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Vadadustat, an Oral HIF-PHI, Is Not Associated With Risk of Neoplasm in Patients With Anemia Due to CKD

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BACKGROUND

- Chronic kidney disease (CKD), estimated to affect nearly 10% of the global population, is frequently associated with anemia, and may be associated with an increased risk of some forms of neoplasia, including renal cell carcinoma (RCC)[1–3]
- The oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) vadadustat (VADA) stimulates endogenous erythropoietin, resulting in increased red blood cell production[4,5]
- The hematologic efficacy of VADA was demonstrated to be noninferior to darbepoetin alfa (DA) in patients with dialysis-dependent (DD) and non–dialysis-dependent (NDD) CKD[4,5]
- HIF activation is evident in many neoplasms, and the HIF pathway can be co-opted to promote angiogenesis; thus, there is a potential increased risk of neoplasia with HIF-PHI therapy[6,7]
- Initial reports on HIF-PHIs have not shown an increased risk of neoplasm or neoplasm-related adverse events (AEs)[8]

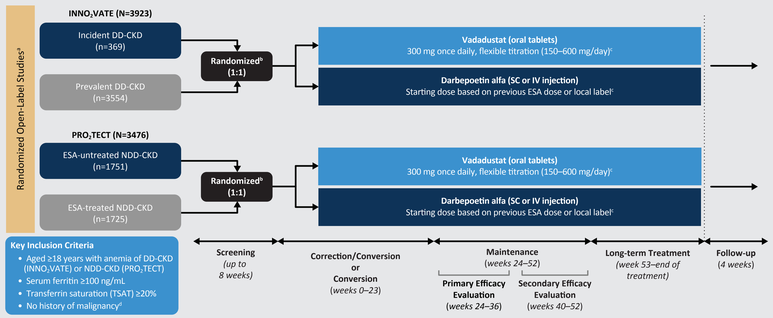
OBJECTIVE

- To investigate the risk of neoplasia in patients with CKD treated with VADA and DA in 4 global phase 3 trials

METHODS

- We pooled data for a total population analysis from 4 global phase 3, randomized, open-label studies in patients with DD-CKD (INNO$_2$VATE trials) and NDD-CKD (PRO$_2$TECT trials)

Figure 1. Study Design



[a]Population: Incident (NCT02865850); Prevalent (NCT02892149); ESA-untreated (NCT02648347); ESA-treated (NCT02680574).
[b]Stratified by: Geographic region; NYHA CHF class; Hb level at study entry.
[c]Study drug is titrated to achieve target Hb levels (US: 10–11 g/dL; non-US: 10–12 g/dL).
[d]Patients were excluded if they had myelodysplastic syndromes, hematologic malignancy, myeloma or a history of active malignancy within 2 years prior to or during screening, except for treated basal cell carcinoma of the skin, curatively resected squamous cell carcinoma of the skin, or cervical carcinoma in situ.
CKD, chronic kidney disease; DD, dialysis-dependent; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IV, intravenous; NDD, non–dialysis-dependent; NYHA CHF, New York Heart Association Congestive Heart Failure; SC, subcutaneous.

Pooled Safety Analysis

- A treatment-emergent adverse event (TEAE) was defined as an AE that started (or a pre-existing AE that worsened) on or after the first dose of study drug
- AEs of special interest (AESI) were identified over the course of the clinical development program, from nonclinical findings, potential class effects of other HIF stabilizers, and ongoing safety surveillance
- 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

