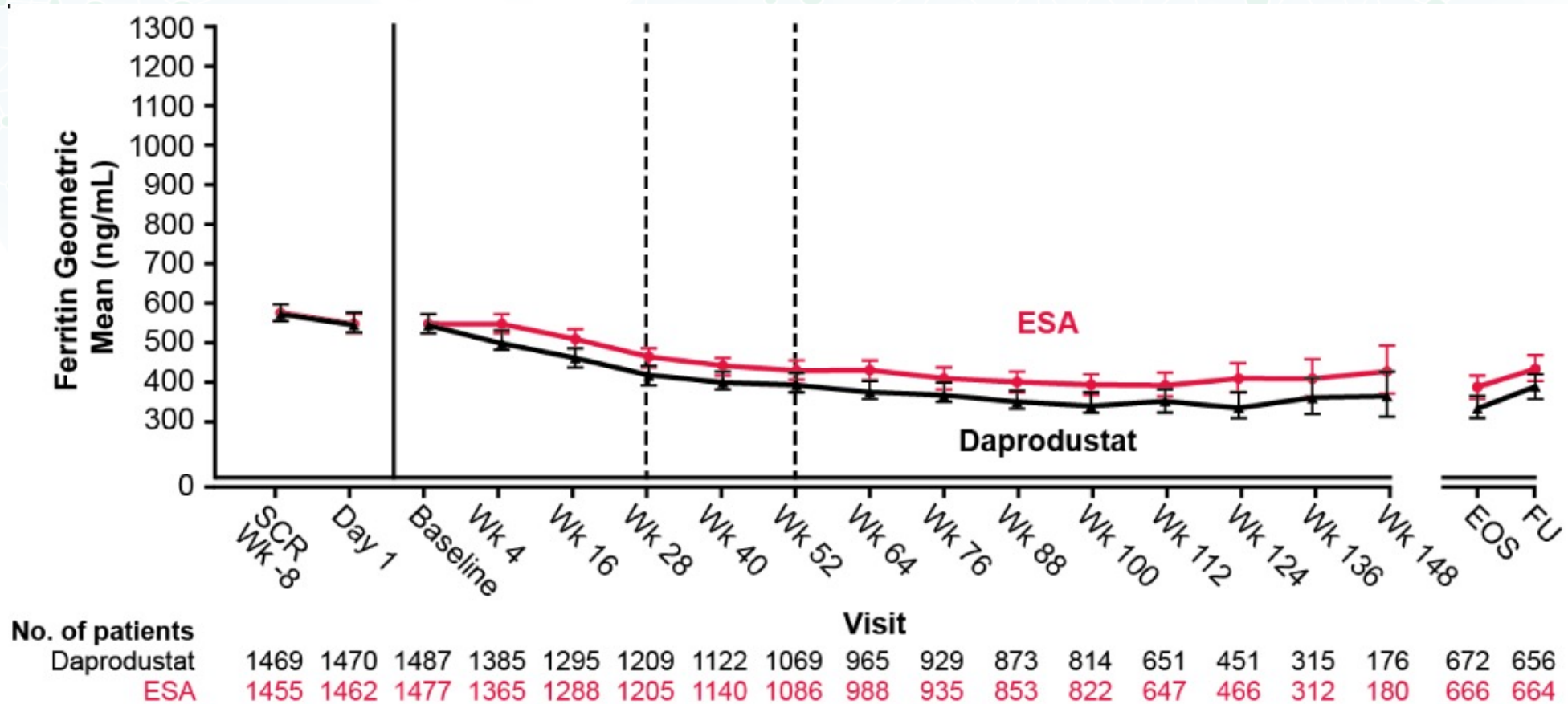
- TSAT similar in 2 arms



Singh *et al.* *N Engl J Med.* 2021 Nov 5. epub ahead of print

HIF-PHI PHASE 3 TRIALS: DAPRODUSTAT (ASCEND-D)

- Ferritin similar in 2 arms



Singh et al. *N Engl J Med*. 2021 Nov 5. epub ahead of print



HIF-PHI PHASE 3 TRIALS: DAPRODUSTAT (NDD PATIENTS)

- NDD trial ASCEND (n=3872, 52 weeks, daprodustat vs darbepoetin):
 - Table 3/Suppl. Fig. S9 shows hepcidin lower, TIBC higher, TSAT slightly lower, serum iron/ferritin similar in daprodustat vs ESA arm; no *P* values provided
 - Iron supplementation not mentioned
- NDD trial Nangaku et al (n=299, 52 weeks, daprodustat vs epoetin-beta pegol)
 - Iron parameters overall similar to ASCEND (hepcidin lower, TIBC higher, TSAT slightly lower, serum iron/ferritin similar in daprodustat vs ESA arm, no *P* values provided)
 - No difference in mean monthly dose oral iron (which was used in 52% daprodustat patients vs 45% EPO patients)
 - Only 1 patient used IV iron (in daprodustat arm)

HIF-PHI PHASE 3 TRIALS: DAPRODUSTAT

Daprodustat Summary

- Daprodustat seems to have some impact on iron parameters, namely reduction in hepcidin, increase in transferrin
- Daprodustat does not seem to have a major impact on need for iron supplementation, at least in the largest published trials to date

HIF-PHI PHASE 3 TRIALS: VADADUSTAT (DD PATIENTS)

INNO₂VATE

- Prospective, open label, RCT of vadadustat vs darbepoetin alfa in incident or prevalent DD patients
- N=3923, 52 weeks, dose adjusted to target Hgb 10-11 (US) or 10-12
- Encouraged use of iron supplementation (IV, oral, or intra-dialytic) to maintain serum ferritin >100 or TSAT >20%
- Primary outcomes: Time to first MACE, mean Hgb change from baseline to weeks 24-36 (non-inferiority)
- Iron parameters/utilization not mentioned as primary or secondary outcomes
- Results report: In both trials, mean serum concentrations of hepcidin, ferritin, and TSAT were similar in the 2 groups
- No discussion of iron supplementation needs

HIF-PHI PHASE 3 TRIALS: VADADUSTAT (DD PATIENTS)

Nangaku et al.

