PO0462

PRESENTED AT ASN KIDNEY WEEK 2021

Assessment of Thromboembolic Events With Vadadustat vs Darbepoetin Alfa for Anemia Treatment in Patients With Non–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 non–dialysis-dependent chronic kidney disease (NDD-CKD)
- In 2 global phase 3, open-label, randomized, non-inferiority trials (PRO_2TECT), VADA was compared with the erythropoiesis-stimulating agent (ESA) darbepoetin alfa (DA) with respect to cardiovascular safety (major adverse cardiovascular event [MACE]) and correction and maintenance of hemoglobin (Hb) concentration[5]
  - The prespecified non-inferiority margin for MACE was 1.25 but the 95th percentile for the hazard ratio (HR) transcended this margin (HR 1.17, 95% confidence interval [CI] 1.01–1.36)
- HIF has a role in coagulation, fibrinolysis, and thrombus resolution, and its activation has a potential risk of thromboembolic events (TEs)[6]
- Given historical safety concerns associated with currently used ESAs, an important safety endpoint of the PRO_2TECT trials was to evaluate 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 TEs (DVT or PE)

METHODS

- Data were pooled from 2 completed global phase 3, open-label, randomized (1:1) non-inferiority trials (PRO_2TECT) that compared the safety and efficacy of VADA with that of DA in adult patients with NDD-CKD
  - PRO_2TECT studies randomized a total of 3476 patients with NDD-CKD[3]
  - The safety population included 3471 patients (5 randomized patients did not receive study drug)
    - NCT02648347: Correction study, ESA-untreated population (N=1748)
    - NCT02680574: Conversion study, ESA-treated population (N=1723)
- The primary safety endpoint of the PRO_2TECT trials was time to first MACE (a composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke), 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 as follows:
  - Investigators identified 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 1739 patients received VADA and 1732 received DA in the 2 studies
- Overall, demographics and other baseline characteristics in the pooled NDD-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 3113.3 patient-years (PY) and 3174.3 PY, respectively

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

Characteristic	VADA (N=1739)	DA (N=1732)
Age, years, mean (SD)	66.2 (13.8)	65.7 (13.6)
>65 years, n (%)	1030 (59.2)	1022 (59.0)
Sex, male, n (%)	797 (45.8)	738 (42.6)
Race, n (%)		
White	1177 (67.7)	1172 (67.7)
Black	280 (16.1)	302 (17.4)
Asian	110 (6.3)	92 (5.3)
American Indian or Alaska Native	54 (3.1)	49 (2.8)
Other[a]	118 (6.8)	117 (6.8)
Region, n (%)[b]		
US	861 (49.5)	862 (49.8)
Europe	295 (17.0)	288 (16.6)
Non-US/Europe	583 (33.5)	582 (33.6)
BMI, kg/m², mean (SD)	29.4 (7.1)	29.7 (7.3)
Diabetes mellitus, n (%)	1098 (63.1)	1115 (64.4)
Statin use, n (%)	1055 (60.7)	1042 (60.2)
Medical history (MedDRA Preferred Terms)		
Arteriovenous fistula thrombosis	2 (0.1)	2 (0.1)
Arteriovenous fistula maturation failure	1 (0.1)	0 (0)
Arteriovenous fistula site complications, other	1 (0.1)	3 (0.2)
Arteriovenous graft site stenosis	0 (0)	1 (0.1)
Vascular access site thrombosis	0 (0)	1 (0.1)
Vascular access site complications, other	0 (0)	1 (0.1)
Vascular pseudoaneurysm	1 (0.1)	2 (0.1)

[a]Includes Native Hawaiian or other Pacific Islander, multiple race, or race not reported.
[b]Europe included Austria, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Poland, Romania, Serbia, Slovakia, Spain, Turkey, and the United Kingdom; Non-US/Europe included Argentina, Australia, Brazil, Canada, Chile, Colombia, Israel, Malaysia, Mexico, New Zealand, Russia, South Africa, South Korea, and Ukraine.
BMI, body mass index; DA, darbepoetin alfa; MedDRA, Medical Dictionary for Regulatory Activities; NDD-CKD, non–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 33 patients (1.9%) in the VADA treatment group and 38 patients (2.2%) in the DA treatment group; HR was 0.88 (95% CI, 0.554, 1.408; *P* value of Gray's test=0.5693; **Table 2**)
  - VAT was reported as 0.5 events/100 PY in the VADA treatment group and 0.6 events/100 PY in the DA treatment group

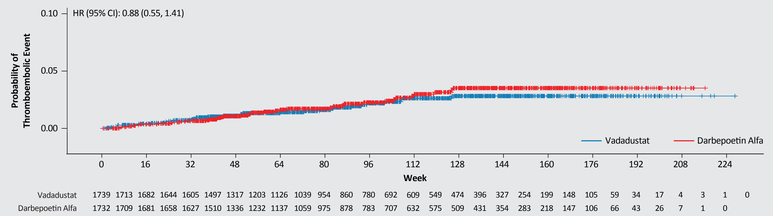
Table 2. Patients With First Thromboembolic Events (CEC-Adjudicated Positive)

