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Vadadustat for Treatment of Anemia in Patients With Dialysis-Dependent CKD Receiving Peritoneal Dialysis

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BACKGROUND

- Chronic kidney disease (CKD) is estimated to affect nearly 10% of the global population, and is frequently associated with anemia[1,2]
- The oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) vadadustat (VADA) stimulates endogenous erythropoietin and red blood cell (RBC) production and is currently approved for the treatment of anemia in patients with CKD in Japan, and is under review by the United States Food and Drug Administration[3–5]
- In 2 recently completed global phase 3 trials in patients with dialysis-dependent chronic kidney disease (DD-CKD) (INNO$_2$VATE), VADA was non-inferior (NI) to darbepoetin alfa (DA) for the primary safety endpoint (time to first major adverse cardiovascular event [MACE]: a composite of all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke) and the primary efficacy endpoint (correction/maintenance of hemoglobin [Hb])[4]
- Here we describe the safety and efficacy of VADA compared to DA in the subgroup of patients who received peritoneal dialysis (PD)

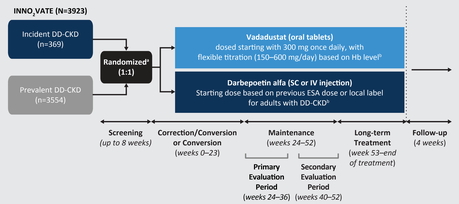
OBJECTIVE

- To describe key efficacy and safety data of VADA in the subgroup of patients receiving PD in the INNO$_2$VATE program

METHODS

- Two randomized (1:1), phase 3, global, open-label, sponsor-blind, parallel-group, active-controlled NI trials (INNO$_2$VATE) comparing VADA vs DA were conducted to determine safety and efficacy in patients with anemia of DD-CKD receiving dialysis (either PD or hemodialysis) (**Figure 1**)

Figure 1. INNO$_2$VATE Study Design



[a]Stratified by: Geographic region; NYHA CHF class; Hb level at study entry.
[b]Study drug is titrated to achieve target Hb levels (US: 10–11 g/dL; non-US: 10–12 g/dL).
CKD, chronic kidney disease; DD, dialysis dependent; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IV, intravenous; NYHA CHF, New York Heart Association Congestive Heart Failure; SC, subcutaneous; US, United States.

- Eligible patients were adults (aged ≥18 years) with DD-CKD, who had anemia with serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20%, and who had not received an RBC transfusion within 8 weeks prior to randomization
  - For the incident DD-CKD study, patients were required to have initiated maintenance dialysis (hemodialysis or PD) within 16 weeks prior to screening, with baseline Hb 8–11 g/dL and receipt of limited doses of erythropoiesis-stimulating agents (ESAs)
  - For the prevalent DD-CKD study, patients were required to have received maintenance dialysis for at least 12 weeks prior to screening and to be currently receiving any form of ESA therapy, with baseline Hb 8–11 g/dL (US) or 9–12 g/dL (non-US)
- The primary and key secondary efficacy endpoints were the mean change in Hb from baseline to the primary evaluation period (PEP) (weeks 24–36) and from baseline to the secondary evaluation period (SEP) (weeks 40–52), respectively, in each trial
- The prespecified primary safety endpoint was time to first MACE
- We assessed the incidence of treatment-emergent adverse events (TEAEs)
- The present pre-specified analyses includes only data from patients undergoing PD
  - Efficacy endpoints and TEAE analyses were conducted post hoc

RESULTS

Baseline Characteristics

- Of the 3923 patients randomized in the 2 INNO$_2$VATE trials, 309 (7.87%) were receiving PD at baseline (VADA, N=152; DA, N=157). 52.4% of these patients were male with a mean age of 54.7 years

Table 1. Selected Demographic Baseline Characteristics of Patients Receiving Peritoneal Dialysis at Baseline