- Prospective, double blind, RCT of vadadustat vs darbepoetin alfa in DD patients
- N=323, 52 weeks, dose adjusted to target Hgb 10-12
- Iron supplementation was used to maintain serum ferritin ≥ 100 , TSAT $\geq 20\%$
- Primary outcome: mean Hgb level weeks 20-24 (non-inferiority achieved)
- Other endpoints included mean iron-related parameters and dose of iron supplementation during 52 week treatment period

HIF-PHI PHASE 3 TRIALS: VADADUSTAT (DD PATIENTS)

Nangaku et al.

- TIBC increased in vadadustat group, but no differences in hepcidin, TSAT, serum iron, ferritin
- MCV and MCH also increased and RDW decreased in vadadustat group
- No differences in mean monthly IV iron dose
- Proportion patients receiving IV iron similar (30.9% vadadustat vs 33.3% darbepoetin)
- Oral iron similar (3.3% vadadustat vs 2.2% darbepoetin)

HIF-PHI PHASE 3 TRIALS: VADADUSTAT (NDD PATIENTS)

- PRO₂TECT: Largest phase 3 trial (N=3476): no mention iron parameters or iron utilization
- Nangaku et al (N=304, 52 weeks, vadadustat vs darbepoetin alfa)
 - Some differences in iron parameters (TIBC higher; hepcidin, ferritin, TSAT lower; MCV, MCH, MCHC higher in vadadustat)
 - No difference in mean monthly dose of oral iron (which increased in both arms)
 - Proportion of patients receiving oral iron similar:
 - 23.8% (vadadustat) vs 18.3% (darbepoetin) at screening
 - 33.6% (vadadustat) vs 29% (darbepoetin) at 48-52 weeks

Chertow *et al. N Engl J Med. 2021 Apr 29;384(17):1589-1600.*

Nangaku *et al. J Am Soc Nephrol. 2021 Apr 21. epub*



HIF-PHI PHASE 3 TRIALS: VADADUSTAT

Vadadustat Summary

- Vadadustat has some modest impact on iron parameters in some trials, but not others. Overall appears to have a weaker effect (though many caveats, including no head-to-head comparisons).
- Vadadustat does not seem to have a major impact on need for iron supplementation, at least in the published trials to date.

HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (DD PATIENTS)

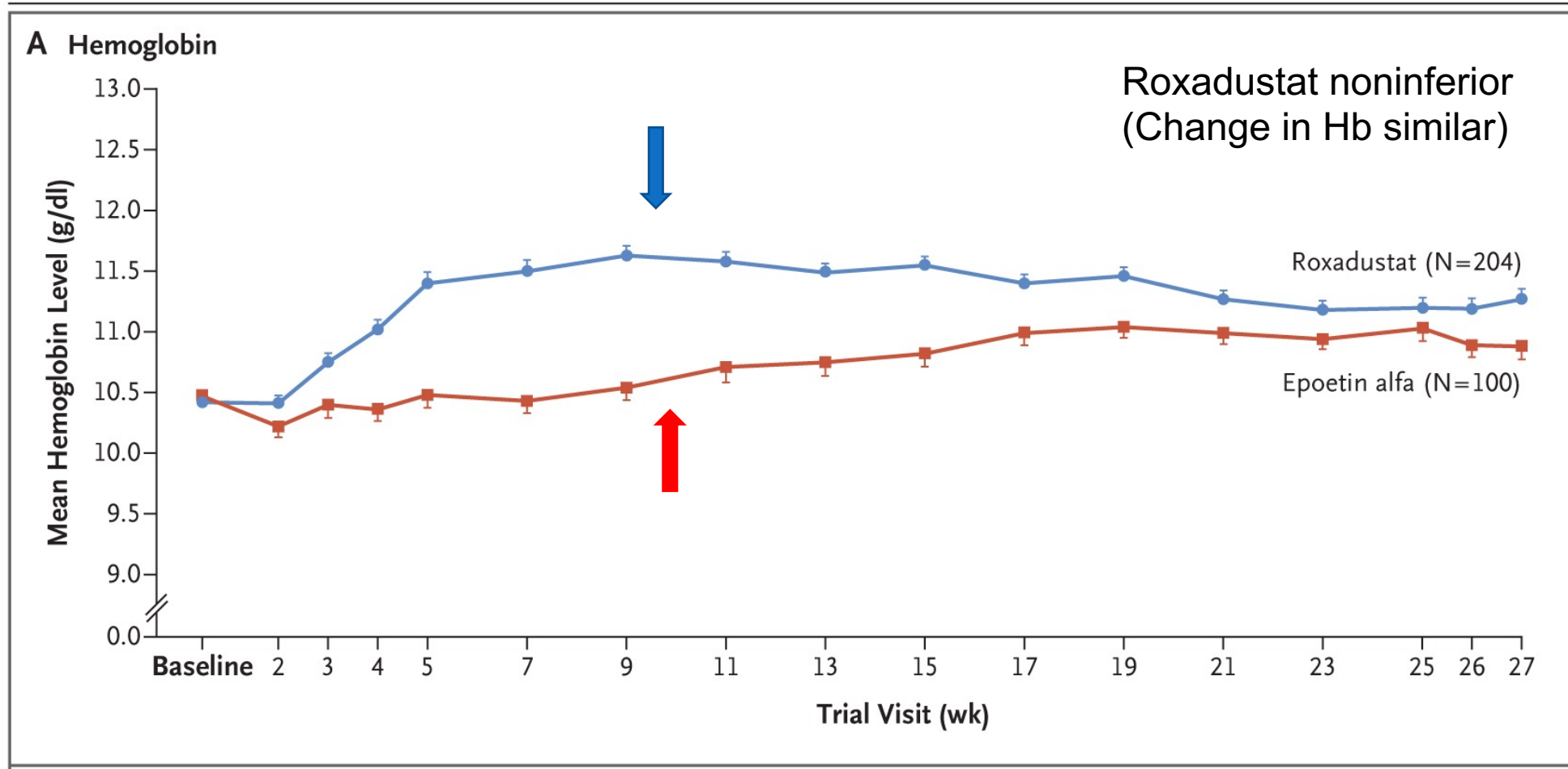
Chen N et al. N Engl J Med. 2019;381(11):1011-1022.

