PO0463

PRESENTED AT ASN KIDNEY WEEK 2021

Thromboembolic Events With Vadadustat vs Darbepoetin Alfa for Anemia Treatment in Patients With Dialysis-Dependent CKD

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American Society of Nephrology (ASN) Kidney Week 2021, Virtual, November 4–7, 2021

BACKGROUND

- Chronic kidney disease (CKD) is estimated to affect nearly 10% of the global population, and is frequently associated with anemia[1,2]
- Vadadustat (VADA) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), a class of drugs that stabilizes HIF and stimulates endogenous erythropoietin and red blood cell production[3,4]
- VADA is being investigated for treatment of anemia in patients with incident or prevalent dialysis-dependent chronic kidney disease (DD-CKD)
- In 2 global phase 3, open-label, randomized, non-inferiority trials (INNO$_2$VATE), VADA was non-inferior to darbepoetin alfa (DA) with respect to cardiovascular safety (major adverse cardiovascular event [MACE] hazard ratio (HR), 0.96; 95% confidence interval [CI], 0.83 to 1.11) and correction and maintenance of hemoglobin (Hb) concentration[5]
  - The prespecified non-inferiority margin for MACE was 1.25
- HIF has a role in coagulation, fibrinolysis, and thrombus resolution, and activation causes a potential risk for thromboembolic events[6]
- Given the historical safety concerns associated with currently used erythropoietin-stimulating agents (ESAs), an important safety endpoint of the INNO$_2$VATE trials was to evaluate thromboembolic events (TEs) during treatment with VADA

OBJECTIVE

- Here we describe the prespecified pooled analysis of the secondary safety endpoints of time to first TE, including (1) any TE (a composite of events of vascular access thrombosis [VAT], arterial thrombosis [AT], deep vein thrombosis [DVT], and pulmonary embolism [PE]), (2) AT, DVT, or PE, and (3) venous TE (DVT or PE)

METHODS

- Data were pooled from 2 completed global phase 3, open-label, randomized (1:1) non-inferiority trials (INNO$_2$VATE), which compared the safety and efficacy of VADA with that of DA in adult patients with DD-CKD
  - INNO$_2$VATE studies randomized a total of 3923 patients with DD-CKD[5]
  - The safety population included 3902 patients (21 randomized patients did not receive study drug)
    - NCT02865850: Correction/Conversion study, incident dialysis population (N=365)
    - NCT02892149: Conversion study, prevalent dialysis population (N=3537)
- The primary safety endpoint of the INNO$_2$VATE trials was time to first MACE (a composite of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke), which was prespecified as a pooled event-driven analysis of both trials
- The Clinical Endpoint Committee (CEC) adjudicated all potential cardiovascular events; they were blinded to patient treatment assignment, and adjudication outcomes were not provided to the investigators during the course of the studies. The formal cardiovascular safety analyses only included events positively adjudicated by CEC (ie, CEC confirmed that the specified endpoint met definitions). Among adjudicated cardiovascular events, TEs included AT, DVT, PE, and VAT
- Treatment-emergent adverse events (TEAEs) were identified by investigators and summarized by:
  - Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term overall, seriousness, relationship to study drug (related or not related as assessed by the investigator), and whether the TEAE led to death
    - TEAEs were defined as adverse events (AEs) that started (or a preexisting AE that worsened) on or after the first dose of study drug
- All analyses were performed using the safety population, which included all enrolled patients who received ≥1 dose of study drug
- Duration of exposure was defined as the number of days between the date the patient received the first dose of study drug and the date the patient received the last dose of study drug

RESULTS

- A total of 1947 patients received VADA and 1955 received DA in the 2 studies
- Overall, demographics and other baseline characteristics in the pooled DD-CKD populations for the 2 global phase 3 studies were well balanced across the VADA and DA treatment groups (**Table 1**)
- Total exposure to VADA and DA was 3222.0 patient-years (PY) and 3245.8 PY, respectively

