Vadadustat Demonstrates Controlled Hemoglobin Response in a Phase 2b Study for the Treatment of Anemia in Patients with Non-Dialysis-Dependent Chronic Kidney Disease

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Abstract

Introduction: Vadadustat (formerly known as AKB-6548) is a novel, once-daily, oral hypoxia-inducible factor (HIF) prolyl-hydroxylase inhibitor that preferentially stabilizes HIF-2α. Current standard of care for anemia in non-dialysis dependent chronic kidney disease (NDD-CKD) with recombinant erythropoiesis-stimulating agents (ESAs) often results in overshoots and oscillations of hemoglobin (Hb) levels. It has been suggested that fluctuations in Hb concentrations, rapidly increasing Hb levels, and overshoots of the Hb target are associated with an increased risk of cardiovascular events. Presented here are data assessing the control and predictability of Hb response from a Phase 2b study.

Methods: A randomized, double-blind, placebo-controlled study was conducted to assess the Hb response of vadadustat over 20 weeks of dosing in NDD-CKD patients with anemia. 210 patients were randomized 2:1 (138 vadadustat, 72 placebo) to once-daily vadadustat (450 mg) or placebo. Hb was monitored at each study visit and a protocol-defined dose adjustment algorithm was used to raise and maintain Hb and to minimize excursions ≥13 g/dL.

Results: The starting dose of 450 mg once-daily was validated by the final average dose of 450 mg/day in the vadadustat-treated patients. Only 15 patients (11%) had a confirmed Hb ≥12 g/dL and only 2 patients (1%) had a confirmed Hb ≥13 g/dL. From Weeks 12 to 20, 74% and 81% of all Hb measurements were between 10–12 g/dL and 10–13 g/dL, respectively. The majority of patients (120 of 135, 89%) achieved and maintained a stable Hb level with two or fewer dose adjustments throughout the 20-week treatment period, and 24% (33 of 135) of patients required no dose adjustment.

Conclusions: Vadadustat increased and maintained Hb levels in NDD-CKD patients in a controlled and predictable manner with minimal dose adjustments. The study provides support that targeting the HIF oxygen-sensing pathway is likely to represent a more physiologic and potentially safer approach to treating anemia than currently available therapy.

Background

- Current standard of care for anemia in NDD-CKD is injectable ESA therapy; however, ESA use often results in substantial Hb oscillations and excursions above the target range
  - Hb variability, rate of rise, and excursions beyond the Hb target range have been associated with an increased risk of cardiovascular events[1]
- Vadadustat is a once-daily, oral inhibitor of HIF prolyl-hydroxylases in development for treatment of anemia in NDD-CKD and dialysis-dependent chronic kidney disease (DD-CKD) patients
  - It facilitates iron homeostasis by decreasing hepcidin and increasing transferrin levels
  - It was well tolerated in prior studies, with the most common adverse events (AEs) being mild-to-moderate nausea and diarrhea. Safety data from this study have been presented previously[2]
- Presented here are post-hoc analyses demonstrating the predictable Hb response achieved with vadadustat when dosed in accordance with protocol-defined dose adjustment guidelines

Methods

- We conducted a double-blind, randomized, parallel-group, placebo-controlled study
- The primary objective was to assess the Hb response (Hb ≥11 g/dL or an increase in Hb ≥1.2 g/dL) to orally administered vadadustat over 20 weeks in NDD-CKD patients with glomerular filtration rate (GFR) categories G3a–G5
- Patients were assigned to one of three study groups based on ESA status at screening:
  - ESA-naïve with Hb level ≤10.5 g/dL
  - Previously treated with ESA (off therapy for ≥11 weeks), and Hb level ≤10.5 g/dL
  - Actively treated with ESA; Hb level ≥9.5 g/dL and ≤12.0 g/dL
- 210 patients assigned in a 2:1 ratio to once-daily vadadustat or placebo
  - Vadadustat was initiated at 450 mg once daily, and titrated by 150 mg increments (1 tablet) according to Hb response (to a maximum of 600 mg once-daily and a minimum of 150 mg once-daily)
- Randomization was stratified by CKD status (GFR categories G3a/b, G4, or G5) and the presence/absence of diabetes mellitus
- Hb was monitored at each study visit and study medication doses were adjusted in accordance with protocol-defined dose adjustment guidelines
  - Dose increases were allowed between weeks 4–12; dose decreases were allowed at any time

Patient Disposition and Demographics (Table 1)

	Vadadustat N (%)*	Placebo N (%)*
Patients dosed (intent-to-treat population)†	138 (100.0)	72 (100.0)
Patients completing through to Week 20	112 (81.2)	63 (87.5)
Per protocol population#	102 (73.9)	58 (80.6)
Male	57 (41.3)	38 (52.8)
Age, mean (years)	66.6	65.9
Diabetes mellitus	106 (76.8)	57 (79.2)
Chronic kidney disease stage G3a/b G4 G5	 36 (26.1) 85 (61.6) 17 (12.3)	 18 (25.0) 42 (58.3) 12 (16.7)
eGFR, mean (mL/min/1.73m²)	25.2	25.0
Urine albumin-to-creatinine ratio, mean/median (mg/g)	1146/416	1455/487