- Prospective, open label, RCT of roxadustat vs epoetin alfa in DD patients
- N=305, duration 26 weeks. Dose adjusted to achieve Hb target 10-12
- No IV iron allowed (except rescue therapy)
- Primary end point: change in Hb level from baseline to avg of weeks 23-27 (non-inferiority)
- Secondary endpoints included change in iron biomarkers

Chen N et al. N Engl J Med. 2019;381(11):1011-1022.



HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (CHEN ET AL)

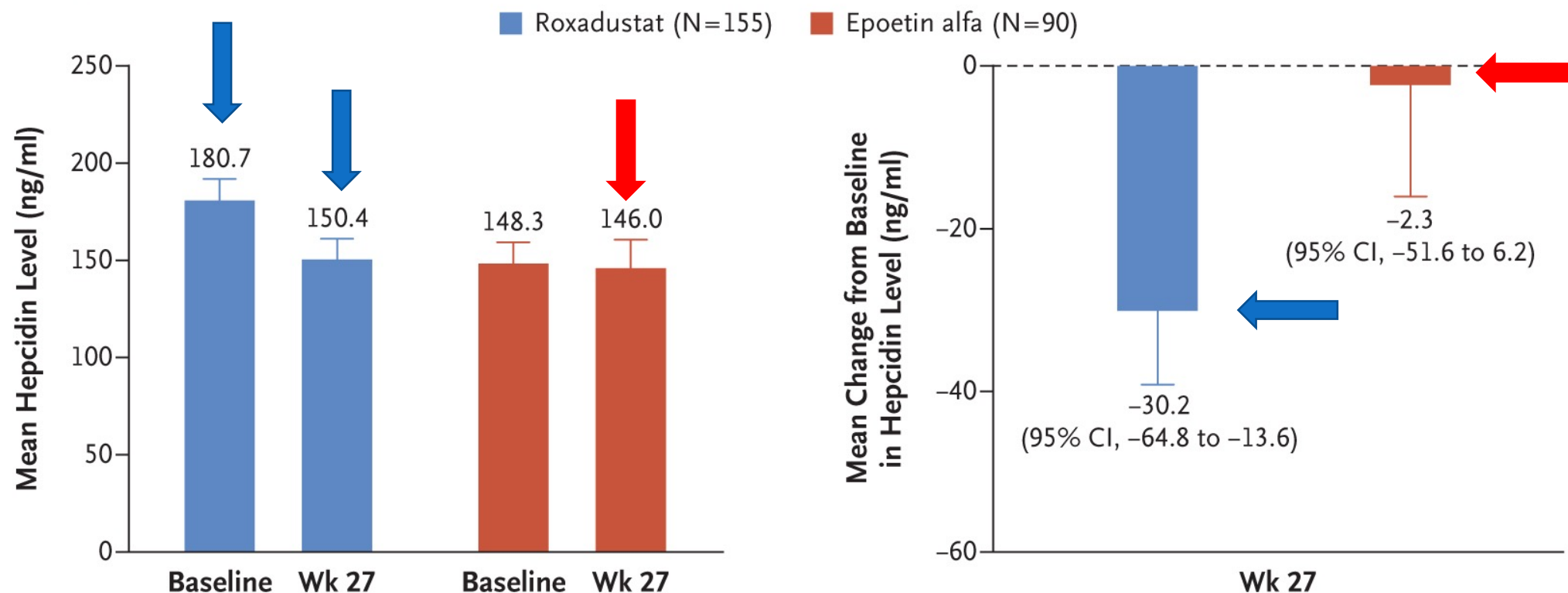


Percentage of patients with Hb response, Hb above lower target, need for rescue therapy also similar

Chen N *et al.* *N Engl J Med.* 2019;381(11):1011-1022.

HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (CHEN ET AL)

B Hepcidin



HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (CHEN ET AL)

- Transferrin increased in roxadustat arm, but not ESA arm

Table 2. Mean Change from Baseline in Iron Biomarker Levels at Week 27 (Intention-to-Treat Population).*

Variable	Roxadustat		Epoetin Alfa		Treatment Difference (95% CI)
	End-of-Treatment Assessment	Change from Baseline	End-of-Treatment Assessment	Change from Baseline	
Transferrin					
No. of patients	160	160	94	94	
Mean (g/liter)	2.29±0.66	0.40±0.48	1.86±0.45	-0.04±0.36	
Least-squares mean (g/liter)		0.38±0.05		-0.05±0.04	0.43±0.05 (0.32 to 0.53)
Total iron-binding capacity					
No. of patients	160	159	94	93	
Mean (μmol/liter)	57.4±16.5	10.0±11.9	46.6±11.3	-1.1±9.0	
Least-squares mean (μmol/liter)		9.5±1.2		-1.2±1.1	10.7±1.3 (8.1 to 13.3)

HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (CHEN ET AL)

- Iron not changed in roxadustat arm, but reduced in ESA arm

Variable	Roxadustat		Epoetin Alfa		Treatment Difference (95% CI)
	End-of-Treatment Assessment	Change from Baseline	End-of-Treatment Assessment	Change from Baseline	
Iron					
No. of patients	160	160	94	94	
Mean ($\mu\text{mol/liter}$)	15.2 \pm 8.1	0.1 \pm 8.3	10.6 \pm 4.0	-3.7 \pm 7.2	
Least-squares mean ($\mu\text{mol/liter}$)		0.6 \pm 0.7		-3.9 \pm 0.5	4.4 \pm 0.7 (3.0 to 5.9)

HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (CHEN ET AL)

- TSAT reduced in both arms, but more in ESA arm

Table 2. Mean Change from Baseline in Iron Biomarker Levels at Week 27 (Intention-to-Treat Population).*

Variable	Roxadustat		Epoetin Alfa		Treatment Difference (95% CI)
	End-of-Treatment Assessment	Change from Baseline	End-of-Treatment Assessment	Change from Baseline	
Transferrin saturation					
No. of patients	160	159	94	93	
Mean (%)	28.0±15.8	-5.7±15.4	23.0±8.5	-7.6±13.8	
Least-squares mean (%)		-4.5±1.2		-8.7±1.0	4.2±1.4 (1.5 to 6.9)

HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (CHEN ET AL)

- Ferritin reduced in both arms, not significantly different

Table 2. Mean Change from Baseline in Iron Biomarker Levels at Week 27 (Intention-to-Treat Population).*

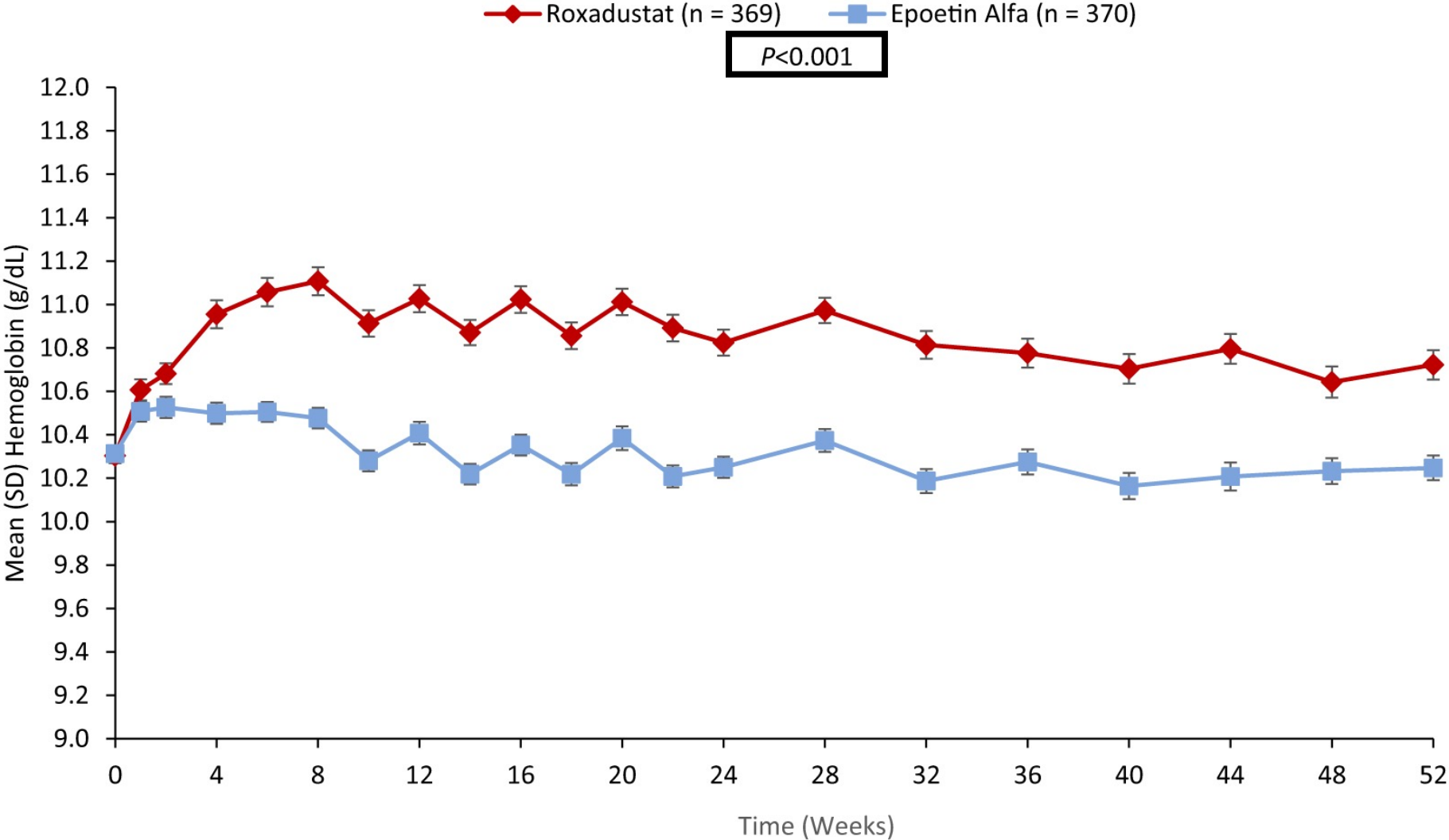
Variable	Roxadustat		Epoetin Alfa		Treatment Difference (95% CI)
	End-of-Treatment Assessment	Change from Baseline	End-of-Treatment Assessment	Change from Baseline	
Ferritin					
No. of patients	160	160	94	94	
Mean ($\mu\text{g/liter}$)	373 \pm 470	-119 \pm 208	294 \pm 294	-136 \pm 220	
Least-squares mean ($\mu\text{g/liter}$)		-99 \pm 19		-133 \pm 21	35 \pm 24 (-12 to 82)

- 3 patients in roxadustat arm and 1 in ESA arm received rescue therapy (IV iron, ESA, or transfusion). Hazard ratio, 1.68; 95% CI, 0.18 to 16.19
- 67 patients (32.8%) in roxadustat arm received oral iron vs 43 (43.0%) in ESA arm

HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (SIERRAS)

- SIERRAS
- Prospective, open label randomized controlled trial of Roxadustat vs epoetin alfa in DD patients
- N=741, duration 52 weeks. Dose adjusted to maintain Hgb 11 in Roxadustat arm vs “according to US package insert” in ESA arm
- In both groups, all patients encouraged to take oral iron. IV iron permitted if patient did not respond adequately to oral iron, could not tolerate or iron, and was iron deficient (ferritin <100 or Tsat <20%)
- Primary outcomes: Mean Hgb change from baseline averaged over weeks 28-52 (non-inferiority)
- Other secondary endpoints included mean monthly IV iron use averaged over weeks 28-52. Other efficacy endpoints included measurements of iron-related parameters.

HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (SIERRAS)

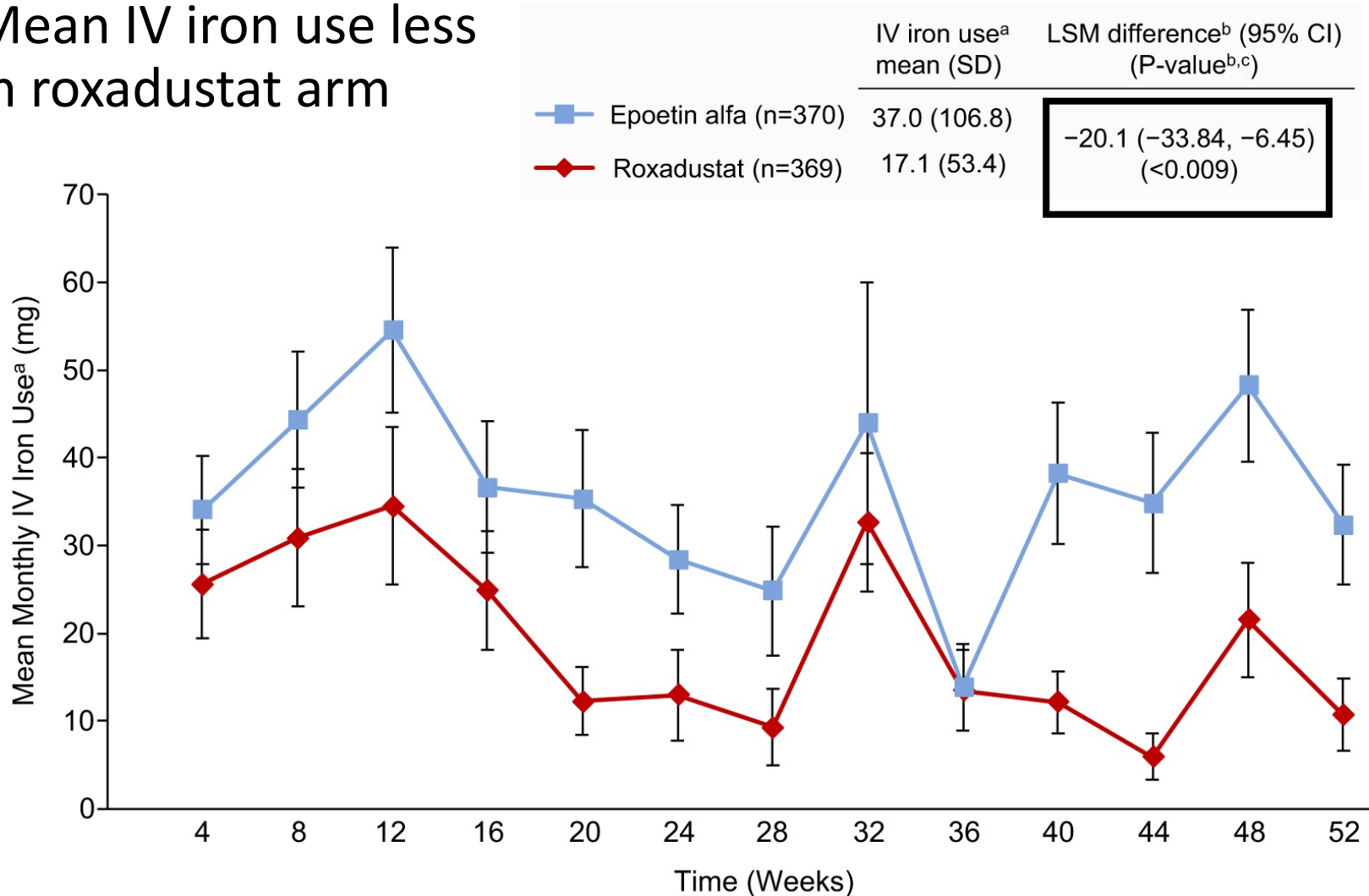


SIERRAS: Charytan *et al.* *KI Reports*. 2021;6:1829-1839.



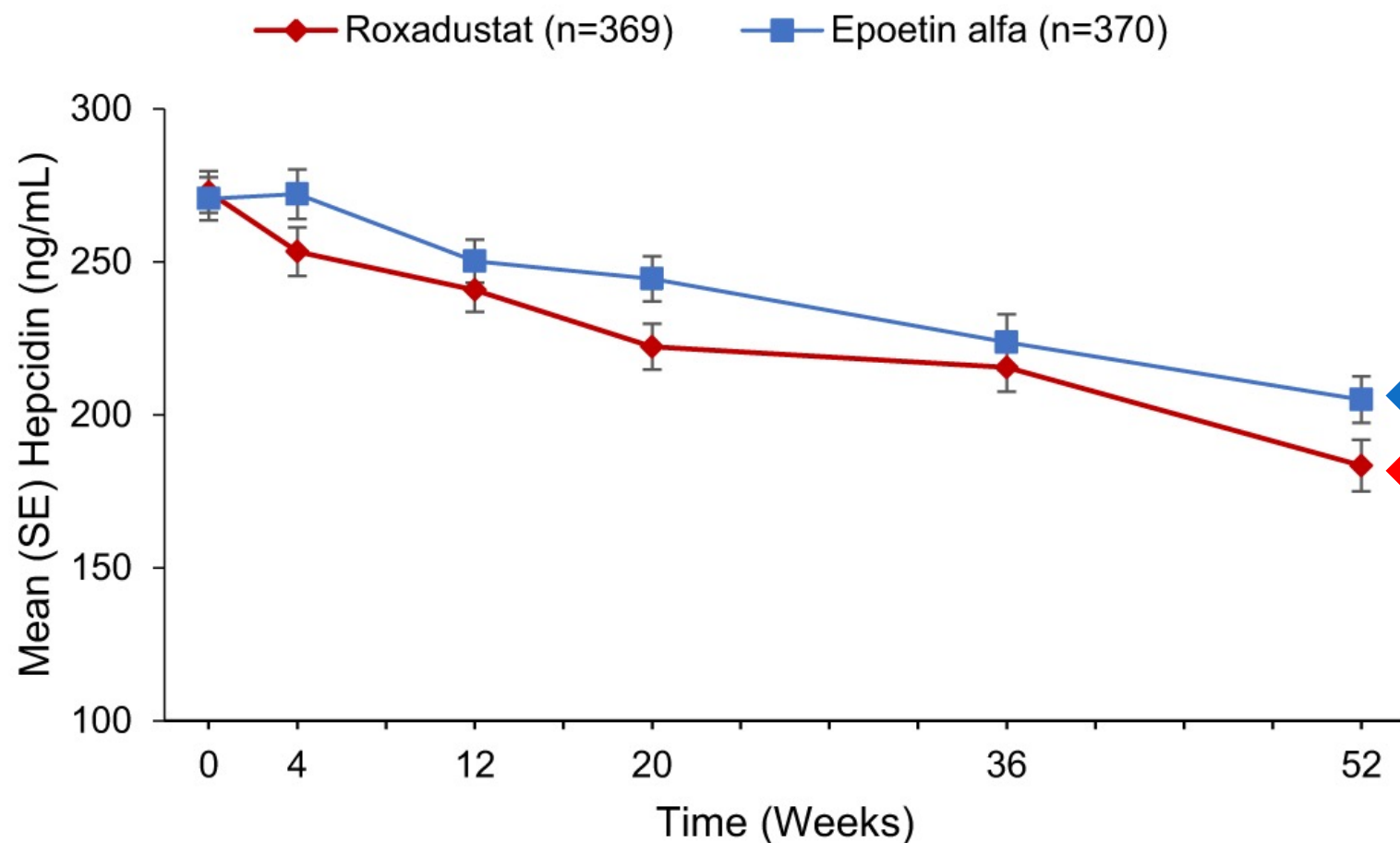
HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (SIERRAS)

