Randomized, Placebo-Controlled Phase 2 Trials of Vadadustat, an Oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor (HIF-PHI), to Treat Anemia of Chronic Kidney Disease (CKD)

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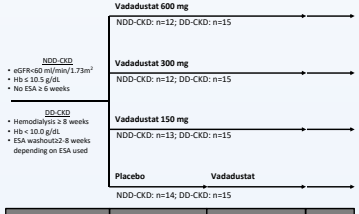
BACKGROUND

- Vadadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor in development for the treatment of anemia associated with non-dialysis-dependent CKD and dialysis-dependent CKD
- In prior phase 2 studies, vadadustat increased 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 subjects with anemia due to NDD-CKD (CI-0021, NCT03054337) and DD-CKD (CI-0022, NCT03054350)
- The primary objective of these studies was to assess the dose-response relationship based on the change in the Hb concentration following daily oral administration of vadadustat for 6 weeks

METHODS

- The two trials consisted of a 6-week fixed-dose, 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 (**Figure 1**)
- During the dose adjustment and maintenance period, vadadustat dose was adjusted to achieve the target Hb range (10-12 g/dL)
- 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
  - Missing values were imputed using last observation carried forward (LOCF)
- Selected secondary efficacy endpoints included
  - Mean Hb levels in primary efficacy period (at Week 6) and at end of the dose adjustment and maintenance period (Week 16)
  - Mean changes in biomarkers associated with iron utilization and mobilization in primary efficacy period (at Week 6)
  - Proportion of subjects who achieve target Hb 10-12 g/dL at EOT (Week 16)
  - Proportion of subjects receiving ESA and RBC requiring rescue at EOT (Week 16)
  - Mean change in Hb between pre-treatment and end of the dose adjustment and maintenance period (Week 16)
- Safety endpoints included:
  - Standard safety endpoints including adverse events (AEs), vital signs, and laboratory studies
  - Proportion of subjects requiring rescue with RBC transfusion and ESAs from baseline to the end of the primary efficacy period (Week 6) and the end of the dose adjustment and maintenance period (Week 16)

Figure 1. Design of the NDD and DD trials



[1] Dose increases not permitted; dose decrease as needed per protocol-specified guidelines for rapid Hb rise or Hb>13 g/dL.
[2] 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. Subject Disposition

	NDD Study	DD Study
Randomized	51	60
Completed Primary Efficacy Period	55	43
Completed Dose Adjustment and Maintenance Period	46	40
Safety Population	51	60
mITT Population[2]	51	58

[2]Pre-treatment Hb average, post-treatment Hb value (Week 2 or later)

Table 2. Baseline characteristics of NDD and DD patients – mITT population

	NDD Study		DD Study	
	Vadadustat	Placebo	Vadadustat	Placebo
Modified ITT 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 Stage, n (%)		Vintage dialysis, years	
CKD Status	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)		

*Multiple etiologies were allowed in this field
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

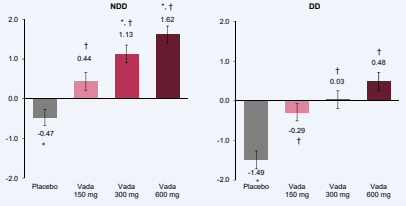
NDD Study – mITT population

- Statistically significant dose-dependent increases from baseline in mean Hb levels were observed with each of the 3 vadadustat treatment groups as compared with placebo at the end of the primary efficacy period (Week 6) (**Figure 2** and **Figure 3**)
- Among subjects initially randomized to vadadustat who completed 16 weeks of treatment (primary efficacy period and dose adjustment and maintenance period), 90.9% exhibited a Hb level within the target range of 10 to 12 g/dL at the end of treatment visit and 9.1% exhibited a Hb level above the target range

DD Study – mITT population

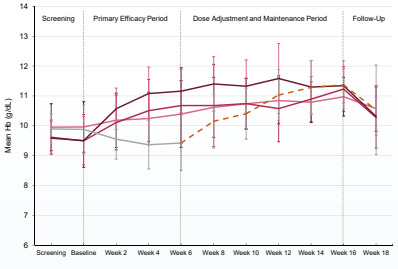
- Statistically significant dose-dependent increases from baseline in mean Hb levels were observed with each of the 3 vadadustat treatment groups as compared with placebo at the end of the primary efficacy period (Week 6) (**Figure 2** and **Figure 4**)
- Among subjects initially randomized to vadadustat who completed 16 weeks of treatment (primary efficacy period and dose adjustment and maintenance period), 71.4% exhibited a Hb level within the target range of 10 to 12 g/dL at the end of treatment visit and 8.6% exhibited a Hb level above the target range

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



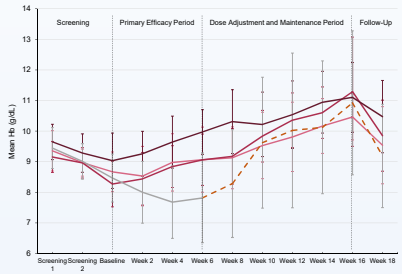
Vada = vadadustat. Statistical methodology: ANCOVA[p<0.0001].MITT LOCF. *p<0.05 v baseline. †p0.05 v placebo. Error bars = standard error