Characteristic	VADA (N=152)	DA (N=157)
Mean age, years (SD)	54.8 (13.4)	54.6 (13.9)
Sex, male, n (%)	76 (50.0)	86 (54.8)
Racial or ethnic group, n (%)		
White	87 (57.2)	86 (54.8)
Asian	35 (23.0)	37 (23.6)
Black or African American	21 (13.8)	24 (15.3)
Other[a]	9 (5.9)	10 (6.4)
Hispanic ethnic group, n (%)		
Hispanic/Latino	52 (34.2)	56 (35.7)
Not Hispanic/Latino	96 (63.2)	99 (63.1)
Region of enrollment, n (%)		
United States	73 (48.0)	90 (57.3)
Europe	14 (9.2)	5 (3.2)
Non-US/Europe	65 (42.8)	62 (39.5)
Mean time since dialysis started, years (SD)	2.8 (3.2)	2.5 (3.0)
Disease history, n (%)		
Diabetes mellitus	75 (49.3)	87 (55.4)
Cardiovascular disease	46 (30.3)	56 (35.7)
NYHA CHF class, n (%)		
Class 0 (no CHF) or I	141 (92.8)	147 (93.6)
II or III	11 (7.2)	10 (6.4)
Mean BMI, kg/m^2 (SD)	28.0 (6.2)	28.7 (8.1)
Mean Hb concentration, g/dL (SD)	10.1 (0.9)	10.0 (0.9)
Iron-related parameters, mean (SD)		
Hepcidin (ng/mL)	195.382 (145.6)	189.526 (153.1)
Ferritin (ng/mL)	585.85 (450.4)	629.17 (507.5)
TIBC (µg/dL)	224.12 (36.2)	222.52 (38.2)
Serum iron (µg/dL)	81.60 (28.6)	87.11 (35.3)
TSAT (%)	36.85 (12.9)	39.04 (13.9)

[a]Includes Native Hawaiian or other Pacific Islander, multiple or not reported.
BMI, body mass index; DA, darbepoetin alfa; Hb, hemoglobin; NYHA CHF, New York Heart Association Congestive Heart Failure; SD, standard deviation; TIBC, total iron-binding capacity; TSAT, transferrin saturation; VADA, vadadustat.

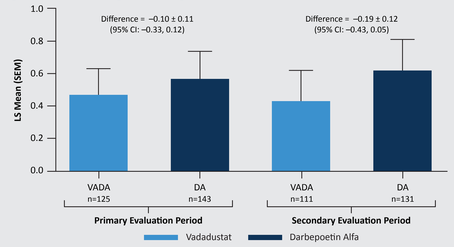
MACE in PD Patients

- Among patients receiving PD, the risk of MACE was similar in the VADA and DA groups (hazard ratio [HR] 1.10; 95% confidence interval [CI]: 0.62, 1.93)

Efficacy in PD Patients

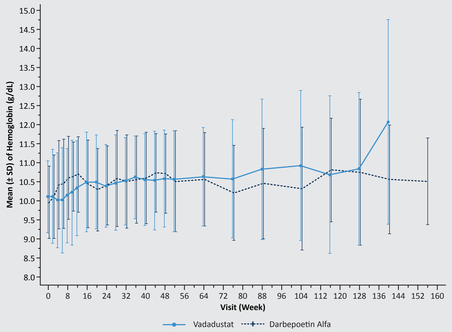
- During the primary efficacy period, the mean Hb concentrations were 10.5 (Min, Max: 7.8, 13.1) in the VADA group, and 10.5 (Min, Max: 7.4, 12.5) in the DA group
- The least squares mean difference in change in Hb from baseline was –0.10 g/dL (95% CI: –0.33, 0.12) during the PEP and –0.19 g/dL (95% CI: –0.43, 0.05) during the SEP (**Figure 2**)
  - Hb concentration remained within target range throughout 156 weeks of treatment (**Figure 3**)
- Primary and key secondary efficacy endpoints met the prespecified NI margin of –0.75 g/dL

Figure 2. Mean Change in Hemoglobin From Baseline



CI, confidence interval; DA, darbepoetin alfa; LS, least squares; SEM, standard error of the mean; VADA, vadadustat.

Figure 3. Mean Hemoglobin Over Time Up to Week 156



SD, standard deviation.

- Of the patients undergoing PD who were treated with VADA and DA, 55.4% (n=84; 95% CI: 51.97, 58.55) of patients treated with VADA and 56.4% (n=89; 95% CI: 54.14, 58.60) of patients treated with DA maintained Hb levels within the geography-specific target ranges during the PEP (weeks 24–36; difference, % [95% CI]: –0.0 [–0.1, 0.1]; odds ratio [95% CI]: 1.0 [0.6, 1.6]) (10–11 g/dL in the United States; 10–12 outside the United States)