- Mean IV iron use less in roxadustat arm



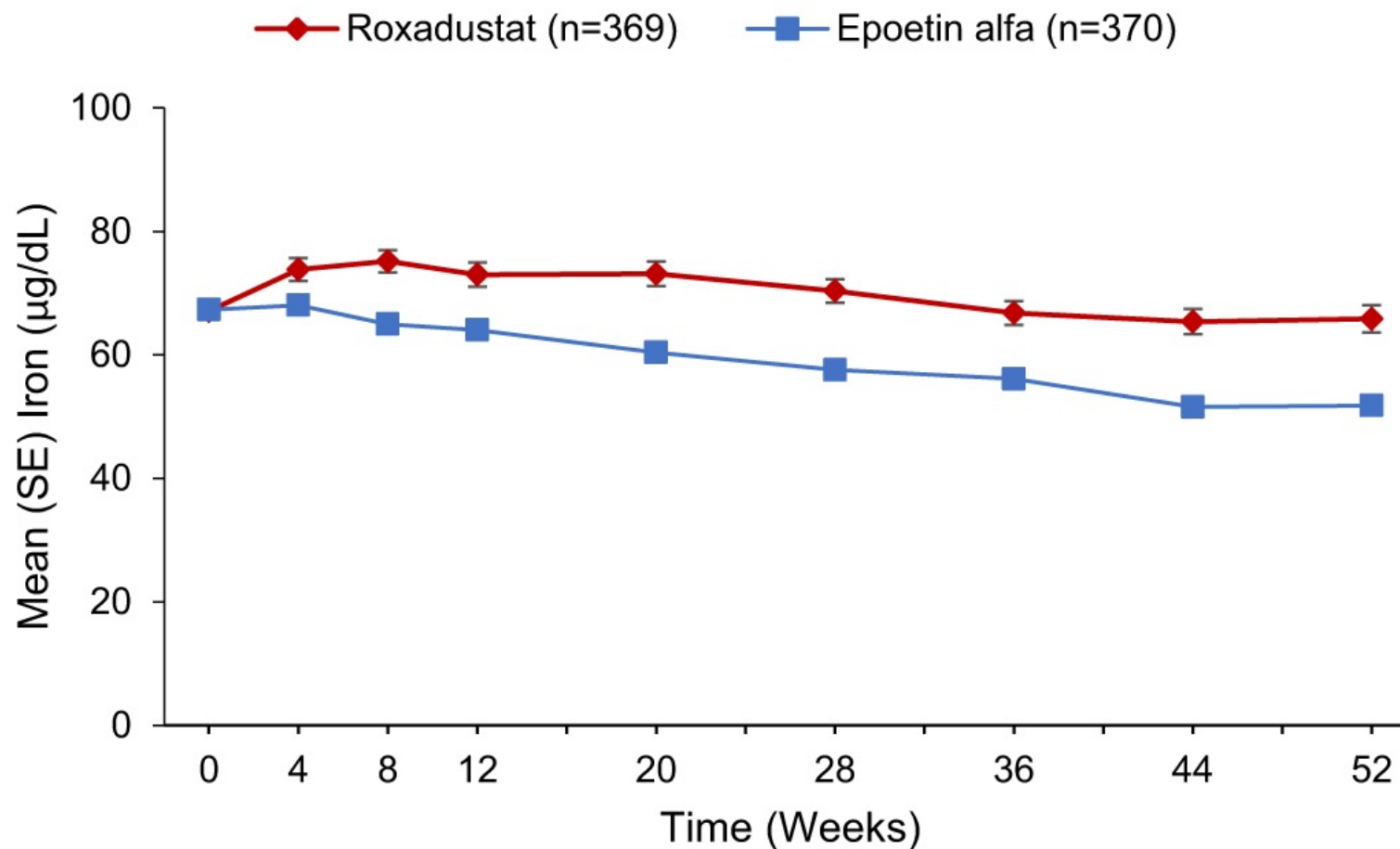
HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (SIERRAS)

- Hepcidin levels tended to be reduced more in roxadustat arm vs ESA, but not significant



