Hemoglobin Response in a Phase 2b Study of Vadadustat for the Treatment of Anemia in Patients with Non-Dialysis Dependent Chronic Kidney Disease

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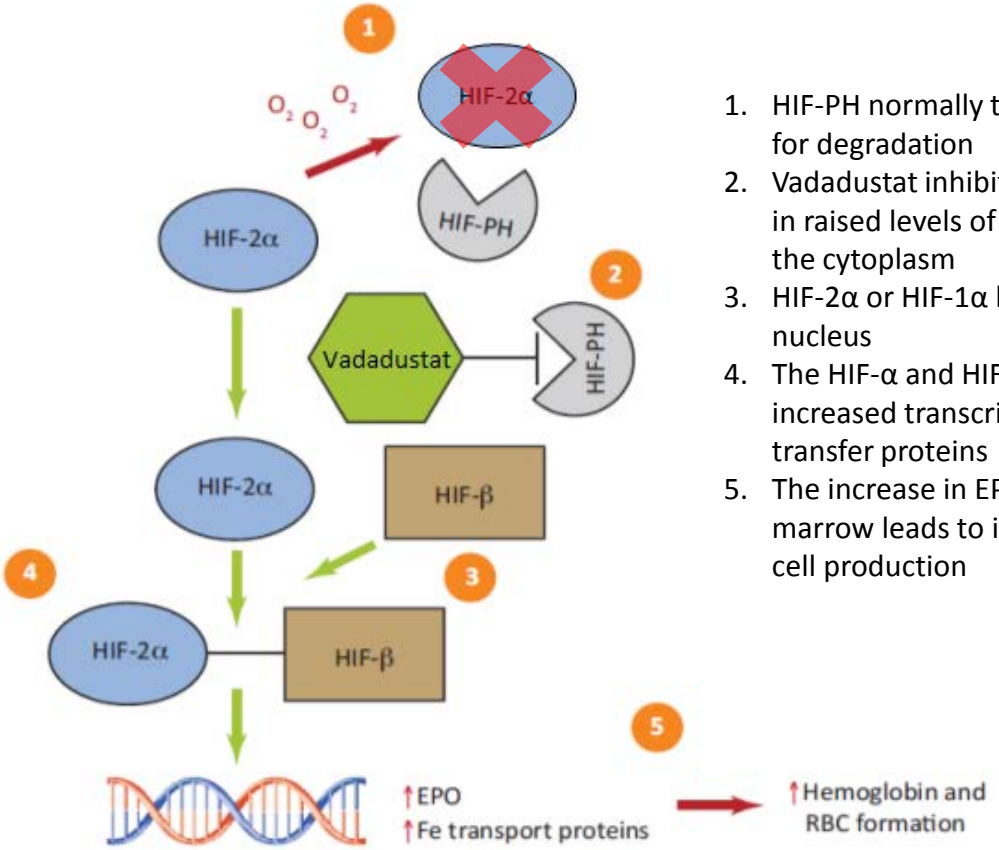
Vadadustat*: A Small-Molecule HIF-PH Inhibitor

- A novel, oral inhibitor of hypoxia-inducible factor prolyl-hydroxylases (HIF-PHs)
- In development for treatment of anemia related to chronic kidney disease (CKD) in patients not on dialysis and those requiring dialysis
  - Thirteen completed studies and >29,000 patient exposure days
- Well tolerated in studies of healthy volunteers and patients with CKD
  - Dose-response relationship observed between dose and erythropoietin (EPO), reticulocyte and hemoglobin (Hb) levels
  - Magnitude of EPO response comparable to that seen at moderate altitude with restoration of normal diurnal pattern
- Facilitates iron homeostasis by decreasing hepcidin and increasing transferrin levels
  - Enhancing iron transport mechanisms that should increase terminal steps of erythropoiesis

*Formerly known as AKB-6548

Vadadustat: Mechanism of Action



1. HIF-PH normally targets HIF-1α and HIF-2α for degradation
2. Vadadustat inhibits HIF-PH activity resulting in raised levels of HIF-α (HIF-2α > HIF-1α) in the cytoplasm
3. HIF-2α or HIF-1α binds with HIF-β in the nucleus
4. The HIF-α and HIF-β complex leads to increased transcription of EPO and iron transfer proteins
5. The increase in EPO and iron in the bone marrow leads to increased Hb and red blood cell production