Hb-Related Safety Endpoints

- Hb excursions >12.0–14.0 g/dL were similar between the VADA and DA groups during the PEP (weeks 24–36) and SEP (weeks 40–52) (**Table 2**)
- Hb increases >1.0–2.0 g/dL within any 2-week interval were similar between the VADA and DA groups during the PEP (weeks 24–36) and SEP (weeks 40–52)
- Hb excursions below 9 g/dL were similar between VADA and DA groups during the PEP (weeks 24–36) and SEP (weeks 40–52)

Table 2. Hemoglobin Excursions and Rate of Rise During the Primary and Secondary Efficacy Periods

	PEP (Weeks 24–36)		SEP (Weeks 40–52)	
	VADA (n=125)	DA (n=143)	VADA (n=111)	DA (n=131)
Hb >12.0 g/dL, n (% [95% CI])	24 (19.2 [12.7, 27.2])	29 (20.3 [14.0, 27.8])	27 (24.3 [16.7, 33.4])	28 (21.4 [14.7, 29.4])
Hb >13.0 g/dL, n (% [95% CI])	4 (3.2 [0.9, 8.0])	7 (4.9 [2.0, 9.8])	9 (8.1 [3.8, 14.8])	8 (6.1 [2.7, 11.7])
Hb >14.0 g/dL, n (% [95% CI])	0 (0.0 [0.0, 2.9])	0 (0.0 [0.0, 2.6])	1 (0.9 [0.0, 4.9])	2 (1.5 [0.2, 5.4])
Hb increase >1.0 g/dL within any 2-week interval, n (% [95% CI])	1 (0.8 [0.0, 4.4])	1 (0.7 [0.0, 3.8])	2 (1.8 [0.2, 6.4])	2 (1.5 [0.2, 5.4])
Hb increase >2.0 g/dL within any 2-week interval, n (% [95% CI])	7 (5.6 [2.3, 11.2])	10 (7.0 [3.4, 12.5])	6 (5.4 [2.0, 11.4])	3 (2.3 [0.5, 6.6])
Hb <9 g/dL, n (% [95% CI])	29 (23.2 [16.1, 31.6])	28 (19.6 [13.4, 27.0])	25 (22.5 [15.1, 31.4])	28 (21.4 [14.7, 29.4])
Hb <8 g/dL, n (% [95% CI])	6 (4.8 [1.8, 10.2])	10 (7.0 [3.4, 12.5])	7 (6.3 [2.6, 12.6])	7 (5.3 [2.2, 10.7])

Hb increase of >2.0 g/dL within any 2-week period included increase >1 g/dL. Hb increase of >1 g/dL is not included in >2 g/dL increase.
CI, confidence interval; DA, darbepoetin alfa; Hb, hemoglobin; PEP, primary evaluation period; SEP, secondary evaluation period; VADA, vadadustat.

Study Treatment Modifications

- During the PEP (weeks 24–36), patients receiving VADA required fewer mean dose modifications than those receiving DA (VADA: 1.3; DA: 2.0) (**Table 3**)
- During the SEP (weeks 40–52), patients receiving VADA required fewer mean dose modifications than those receiving DA (VADA: 1.2; DA: 2.1)

Table 3. Study Treatment Modifications Throughout the Study

	Weeks 2–8		Weeks 10–20		PEP (Weeks 24–36)		SEP (Weeks 40–52)	
	VADA (n=152)	DA (n=157)	VADA (n=152)	DA (n=157)	VADA (n=152)	DA (n=157)	VADA (n=152)	DA (n=157)
Patients with a dose modification, n (%)	152 (100.0)	157 (100.0)	140 (92.1)	152 (96.8)	123 (80.9)	141 (89.8)	101 (66.4)	128 (81.5)
Number of dose changes								
Mean (SD)	1.4 (0.89)	1.5 (1.18)	1.4 (1.18)	1.9 (1.32)	1.3 (1.2)	2.0 (1.6)	1.2 (1.3)	2.1 (1.8)
Median	1.0	1.0	1.0	2.0	1.0	2.0	1.0	2.0
Min, Max	0, 4	0, 6	0, 4	0, 7	0, 5	0, 7	0, 5	0, 10
Reasons for dose modifications, n (%)								
Increased or decreased based on Hb assessment	102 (67.1)	96 (61.1)	65 (46.4)	98 (64.5)	46 (37.4)	89 (63.1)	34 (33.7)	83 (64.8)
Decreased due to AE	0	0	0	0	0	0	0	0
Interrupted due to elevated Hb	23 (15.1)	47 (29.9)	28 (20.0)	31 (20.4)	21 (17.1)	42 (29.8)	22 (21.8)	31 (24.2)
Interrupted due to ESA rescue*	13 (8.6)	0	18 (12.9)	0	12 (9.8)	1 (0.7)	14 (13.9)	1 (0.8)
Interrupted due to AE	8 (5.3)	2 (1.3)	9 (6.4)	5 (3.3)	8 (6.5)	4 (2.8)	2 (2.0)	2 (1.6)
Restarted	17 (11.2)	23 (14.6)	51 (36.4)	52 (34.2)	39 (31.7)	39 (27.7)	32 (31.7)	36 (28.1)
Other	2 (1.3)	3 (1.9)	2 (1.4)	12 (7.9)	5 (4.1)	4 (2.8)	1 (1.0)	7 (5.5)

