Vadadustat—a Novel, Oral Treatment for Anemia of CKD—Maintains Stable Hemoglobin Levels in Dialysis Patients Converting From Erythropoiesis-Stimulating Agent (ESA)

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Abstract

Background: Vadadustat is a novel, oral agent that stimulates erythropoiesis by stabilizing hypoxia-inducible factor. In pre-dialysis patients with chronic kidney disease, vadadustat results in controlled increases in hemoglobin (Hb) and enhances iron utilization. Here we present data from a Phase 2 trial of vadadustat in hemodialysis (HD) patients.

Methods: A multi-center, open-label, 16-week trial to assess Hb response and safety of vadadustat enrolled 94 HD patients (Hb 9-12 g/dL) maintained on ESA therapy prior to study entry. Patients were converted to vadadustat, and assigned to 1 of 3 oral dose cohorts. The primary efficacy analysis was to evaluate mean Hb changes from baseline at weeks 7/8, and weeks 15/16. Plasma concentrations of vadadustat and its O-glucuronide and acyl-glucuronide metabolites were determined pre- and post-dialysis at weeks 2 and 16.

Results: Vadadustat maintained stable Hb levels in all 3 dose cohorts during the 16 week treatment period following conversion from ESA.

Dose Cohort	Mean Hb Levels (g/dL)*		
	Baseline	Weeks 7/8	Weeks 15/16
300 mg QD	10.4	10.4	10.3
450 mg QD	10.6	10.3	10.5
450 mg TIW	10.5	10.2	10.4

QD, one dose per day; TIW, three doses per week.
**Modified intent-to-treat (MITT) population*

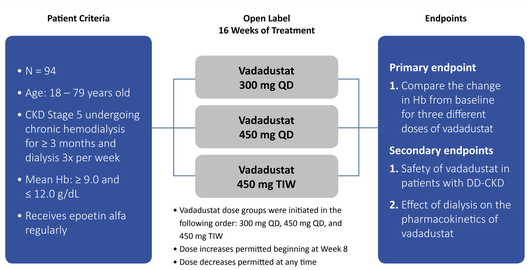
One subject in the 300mg QD cohort had a single Hb excursion to 13.1 g/dL. Serious adverse events (SAEs) were reported in 13 subjects (13.8%), within the expected range (13-17 subjects). No drug-related SAEs, nor deaths, were reported. Plasma concentrations of vadadustat and its glucuronide metabolites exhibited dose-related increases across the 3 treatment cohorts. The dialysis procedure did not impact the plasma level of vadadustat, but the expected decreases in the glucuronide metabolites following dialysis were observed.

Conclusions: Vadadustat safely and effectively maintained Hb levels in dialysis patients who were converted from injectable ESAs. Vadadustat can be administered without regard to the patient's dialysis schedule.

Background

- Current standard of care for anemia is ESAs, which are associated with Hb excursions and an increased risk of SAEs and death
- Vadadustat is an oral inhibitor of hypoxia-inducible factor prolyl-hydroxylases (HIF-PHs) in development for treatment of anemia in CKD patients not on dialysis and those requiring dialysis
- Vadadustat has been well tolerated in healthy volunteers and CKD patients
  - 15 completed studies and over 29,000 patient exposure days (over 20,000 patient exposure days in placebo-controlled trials)
  - Direct dose-response relationship observed between drug dose and erythropoietin (EPO) and Hb levels
  - Facilitates iron homeostasis by decreasing hepcidin and ferritin, and increasing total-iron binding capacity (TIBC)
- Here we present data from a Phase 2 trial of vadadustat in patients with dialysis-dependent CKD (DD-CKD)