- Vadadustat preferentially stabilizes HIF-2α, leading to:
  - EPO levels maintained within physiologic range and physiologic effect on reticulocytes
  - Enhanced iron mobilization

Phase 2b Randomized, Double-blind, Placebo-Controlled Study of Vadadustat in Patients with CKD

Patient Criteria

- Group 1: (50%) ESA-naïve with Hb ≤10.5 g/dL (1)
- Group 2: (30%) previously treated with Hb ≤10.5 g/dL and off ESA >11 weeks (1)
- Group 3: (20%) actively treated (2) with Hb ≥ 9.5 and ≤ 12.0 g/dL (1)(3)

20 Weeks of Treatment
Follow-up = 4 weeks

Randomized 2:1
Active treatment to Placebo

- Vadadustat
- Placebo

Initiate treatment at 450 mg QD; adjust dose according to Hb response

Patients received oral iron as required to maintain ferritin between 50 and 300 ng/mL

Endpoints

Percent of patients:

1. Achieving or maintaining mean Hb ≥11.0 g/dL (average of Weeks 19 and 20)

OR

2. Increasing Hb by ≥1.2 g/dL (average of Weeks 19 and 20) over their pre-dose average

ESA Rescue

Allow rescue with ESA after Week 6 if worsening anemia

(1) At the time of screening.
(2) Patients being treated with an ESA (erythropoiesis-stimulating agent) for a minimum of 4 months prior to screening.
(3) Randomization and 1st dose of study medication in Group 3 occurred at approximately the same time that the patient would have otherwise received the next dose of ESA.

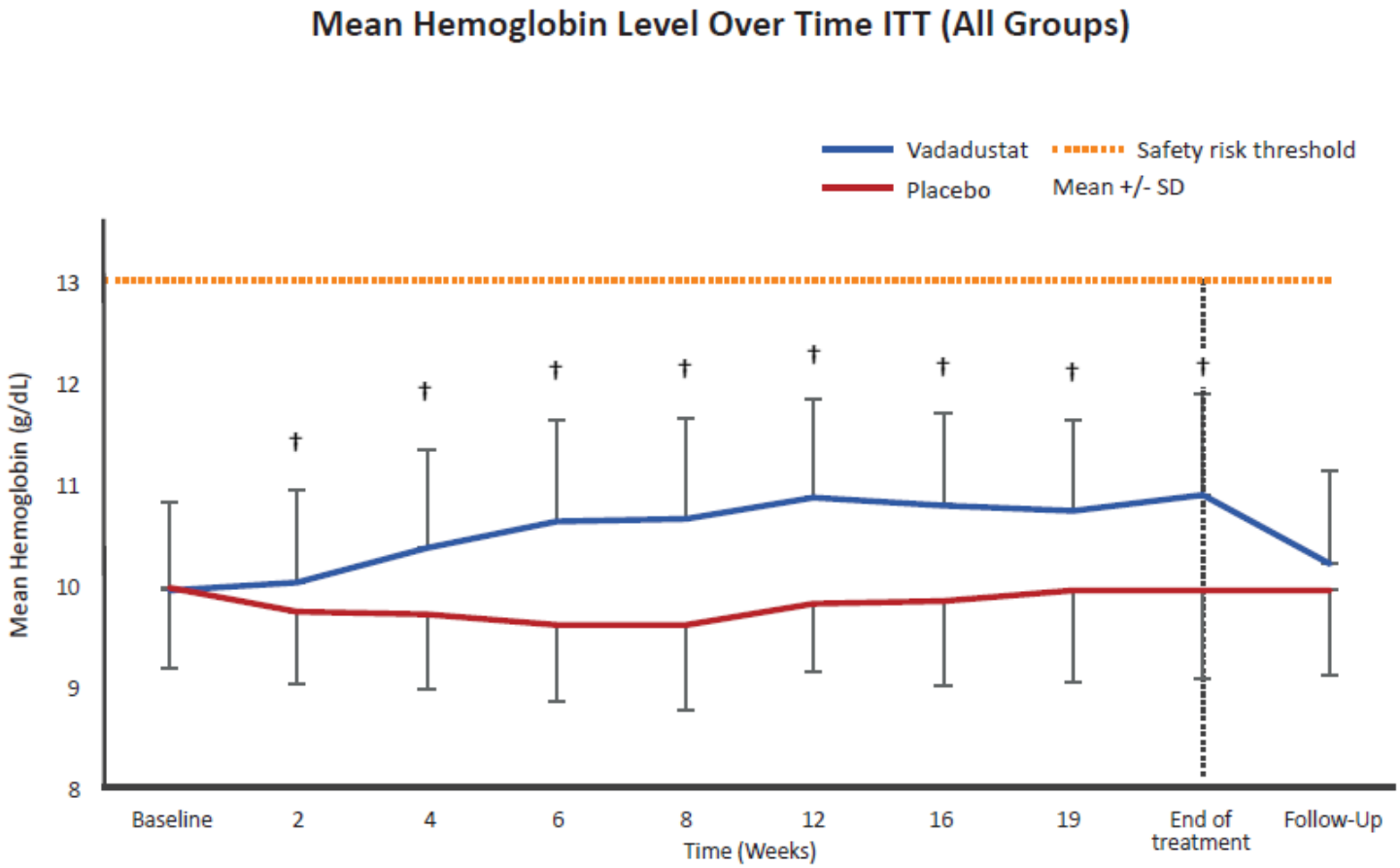
Phase 2b Patient Population Well Balanced Between the Two Groups

