Efficacy and Safety of Vadadustat, an Oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor, Being Evaluated for the Treatment of Anemia Due to Chronic Kidney Disease (CKD) in Japanese Subjects: Results from Phase 2 Studies

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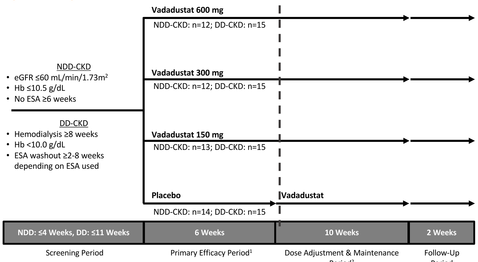
BACKGROUND

- Vadadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) in development for the treatment of anemia associated with non-dialysis-dependent (NDD) and dialysis-dependent (DD) chronic kidney disease (CKD)
- In prior phase 2 studies, vadadustat increased hemoglobin (Hb) levels and improved biomarkers associated with iron utilization and mobilization in anemic CKD patients (Pergola et al., *Kidney Int*, 2016; Martin et al., *AJN*, 2017; Haase et al., *NDT*, 2018)
- Vadadustat was investigated in two phase 2, randomized, double-blind, placebo-controlled trials in Japanese CKD subjects with anemia due to NDD (CI-0021, NCT03054337) and DD (CI-0022, NCT03054350)
- The primary objective of these studies was to assess the dose-response relationship based on the change in Hb concentration following daily oral administration of vadadustat for 6 weeks

METHODS

- The two trials included a 6-week fixed-dose, double-blind, placebo-controlled, primary efficacy period and a 10-week active treatment, dose adjustment and maintenance period
- At the start of the primary efficacy period, subjects were randomized 1:1:1:1 to vadadustat 150 mg, 300 mg, 600 mg, or placebo (**Figure 1**)
- At the start of the dose adjustment and maintenance period, subjects randomized to placebo were switched to vadadustat 150 mg, 300 mg, or 600 mg (**Figure 1**). For all subjects, vadadustat dose was adjusted to achieve target Hb range (10-12 g/dL) during this period.
- Statistical analysis: For the primary efficacy analysis in each study, an analysis of covariance (ANCOVA) model was used in the modified intention-to-treat (mITT) population (**Figure 2**) to compare mean change in Hb from baseline (pretreatment average) to Week 6 between the vadadustat and placebo groups
  - mITT population included all randomized subjects receiving at least one dose of study medication and had pre-treatment Hb average and at least one post-baseline Hb measurement. Safety population included all enrolled subjects receiving at least one dose of study medication
  - Missing values were imputed using last observation carried forward (LOCF)

Figure 1. Design of the NDD and DD trials



eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin.
†Dose increases not permitted; dose decrease as needed per protocol-specified guidelines for rapid Hb rise or Hb>13 g/dL.
‡Dose adjusted per protocol-specified guidelines to achieve target Hb 10-12 g/dL. Subjects randomized to placebo were switched to vadadustat at the beginning of the dose adjustment and maintenance period.

RESULTS

Table 1. Baseline characteristics of NDD and DD subjects: mITT population

	NDD Study		DD Study	
	Vadadustat	Placebo	Vadadustat	Placebo
mITT population, n	37	14	44	14
Age, years	69.8 (11.7)	71.4 (11.6)	63.3 (9.2)	65.7 (11.6)
Female, n (%)	18 (49)	4 (29)	12 (27)	6 (43)
Weight, kg	59.2 (12.4)	58.0 (10.3)	60.7 (14.8)	52.6 (11.0)
BMI, kg/m²	24.3 (4.5)	22.4 (3.4)	24.0 (4.5)	22.4 (4.0)
Diabetes mellitus*, n (%)	12 (32)	8 (57)	22 (50)	6 (43)
Etiology of CKD*, n (%)				
Hypertension	15 (41)	8 (57)	13 (30)	6 (43)
Diabetes	6 (16)	6 (43)	19 (43)	5 (36)
Autoimmune/GN/Vasculitis	8 (22)	2 (14)	13 (30)	5 (36)
Pre-treatment Hb, g/dL	9.7 (0.7)	9.9 (0.6)	9.0 (0.6)	8.97 (0.6)
eGFR, mL/min/1.73m²	17.8 (10.3)	22.0 (9.8)	NA	NA
CKD status	CKD Stage, n (%)		Vintage dialysis, years	
	G3a 1 (3)	0	6.1 (6.5)	7.6 (9.9)
	G3b 6 (16)	2 (14)		
	G4 10 (27)	8 (57)		
	G5 20 (54)	4 (29)		

BMI, body mass index; eGFR, estimated glomerular filtration rate; Hb, hemoglobin.
*Multiple etiologies were allowed in this field. Only the 3 most frequent are listed.
Data are presented as n (%) or mean (SD).
G3a, eGFR 45-59 mL/min/1.73m²; G3b, eGFR 30-44 mL/min/1.73m²; G4, eGFR 15-29 mL/min/1.73m²; G5, eGFR <15 mL/min/1.73m².

