Efficacy and Dose Requirements of Vadadustat Are Independent of Systemic Inflammation and Prior Erythropoiesis-Stimulating Agent (ESA) Dose in Patients With Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD)

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Introduction

Chronic Kidney Disease (CKD) and Inflammation

- In patients with CKD, both absolute and functional iron deficiency and inflammation can contribute to resistance to ESAs.[1] Patients with CKD may therefore require high doses of ESAs, which are associated with hemoglobin (Hb) excursions and an increased risk of serious adverse events and death[2]

Vadadustat

- Vadadustat is a small molecule inhibitor of hypoxia-inducible factor prolyl-hydroxylase domains (HIF-PHDs) that is dosed orally, and is currently in Phase 3 studies for the treatment of anemia secondary to CKD in patients with NDD-CKD and dialysis-dependent (DD-) CKD
- In a Phase 2b study, vadadustat increased Hb levels in patients with NDD-CKD in a controlled and predictable manner with few Hb excursions ≥13 g/dL and improved iron homeostasis by decreasing hepcidin and increasing transferrin levels[3]
- When vadadustat was administered to patients with DD-CKD in a Phase 2 study, Hb was maintained in the target range with only one Hb excursion of 13.1 g/dL. Repeated dosing over a 16-week period did not result in the accumulation of vadadustat or its metabolites[4]
- Here we present a post hoc analysis of data from a Phase 2b trial of vadadustat in patients with NDD-CKD

Demographics and Baseline Characteristics

	Vadadustat (n=138)	Placebo (n=72)
Age (years)	66.6 ± 10.0	65.9 ± 12.3
Gender		
Male	57 (41.3)	38 (52.8)
Female	81 (58.7)	34 (47.2)
Race		
White/Caucasian	83 (60.1)	49 (68.1)
Black/African American	49 (35.5)	19 (26.4)
Other	6 (4.3)	4 (5.5)
Body Mass Index, kg/m²	31.9 ± 6.6	30.0 ± 7.3
eGFR, mL/min/1.73 m²	25.2 ± 10.4	25.0 ± 11.7
CKD Status[a]		
G3a/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 and large vessel disease	78 (56.5)	36 (50.0)
Other	5 (3.6)	7 (9.7)
Hepcidin, ng/mL	249.1 ± 133.5	233.1 ± 123.5
C-Reactive Protein, mg/dL	0.7 ± 1.0	0.5 ± 0.6

Data are presented as n (%) or mean ± standard deviation.
eGFR, estimated glomerular filtration rate.
[a]Stratified by eGFR (mL/min/1.73 m²): G3a/b, 30–59; G4, 15–29; G5,<15.

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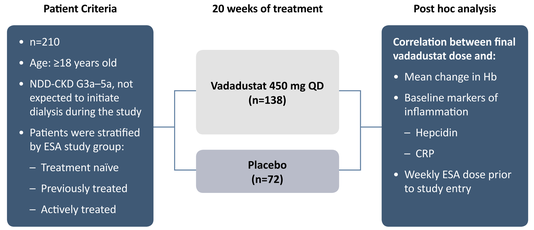
Study Design

- Post hoc analysis of a Phase 2b, multicenter, randomized, double-blind, placebo-controlled study in patients with NDD-CKD



QD, once daily.
Doses stated are initial doses. From Week 4, the actual dose could vary from 150–600 mg QD.

- Patients were randomized 2:1 for vadadustat versus placebo
- For the vadadustat treatment arm, the number of study participants actively treated with ESAs at baseline was 27/138 (19.6%)

Results

Mean Hb Levels Over the Course of Study Duration (MITT Population[a])

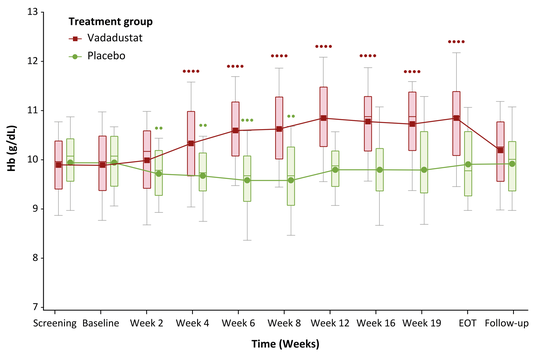
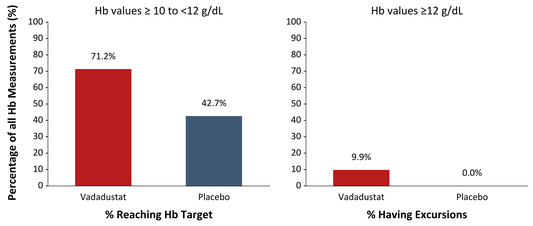


Figure taken from Pergola et al. *Kidney Int* 2016;90:1115–22.
EOT, end of treatment; MITT, modified intent to treat; RBC, red blood cell.
[a] The MITT population included all randomized subjects who received at least one dose of study medication and had a Hb and RBC count measurement at Screening or baseline, and at least one post-baseline measurement for Hb and RBC count.
Box-and-whisker plots represent 10th, 25th, 75th and 90th percentiles. Medians are indicated by the line within the boxes, means by the symbol within the boxes. Comparison of baseline to weekly and EOT means for vadadustat or placebo groups was performed with a 2-sided Student t-test at α=0.05: **p<0.01; ***p<0.001; ****p<0.0001.