		Vadadustat	Placebo
Patients dosed (ITT Population)[(1)]		138 (100.0%)	72 (100.0%)
Mean age (years)		66.6	65.9
Mean eGFR (mL/min/1.73m^2)		25.2	25.0
CKD Status	**G3 a/b**	36 (26.1%)	18 (25.0%)
	G4	85 (61.6%)	42 (58.3%)
	G5	17 (12.3%)	12 (16.7%)
Diabetes Mellitus		106 (76.8%)	57 (79.2%)
Etiology of CKD	**Diabetes**	103 (74.6%)	51 (70.8%)
	Hypertension	78 (56.6%)	36 (50.0%)
	Other	7 (5.0%)	11 (15.3%)
Mean Urine ACR (mg/g)		1,146	1,455

(1) Intent-to-treat (ITT) Population: all randomized patients who received at least one dose of study medication. All safety analyses were performed using the ITT population.

ACR=albumin:creatinine ratio; eGFR=estimated glomerular filtration rate.

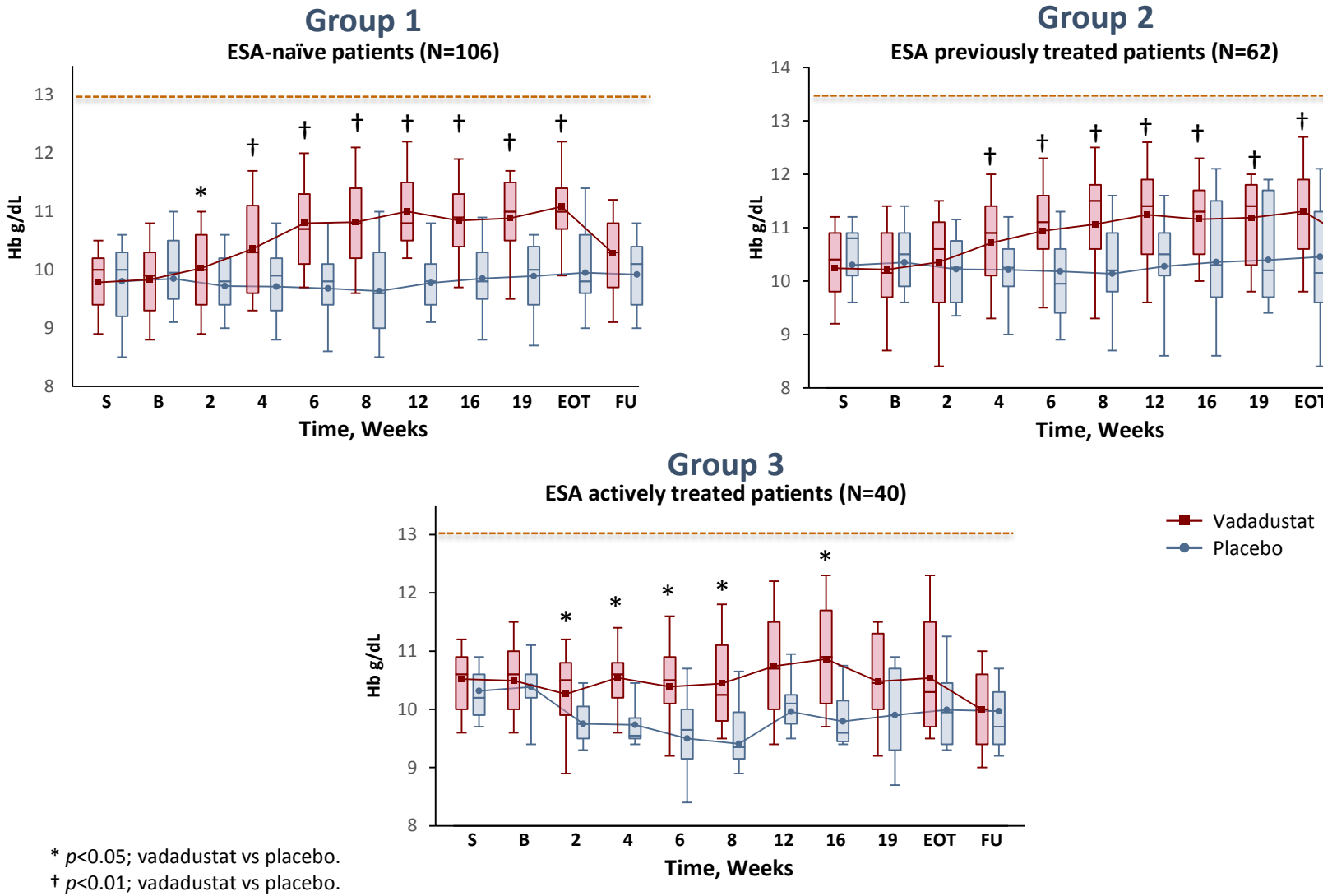
Maintained Hb Throughout 20-week Treatment Period With Limited Excursions >13 g/dL



