Impact of Vadadustat on Iron Regulation in Japanese Patients With Chronic Kidney Disease

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BACKGROUND

- Vadadustat, an investigational oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIP-PHI), is under clinical development for the treatment of anemia due to chronic kidney disease (CKD).
- Previous Phase 2 studies have shown that vadadustat was associated with increased hemoglobin (Hb) levels and changes in iron-related parameters in patients with anemia due to CKD (Pergola 2016; Martin 2017; Haase 2019).
- In this study, the effect of daily oral doses of vadadustat was investigated in two Phase 2, multicenter, double-blind, placebo-controlled clinical trials in Japanese patients with CKD who were non-dialysis dependent (NDD) (Study CI-0021, NCT03054337) and dialysis-dependent (DD) (Study CI-0022, NCT03054350).

STUDY OBJECTIVES

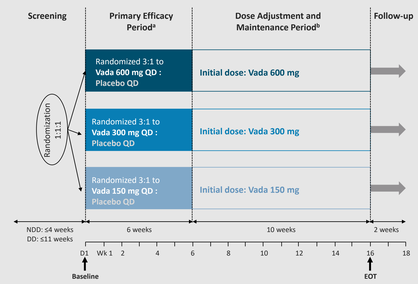
- To observe changes in Hb and iron parameters with a daily oral dose of vadadustat 150, 300, or 600 mg or placebo in patients with anemia due to CKD over 16 weeks.
- These post-hoc analyses investigated the effect of pre-treatment iron supplementation on iron utilization and mobilization in patients taking vadadustat.

METHODS

Study Design

- Studies CI-0021 (NDD-CKD) and CI-0022 (DD-CKD) were both Phase 2, randomized, double-blind, placebo-controlled, dose-finding trials to assess the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of vadadustat in Japanese patients.
  - The study population consisted of male and female patients ≥20 years of age with a CKD diagnosis (estimated glomerular filtration rate of ≤60 mL/min/1.73 m^2 and Hb ≤10.5 g/dL)
  - Inclusion criteria for both studies during screening, included serum ferritin ≥50 ng/mL, transferrin saturation (TSAT) ≥20%; for the CI-0021 (NDD-CKD) study, patients were eligible if they were not being treated with dialysis and not expected to start dialysis within 3 months of screening.
  - Exclusion criteria included anemia due to a cause other than CKD or the presence of active bleeding or recent blood loss, and for the CI-0021 (NDD-CKD) study, intravenous iron within 4 weeks prior to or during screening.
- Patients with NDD-CKD or DD-CKD were randomized in a 3:1 ratio to once-daily vadadustat (150, 300, or 600 mg) or placebo (**Figure 1**).

Figure 1. Design of the NDD-CKD and DD-CKD Studies



[a]Dose increases not permitted; dose decrease as needed per protocol-specified guidelines for rapid Hb rise or Hb >13 g/dL.
[b]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. After the Week 6 visit, investigators prescribed iron supplementation for subjects with ferritin <100 ng/mL and TSAT <20%, and the iron dose was selected at the investigator's discretion.
EOT, end of treatment; Hb, hemoglobin; QD, once daily; Vada, vadadustat.

- A 6-week primary efficacy period was followed by a 10-week dose adjustment and maintenance period.
- At the start of the dose adjustment and maintenance period, subjects who received placebo switched to vadadustat.
- The primary efficacy endpoint was mean change in Hb from baseline to Week 6 between the vadadustat and placebo groups.
- Selected secondary efficacy endpoints included:
  - Mean Hb levels at Week 6 (end of primary efficacy period) and Week 16 (end of dose adjustment and maintenance period).
  - Mean changes in iron-related parameters in primary efficacy period at Week 6.
- Post-hoc analyses of iron-related parameters from baseline to Week 16 were based on pre-treatment iron supplementation status, defined as follows:
  - Iron user: A study subject who was receiving iron supplementation at baseline (i.e., within 28 days prior to study start) and continued receiving iron throughout the study.
  - Non-iron user: A study subject who was not receiving iron supplementation at study baseline (i.e., within 28 days prior to study start) and received no iron throughout the study.

RESULTS

Tables 1 and **2** present the subject disposition and baseline demographics, respectively.