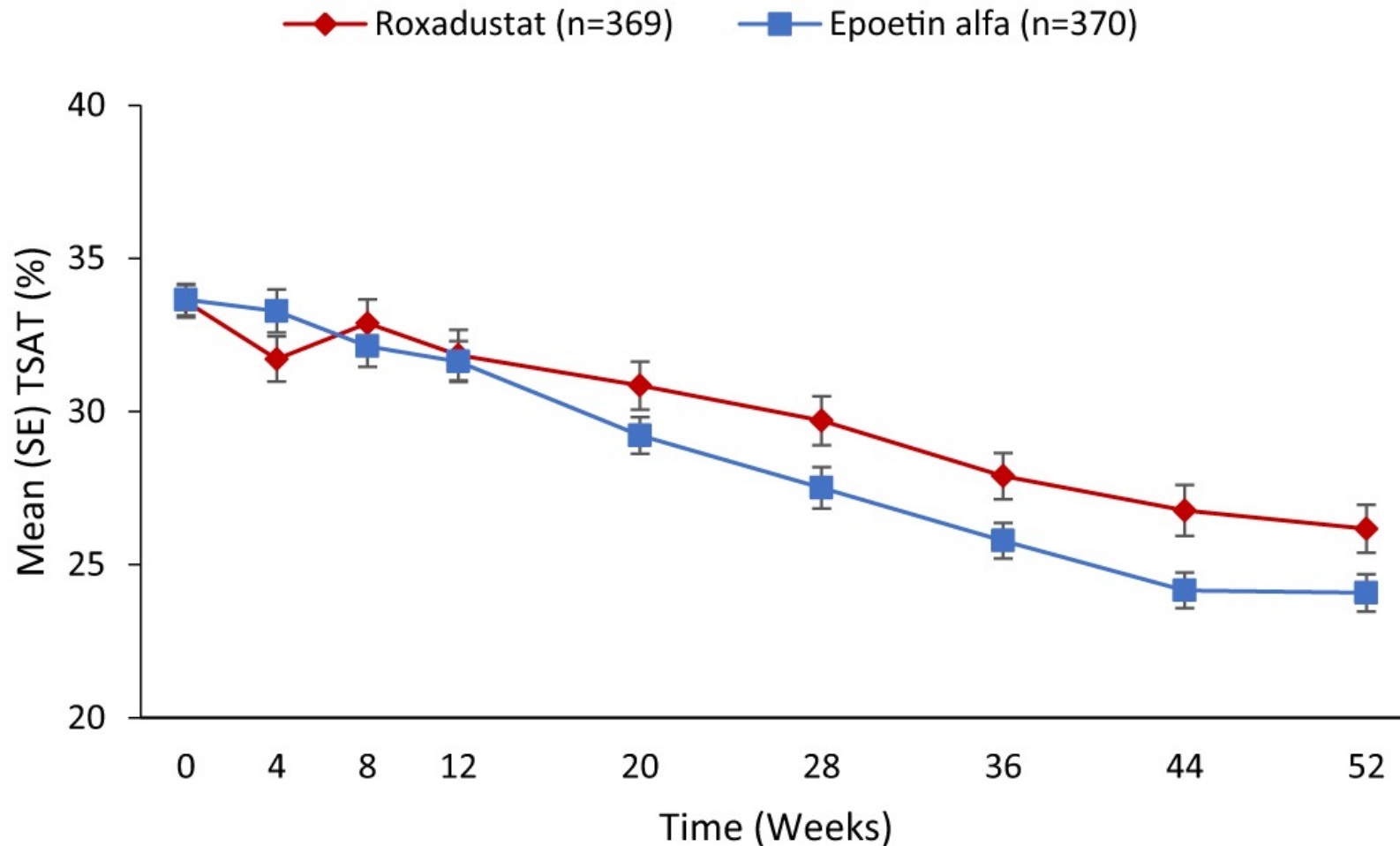
HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (SIERRAS)

- Serum iron was higher in roxadustat arm vs ESA



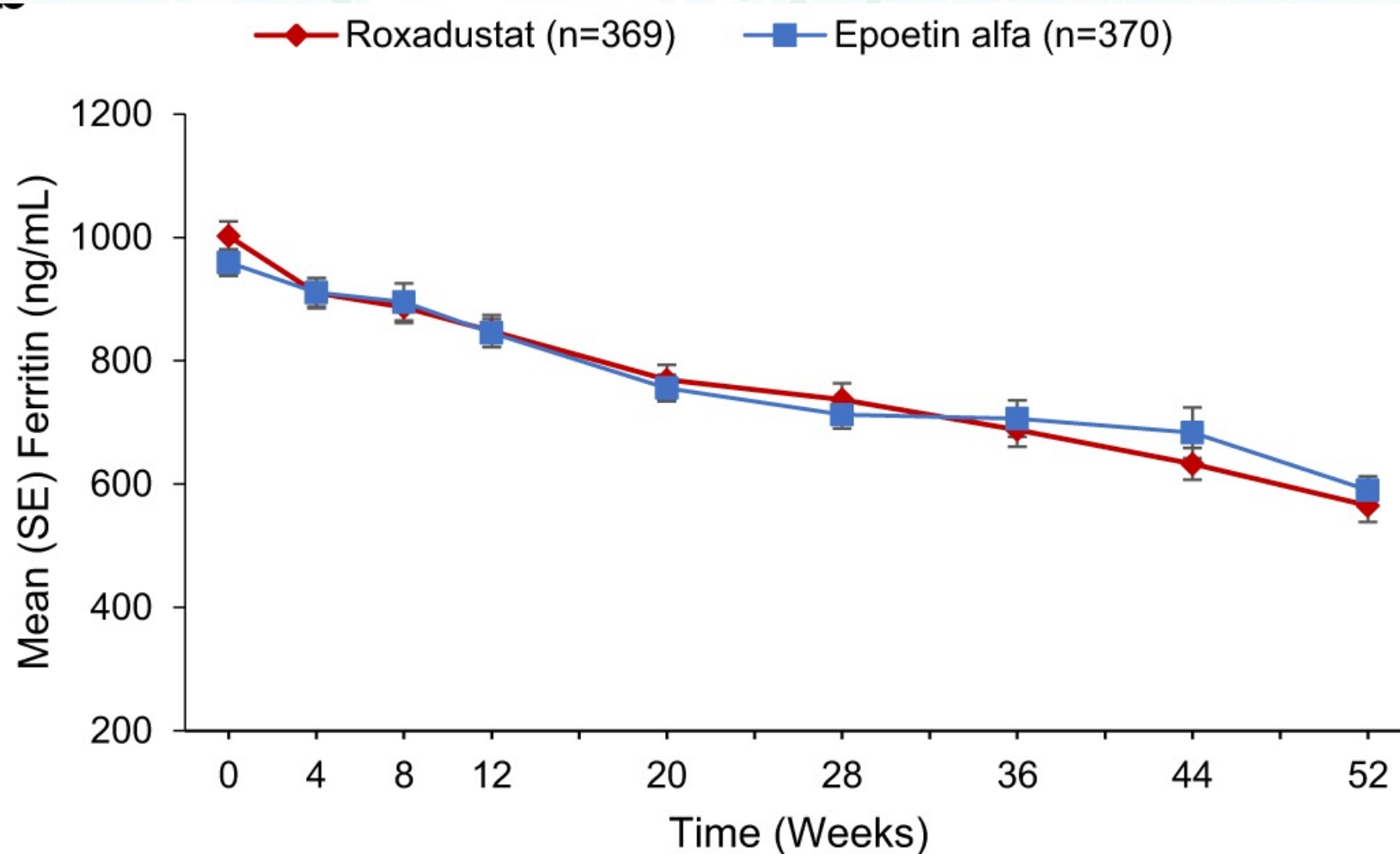
HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (SIERRAS)