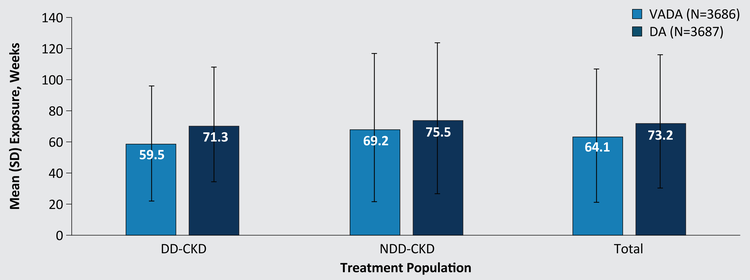
- Overall, demographics and other baseline characteristics in the pooled DD-CKD, NDD-CKD, and total populations for global phase 3 studies were well-balanced across the VADA and DA treatment groups (**Table 1**)
- In total, 3686 patients were exposed to VADA and 3687 to DA for a median (interquartile range) duration of 56.7 weeks (31.9–91.7) and 70.0 weeks (39.9–102.1). Treatment exposure in NDD-CKD, DD-CKD, and total populations are reported in **Figure 2**
  - 54.6% of VADA-treated patients and 64.2% of DA-treated patients were exposed for ≥52 weeks, and 18.9% and 24.1% for >104 weeks in the total population, respectively

Table 1. Demographics and Other Baseline Characteristics

Characteristic	DD-CKD Population		NDD-CKD Population		Total Population	
	VADA (N=1947)	DA (N=1955)	VADA (N=1739)	DA (N=1732)	VADA (N=3686)	DA (N=3687)
Age, years, mean (SD)	57.8 (14.0)	58.1 (13.9)	66.2 (13.8)	65.7 (13.6)	61.8 (14.5)	61.7 (14.3)
Sex, Female, n (%)	858 (44.1)	845 (43.2)	942 (54.2)	994 (57.4)	1800 (48.8)	1839 (49.9)
Race, n (%)						
White	1255 (64.5)	1231 (63.0)	1177 (67.7)	1172 (67.7)	2432 (66.0)	2403 (65.2)
Black	470 (24.1)	478 (24.5)	280 (16.1)	302 (17.4)	750 (20.3)	780 (21.2)
Asian	88 (4.5)	106 (5.4)	110 (6.3)	92 (5.3)	198 (5.4)	198 (5.4)
American Indian or Alaska Native	20 (1.0)	30 (1.5)	54 (3.1)	49 (2.8)	74 (2.0)	79 (2.1)
Other[a]	114 (5.9)	110 (5.6)	118 (6.8)	117 (6.8)	232 (6.3)	227 (6.2)
Region, n (%)[b]						
US	1180 (60.6)	1181 (60.4)	861 (49.5)	862 (49.8)	2041 (55.4)	2043 (55.4)
Europe	277 (14.2)	295 (15.1)	295 (17.0)	288 (16.6)	572 (15.5)	583 (15.8)
Other	490 (25.2)	479 (24.5)	583 (33.5)	582 (33.6)	1073 (29.1)	1061 (28.8)
BMI, kg/m^2, mean (SD)	28.5 (7.1)	28.4 (7.1)	29.4 (7.1)	29.7 (7.3)	28.9 (7.2)	29.1 (7.2)

[a]Includes Native Hawaiian or other Pacific Islander, multiple or not reported. [b]Europe (DD-CKD population) included Bulgaria, France, Germany, Italy, Poland, Portugal, Serbia, Ukraine, and the United Kingdom; Europe (NDD-CKD population) included Austria, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Poland, Romania, Serbia, Slovakia, Spain, Turkey, and the United Kingdom; Non-US/Europe (DD-CKD population) included Argentina, Australia, Brazil, Canada, Israel, Mexico, Russia, and South Korea; Non-US/Europe (NDD-CKD population) included Argentina, Australia, Brazil, Canada, Chile, Colombia, Israel, Malaysia, Mexico, New Zealand, Russia, South Africa, South Korea, and Ukraine.
BMI, body mass index; CKD, chronic kidney disease; DA, darbepoetin alfa; DD, dialysis-dependent; NDD, non–dialysis-dependent; SD, standard deviation; US, United States; VADA, vadadustat.

Figure 2. Mean Duration of Treatment Exposure in NDD-CKD, DD-CKD, and Total Populations



CKD, chronic kidney disease; DA, darbepoetin alfa; DD, dialysis-dependent; NDD, non–dialysis-dependent; SD, standard deviation; VADA, vadadustat.