Efficacy

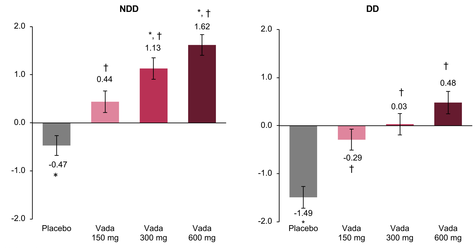
NDD study: mITT population (N=51)

- Statistically significant dose-dependent increases from baseline in mean Hb levels were observed for each vadadustat treatment group vs placebo at the end of the primary efficacy period (Week 6) (**Figure 2** and **Figure 3**)
- All NDD subjects who received vadadustat achieved or exceeded target Hb levels at some point during the trial
  - All subjects initially randomized to vadadustat who completed 16 weeks of treatment (primary efficacy period and dose adjustment and maintenance period) exhibited Hb levels of ≥10 g/dL. 90.9% exhibited Hb levels within the target range of 10 to 12 g/dL at the end of treatment visit and 9.1% exhibited Hb levels above the target range
- No subjects required ESA or RBC transfusion rescue during the primary efficacy period. During the dose adjustment and maintenance period, 1 subject each in the 300 mg vadadustat, 600 mg vadadustat, and placebo converting to vadadustat groups required RBC transfusion rescue; 2 subjects in the 300 mg group and 1 in the 600 mg group required ESA rescue

DD study: mITT population (N=58)

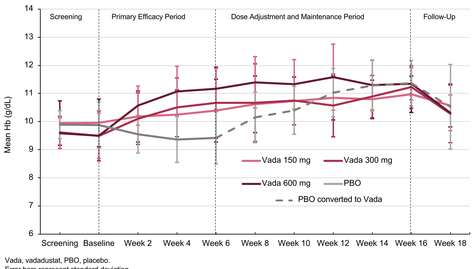
- Statistically significant dose-dependent increases from baseline in mean Hb levels were observed for each vadadustat treatment group vs placebo at the end of the primary efficacy period (Week 6) (**Figure 2** and **Figure 4**)
- Among subjects initially randomized to vadadustat who completed 16 weeks of treatment (primary efficacy period and dose adjustment and maintenance period), 71.4% exhibited Hb levels within the target range of 10 to 12 g/dL at the end of treatment visit, 8.6% exhibited Hb levels above the target range, and 20.0% exhibited Hb levels below the target range
- During the primary efficacy period, 3 (21%) subjects in the placebo group and 1 (8%) in the 600 mg group required RBC transfusion rescue, and 8 (57%) in the placebo group, and 4 (27%), 2 (13%), and 1 (7%) in the 150, 300, and 600 mg groups, respectively, required ESA. During the dose adjustment and maintenance period, 1 (7%) in the 150 mg group required RBC transfusion, and 1 (7%) in the placebo group and 1 (7%) in the 600 mg group required ESA rescue

Figure 2. Observed mean change in Hb (g/dL) between baseline (pretreatment average) and Week 6: mITT population



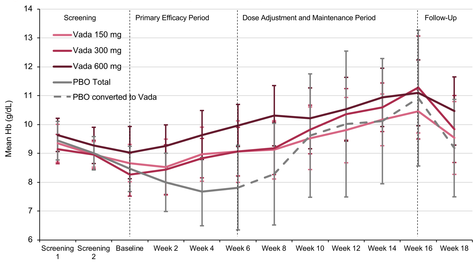
Vada, vadadustat.
Statistical methodology: ANCOVA [P<0.0001]; mITT LOCF. *P<0.05 vs baseline. †P<0.05 vs placebo. Error bars represent standard error.

Figure 3. Mean Hb over time in NDD subjects: mITT population



Vada, vadadustat; PBO, placebo.
Error bars represent standard deviation.

Figure 4. Mean Hb over time in DD subjects: mITT population



Vada, vadadustat, PBO, placebo.
Error bars represent standard deviation.

