Vadadustat, a Novel, Oral Treatment for Anemia of CKD, Maintains Stable Hemoglobin Levels in Dialysis Patients Converting from Erythropoiesis-Stimulating Agents

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Abstract

Background: Vadadustat is a novel, oral agent that stimulates erythropoiesis by stabilizing hypoxia-inducible factor (HIF). Prior studies in patients with non-dialysis dependent chronic kidney disease (NDD-CKD) have shown that vadadustat results in controlled, dose-dependent increases in hemoglobin (Hb) and enhances iron mobilization and utilization. Here we present data from a Phase 2 trial of vadadustat in hemodialysis patients.

Methods: A multi-center, open-label, 16-week trial was designed to assess Hb response, safety, and tolerability of vadadustat. The trial enrolled 94 hemodialysis patients (Hb 9–12 g/dL), who were maintained on erythropoiesis-stimulating agents (ESAs) prior to study entry. Patients were converted from ESA to vadadustat, and assigned to 1 of 3 dose cohorts: 300 mg once daily (QD); 450 mg QD; or 450 mg three times weekly (TIW). The primary efficacy analysis was to evaluate mean Hb changes from baseline at weeks 7/8, and weeks 15/16. From week 8, dose could be adjusted as needed to maintain Hb. All patients were iron replete at baseline and throughout the study; IV iron use was allowed.

Results: Vadadustat maintained stable Hb levels in all 3 dose cohorts during the 16-week treatment period following conversion from ESAs. One patient in the 300 mg QD cohort had a single Hb excursion to 13.1 g/dL. Adverse events (AEs) were balanced across the 3 cohorts. Serious adverse events (SAEs) were reported in 13 patients (13.8%), which was within the expected range (13–17 patients). No drug-related SAEs, nor deaths, were reported.

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

Modified intent-to-treat (MITT) population

Conclusions: Vadadustat safely and effectively maintained Hb levels in dialysis patients who were converted from injectable ESAs.

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
  - 13 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

Patient Criteria

- N = 94
- Age: 18 – 79 years old
- CKD Stage 5 undergoing chronic hemodialysis for ≥ 3 months and dialysis 3x per week
- Mean Hb: ≥ 9.0 and ≤ 12.0 g/dL
- Receives epoetin alfa regularly

Open Label 16 Weeks of Treatment

Vadadustat 300 mg QD

Vadadustat 450 mg QD

Vadadustat 450 mg TIW

Dose increases permitted beginning at Week 8.
Dose decreases permitted at any time.

Endpoints

Primary endpoint

1. Compare the change in Hb from baseline for three different doses of vadadustat

Secondary endpoints

1. Safety of vadadustat in End Stage Renal Disease patients on dialysis
2. Effect of dialysis on the pharmacokinetics of vadadustat

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Demographics

	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%)
Mean Age (years)	55.5	59.4	57.8	57.6
Mean Body Mass Index (kg/m²)	29.8	29.6	29.2	29.5
Mean time on dialysis (years)	4.9	4.9	3.9	4.6
Mean Hb (g/dL)	10.4	10.6	10.5	10.5
Mean Ferritin (ng/mL)	763	782	808	784
Etiology of CKD				
Diabetes	16 (53.3%)	23 (69.7%)	21 (67.7%)	60 (63.8%)
Hypertension & 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%)

Patient Disposition

	300 mg QD N=30	450 mg QD N=33	450 mg TIW N=31	All Patients N=94
Patients enrolled	30	33	31	94
ITT population	30 (100.0%)	33 (100.0%)	31 (100.0%)	94 (100.0%)
MITT 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%)
Patients discontinuing study early	6 (20.0%)	9 (27.3%)	10 (32.3%)	25 (26.6%)

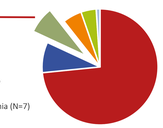
Population Definitions:

- **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.

Reasons for Early Withdrawal

7 of **94** patients (7.4%) discontinued due to worsening anemia

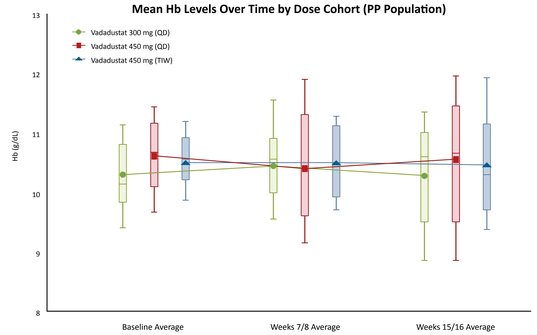
- 3 received transfusion (1) or ESA (2) while hospitalized for other reasons
- 2 withdrew prior to the first allowed dose increase at Week 8
- 2 withdrew before Week 8 dose increase could be expected to impact Hb



Results

Vadadustat maintained stable Hb levels in all 3 dose cohorts

Mean Hb Levels Over Time by Dose Cohort (PP Population)



Box and whiskers 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 (PP 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)

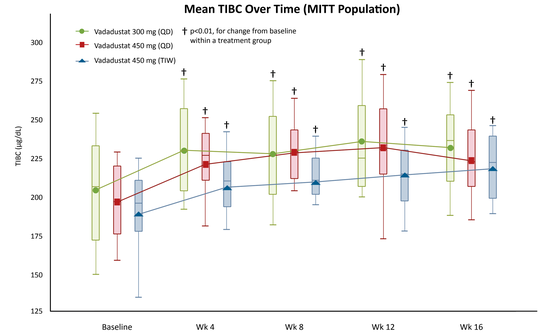
Difference in Mean Hb Change (g/dL) Between Dose Cohorts (PP Population)

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

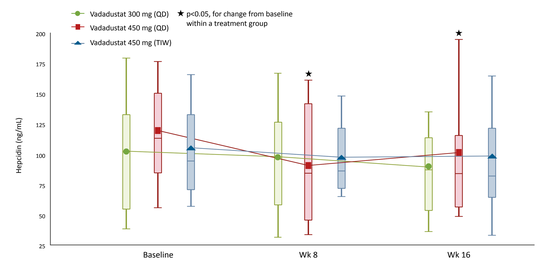
Sustained improvement in iron mobilization, consistent with previous studies

Mean TIBC Over Time (MITT Population)



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

Mean Hepcidin Results Over Time (MITT Population)



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

Results (cont.)

AEs were balanced across the 3 dose cohorts

Summary of AEs and SAEs (ITT 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
Death	0	6
Non-fatal and fatal stroke and TIA	0	7
Non-fatal MI	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
- Improvements in iron mobilization were consistent with previous studies
- 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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