- A summary of TEAEs and treatment-emergent serious AEs (SAEs) of neoplasm are presented in **Table 2**

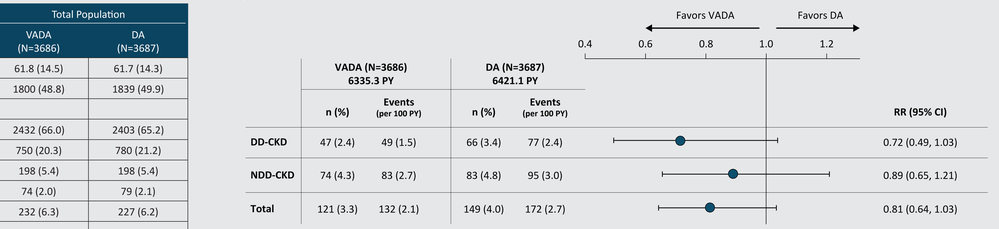
Table 2. TEAEs and SAEs of Neoplasm

	DD-CKD				NDD-CKD				Total Population			
	VADA (N=1947)		DA (N=1955)		VADA (N=1739)		DA (N=1732)		VADA (N=3686)		DA (N=3687)	
	n (%)	Events (per 100 PY)	n (%)	Events (per 100 PY)	n (%)	Events (per 100 PY)	n (%)	Events (per 100 PY)	n (%)	Events (per 100 PY)	n (%)	Events (per 100 PY)
TEAEs of neoplasm	71 (3.6)	77 (2.4)	100 (5.1)	118 (3.6)	103 (5.9)	122 (3.9)	123 (7.1)	146 (4.6)	174 (4.7)	199 (3.1)	223 (6.0)	264 (4.1)
Drug-related AEs of neoplasm	4 (0.2)	4 (0.1)	0	0	1 (0.1)	1 (0)	1 (0.1)	1 (0)	5 (0.1)	5 (0.1)	1 (0)	1 (0)
Treatment-emergent SAEs of neoplasm	40 (2.1)	40 (1.2)	62 (3.2)	68 (2.1)	59 (3.4)	64 (2.1)	69 (4.0)	75 (2.4)	99 (2.7)	104 (1.6)	131 (3.6)	143 (2.2)
Drug-related SAEs of neoplasm	1 (0.1)	1 (0)	0	0	1 (0.1)	1 (0)	1 (0.1)	1 (0)	2 (0.1)	2 (0)	1 (0)	1 (0)
TEAEs of neoplasm leading to study drug withdrawal	4 (0.2)	4 (0.1)	2 (0.1)	2 (0.1)	9 (0.5)	9 (0.3)	10 (0.6)	11 (0.3)	13 (0.4)	13 (0.2)	12 (0.3)	13 (0.2)
TEAEs of neoplasm resulting in death	5 (0.3)	5 (0.2)	10 (0.5)	10 (0.3)	11 (0.6)	11 (0.4)	21 (1.2)	21 (0.7)	16 (0.4)	16 (0.3)	31 (0.8)	31 (0.5)

AEs, adverse events; CKD, chronic kidney disease; DA, darbepoetin alfa; DD, dialysis-dependent; NDD, non–dialysis-dependent; PY, patient-years; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; VADA, vadadustat.

- Neoplasms were observed at a rate of 2.1 events/100 PY and 2.7 events/100 PY in the VADA and DA treatment groups, respectively (relative risk [RR], 0.81; 95% confidence interval [CI], 0.64, 1.03) (**Figure 3**)
  - Rates of neoplasms in patients with DD-CKD were 1.5 vs 2.4 events/100 PY (RR, 0.72; 95% CI, 0.45, 1.03)
  - Rates of neoplasms in patients with NDD-CKD were 2.7 vs 3.0 events/100 PY (RR, 0.89; 95% CI, 0.65, 1.21)