† $p<0.01$; vadadustat vs placebo.

- Met primary endpoint (54.9% vs. 10.3%, $p<0.0001$)
- Mean hemoglobin change of 1 g/dL
- Only 4.4% of patients experienced excursions beyond 13 g/dL (6 patients)

Mean Hemoglobin Over Time by ESA study Group (MITT Population)



* $p<0.05$; vadadustat vs placebo.

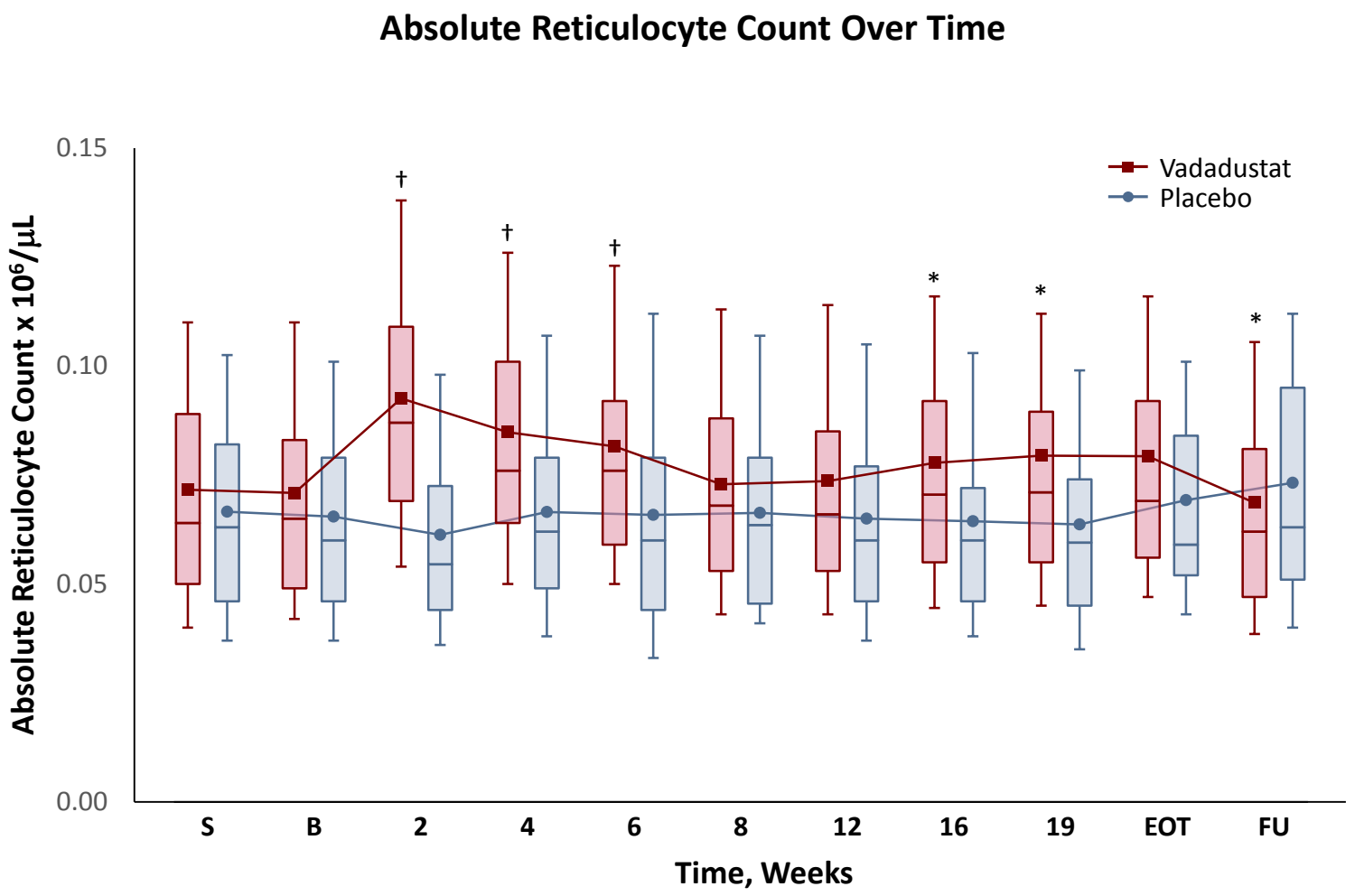
† $p<0.01$; vadadustat vs placebo.