	VADA (N=1739)		DA (N=1732)		Hazard Ratio (95% CI); *P* value[a]
	n (%)	Events (per 100 PY)	n (%)	Events (per 100 PY)	
Any thromboembolic event (composite)	33 (1.9)	40 (1.3)	38 (2.2)	44 (1.4)	0.88 (0.554, 1.408); *P*=0.5693
Vascular access thrombosis[b]	12 (0.7)	17 (0.5)	14 (0.8)	19 (0.6)	–
Arterial thrombosis	3 (0.2)	3 (0.1)	2 (0.1)	2 (0.1)	–
Deep vein thrombosis	15 (0.9)	16 (0.5)	20 (1.2)	20 (0.6)	–
Pulmonary embolism	5 (0.3)	5 (0.2)	4 (0.2)	4 (0.1)	–
Arterial thrombosis, DVT, or PE	21 (1.2)	–	25 (1.4)	–	0.86 (0.480, 1.544); *P*=0.5685
Venous thromboembolic events (DVT or PE)	18 (1.0)	–	23 (1.3)	–	0.80 (0.430, 1.485); *P*=0.4450

[a]*P* value assessed using Gray's test.
[b]Number of patients with access varied throughout the study timepoints.
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) were similar between treatment groups (**Figure 1**)

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



Vadadustat	1739	1713	1682	1644	1605	1497	1317	1203	1126	1039	954	860	780	692	609	549	474	396	327	254	199	148	105	59	34	17	4	3	1	0
Darbepoetin Alfa	1732	1709	1681	1658	1627	1510	1336	1232	1137	1059	975	878	783	707	632	575	509	431	354	283	218	147	106	66	43	26	7	1	0	

CEC, Clinical Endpoint Committee; CI, confidence interval; HR, hazard ratio.

- Median time to first TE (any) was similar between 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=1739)	DA (N=1732)
Any thromboembolic event (composite)[a]	38.0 (22.29, 82.14)	52.9 (28.00, 86.71)
Arterial thrombosis, DVT, or PE	38.0 (23.14, 78.14)	51.9 (30.00, 83.00)
Venous thromboembolic events (DVT or PE)	40.8 (23.14, 78.14)	51.9 (30.00, 83.00)

[a]Any thromboembolic event includes AT+DVT+PE+VAT.
AT, arterial thrombosis; 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 not significantly different between treatment groups (*P*=0.5693) (**Table 4**)

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

Study Duration	Cumulative Incidence (95% CI)[b] VADA (N=1739)	DA (N=1732)
52 Weeks	0.013 (0.008, 0.019)	0.011 (0.007, 0.017)
104 Weeks	0.021 (0.014, 0.030)	0.022 (0.015, 0.031)
156 Weeks	0.025 (0.017, 0.035)	0.031 (0.022, 0.043)
208 Weeks	0.025 (0.017, 0.035)	0.031 (0.022, 0.043)

[a]Includes AT+DVT+PE+VAT.
[b]Based on nonparametric analysis. For the analysis of pooled data (ESA-untreated + ESA treated 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.

- The 30-day mortality rate from any TE was 4/33 (12.1%) and 4/38 (10.4%) in the VADA and DA groups, respectively (proportion difference [VADA-DA], 0.021 [95% CI, –0.130, 0.173])

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 acute myocardial infarction, DVT, and ischemic stroke (**Table 5**)
- In the DA treatment group, the most common treatment-emergent thrombosis events occurring in ≥3 patients were acute myocardial infarction, DVT, and arteriovenous fistula thrombosis
- Between treatment groups, similar rates were observed with thrombosis AEs (relative risk 1.03) and serious AEs (relative risk 1.17)

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

	VADA (N=1739)				DA (N=1732)			
	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]	143 (8.2)	165 (5.3)	112 (6.4)	128 (4.1)	138 (8.0)	164 (5.2)	102 (5.9)	112 (3.5)
Acute myocardial infarction	69	73	66	70	53	60	51	56
DVT	15	16	11	12	23	23	10	10
Ischemic stroke	13	15	13	15	9	9	8	8
Myocardial infarction	13	13	12	12	12	12	12	12
Arteriovenous fistula thrombosis	10	12	4	5	18	23	10	10

*The preferred terms listed in the table were reported in ≥3 patients for any TEAEs and for serious TEAEs in both treatment groups. Other TEAEs reported in ≥3 patients for any TEAEs or for serious TEAEs in either treatment group were (in decreasing order of events) cerebral infarction, vascular access site thrombosis, peripheral artery thrombosis, arteriovenous graft thrombosis, thrombophlebitis superficial, venous thrombosis limb, and thrombophlebitis. Other TEAEs with rates fewer than 3 patients were atrial thrombosis, brain stem stroke, cerebellar infarction, embolic cerebral infarction, embolic stroke, jugular vein thrombosis, lacunar infarction, lacunar stroke, shunt thrombosis, subclavian vein thrombosis, thrombosis, and vein thrombosis.
[a]Type of access varied throughout the study timepoints, 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

- Lower rates of device/shunt thrombosis AEs (relative risk 0.56) and serious AEs (relative risk 0.58) were observed in the VADA treatment group versus the DA treatment group
  - Any TEAEs categorized as device/shunt thrombosis were reported in 17 patients (22 events) and 28 patients (40 events) in the VADA and DA treatment groups, respectively
  - Serious TEAEs categorized as device/shunt thrombosis were reported in 5 patients (8 events) and 13 patients (14 events) in the VADA and DA treatment groups, respectively

LIMITATIONS

- The PRO_2TECT 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.

CONCLUSION

- In the phase 3 PRO_2TECT trials in patients with anemia and NDD-CKD, the rate of TEs was similar between 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 PRO_2TECT 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 part, except in abstract format.

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

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