Figure 3. Rates of Neoplasm as AESI in NDD-CKD, DD-CKD, and Total Populations



	VADA (N=3686) 6335.3 PY		DA (N=3687) 6421.1 PY		
	n (%)	Events (per 100 PY)	n (%)	Events (per 100 PY)	RR (95% CI)
DD-CKD	47 (2.4)	49 (1.5)	66 (3.4)	77 (2.4)	0.72 (0.49, 1.03)
NDD-CKD	74 (4.3)	83 (2.7)	83 (4.8)	95 (3.0)	0.89 (0.65, 1.21)
Total	121 (3.3)	132 (2.1)	149 (4.0)	172 (2.7)	0.81 (0.64, 1.03)

AESI, adverse events of special interest; CI, confidence interval; CKD, chronic kidney disease; DA, darbepoetin alfa; DD, dialysis-dependent; NDD, non–dialysis-dependent; RR, relative risk; VADA, vadadustat.

- Neoplasms were reported in 3.3% of total patients administered VADA and 4.0% of patients administered DA (RR, 0.81; 95% CI, 0.64, 1.03) (**Table 3**)
  - RCC was reported for 0.1% of patients in each of the VADA and DA treatment groups
- Neoplasms were reported for 2.4% of patients with DD-CKD administered VADA and 3.4% of patients administered DA (RR, 0.72; 95% CI, 0.49, 1.03)
  - RCC was reported for 0.1% of patients in the VADA treatment group and 0.2% of patients in the DA treatment group
- Neoplasms were reported for 4.3% of patients with NDD-CKD who were administered VADA and 4.8% of patients administered DA (RR, 0.89; 95% CI, 0.65, 1.21)
  - The most frequent neoplasms by preferred terms were non-melanoma skin cancer (basal cell carcinoma: 0.8% and 0.7% of patients in the VADA and DA treatment groups, respectively; and squamous cell carcinoma of the skin: 0.8% and 0.6% of patients, respectively)
  - No cases of RCC were reported in the VADA treatment group, and the DA treatment group showed reported cases in 0.1% of patients

Table 3. Neoplasm-Related Treatment-Emergent AESI in ≥1 Patients—Pooled Total Population

System organ class Preferred term, n (%)	VADA (N=3686)	DA (N=3687)
Malignant or unspecified tumors	121 (3.3)	149 (4.0)
Basal cell carcinoma	15 (0.4)	20 (0.5)
Squamous cell carcinoma of the skin	14 (0.4)	11 (0.3)
Invasive ductal breast carcinoma	5 (0.1)	2 (0.1)
Prostate cancer	4 (0.1)	12 (0.3)
Breast cancer	4 (0.1)	3 (0.1)
Plasma cell myeloma	4 (0.1)	7 (0.2)
Adenocarcinoma of the colon	3 (0.1)	6 (0.2)
Malignant melanoma	3 (0.1)	3 (0.1)
Hepatocellular carcinoma	3 (0.1)	2 (0.1)
Lung adenocarcinoma	3 (0.1)	1 (0.0)
Prostate cancer metastatic	3 (0.1)	1 (0.0)
RCC	2 (0.1)	5 (0.1)
Clear cell RCC	2 (0.1)	3 (0.1)
Colon cancer	2 (0.1)	3 (0.1)
Adenocarcinoma	1 (0.0)	3 (0.1)
Bladder cancer	1 (0.0)	3 (0.1)
Squamous cell carcinoma	1 (0.0)	3 (0.1)

AESI, adverse events of special interest; DA, darbepoetin alfa; RCC, renal cell carcinoma; VADA, vadadustat.

CONCLUSIONS

- A pooled analysis was conducted on the safety populations from 4 global phase 3 trials evaluating VADA for the treatment of anemia due to CKD in patients with DD-CKD or NDD-CKD
- The risk of neoplasia among >3600 patients treated with VADA for a median duration of 56 weeks was comparable to treatment with DA

ACKNOWLEDGMENTS

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DISCLOSURES

RA and GC currently serve as study consultants for Akebia Therapeutics, Inc. DV, WL, and CS 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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