NDD and DD iron-related parameters: mITT Population

- Statistically significant, dose-dependent decreases in ferritin and hepcidin and increases in total iron binding capacity (TIBC) were observed with vadadustat administration from baseline to Week 6 (**Table 2**)
- In the NDD study, all vadadustat dosages resulted in a statistically significant decrease from baseline in transferrin saturation (TSAT) at Week 6 but not compared with placebo. In the DD study, vadadustat at 300 and 600 mg resulted in a statistically significant decrease in TSAT from baseline, but only the 600 mg dosage was significantly different from placebo (**Table 2**)

Table 2. Mean absolute changes in iron indices from baseline to Week 6 in NDD and DD subjects: mITT population

	NDD Study				DD Study			
Iron Index	Placebo* (n=14)	Vadadustat 150 mg (n=12)	Vadadustat 300 mg (n=12)	Vadadustat 600 mg (n=13)	Placebo* (n=6)	Vadadustat 150 mg (n=11)	Vadadustat 300 mg (n=13)	Vadadustat 600 mg (n=13)
TIBC, µg/dL Mean (SD)	7.6 (23.55)	44.9‡,† (32.99)	75.2‡,† (35.60)	93.8‡,† (44.74)	15.8‡ (8.08)	35.4‡ (28.72)	67.5‡,† (25.72)	80.7‡,† (39.04)
TSAT, % Mean (SD)	-4.72 (8.93)	-4.96‡ (7.34)	-7.3‡† (8.38)	-6.78‡ (10.61)	-2.78 (12.82)	-6.51 (11.62)	-10.14‡ (11.29)	-12.46‡,† (9.54)
Ferritin, ng/mL Mean (SD)	-11.44 (31.41)	-38.48‡ (34.23)	-69.36‡,† (49.97)	-101.54‡,† (57.70)	12.63 (32.42)	-51.20‡,† (58.86)	-68.67‡,† (54.71)	-104.49‡,† (49.56)
Hepcidin, ng/mL Mean (SD)	-3.82 (18.50)	-24.62‡ (20.02)	-40.82‡,† (27.25)	-37.96‡,† (21.08)	-11.80 (13.65)	-53.47‡,† (43.55)	-73.59‡,† (32.35)	-104.30‡,† (36.76)

n reflects the subset of patients for whom iron indices were collected.
*Placebo group switched to vadadustat at the beginning of the dose adjustment and maintenance period.
‡P<0.05 vs baseline; †P<0.05 vs placebo.

Safety

- During the primary efficacy period of both studies, adverse events (AEs) were reported at a higher rate in the vadadustat 300 and 600 mg groups than in the 150 mg or placebo groups
- In both studies, most AEs were mild or moderate and assessed by investigator as unrelated to study drug

NDD study: safety population (N=51)

- No serious AEs (SAEs) were reported during the primary efficacy period. During the dose adjustment and maintenance period, 11 subjects reported a total of 13 SAEs. Only one reported SAE was determined to be drug-related (abnormal hepatic function). No deaths were reported
- Treatment-emergent AEs (TEAEs) occurring in >2 of the 37 vadadustat-treated subjects during the primary efficacy period were hypertension (13.5%) and nausea (8.1%). No placebo-treated subjects experienced either of these, and no AE was reported by more than one placebo-treated subject
- TEAEs occurring in >2 of the 51 vadadustat-treated subjects during the dose adjustment and maintenance period included viral upper respiratory tract infection (7.8%), arteriovenous shunt operation (5.9%), constipation (5.9%), and diarrhea (5.9%)
- Three subjects (25%) in the 300 mg and 9 subjects (69.2%) in the 600 mg group had a dose decrease or interruption during the primary efficacy period according to a protocol-defined dose adjustment algorithm

DD study: safety population (N=60)

- Five SAEs were reported in 3 vadadustat-treated subjects. During the dose adjustment and maintenance period, 3 subjects reported a total of 4 SAEs. None of these were determined to be drug-related. No deaths were reported
- TEAEs occurring in >2 of the 45 vadadustat-treated subjects during the primary efficacy period included nasopharyngitis (15.6%), diarrhea (8.9%), and shunt stenosis (6.7%). No TEAE was reported by more than one placebo-treated subject during this period
- TEAEs occurring in >2 of the 45 vadadustat-treated subjects during the dose adjustment and maintenance period included nasopharyngitis (13.3%) and headache (6.7%). No TEAE was reported by >2 placebo-to-vadadustat subjects after they were switched to vadadustat
- One subject (6.7%) in the 150 mg and 3 subjects (21.4%) in the 600 mg group had a dose decrease or interruption during the primary efficacy period according to a protocol-defined dose adjustment algorithm

