Vadadustat Maintains Hemoglobin (Hb) Levels in Dialysis-Dependent Chronic Kidney Disease (DD-CKD) Patients Independent of Systemic Inflammation or Prior Dose of Erythropoiesis-Stimulating Agent (ESA)

Volker H. Haase,[1] Glenn Chertow,[2] Geoffrey Block,[3] Pablo Pergola,[4] Qing Zuraw,[5] Zeeshan Khawaja,[5] Amit Sharma,[5] Bradley J. Maroni,[5] Peter A. McCullough[6]

[1]Vanderbilt University, Nashville, TN; [2]Stanford University School of Medicine, Palo Alto, CA; [3]Denver Nephrology, Denver, CO; [4]Renal Associates PA, San Antonio, TX; [5]Akebia Therapeutics, Inc., Cambridge, MA; [6]Baylor University Medical Center, Dallas, TX

Introduction

- Partial correction of anemia with ESAs is the cornerstone of therapy for patients undergoing dialysis[1]
  - ESA administration often results in substantial Hb oscillations and excursions above target range, which are associated with increased risk of cardiovascular disease and death[2,3]
- Levels of the inflammation marker hepcidin are increased in many patients with DD-CKD, which leads to decreased iron absorption and recycling[4]
- Vadadustat is an oral inhibitor of hypoxia-inducible factor prolyl-hydroxylase domains (HIF-PHDs) in development for the treatment of anemia in patients with non-dialysis dependent CKD (NDD-CKD) and DD-CKD
- In a Phase 2 study, vadadustat increased Hb levels in patients with DD-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[5]
  - A post hoc analysis on this study was performed to explore the relationship between final vadadustat dose, mean change in Hb, baseline markers of inflammation (hepcidin and C-reactive protein [CRP]), and weekly ESA dose prior to study entry

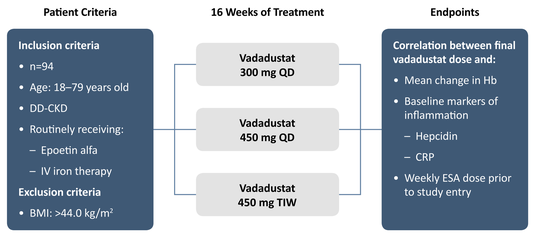
Demographics and Baseline Characteristics

	Vadadustat Treatment Group		
	300 mg QD (n=30)	450 mg QD (n=33)	450 mg TIW (n=31)
Age (years)	55.5 ± 12.4	59.4 ± 11.6	57.8 ± 8.3
Gender			
Male	17 (56.7)	18 (54.5)	19 (61.3)
Female	13 (43.3)	15 (45.5)	12 (38.7)
Body Mass Index (kg/m²)	29.8 ± 7.7	29.6 ± 6.0	29.2 ± 5.4
Race			
Black/African American	6 (20.0)	9 (27.3)	9 (29.0)
White/Caucasian	24 (80.0)	21 (63.6)	19 (61.3)
Other	0 (0.0)	3 (9.1)	3 (9.7)
Etiology of CKD[a]			
Diabetes	16 (53.3)	23 (69.7)	21 (67.7)
Hypertension and large vessel disease	15 (50.0)	17 (51.5)	21 (67.7)
Other	7 (23.3)	4 (12.1)	1 (3.2)
Time on Dialysis (years)	4.9 ± 4.3	4.9 ± 6.7	3.9 ± 3.6
Epoetin Alfa Dose (units/week)	4460 ± 3595	5986 ± 3861	6884 ± 5223
Hemoglobin (g/dL)	10.4 ± 0.6	10.6 ± 0.6	10.5 ± 0.5
Hepcidin (ng/mL)	102.6 ± 58.9	119.6 ± 54.8	105.4 ± 46.8
C-Reactive Protein (mg/dL)	1.2 ± 2.4	1.1 ± 1.5	1.6 ± 3.3

Data are presented as n (%) or mean ± standard deviation.
[a]More than one etiology of CKD could be given per patient.

Study Design

- Post hoc analysis of a randomized, multicenter, open-label, Phase 2 study in patients with DD-CKD

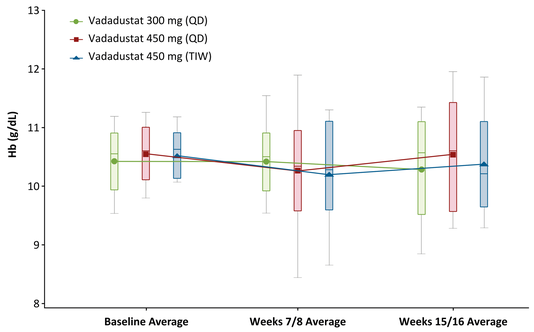


BMI, body mass index; CRP, C-reactive protein; IV, intravenous; QD, once daily; TIW, three times weekly

- Patients were converted from ESA to vadadustat and assigned to one of the three sequential dose cohorts
- From Week 8, vadadustat dose could be adjusted (150–600 mg) as needed to maintain Hb target

Results

Mean Hb Levels Over Time by Dose Cohort (MITT Population[a])



MITT, modified intent-to-treat.
[a] The MITT population included all randomized subjects who were assigned to study medication, received at least one dose of study medication, and had a pre-dose average and at least one post-Baseline Hb measurement.
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.