Study Design



Demographics and Baseline Characteristics

	300 mg QD n=30	450 mg QD n=33	450 mg TIW n=31	All Patients N=94
Gender (female)	13 (43.3%)	15 (45.5%)	12 (38.7%)	40 (42.6%)
Race				
White/Caucasian	24 (80.0%)	21 (63.6%)	19 (61.3%)	64 (68.1%)
Black or African American	6 (20.0%)	9 (27.3%)	9 (29.0%)	24 (25.5%)
Other	0 (0.0%)	3 (9.1%)	3 (9.7%)	6 (6.4%)
Age (mean ± SD; years)	55.5 (± 12.4)	59.4 (± 11.6)	57.8 (± 8.3)	57.6 (± 10.9)
Body Mass Index (mean ± SD; kg/m^2)	29.8 (± 7.7)	29.6 (± 6.0)	29.2 (± 5.4)	29.5 (± 6.4)
Time on Dialysis (mean ± SD; years)	4.9 (± 4.3)	4.9 (± 6.7)	3.9 (± 3.6)	4.6 (± 5.0)
Baseline Hemoglobin (mean ± SD; g/dL)	10.4 (± 0.6)	10.6 (± 0.6)	10.5 (± 0.5)	10.5 (± 0.7)
Baseline Ferritin (mean ± SD; ng/mL)	763 (± 471)	782 (± 465)	808 (± 431)	784 (± 451)
Etiology of CKD				
Diabetes	16 (53.3%)	23 (69.7%)	21 (67.7%)	60 (63.8%)
Hypertension and Large Vessel Disease	15 (50.0%)	17 (51.5%)	21 (67.7%)	53 (56.4%)
Other	7 (23.3%)	4 (12.1%)	1 (3.2%)	12 (12.8%)

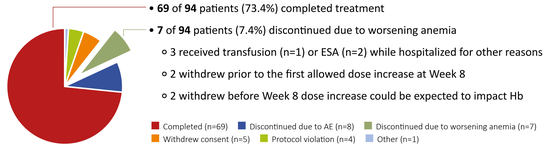
SD, standard deviation

Analysis Populations

	300 mg QD n=30	450 mg QD n=33	450 mg TIW n=31	All Patients N=94
Intent-to-Treat Population	30 (100.0%)	33 (100.0%)	31 (100.0%)	94 (100.0%)
Modified Intent-to-Treat Population	30 (100.0%)	33 (100.0%)	31 (100.0%)	94 (100.0%)
Per Protocol Population	21 (70.0%)	23 (69.7%)	20 (64.5%)	64 (68.1%)

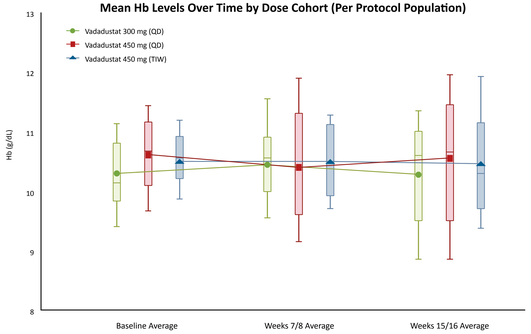
Population Definitions:
- **Intent-to-treat (ITT) population** – included all randomized patients who received at least one dose of study medication.
- **Modified intent-to-treat (MITT) population** – included patients in the ITT population who had a pre-dose average and at least one post-baseline Hb measurement. All efficacy endpoints were analyzed using the MITT population.
- **Per protocol (PP) population** – included patients in the MITT population who had efficacy data through Week 16, had a study medication compliance of ≥ 80%, and did not have any major protocol deviations. The primary efficacy endpoint was analyzed using the PP population.

Patient Disposition



Results

Vadadustat maintained stable Hb levels in all 3 dose cohorts



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

Mean Hb Change (g/dL) By Dose Cohort (Per Protocol Population)

Study Stage	300 mg QD n=30	450 mg QD n=33	450 mg TIW n=31
Baseline to Week 8 Mean (95% CI)	0.15 (-0.28, 0.58) n = 21	-0.22 (-0.63, 0.19) n = 23	-0.01 (-0.35, 0.33) n = 20
Baseline to Week 16 Mean (95% CI)	-0.02 (-0.46, 0.42) n = 21	-0.04 (-0.46, 0.39) n = 23	-0.04 (-0.53, 0.46) n = 20