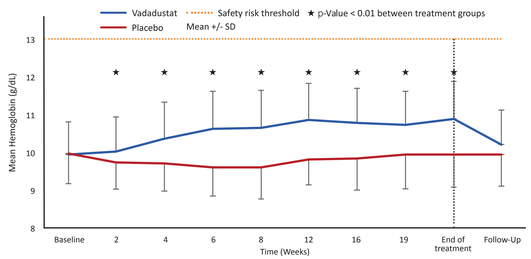
*Number of patients unless otherwise stated
†Number of patients dosed was used to calculate percentages
#Completed through Week 20 with compliance ≥80%
eGFR, estimated glomerular filtration rate

Results

Met Primary Endpoint

- A significantly greater percentage of vadadustat-treated patients than placebo-treated patients achieved a successful Hb response (54.9% versus 10.3%, p<0.0001)
- Increases in Hb were observed by Week 4 and plateaued by Week 12 (Fig.1)
- Hb was maintained in the desired range while minimizing Hb excursions ≥13.0 g/dL

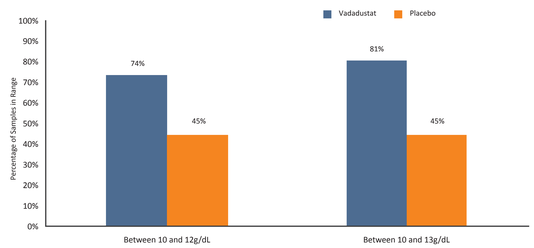
Mean Hemoglobin Level Over Time ITT (All Groups) (Fig.1)



Controlled and Consistent Hb Response

- From Weeks 12 to 20, 74% (330 of 449) and 81% (365 of 449) of all Hb values in vadadustat-treated patients were between 10–12 g/dL and 10–13 g/dL, respectively (Fig.2)
- Only 15 vadadustat-treated patients (11%) had a confirmed (next measured value) Hb ≥12 g/dL and only 2 patients (1%) had a confirmed Hb ≥13 g/dL

Hb Measurements from Weeks 12 to 20 Within Two Ranges (Fig.2)



Minimal Dose Adjustments Were Required (Table 2)

- The majority of patients (120 of 135, 89%) achieved and maintained a stable Hb level with two or fewer dose adjustments throughout the 20-week treatment period
- 24% (33 of 135) of patients required no dose adjustment

Number of Dose Adjustments per Patient from Week 2 through End of Treatment (ITT* Population) (Table 2)

Number of Dose Adjustments	Vadadustat N=135
0	33 (24.4%)
1	62 (45.9%)
2	25 (18.5%)
3	13 (9.6%)
4	2 (1.5%)
Subjects with ≥1 dose reduction	56 (41.5%)
Subjects with ≥1 dose increase	75 (55.6%)

*ITT – Intent-to-treat

Results (cont.)

Vadadustat Dose Requirements During the Study (Table 3)

Treatment Group		Study Visit	Number of Patients on Prescribed Regimen (tablets/day)					Average Dose
			0	1	2	3	4	
All Vadadustat Subjects (N=138)		Baseline (N=138)	-	-	-	138 (100.0%)	-	3.0
		Week 2 (N=135)	2 (1.5%)	4 (3.0%)	3 (2.2%)	126 (93.3%)	0 (0.0%)	2.9
		Week 4 (N=130)	2 (1.5%)	12 (9.2%)	15 (11.5%)	64 (49.2%)	37 (28.5%)	2.9
		Week 6 (N=126)	3 (2.4%)	14 (11.1%)	22 (17.5%)	52 (41.3%)	35 (27.8%)	2.8
		Week 8 (N=127)	1 (0.8%)	18 (14.2%)	22 (17.3%)	37 (29.1%)	49 (38.6%)	2.9
		Week 12 (N=121)	3 (2.5%)	15 (12.4%)	19 (15.7%)	32 (26.4%)	52 (43.0%)	3.0
		Week 16 (N=117)	1 (0.9%)	14 (12.0%)	20 (17.1%)	34 (28.4%)	48 (41.0%)	3.0
		Week 19 (N=116)	2 (1.7%)	14 (12.1%)	19 (16.4%)	33 (29.1%)	48 (41.4%)	3.0
CKD Stage	G3a/b	Week 19 (N=32)	1 (3.1%)	1 (3.1%)	3 (9.4%)	11 (34.4%)	16 (50.0%)	3.3
	G4	Week 19 (N=73)	1 (1.4%)	10 (13.7%)	12 (16.4%)	21 (28.8%)	29 (39.7%)	2.9
	G5	Week 19 (N=11)	0 (0.0%)	3 (27.3%)	4 (36.4%)	1 (9.1%)	3 (27.3%)	2.4

- On average, a dose of 450 mg once-daily (3 tablets) was required during the study
- However, dose requirement decreased with the severity of CKD

Conclusions

- Vadadustat increased and maintained Hb levels in NDD-CKD patients in a controlled and consistent manner, with minimal excursions
- The majority of patients (120 of 135, 89%) achieved and maintained a stable Hb level with two or fewer dose adjustments throughout the 20-week treatment period
- These findings support the initiation of the global Phase 3 program for vadadustat in NDD-CKD

References

1. Unger EF, Thompson AM, Blank MJ, Temple R. N Engl J Med 2010:21;362(3):189–92
2. Pergola PE, Spinowitz B, Haase VH, *et al*. Poster presented at the World Congress of Nephrology 2015, Cape Town, South Africa, 13–17 March, 2015 (Poster #MON-357; Abstract #WCN15-1252)

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