Table 3. Overview of TEAEs by randomized dose: safety population

	NDD Study				DD Study			
TEAE n (%)	Placebo*	Vadadustat 150 mg	Vadadustat 300 mg	Vadadustat 600 mg	Placebo	Vadadustat 150 mg	Vadadustat 300 mg	Vadadustat 600 mg
Primary Efficacy Period								
	N=14	N=12	N=12	N=13	N=15	N=15	N=15	N=15
Any TEAE	5 (35.7)	4 (33.3)	7 (58.3)	7 (53.8)	6 (40)	8 (53.3)	11 (73.3)	6 (40)
- Mild	4 (28.6)	4 (33.3)	6 (50.0)	7 (53.8)	6 (40)	7 (46.7)	11 (73.3)	5 (33.3)
- Moderate	1 (7.1)	-	1 (8.3)	-	1 (6.7)	1 (6.7)	-	2 (13.3)
- Severe	-	-	-	-	-	-	-	1 (6.7)
Any drug-related TEAE	-	1 (8.3)	3 (25.0)	3 (23.1)	-	-	3 (20.0)	1 (6.7)
TEAE leading to withdrawal	-	-	-	-	-	-	-	1 (6.7)
Serious adverse event	-	-	-	-	1 (6.7)	-	-	3 (20)
Death	-	-	-	-	-	-	-	-
Dose Adjustment and Maintenance Period								
	N=14	N=12	N=12	N=13	N=15	N=15	N=15	N=15
Any TEAE	9 (64.3)	9 (75.0)	10 (83.3)	6 (46.2)	4 (26.7)	9 (60)	9 (60)	9 (60)
- Mild	9 (42.9)	7 (58.3)	10 (83.3)	5 (38.5)	4 (26.7)	9 (60)	9 (60)	9 (60)
- Moderate	3 (21.4)	5 (41.7)	3 (25.0)	2 (15.4)	1 (6.7)	-	2 (13.3)	-
- Severe	1 (7.1)	-	2 (16.7)	1 (7.7)	-	1 (6.7)	-	-
Any drug-related TEAE	1 (7.1)	2 (16.7)	1 (8.3)	-	2 (13.3)	-	-	-
TEAE leading to withdrawal	1 (7.1)	-	2 (16.7)	1 (7.7)	-	1 (6.7)	-	1 (6.7)
Serious adverse event	4 (28.6)	-	5 (41.7)	2 (15.4)	-	1 (6.7)	1 (6.7)	1 (6.7)
Death	-	-	-	-	-	-	-	-

*Placebo group switched to vadadustat at the beginning of the dose adjustment and maintenance period

NDD study Hb excursions: mITT population

- No vadadustat-treated subject had Hb levels >13 g/dL during the primary efficacy period. Three subjects in the dose adjustment and maintenance period each had 1 occurrence of Hb levels >13 g/dL. Hb levels fell below 13 g/dL for all 3 of these subjects within 2 weeks after protocol-specified interruption of treatment with vadadustat
- During the 6-week primary efficacy period, Hb values in the >12 to 13 g/dL range were reported for 8 (21.6%) subjects randomized to receive vadadustat
- During the dose adjustment and maintenance period, Hb values in the >12 to 13 g/dL range occurred in 13 (35.1%) subjects in the vadadustat group, and 5 (35.7%) in the placebo group that switched to vadadustat

DD study Hb excursions: mITT population

- No vadadustat-treated subject had Hb levels >13 g/dL during the primary efficacy period. Two subjects in the dose adjustment and maintenance period each had 1 occurrence of Hb levels >13 g/dL. Hb levels fell below 13 g/dL for both of these subjects within 2 weeks after protocol-specified interruption of treatment with vadadustat
- During the 6-week primary efficacy period, no Hb values in the >12 to 13 g/dL range were reported for any subjects randomized to receive either vadadustat or placebo
- During the dose adjustment and maintenance period, Hb values in the >12 to 13 g/dL range were reported for 5 (11.4%) subjects in the vadadustat group, and 1 (7.1%) subject in the placebo group that switched to vadadustat

CONCLUSIONS

Overall, efficacy and safety results from the phase 2 studies of vadadustat support its continued development for patients with anemia due to CKD. Further investigation of daily doses of vadadustat from 150 to 600 mg in phase 3 trials for treatment of anemia in Japanese patients with NDD-CKD or DD-CKD is ongoing.

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DISCLOSURES

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