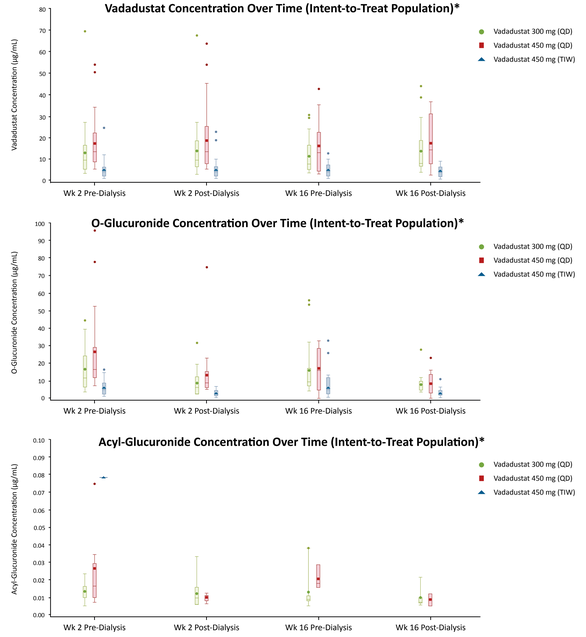
- Mean change in Hb level within each dose cohort remained stable throughout the study (e.g. baseline to Week 16 ranged from -0.02 g/dL to -0.04 g/dL)

Difference in Mean Hb Change (g/dL) Between Dose Cohorts (Per Protocol Population)

Study Stage	300 mg QD vs. 450 mg QD	300 mg QD vs. 450 mg TIW	450 mg QD vs. 450 mg TIW
Baseline to Week 8 Mean (95% CI)	0.37 (-0.16, 0.90)	0.16 (-0.39, 0.71)	-0.21 (-0.75, 0.33)
Baseline to Week 16 Mean (95% CI)	0.02 (-0.59, 0.62)	0.02 (-0.61, 0.64)	0.00 (-0.61, 0.61)

- There was no significant difference in the mean Hb change from baseline between the 3 dose cohorts

Plasma concentrations of vadadustat and its O-glucuronide metabolite exhibited dose-related increases



* Box-and-whisker plots representing 10th, 25th, 75th, and 90th percentiles; median is the line within the box; mean is symbol within the box.

- Limited number of patients in the 300 mg QD and 450 mg QD groups had detectable levels of the acyl-glucuronide metabolite of vadadustat
- Only 1 patient in the 450 mg TIW dose group had detectable levels of the acyl-glucuronide metabolite of vadadustat; detected at the Week 2 pre-dialysis time point

Results (continued)

Adverse events were balanced across the 3 dose cohorts

Summary of Adverse Events (AEs) and Serious Adverse Events (SAEs) (Intent-to-Treat Population)

	300 mg QD n=30	450 mg QD n=33	450 mg TIW n=31	All Patients N=94
Number of AEs	110	95	89	294
Patients With ≥1 AE	26 (86.7%)	26 (78.8%)	26 (83.9%)	78 (83.0%)
Patients With ≥1 SAE	2 (6.7%)	6 (18.2%)	5 (16.1%)	13 (13.8%)
Patients With SAE Reported as Related	0	0	0	0
Deaths	0	0	0	0

- The observed SAEs were consistent with events described in the dialysis population with multiple comorbidities
- No drug-related SAEs or deaths were reported

Observed vs. Expected AEs

	Observed Count in Study CI-0011	Expected Count for Study CI-0011 Based on Published DD-CKD Data‡
	n	n
Patients With ≥1 SAE	13	13–17
Deaths	0	6
Non-Fatal or Fatal Stroke and Transient Ischemic Attack	0	7
Non-Fatal Myocardial Infarction	2	2

‡Expected counts were estimated from USRDS data, except for SAE counts, which were estimated from pooled dialysis study publications: *Van Buren et al., AJKD, 66(3): 479–88, 2015; Besarab et al., BMC Nephrology, 13: 95, 2012; Covic et al., NDT, 25: 2722–2730, 2010; Fishbane et al., NEJM, 368:307–19, 2013.*

Conclusions

- This Phase 2 study demonstrated the safety and efficacy of vadadustat in dialysis patients
- Across the 3 dosing regimens, Hb was maintained in the desired range with only one Hb excursion to 13.1 g/dL observed
- Plasma concentrations of vadadustat and its O-glucuronide metabolite exhibited dose-related increases
- The dialysis procedure did not impact the plasma concentrations of vadadustat, whereas the plasma concentration of the O-glucuronide metabolite was lower following the dialysis treatment
- Of the limited number of patients with detectable levels of the acyl-glucuronide metabolite of vadadustat, plasma concentrations were lower in the post-dialysis samples compared to the pre-dialysis samples
- Repeated dosing of vadadustat over a 16-week period did not result in the accumulation of vadadustat or its metabolites
- There were no apparent differences in the type or frequency of AEs reported across the 3 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 dialysis patients

Acknowledgments

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