- TSAT decreased slightly less in roxadustat arm vs ESA



HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (SIERRAS)

- Ferritin levels similar



SIERRAS: Charytan *et al.* *KI Reports*. 2021;6:1829-1839.

HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (POOLED DD)

Barratt et al. Adv Ther. 2021;38:5345-5360

- Pooled analysis of 4 phase 3 studies in DD patients treated with roxadustat vs ESA (PYRENEES, SIERRAS, HIMALAYAS, ROCKIES)
- Caveats:
 - Trials were different in how they handled iron
 - Some trials had imbalances between arms in iron supplementation protocol, baseline parameters (e.g. PYRENEES)
 - ROCKIES trial is still not published so cannot assess details of this trial
 - all open label
- N=4714 patients, stratified by incident HD or stable HD
- Outcomes: Mean Hgb change from baseline averaged over weeks 28-36 without rescue or weeks 28-52 regardless of rescue; time to MACE, MACE +, all-cause mortality; TEAE (non-inferiority)
- Secondary efficacy endpoints included monthly IV iron use

HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (POOLED DD)

Endpoint/parameter	Incident dialysis subgroup		Stable dialysis subgroup	
	Roxadustat (<i>n</i> = 673)	ESA (<i>n</i> = 669)	Roxadustat (<i>n</i> = 1379)	ESA (<i>n</i> = 1417)
Monthly intravenous iron use over weeks 28–52 (SAF)				
<i>n</i> (%)	606/756 (80.2)	621/759 (81.8)	1414/1586 (89.2)	1486/1589 (93.5)
Mean (SD), mg	53.57 (143.10)	70.22 (173.33)	42.45 (229.80)	61.99 (148.02)
Median, mg	0	0	0	0
Minimum, maximum, mg	0, 1600	0, 2800	0, 5504	0, 1589.7

HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (POOLED DD)

Endpoint/parameter	Incident dialysis subgroup		Stable dialysis subgroup	
	Roxadustat (<i>n</i> = 673)	ESA (<i>n</i> = 669)	Roxadustat (<i>n</i> = 1379)	ESA (<i>n</i> = 1417)
Monthly intravenous iron use over weeks 28–52 (SAF)				
<i>n</i> (%)	606/756 (80.2)	621/759 (81.8)	1414/1586 (89.2)	1486/1589 (93.5)
Mean (SD), mg	53.57 (143.10)	70.22 (173.33)	42.45 (229.80)	61.99 (148.02)
Median, mg	0	0	0	0
Minimum, maximum, mg	0, 1600	0, 2800	0, 5504	0, 1589.7

HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (POOLED DD)

Endpoint/parameter	Incident dialysis subgroup		Stable dialysis subgroup	
	Roxadustat (<i>n</i> = 673)	ESA (<i>n</i> = 669)	Roxadustat (<i>n</i> = 1379)	ESA (<i>n</i> = 1417)
Monthly intravenous iron use over weeks 28–52 (SAF)				
<i>n</i> (%)	606/756 (80.2)	621/759 (81.8)	1414/1586 (89.2)	1486/1589 (93.5)
Mean (SD), mg	53.57 (143.10)	70.22 (173.33)	42.45 (229.80)	61.99 (148.02)
Median, mg	0	0	0	0
Minimum, maximum, mg	0, 1600	0, 2800	0, 5504	0, 1589.7

HIF-PHI PHASE 3 TRIALS: ROXADUSTAT (POOLED DD)

Endpoint/parameter	Incident dialysis subgroup		Stable dialysis subgroup	
	Roxadustat (<i>n</i> = 673)	ESA (<i>n</i> = 669)	Roxadustat (<i>n</i> = 1379)	ESA (<i>n</i> = 1417)
Monthly intravenous iron use over weeks 28–52 (SAF)				
<i>n</i> (%)	606/756 (80.2)	621/759 (81.8)	1414/1586 (89.2)	1486/1589 (93.5)
Mean (SD), mg	53.57 (143.10)	70.22 (173.33)	42.45 (229.80)	61.99 (148.02)
Median, mg	0	0	0	0
Minimum, maximum, mg	0, 1600	0, 2800	0, 5504	0, 1589.7

HIF-PHI PHASE 3 TRIALS: ROXADUSTAT NDD

- Most roxadustat NDD trials were compared with placebo or no treatment
- One ESA comparator trial (DOLOMITES), but significant flaws in this trial with regard to iron outcomes
 - 44-48% patients iron deficient at baseline
 - Baseline iron deficiency more in ESA arm
 - Iron supplementation managed differently in the 2 arms

HIF-PHI PHASE 3 TRIALS: ROXADUSTAT

Roxadustat Summary

- Roxadustat seems to have some impact on iron parameters, namely increase in transferrin, tendency toward reduced hepcidin, increase in serum iron; changes in TSAT, ferritin more variable among trials
- There is some evidence that roxadustat may decrease need for iron supplementation in DD patients.
- However, many problematic trials with regards to iron outcomes; more data is needed

CONCLUSIONS

- Will we need to give any iron when we prescribe HIF-PHIs?
 - Yes
 - Possibly less, at least with some HIF-PHIs, but the current data is not sufficient to fully answer this question
- We need better RCTs designed to look specifically at this question
- Not all HIF-PHIs are the same when it comes to impact on iron parameters and iron utilization. This needs to be investigated for each agent.