*Starting at week 6, patients in both treatment groups could receive ESAs as rescue therapy if they had worsening symptoms of anemia and a hemoglobin concentration of less than 9.5 g per deciliter. In the darbepoetin alfa group, an ESA was defined post hoc as a rescue medication if the dose was at least double that of the previous dose of darbepoetin alfa.
AE, adverse event; DA, darbepoetin alfa; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; PEP, primary evaluation period; SD, standard deviation; SEP, secondary evaluation period; VADA, vadadustat.

Incidence of TEAEs and Serious Adverse Events (SAEs)

- The incidence of overall TEAEs was 88.2% vs 95.5% and of SAEs was 52.6% vs 73.2% in the VADA and DA groups, respectively (**Table 4**)
- The most common TEAEs were peritonitis (17.8%), hypertension (14.5), nasopharyngitis (13.8%), and pneumonia (11.8%) in the VADA group; while in the DA group, peritonitis (27.4%), hypertension (19.1), nasopharyngitis (12.7%), and hyperkalemia (14.0%) were most common

Table 4. Overall Summary of TEAEs, SAEs, and TEAEs Occurring in ≥10% of Patients

	VADA (N=152; Exposure=242.0 PY)		DA (N=157; Exposure=262.2 PY)	
Category	n (%)	Events (Events per 100 PY)	n (%)	Events (Events per 100 PY)
Overall Summary of TEAEs				
Any TEAEs	134 (88.2)	1069 (441.7)	150 (95.5)	1464 (558.4)
Any drug-related TEAEs	15 (9.9)	25 (10.3)	8 (5.1)	9 (3.4)
Any severe TEAEs	52 (34.2)	148 (61.2)	75 (47.8)	218 (83.1)
Any SAEs	80 (52.6)	263 (108.7)	115 (73.2)	347 (132.3)
Any drug-related SAEs	2 (1.3)	2 (0.8)	2 (1.3)	2 (0.8)
Any TEAEs leading to study treatment discontinuation	6 (3.9)	6 (2.5)	5 (3.2)	5 (1.9)
Any drug-related TEAEs leading to study treatment discontinuation	4 (2.6)	4 (1.7)	2 (1.3)	2 (0.8)
Any TEAEs leading to death	16 (10.5)	16 (6.6)	19 (12.1)	19 (7.2)
All deaths	16 (10.5)	16 (6.6)	20 (12.7)	20 (7.6)
TEAEs Occurring in ≥10% of Patients				
Infections and infestations	84 (55.3)	235 (97.1)	109 (69.4)	309 (117.8)
Peritonitis	27 (17.8)	34 (14.0)	43 (27.4)	53 (20.2)
Nasopharyngitis	21 (13.8)	28 (11.6)	20 (12.7)	29 (11.1)
Pneumonia	18 (11.8)	22 (9.1)	17 (10.8)	18 (6.9)
Gastrointestinal disorders	61 (40.1)	126 (52.1)	74 (47.1)	164 (62.5)
Metabolism and nutrition disorders	56 (36.8)	94 (38.8)	79 (50.3)	172 (65.6)
Hyperkalemia	9 (5.9)	10 (4.1)	22 (14.0)	26 (9.9)
Vascular disorders	47 (30.9)	70 (28.9)	58 (36.9)	94 (35.9)
Hypertension	22 (14.5)	25 (10.3)	30 (19.1)	33 (12.6)
General disorders and administration site conditions	58 (38.2)	74 (30.6)	44 (28.0)	77 (29.4)
Asthenia	16 (10.5)	21 (8.7)	7 (4.5)	11 (4.2)
Nervous system disorders	43 (28.3)	63 (26.0)	41 (26.1)	64 (24.4)
Injury, poisoning, and procedural complications	38 (25.0)	77 (31.8)	45 (28.7)	88 (33.6)
Musculoskeletal and connective tissue disorders	36 (23.7)	48 (19.8)	47 (29.9)	75 (28.6)
Respiratory, thoracic, and mediastinal disorders	32 (21.1)	50 (20.7)	42 (26.8)	57 (21.7)
Cardiac disorders	29 (19.1)	60 (24.8)	40 (25.5)	76 (29.0)
Skin and subcutaneous tissue disorders	21 (13.8)	22 (9.1)	31 (19.7)	41 (15.6)
Blood and lymphatic system disorders	15 (9.9)	22 (9.1)	25 (15.9)	37 (14.1)
Psychiatric disorders	14 (9.2)	14 (5.8)	23 (14.6)	29 (11.1)
Eye disorders	15 (9.9)	18 (7.4)	16 (10.2)	24 (9.2)