Table 1. Demographics and Other Baseline Characteristics—Pooled DD-CKD

Characteristic	VADA (N=1947)	DA (N=1955)
Age, years, mean (SD)	57.8 (14.0)	58.1 (13.9)
>65 years, n (%)	667 (34.3)	663 (33.9)
Sex, male, n (%)	1089 (55.9)	1110 (56.8)
Race, n (%)		
White	1255 (64.5)	1231 (63.0)
Black	470 (24.1)	478 (24.5)
Asian	88 (4.5)	106 (5.4)
American Indian or Alaska Native	20 (1.0)	30 (1.5)
Other[a]	114 (5.9)	110 (5.6)
Region, n (%)[b]		
US	1180 (60.6)	1181 (60.4)
Europe	277 (14.2)	295 (15.1)
Non-US/Europe	490 (25.2)	479 (24.5)
BMI, kg/m^2, mean (SD)	28.5 (7.1)	28.4 (7.1)
Diabetes mellitus, n (%)	1070 (55.0)	1088 (55.7)
Statin use, n (%)	943 (48.4)	969 (49.6)
Type of dialysis vascular access, n (%)[c]		
Not applicable (peritoneal dialysis)	159 (8.2)	159 (8.1)
Arteriovenous fistula	1370 (70.4)	1349 (69.0)
Arteriovenous graft	158 (8.1)	180 (9.2)
Temporary (ie, non-tunneled dialysis) catheter	47 (2.4)	48 (2.5)
Tunneled dialysis catheter	235 (12.1)	226 (11.6)
Other	2 (0.1)	3 (0.2)

[a]Includes Native Hawaiian or other Pacific Islander, multiple race, or race not reported.
[b]Europe (DD-CKD population) included Bulgaria, France, Germany, Italy, Poland, Portugal, Serbia, Ukraine, United Kingdom; Non-US/Europe (DD-CKD population) included Argentina, Australia, Brazil, Canada, Israel, Mexico, Russia, South Korea.
[c]Type of dialysis vascular access that was used for the most recently completed hemodialysis treatment.
BMI, body mass index; DA, darbepoetin alfa; DD-CKD, dialysis-dependent chronic kidney disease; SD, standard deviation VADA, vadadustat.

CEC-adjudicated events

- A first positively adjudicated event of any TE (AT+DVT+PE+VAT) occurred in 169 patients (8.7%) in the VADA treatment group and 148 (7.6%) in the DA treatment group; HR was 1.2 (95% CI, 0.96, 1.50; *P* value of Gray's test=0.161; **Table 2**)
  - VAT was reported as 6.6 events/100 PY in both treatment groups

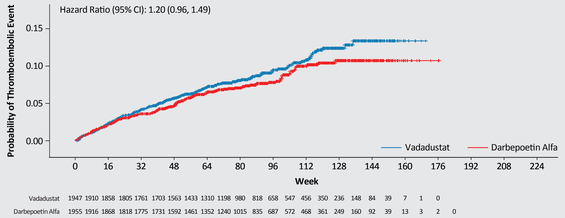
Table 2. Patients With First Thromboembolic Events (CEC-Adjudicated Positive)

	VADA (N=1947)		DA (N=1955)		Hazard Ratio (95% CI); *P* value[a]
	n (%)	Events (per 100 PY)	n (%)	Events (per 100 PY)	
Any thromboembolic event (composite)	169 (8.7)	242 (7.5)	148 (7.6)	249 (7.7)	1.20 (0.96, 1.49); *P*=0.161
Vascular access thrombosis[b]	146 (7.5)	212 (6.6)	120 (6.1)	214 (6.6)	–
Arterial thrombosis	7 (0.4)	8 (0.2)	4 (0.2)	4 (0.1)	–
Deep vein thrombosis	15 (0.8)	17 (0.5)	20 (1.0)	21 (0.6)	–
Pulmonary embolism	5 (0.3)	6 (0.2)	9 (0.5)	10 (0.3)	–
Arterial thrombosis, DVT, or PE	26 (1.3)	–	32 (1.6)	–	0.86 (0.51, 1.44); *P*=0.462
Venous thromboembolic events (DVT or PE)	19 (1.0)	–	28 (1.4)	–	0.71 (0.40, 1.27); *P*=0.206

[a]*P* value assessed using Gray's test.
[b]Number of patients with access varied throughout the study time points.
CEC, Clinical Endpoint Committee; CI, confidence interval; DA, darbepoetin alfa; DVT, deep vein thrombosis; PE, pulmonary embolism; PY, patient-years; VADA, vadadustat..

- Kaplan-Meier estimates of time to first TE (any) was similar between treatment groups (**Figure 1**)

Figure 1. Kaplan-Meier Curve for Time to First Thromboembolic Event (CEC-Adjudicated Positive)



CEC, Clinical Endpoint Committee; CI, confidence interval.