Figure 3. Mean Hb over time in NDD patients – mITT population



Vada = vadadustat, PBO = placebo, error bars = standard deviation

Figure 4. Mean Hb over time in DD patients – mITT population



Vada = vadadustat, PBO = placebo, error bars = standard deviation

Table 3. ESA and RBC Transfusion Rescue – mITT Population

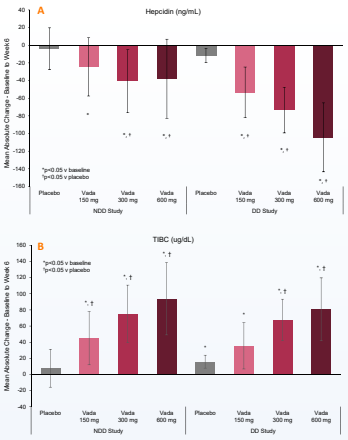
	NDD Study				DD Study			
	Placebo	Vada - 150 mg	Vada - 300 mg	Vada - 600 mg	Placebo	Vada - 150 mg	Vada - 300 mg	Vada - 600 mg
Received RBC Transfusion								
Primary Efficacy Period	0	0	0	0	3 (21%)	0	0	1 (7%)
Dose Adjustment and Maintenance Period*	1 (7%)	0	1 (8%)	1 (8%)	0	1 (7%)	0	0
Received ESA								
Primary Efficacy Period	0	0	0	0	8 (57%)	4 (27%)	2 (13%)	1 (7%)
Dose Adjustment and Maintenance Period*	0	0	2 (17%)	1 (8%)	1 (7%)	0	0	1 (7%)

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

NDD and DD- Iron-Related Parameters – mITT Population (Figure 5)

- Statistically significant, dose-dependent increases in total iron binding capacity (TIBC) and decreases in ferritin (data not shown) and hepcidin were observed with vadadustat administration from baseline to Week 6 (**Figure 5**)

Figure 5. Mean absolute changes in (A) hepcidin and (B) TIBC, from baseline to Week 6, in NDD and DD patients - mITT population



Vada = vadadustat, error bars = standard deviation
*Placebo switched to vadadustat at the beginning of the dose adjustment and maintenance period.

Safety

- NDD study – Safety Population:
  - During the 6-week, double-blind, placebo-controlled primary efficacy period, a higher proportion of subjects reported any AE in the vadadustat 300 mg or 600 mg group compared with the vadadustat 150 mg or placebo groups
  - Most AEs were mild or moderate in severity and assessed by the investigator as unrelated to study drug
  - No SAEs were reported during the primary efficacy period. During the dose adjustment and maintenance period, 11 subjects reported a total of 13 SAEs
  - No deaths were reported
  - AEs reported in >2 vadadustat-treated subjects during either period were hypertension, nausea, viral upper respiratory tract infection, arteriovenous shunt operation, constipation, and diarrhea
  - No clinically meaningful changes from baseline were observed in laboratory values or vital signs
  - Three subjects (25%) in 300 mg and 9 subjects (69.2%) in 600 mg had a dose decrease or interruption during the primary efficacy period.
- DD study – Safety Population:
  - During the 6-week, double-blind, placebo-controlled primary efficacy period, a higher proportion of subjects reported any AE in the vadadustat 150 mg or 300 mg group compared with the vadadustat 600 mg or placebo groups
  - Most AEs were mild or moderate in severity and assessed by the investigator as unrelated to study drug
  - Five SAEs were reported in 3 vadadustat-treated subjects. During the dose adjustment and maintenance period, 3 subjects reported a total of 4 SAEs
  - No deaths were reported
  - AEs reported in >2 vadadustat-treated subjects during either period were nasopharyngitis, diarrhea, shunt stenosis, and headache
  - No clinically meaningful changes from baseline were observed in laboratory values or vital signs
  - One subject (6.7%) in 150 mg and 3 subjects (21.4%) in 600 mg had a dose decrease or interruption during the primary efficacy period.

Table 4. Overview of TEAEs by randomized dose - safety population

	NDD Study				DD Study			
Treatment-Emergent Adverse Event, 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)
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)	-	-
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

Table 5. TEAEs occurring in >10% of subjects by randomized dose - safety population

MedDRA System Preferred Term, n (%)	Placebo*	Vadadustat 150 mg	Vadadustat 300 mg	Vadadustat 600 mg
	NDD Study			
	N=14	N=12	N=12	N=13
Primary Efficacy Period				
Nausea	-	-	2 (16.7)	1 (7.7)
Hypertension	-	-	3 (25.0)	2 (15.4)
Dose Adjustment and Maintenance Period				
Contusion	2 (16.7)	-	-	-
Constipation	-	2 (16.7)	-	1 (7.1)
Arteriovenous shunt operation	-	3 (25.0)	-	-
	DD Study			
	N=15	N=15	N=15	N=15
Primary Efficacy Period				
Diarrhea	1 (6.7)	-	2 (13.3)	2 (13.3)
Nasopharyngitis	-	1 (6.7)	5 (33.3)	1 (6.7)
Shunt Stenosis	-	1 (6.7)	-	2 (13.3)
Dose Adjustment and Maintenance Period				
Diarrhea	-	1 (6.7)	-	2 (13.3)
Contusion	2 (13.3)	0	-	-
Nasopharyngitis	4 (26.7)	2 (13.3)	-	1 (6.7)
Headache	2 (13.3)	-	1 (6.7)	2 (13.3)

*Placebo group switched to vadadustat at the beginning of the dose adjustment and maintenance period
MedDRA = Medical Dictionary for Regulatory Activities

CONCLUSIONS

- Overall, the efficacy results and safety profile observed in the phase 2 studies support further evaluation of vadadustat, inclusive of daily doses of 150 mg to 600 mg, in phase 3 trials for the treatment of anemia in Japanese patients with NDD-CKD or DD-CKD

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SG: Employee, Akebia Therapeutics, Inc.
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