DA, darbepoetin alfa; PY, patient-years; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; VADA, vadadustat.

SAEs Requiring Hospitalization

- Most SAEs by system organ class were more frequent in the DA treated group
- The most common SAEs resulting in hospitalization were peritonitis (11.2%), pneumonia (8.6%), and sepsis (5.3%) in the VADA group; while in the DA group, peritonitis (19.7%), pneumonia (5.7%), sepsis (5.7%), acute MI (5.1%), and hyperkalemia (5.1%) were most common (**Table 5**)

Table 5. Summary of SAEs Resulting in Hospitalization of ≥5% of Patients

	VADA (N=152; Exposure=242.0 PY)		DA (N=157; Exposure=262.2 PY)	
Category	n (%)	Events (per 100 PY)	n (%)	Events (per 100 PY)
Any hospitalization, TEAEs	77 (50.7)	235 (97.1)	113 (72.0)	328 (125.1)
Infections and infestations	41 (27.0)	83 (34.3)	66 (42.0)	114 (43.5)
Peritonitis	17 (11.2)	18 (7.4)	31 (19.7)	34 (13.0)
Pneumonia	13 (8.6)	15 (6.2)	9 (5.7)	9 (3.4)
Sepsis	8 (5.3)	11 (4.5)	9 (5.7)	10 (3.8)
Gastrointestinal disorders	16 (10.5)	22 (9.1)	19 (12.1)	27 (10.3)
Cardiac disorders	15 (9.9)	26 (10.7)	23 (14.6)	36 (13.7)
Acute MI	7 (4.6)	7 (2.9)	8 (5.1)	10 (3.8)
Injury poisoning and procedural complications	12 (7.9)	20 (8.3)	21 (13.4)	25 (9.5)
Nervous system disorders	11 (7.2)	13 (5.4)	11 (7.0)	13 (5.0)
Vascular disorders	12 (7.9)	14 (5.8)	20 (12.7)	23 (8.8)
Respiratory, thoracic, and mediastinal disorders	9 (5.9)	10 (4.1)	7 (4.5)	7 (2.7)
Musculoskeletal and connective tissue disorders	2 (1.3)	2 (0.8)	9 (5.7)	9 (3.4)
Metabolism and nutrition disorders				
Hyperkalemia	0 (0.0)	0 (0.0)	8 (5.1)	9 (3.4)
Blood and lymphatic system disorders	7 (4.6)	7 (2.9)	8 (5.1)	8 (3.1)

DA, darbepoetin alfa; MI, myocardial infarction; PY, patient-years; TEAEs, treatment-emergent adverse events; VADA, vadadustat.

CONCLUSIONS

- In a subgroup analysis of patients receiving peritoneal dialysis in the INNO$_2$VATE phase 3 trials, the safety and efficacy of VADA were largely comparable to DA
  - Among patients receiving PD, the risk of MACE was similar in the VADA and DA groups
  - Hb levels were within the target range in the majority of patients in both the VADA and DA groups
  - VADA therapy was associated with fewer dose adjustments
  - Patients receiving VADA experienced fewer SAEs and a lower incidence of hospitalization than those receiving DA

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DISCLOSURES

NB, PC, CG, LK, and KAN were study investigators. GC and KUE currently serve as study consultants for Akebia Therapeutics, Inc. WL, TM, and DV are employees of Akebia Therapeutics, Inc.

The results presented here have not been published previously in whole or part, except in abstract format.

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