- Median time to first TE (any) was similar in both treatment groups (**Table 3**)

Table 3. Median Time to First Thromboembolic Event (CEC-Adjudicated Positive)

Time to first event, median (Q1, 3), weeks	VADA (N=1947)	DA (N=1955)
Any thromboembolic event (composite)[a]	35.4 (15.43, 62.86)	38.9 (14.79, 58.79)
AT, DVT, or PE	49.4 (16.43, 70.29)	48.8 (19.50, 63.50)
Venous thromboembolic events (DVT or PE)	51.4 (31.43, 76.29)	49.6 (26.36, 63.50)

[a]Any TE includes AT+DVT+PE+VAT.
AT, arterial thrombosis; CEC, Clinical Endpoint Committee; DA, darbepoetin alfa; DVT, deep vein thrombosis; PE, pulmonary embolism; Q1, 3, first quartile, third quartile; VADA, vadadustat; VAT, vascular access thrombosis.

- Cumulative incidence of TEs was were not significantly different between treatment groups (*P*=0.1608) (**Table 4**)

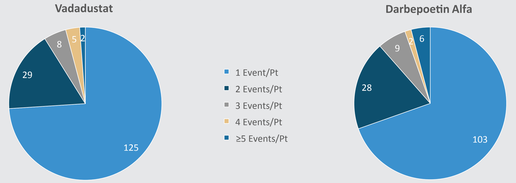
Table 4. Cumulative Incidence of Thromboembolic Events[a] (CEC-Adjudicated Positive)

Study Duration	Cumulative Incidence (95% CI)[b] VADA (N=1947)	DA (N=1955)
52 weeks	0.06 (0.049, 0.071)	0.05 (0.042, 0.062)
104 weeks	0.09 (0.080, 0.110)	0.08 (0.070, 0.098)
156 weeks	0.12 (0.101, 0.143)	0.10 (0.082, 0.115)

[a]Includes AT+DVT+PE+VAT.
[b]Based on non-parametric analysis. For the analysis of pooled data (Incident dialysis + Prevalent dialysis trials), Gray's test stratified by study.
AT, arterial thrombosis; CEC, Clinical Endpoint Committee; CI, confidence interval; DA, darbepoetin alfa; DVT, deep vein thrombosis; PE, pulmonary embolism; VADA, vadadustat; VAT, vascular access thrombosis.

- A recurrent event analysis for TEs showed similar outcomes between the 2 treatment groups (**Figure 2**)
- In the VADA treatment group, 242 TEs were reported in 169 patients, with a median of 1 event/patient (maximum 9 events/patient); in the DA treatment group, 249 TEs were reported in 148 patients, with a median of 1 event/patient (maximum 13 events/patient)
- The median time to TE (first quartile, third quartile) was 42.86 weeks (18.43, 70.43) and 48.43 weeks (20.14, 69.43) in the VADA and DA treatment groups, respectively, with an HR (VADA/DA) of 0.99 (95% CI, 0.831, 1.186)

Figure 2. Number of CEC-Adjudicated Recurrent Thromboembolic Events Per Patient



Pt, patient.

- 30-day mortality rate from any TE was 9/169 (5.3%) and 12/148 (8.1%) in the VADA and DA groups, respectively (proportion difference [VADA-DA], −0.029 [95%CI, −0.085, 0.027])

Investigator-Reported AEs (MedDRA preferred terms)

MedDRA Category: Thrombosis

- The most common treatment-emergent thrombosis events occurring in ≥3 patients in the VADA treatment group were arteriovenous fistula thrombosis, acute myocardial infarction, arteriovenous graft thrombosis, and vascular access site thrombosis (**Table 5**)
- Similarly, in the DA treatment group, the most common treatment-emergent thrombosis events occurring in ≥3 patients were arteriovenous fistula thrombosis, acute myocardial infarction, arteriovenous graft thrombosis, and vascular access site thrombosis
- Between treatment groups, similar rates were observed for thrombosis AEs (relative risk, 0.93 event/100 PY) and serious AEs (relative risk, 1.01 event/100 PY)

Table 5. Thrombosis TEAEs and Serious TEAEs Occurring in ≥3 Patients (Investigator-Reported Preferred Term)