Table 1. Subject Disposition

	NDD-CKD Study	DD-CKD Study
Randomized	51	60
Completed primary efficacy period	51	43
Completed dose adjustment and maintenance period	46	40
Safety population	51	60
mITT population	51	58

mITT, modified intent-to-treat

Table 2. Baseline Characteristics

		NDD-CKD Study		DD-CKD Study	
		Vada (n=37)	PBO → Vada (n=14)	Vada (n=44)	PBO → Vada (n=14)
Age, mean (SD), 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)
CKD etiology[a], n (%)					
Hypertension		15 (41)	8 (57)	13 (29.5)	6 (42.9)
Diabetes		6 (16)	6 (43)	19 (43)	5 (36)
Autoimmune/GN/vasculitis		8 (22)	2 (14)	13 (29.5)	5 (35.7)
CKD stage[b], n (%)	G3a	1 (3)	0	-	-
	G3b	6 (16)	2 (14)	-	-
	G4	10 (27)	8 (57)	-	-
	G5	20 (54)	4 (29)	-	-
ESA user[c], n (%)		-	-	29 (64.4%)	13 (86.7%)
Pre-treatment Hb average[c], mean (SD), g/dL		9.7 (0.7)	9.9 (0.6)	9.0 (0.6)	9.0 (0.6)
Prior iron use[c], n (%)		7 (18.9)	3 (21.4)	17 (37.8)	9 (60.0)
Ferritin, mean (SD), ng/mL		180.6 (113.1)	171.1 (92.0)	217.8 (113.1)	294.6 (215.0)
Transferrin saturation, % (SD)		30.5 (8.9)	32.1 (8.3)	43.6 (16.6)	49.8 (15.4)

[a]Multiple etiologies were allowed in this field.
[b]G3a = eGFR 45-59 mL/min/1.73m^2, G3b = eGFR 30-44 mL/min/1.73m^2, G4 = eGFR 15-29 mL/min/1.73m^2, G5 = eGFR <15 mL/min/1.73m^2.
[c]Data presented for safety population (NDD-CKD study: vadadustat, n=37; placebo, n=14; DD-CKD study: vadadustat, n=45; placebo, n=15).
CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; GN, glomerulonephritis; Hb, hemoglobin; SD, standard deviation; Vada, vadadustat.

Figure 2. NDD-CKD Study: Iron-Related Parameters by Iron Supplementation at Baseline

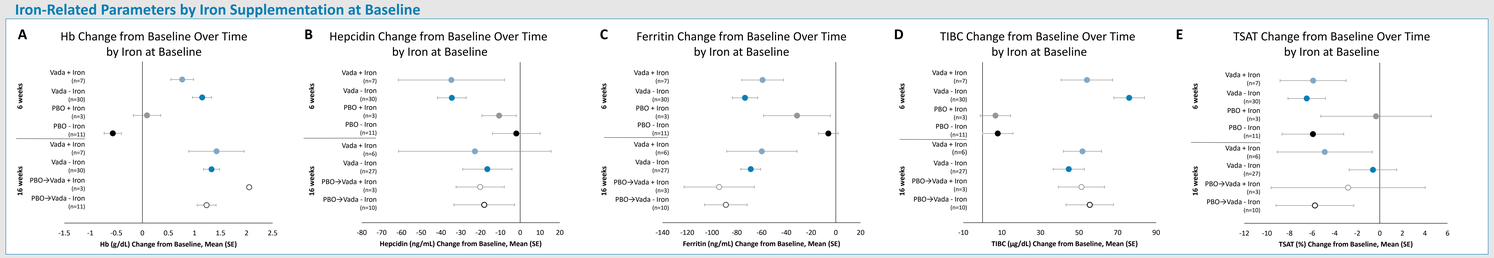
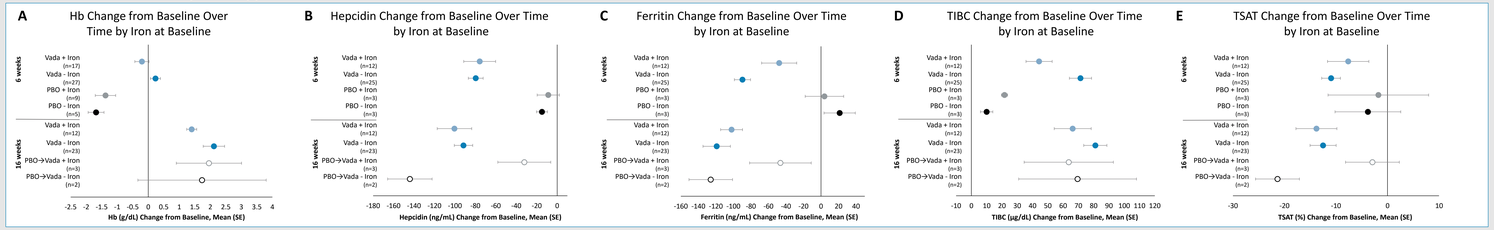