B=baseline; EOT=end of treatment; FU=follow-up; Hb=hemoglobin; S=screening.

Box and whiskers plot represents 10th, 25th, 75th, and 90th percentiles, median is the line within the box, mean is symbol within the box.

Modified intent-to-treat (MITT) population – included patients in the ITT population who had a Baseline and at least one post-baseline Hb measurement.

Physiologic Response Observed: Reticulocytes Rose Then Decreased and Stabilized to Maintain Hb



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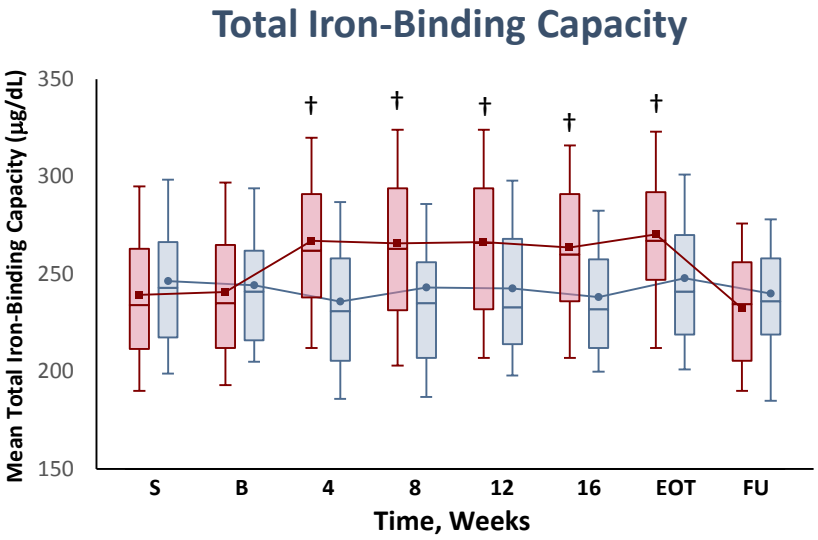
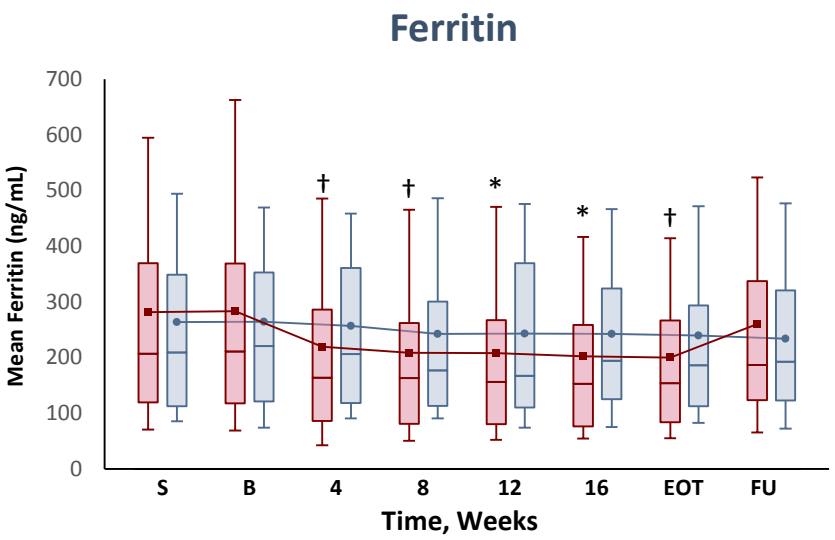
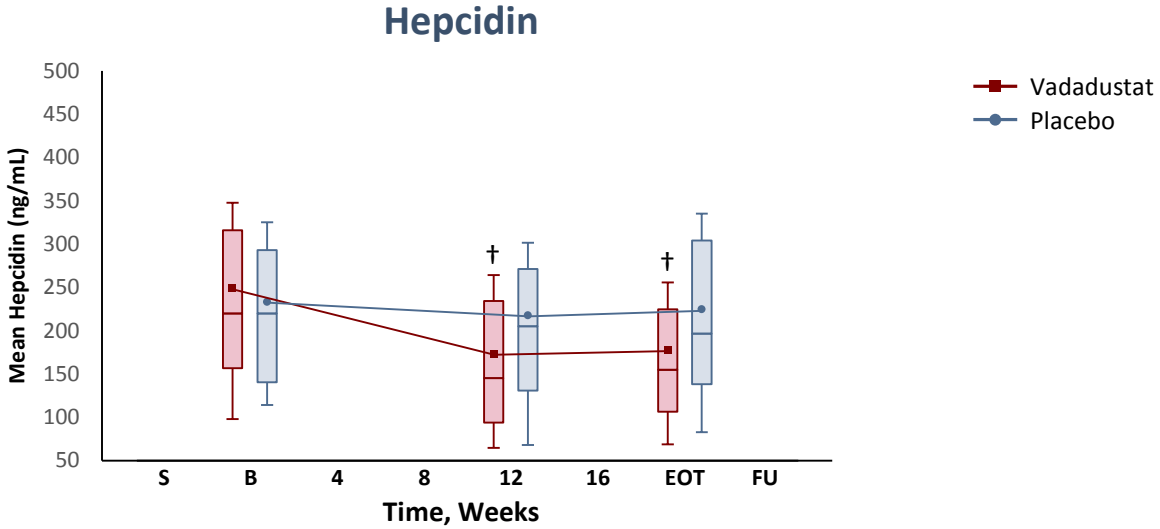
Vadadustat Decreased Serum Hepcidin and Ferritin and Increased Total Iron-Binding Capacity