- Hb levels were assessed in the MITT population; the post hoc analysis was also performed using this patient population
- Each vadadustat dose cohort maintained Hb levels for the duration of the study
- There was no statistically significant change in mean Hb from baseline to Week 7/8 or from baseline to Week 15/16 for any of the three dose cohorts
- There was no statistically significant difference in the magnitude of the change in mean Hb level from baseline to Week 7/8 or from baseline to Week 15/16 between dose cohorts

Results (continued)

Mean Hb Change from Baseline, by Dose Cohort (MITT Population)

	Vadadustat Treatment Group					
	300 mg QD (n=30)		450 mg QD (n=33)		450 mg TIW (n=31)	
Time Period	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
Baseline to Week 7/8	28	0.00 (-0.35, 0.35)	28	-0.29 (-0.66, 0.09)	26	-0.36 (-0.81, 0.10)
Baseline to Week 15/16	24	-0.03 (-0.41, 0.35)	24	-0.07 (-0.48, 0.34)	21	-0.14 (-0.65, 0.37)

CI, confidence interval.

Difference in Mean Hb Change between Dose Cohorts (MITT Population)

	Vadadustat Treatment Group		
	300 mg QD vs 450 mg QD	300 mg QD vs 450 mg TIW	450 mg QD vs 450 mg TIW
Time Period	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Baseline to Week 7/8	0.29 (-0.25, 0.82)	0.36 (-0.19, 0.90)	0.07 (-0.48, 0.61)
Baseline to Week 15/16	0.04 (-0.54, 0.61)	0.10 (-0.49, 0.70)	0.07 (-0.53, 0.66)

Final Vadadustat Dose vs Baseline Markers of Systemic Inflammation and Weekly ESA Dose Prior to Study Entry

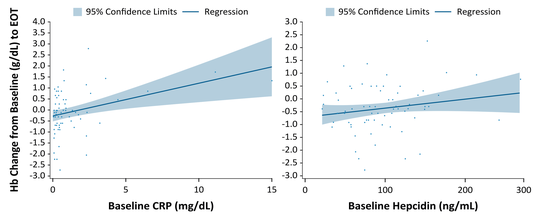
	Baseline Hepcidin (ng/mL)		Baseline CRP (mg/dL)		Weekly ESA dose prior to study entry (units/week)	
Final dose (mg/day)	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
QD Vadadustat Dose						
150	6	144.1 ± 106.1	6	1.8 ± 1.9	6	4816 ± 4256
300	18	106.5 ± 53.2	18	0.8 ± 0.9	18	5005 ± 3699
450	20	116.5 ± 53.5	20	1.2 ± 2.8	20	7025 ± 4963
600	19	100.6 ± 42.6	19	1.0 ± 1.5	19	8152 ± 4834
p-value		0.4		0.6		0.3
TIW Vadadustat Dose						
150	1	87.9	1	0.8	1	8000
300	4	88.4 ± 33.0	4	0.6 ± 0.3	4	6750 ± 5909
450	12	125.1 ± 62.0	12	2.6 ± 4.7	12	8075 ± 7561
600	14	94.4 ± 30.7	14	1.2 ± 1.9	14	6742 ± 4754
p-value		0.3		0.6		0.9

SD, standard deviation.

- No association was found between the final vadadustat dose required, achieved Hb, and markers of systemic inflammation assessed at baseline
- Similarly, there was no statistical correlation between the final vadadustat dose and the mean weekly ESA dose prior to study entry (p=0.9)

Results (continued)

Change in Hb from Baseline to EOT vs Baseline Markers of Systemic Inflammation



- A linear regression analysis was performed to assess the Hb change from baseline to EOT for each vadadustat dose group. Hb was the dependent variable and baseline values of hepcidin/CRP were independent variables
  - No association was observed between the final Hb change and CRP (p=0.08) or hepcidin (p=0.12)

Safety

- The overall incidence of adverse events (AEs) was comparable across the vadadustat dosing groups (86.7% for 300 mg QD, 78.8% for 450 mg QD, and 83.9% for 450 mg TIW) and were within expectations of the frequency observed in pooled studies of dialysis patients with similar comorbidities[5]
- Serious AEs (SAEs) occurred in 6.7%, 18.2% and 16.1% of the 300 mg QD, 450 mg QD, and 450 mg TIW vadadustat dosing groups, respectively. None were reported by the investigators as related to vadadustat

Conclusions

- In patients with CKD undergoing dialysis, whose anemia was maintained previously with ESA therapy, vadadustat treatment resulted in baseline-stable Hb measurements for the duration of the study
- Similarly, there was no difference in the magnitude of the mean Hb change from baseline between different dose cohorts
- The Hb response and vadadustat dose requirements for Hb maintenance were independent of underlying markers of systemic inflammation and prior ESA dose in patients with DD-CKD
- Vadadustat was generally well-tolerated under the studied condition[5]
  - There were no apparent differences in the type or frequency of AEs reported across dosing groups
  - The observed SAEs were consistent with events described in the dialysis population with multiple comorbidities
- These results support the continued development of vadadustat for the treatment of anemia in patients with DD-CKD

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. *Kidney Int Suppl* 2012;2:282.
2. Fishbane S, Berns JS. *Nephrol Dial Transplant* 2007;22:2129–32.
3. Gilbertson DT, Hu Y, Peng Y, et al. *ASN Kidney Week 2015.*
4. Ganz T, Nemeth E. Iron *Semin Nephrol* 2016;36:87–93.
5. Haase VH, Hartman CS, Maroni B, et al. *National Kidney Foundation Spring Clinical Meeting 2016.* Abstract 171.

Acknowledgments

The authors thank Dr. Ramin Farzaneh-Far for initial participation in abstract development for this poster. We also thank Lucid Partners Ltd. for poster layout. The study was funded by Akebia Therapeutics, Inc.
To download an electronic copy of the poster, please visit: www.akebia.com/media/publications.

PRESENTED AT ASN KIDNEY WEEK 2016