Figure 3. DD-CKD Study: Iron-Related Parameters by Iron Supplementation at Baseline



Efficacy

- In both studies, vadadustat was found to increase Hb levels from baseline through Week 16, even among the subjects not receiving prior iron supplementation (**Figure 2A**, **Figure 3A**).
- By week 6, levels of hepcidin declined from baseline in all vadadustat arms across both studies (**Figure 2B, Figure 3B**)
- Levels of ferritin, total iron binding capacity (TIBC), TSAT, all changed from baseline by Week 6 in all vadadustat arms across both studies (**Figure 2 C-E, Figure 3 C-E**).

Safety Population

- Study CI-0021 (NDD-CKD) (**Table 3**):
  - Adverse events (AEs) reported in >2 patients treated with vadadustat during either the primary efficacy period or the dose adjustment and maintenance period were hypertension, nausea, viral upper respiratory tract infection, arteriovenous shunt operation, constipation, and diarrhea.
- Study CI-0022 (DD-CKD) (**Table 3**):
  - AEs reported in >2 vadadustat-treated subjects during either period were nasopharyngitis, diarrhea, shunt stenosis, and headache.

Table 3. Overview of TEAEs – Safety Population

	NDD Study		DD Study	
	Vadadustat Total n=37	Placebo[a] Total n=14	Vadadustat Total n=45	Placebo[a] Total n=15
Primary Efficacy Period				
Any TEAE	18 (48.6)	5 (35.7)	25 (55.6)	6 (40.0)
Mild	17 (45.9)	4 (28.6)	23 (51.1)	6 (40.0)
Moderate	1 (2.7)	1 (7.1)	3 (6.7)	1 (6.7)
Severe	0 (0)	0 (0)	1 (2.2)	0 (0)
TEAEs leading to withdrawal	0 (0)	0 (0)	1 (2.2)	0 (0)
Serious TEAEs	0 (0)	0 (0)	3 (6.7)	1 (6.7)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)
Dose Adjustment and Maintenance Period				
Any TEAE	25 (67.6)	9 (64.3)	27 (60.0)	4 (26.7)
Mild	22 (59.5)	6 (42.9)	27 (60.0)	4 (26.7)
Moderate	10 (27.0)	2 (21.4)	2 (4.4)	1 (6.7)
Severe	3 (8.1)	1 (7.1)	1 (2.2)	0 (0.0)
Any TEAEs leading to withdrawal	3 (8.1)	1 (7.1)	2 (4.4)	0 (0)
Any serious TEAEs	7 (18.9)	4 (28.6)	3 (6.7)	0 (0)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)

[a]Placebo group switched to vadadustat at the beginning of the dose adjustment and maintenance period.
TEAE, treatment-emergent adverse event

CONCLUSIONS

- Findings from the Phase 2 studies emphasize that improvement in hemoglobin was observed in vadadustat-treated subjects regardless of iron supplementation.
- Changes in hepcidin suggest that improvement in iron regulation might be expected.
- Changes in the iron-related parameters in the presence of vadadustat are consistent with the observed drop in hepcidin, suggesting improvement in iron utilization regardless of iron supplementation.
- The safety profile was consistent with the evolving safety profile of vadadustat, and no new safety issues were identified.
- Limitations of these post-hoc analyses include overall small sample size and lower proportion of iron utilization in this population that may confound the interpretation of results.

DISCLOSURES:

This study was funded by Akebia Therapeutics, Inc.

CS, YF, ZK, RA, WL, AC, DV, and **GR:** Employee, Akebia Therapeutics, Inc. **RA:** Consultant, Akebia Therapeutics, Inc. **MN:** Consultant, Akebia Therapeutics, Inc.; Lecture fees and research funds from Mitsubishi Tanabe Pharma Corporation. **CS & YF** contributed equally.

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