- Vadadustat increased and maintained Hb levels in patients with NDD-CKD throughout the 20-week study
- By Week 2, the mean Hb levels for patients in the vadadustat group had increased significantly from baseline; Hb levels plateaued by Weeks 6–8 and were sustained throughout the remainder of study duration
- Throughout the 20-week study, Hb excursions ≥13 g/dL occurred in 4.3% (6/138) of patients administered vadadustat

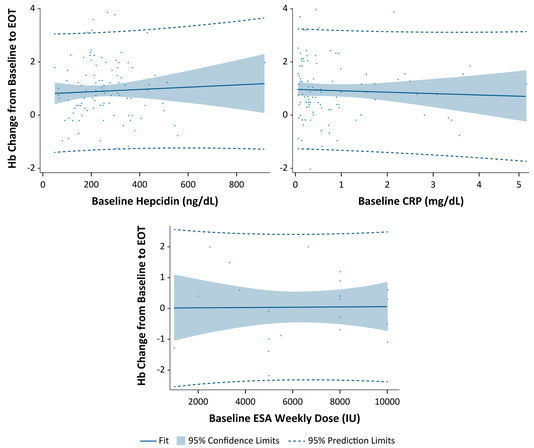
Results (continued)

Percentage of all Hb Measurements from Weeks 8 to 20 (MITT Population)



- From Weeks 8 to 20, 71.2% of all Hb measurements in patients administered vadadustat were in the target range of ≥10 to <12 g/dL, compared to 42.7% of Hb measurements in patients administered placebo
- Overall, 9.9% of Hb measurements were ≥12.0 g/dL in patients administered vadadustat versus none in the placebo group

Change in Hb from Baseline to End of Treatment With Respect to Baseline Markers of Inflammation and Baseline Weekly ESA Dose



- No correlation was found between the magnitude of the mean increase in Hb from baseline to Week 20 and markers of inflammation assessed at baseline (hepcidin, p=0.6; CRP, p=0.6)
- Similarly, there was no correlation between the magnitude of the mean increase in Hb and the mean weekly ESA dose in patients actively treated with ESAs at baseline (p=0.9)

Safety

- The overall incidence of adverse events (AEs) was comparable between the vadadustat (74.6%) and placebo (73.6%) groups
- Serious AEs (SAEs) occurred in 23.9% and 15.3% of the vadadustat- and placebo-treated patients, respectively
  - The imbalance was driven by renal SAE reporting – renal SAEs requiring dialysis initiation occurred in 8.0% and 9.7% of the vadadustat- and placebo-treated patients, respectively

Results (continued)

Final Vadadustat Dose at Week 20 vs Baseline Inflammatory Markers and Weekly ESA Dose

	Baseline Hepcidin (ng/mL)		Baseline CRP (mg/dL)		Weekly ESA dose prior to study entry (units/week)[a]	
Final dose (mg/day)	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
150	18	221.7 ± 112.4	18	0.34 ± 0.50	0	–
300	22	246.7 ± 136.0	22	0.78 ± 1.36	4	9083 ± 7530
450	47	268.4 ± 157.9	46	0.66 ± 0.90	12	6597 ± 2961
600	51	242.0 ± 112.0	51	0.83 ± 0.96	11	6841 ± 2748
p-value		0.6		0.3		0.4

[a]Only patients actively treated with ESA therapy at baseline were included in this analysis.

- The vadadustat mean dose at Week 19 was 450 mg QD, the same as the starting dose (at study entry)
- The majority of patients in the vadadustat group achieved and maintained a stable Hb level with ≤2 dose adjustments throughout the 20-week treatment period
- No correlation was found between the final vadadustat dose at Week 20 and:
  - Markers of inflammation assessed at baseline (hepcidin, p=0.6; CRP, p=0.3), or
  - Weekly ESA dose in patients undergoing active treatment with ESAs (p=0.4)

Conclusions

- This Phase 2b study of vadadustat administered to patients with NDD-CKD showed that vadadustat raised and maintained Hb levels in a controlled and predictable manner
  - There were few Hb excursions ≥13 g/dL
- Vadadustat improved iron absorption and mobilization[3]
- This post hoc analysis showed that the Hb response and dose requirement for the correction and maintenance of Hb were independent of underlying systemic inflammation and baseline ESA dose
- Vadadustat was generally well-tolerated in patients with NDD-CKD: the overall incidence of AEs/SAEs were comparable between vadadustat- and placebo-treated patients and were within expectations of the NDD-CKD population
- These results support the continued development of vadadustat for the treatment of anemia in patients with NDD-CKD

References

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