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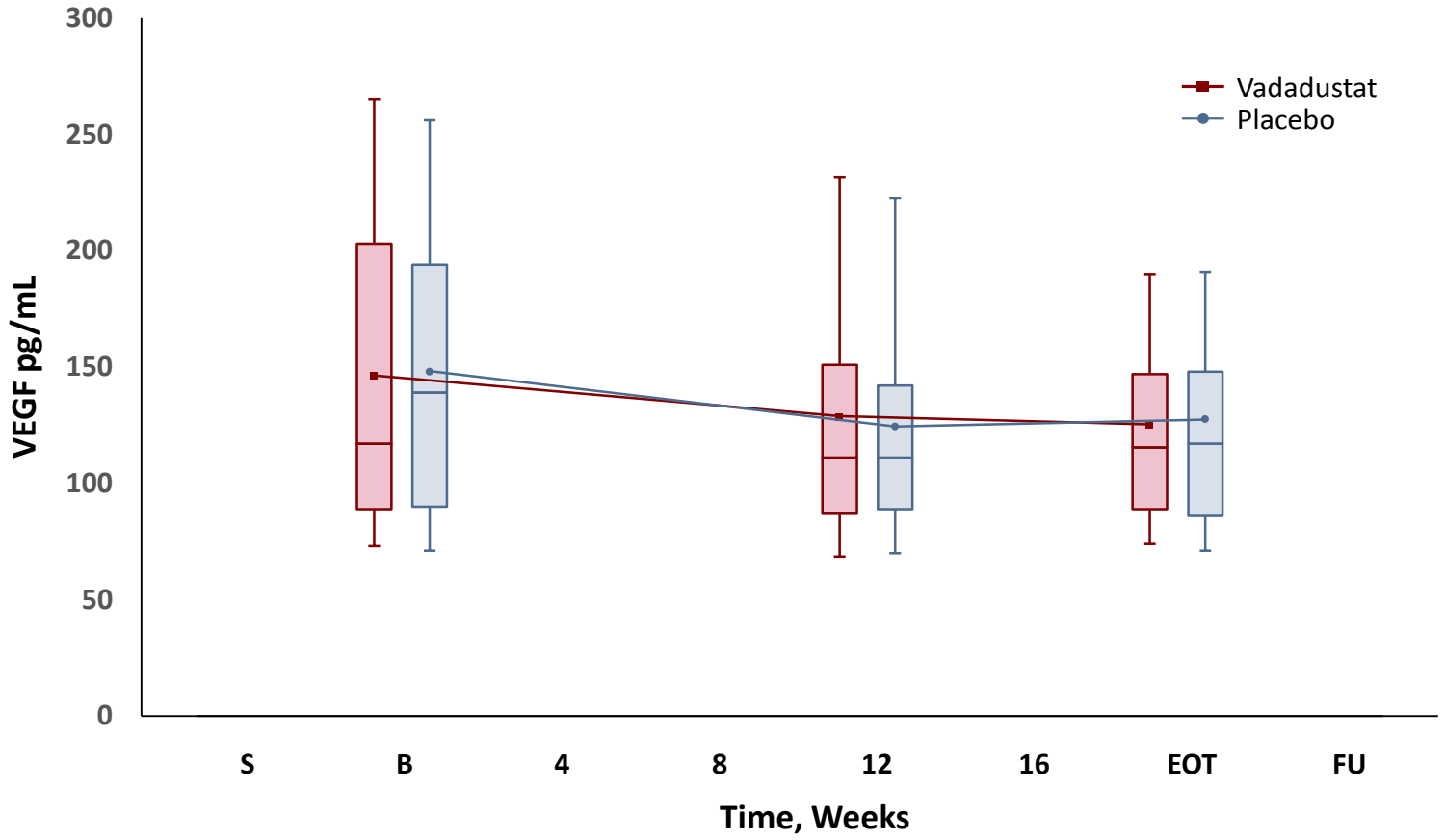
Vadadustat was Generally Well Tolerated in Phase 2b Study, with no Safety Concern Identified

		Vadadustat N = 138	Placebo N = 72
Treatment Emergent Adverse Events	Evenly distributed across groups	103 (74.6%)	53 (73.6%)
Serious Adverse Events (SAEs)	Imbalance driven by how renal SAEs were reported	33 (23.9%)	11 (15.3%)
Non-Renal SAEs	No signal or pattern identified	20 (14.5%)	9 (12.5%)
Renal SAEs	Variability in classification None considered treatment related	13 (9.4%)[1]	2 (2.8%)
	➡ **Dialysis initiations -** objective measure for severity of renal SAEs	11 (8.0%)[1]	7 (9.7%)[2]
Deaths	Based on TREAT and CHOIR, the expected deaths were 2-4 in vadadustat & 1-2 in placebo	3	0

[1] Includes 3 renal SAEs that occurred > 3 weeks after end of treatment
[2] Includes 1 dialysis initiation that occurred 1 week after the end of treatment