	VADA (N=1947)				DA (N=1955)			
	Any TEAE		Serious TEAE		Any TEAE		Serious TEAE	
Category MedDRA Preferred Term[a]	n (%)	Events (per 100 PY)	n (%)	Events (per 100 PY)	n (%)	Events (per 100 PY)	n (%)	Events (per 100 PY)
Thrombosis[b]	306 (15.7)	466 (14.5)	206 (10.6)	276 (8.6)	312 (16.0)	504 (15.5)	210 (10.7)	276 (8.5)
Arteriovenous fistula thrombosis	112	141	59	69	88	116	44	52
Arteriovenous graft thrombosis	43	64	22	28	42	98	21	32
Vascular access site thrombosis	34	48	8	9	41	58	16	21
Graft thrombosis	11	13	5	5	9	16	1	1
Acute myocardial infarction	87	104	84	101	84	95	82	93
Deep vein thrombosis	20	23	13	13	17	17	10	10
Ischemic stroke	14	14	14	14	13	13	13	13
Thrombophlebitis superficial	7	9	2	3	4	4	0	0
Jugular vein thrombosis	5	6	3	4	11	11	8	8
Peripheral artery thrombosis	5	6	4	4	3	3	3	3
Lacunar infarction	2	2	0	0	7	7	4	4
Cerebral infarction	3	3	3	3	5	5	4	4
Venous thrombosis	1	1	0	0	4	4	3	3

[a]Terms presented in the table were reported in ≥3 patients for any TEAEs and for serious TEAEs in any treatment groups. Accordingly, TEAEs not included in the table are: arterial thrombosis, atrial thrombosis, brachiocephalic vein thrombosis, cerebellar infarction, embolic stroke, intracardiac thrombus, lacunar stroke, shunt thrombosis, subclavian vein thrombosis, thrombophlebitis, thrombosis, thrombosis in device, vascular graft thrombosis, vena cava thrombosis, and venous thrombosis limb. [b]Type of access varied throughout the study time points; hence, n/events for preferred terms may not add up to the category total.
DA, darbepoetin alfa; MedDRA, Medical Dictionary for Regulatory Activities; PY, patient-years; TEAE, treatment-emergent adverse event; VADA, vadadustat..

MedDRA Category: Device/Shunt Thrombosis

- Between treatment groups, similar rates were observed for device/shunt thrombosis AEs (**Table 6**)
  - AE relative risk: 0.94 event/100 PY; serious AE relative risk: 1.06 event/100 PY (data not shown)

Table 6. Device/Shunt Thrombosis TEAEs and Serious TEAEs (Investigator-Reported Preferred Term)

	VADA (N=1947)				DA (N=1955)			
	Any TEAE		Serious TEAE		Any TEAE		Serious TEAE	
Category MedDRA Preferred Term	n (%)	Events (per 100 PY)	n (%)	Events (per 100 PY)	n (%)	Events (per 100 PY)	n (%)	Events (per 100 PY)
Device/shunt thrombosis[a]	185 (9.5)	274 (8.5)	91 (4.7)	115 (3.6)	161 (8.2)	295 (9.1)	77 (3.9)	109 (3.4)
Arteriovenous fistula thrombosis	112	141	59	69	88	116	44	52
Arteriovenous graft thrombosis	43	64	22	28	42	98	21	32
Vascular access site thrombosis	34	48	8	9	41	58	16	21
Graft thrombosis	11	13	5	5	9	16	1	1
Device-related thrombosis	3	3	0	0	0	0	0	0
Shunt thrombosis	2	2	2	2	1	1	1	1
Vascular graft thrombosis	2	2	1	1	2	3	1	1
Thrombosis in device	1	1	1	1	3	3	1	1

DA, darbepoetin alfa; MedDRA, Medical Dictionary for Regulatory Activities; PY, patient-years; TEAE, treatment-emergent adverse event; VADA, vadadustat.
[a]Type of access varied throughout the study time points, hence, n/events for preferred terms may not add up to the category total.

LIMITATIONS

- The INNO$_2$VATE studies included 2 safety databases – one database for the CEC-Adjudicated events, and a second safety database. AEs were only adjudicated, and thus included in the CEC-Adjudicated event database, if necessary clinical information was available (eg, imaging reports of thrombosis and clinical description of TE). Conversely, the Safety database included all investigator-reported AEs, regardless of clinical documentation. This may have led to differences between the 2 databases in similar terms
- Patients' vascular access type may have changed throughout the INNO$_2$VATE study, and the number of patients with access also varied throughout the study time points

CONCLUSION

- In the phase 3 INNO$_2$VATE trials in patients with anemia and DD-CKD, the rate of TEs was similar in both the VADA and DA treatment groups

ACKNOWLEDGMENTS

This study was funded by Akebia Therapeutics, Inc., and Otsuka Pharmaceutical. Medical writing assistance was provided by Cadent Medical Communications, LLC, a Syneos Health® group company, and was supported by Akebia Therapeutics, Inc.

DISCLOSURES

PP and PM serve as members of the executive committee of INNO$_2$VATE trials 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 in part, except in abstract format.

Presented during American Society of Nephrology (ASN) Kidney Week 2021, Virtual, November 4–7, 2021.

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