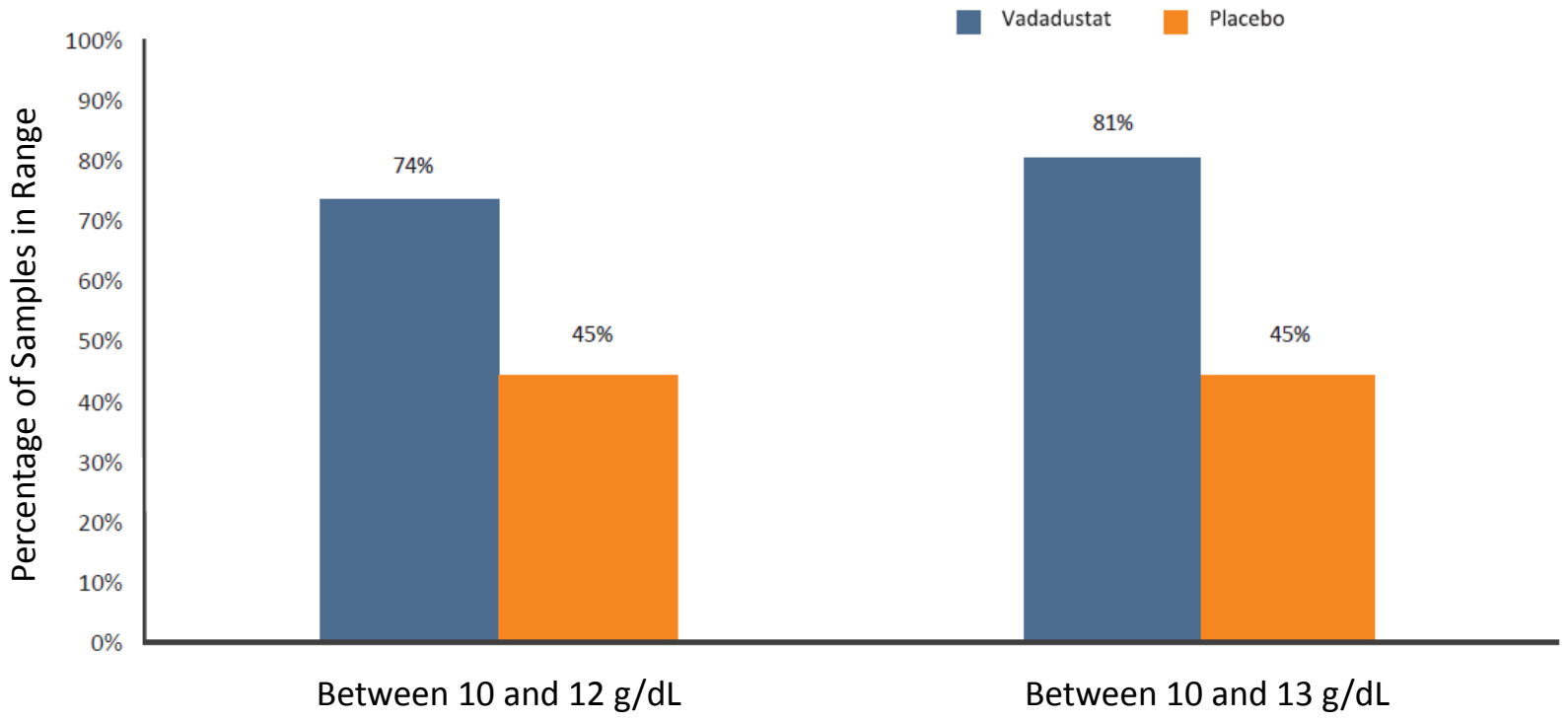
No Change From Baseline Observed in VEGF Levels (Regulated by HIF-1α)



B=baseline; EOT=end of treatment; FU=follow-up; S=screening; VEGF=vascular endothelial growth factor.
Box and whiskers plot represents 10th, 25th, 75th, and 90th percentiles, median is the line within the box, mean is symbol within the box

Dosing Algorithm Designed to Minimize Excursions Also Maintained Hb Over Time Effectively Between 10 and 12 g/dL

% of all Hb measurements from week 8 to week 20 that are within 2 ranges (10-12, 10-13)



Phase 2b Study – Summary

- Treatment with vadadustat using the prescribed dosing algorithm resulted in:
  - Increases in Hb that were maintained at the clinically desired range while minimizing excursions ≥13.0 g/dL
  - A reticulocyte profile that closely mimicked the predicted response to altitude-associated hypoxia
  - Improvements in iron mobilization consistent with previous studies
  - Maintenance of stable Hb in patients that were converted from ESA to vadadustat (Group 3)
- Safety profile consistent with previous studies
  - AEs were balanced between vadadustat and placebo and were those expected in a trial conducted in this patient population
  - The imbalance in SAEs was primarily related to renal events which was attributable to variability in AE reporting

Acknowledgments

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