Akebia® THERAPEUTICS

BETTERING THE LIVES OF PEOPLE IMPACTED BY KIDNEY DISEASE

ASN Investor Briefing Webcast
October 23, 2020

CAUTIONARY NOTE ON FORWARD-LOOKING STATEMENTS

Statements in this presentation regarding Akebia's strategy, plans, prospects, expectations, beliefs, intentions and goals are forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995, as amended, including but not limited to statements regarding the path forward for vadadustat in dialysis; the assessment of the data from the global Phase 3 program for vadadustat; the expectation that treatment of non-dialysis patients with vadadustat will be a review issue for the U.S. Food and Drug Administration (FDA); the belief that the newly presented analyses and totality of the data from the global Phase 3 program of vadadustat will inform FDA's review of vadadustat in non-dialysis; safety and efficacy of vadadustat; the potential indications for and benefits of vadadustat; sharing vadadustat clinical data in peer reviewed journals and with health authorities and others, as well as the timing and forum thereof; the timing of meetings with regulators, including the pre-NDA meeting with the FDA; working with regulators to make vadadustat available to dialysis patients, subject to approval; submitting filings, including the totality of the global Phase 3 data, for marketing approval of vadadustat, and the timing thereof; the potential launch and commercialization of vadadustat if approved by regulatory authorities; implications for Japan; and market opportunity, clinical opportunity, commercial potential, prevalence, and the growth in, and potential demand for, vadadustat. The terms "believe," "confident," "expect," "look forward," "on track," "opportunity," "plan," "potential," "promising," "working" and similar references are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement, including the timing and content of advice given and decisions made by health authorities, including approval and labeling decisions; the actual time it takes to make regulatory submissions for vadadustat to health authorities, including the submission of the NDA to the FDA; risks associated with the Priority Review Voucher for vadadustat; the potential direct or indirect impact of the COVID-19 pandemic on our business, operations, and the markets and communities in which we and our partners, collaborators, vendors and customers operate; manufacturing and quality risks; risks associated with management and key personnel changes and transitional periods; the actual funding required to continue to commercialize our commercial product, to develop and commercialize vadadustat, and to operate the Company; market acceptance and coverage and reimbursement of our commercial product and vadadustat, if approved; the risks associated with potential generic entrants for our commercial product and vadadustat, if approved; early termination of any of Akebia's collaborations; Akebia's and its collaborators' ability to satisfy their obligations under Akebia's collaboration agreements; the competitive landscape for our commercial product and vadadustat; the scope, timing, and outcome of any legal, regulatory and administrative proceedings; changes in the economic and financial conditions of the businesses of Akebia and its collaborations partners and vendors; and Akebia's ability to obtain, maintain and enforce patent and other intellectual property protection for our commercial product, vadadustat and any other product candidates. Other risks and uncertainties include those identified under the heading "Risk Factors" in Akebia's Quarterly Report on Form 10-Q for the quarter ended June 30, 2020 and other filings that Akebia may make with the U.S. Securities and Exchange Commission in the future. These forward-looking statements (except as otherwise noted) speak only as of the date of this presentation, and Akebia does not undertake, and specifically disclaims, any obligation to update any forward-looking statements contained in this presentation.

Vadadustat is an investigational drug and has not yet been approved by the U.S. Food and Drug Administration or any regulatory authority with the exception of Japan's Ministry of Health, Labour and Welfare.

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AGENDA

- Opening Remarks
  John P. Butler, President and Chief Executive Officer
- Review of INNO$_2$VATE and PRO$_2$TECT Global Phase 3 Data Presented at *American Society of Nephrology Kidney Week 2020 Reimagined*
  Glenn Chertow, M.D., M.P.H., Professor of Medicine, Chief of the Division of Nephrology at Stanford University and Co-Chair of the independent Executive Steering Committee for PRO$_2$TECT and INNO$_2$VATE
- Discussion of INNO$_2$VATE and PRO$_2$TECT Global Phase 3 Safety Data
  Steven K. Burke, M.D., Senior Vice President, Research & Development and Chief Medical Officer
- Question and Answer Session
- Closing Remarks
  John P. Butler, President and Chief Executive Officer

INNO$_2$VATE Program

Global Phase 3 Clinical Trials of Vadadustat for Treatment of Anemia in Patients With Dialysis-Dependent Chronic Kidney Disease

Introduction

Background

- Vadadustat is an investigational oral HIF-PHI under development for the treatment of anemia of CKD[1]
  - In phase 2 studies, vadadustat raised and maintained hemoglobin concentrations within target range in patients with non dialysis-dependent (NDD-) and dialysis-dependent (DD-)CKD[2-4]
- Long-term safety and efficacy of vadadustat compared with ESA are unknown

Objectives of the INNO$_2$VATE Program

- To evaluate the long-term safety and efficacy of vadadustat compared to darbepoetin alfa in **DD-CKD patients** with anemia in **two trials** in

  - *incident* DD-CKD with limited ESA exposure (baseline Hb 8-11 g/dL)

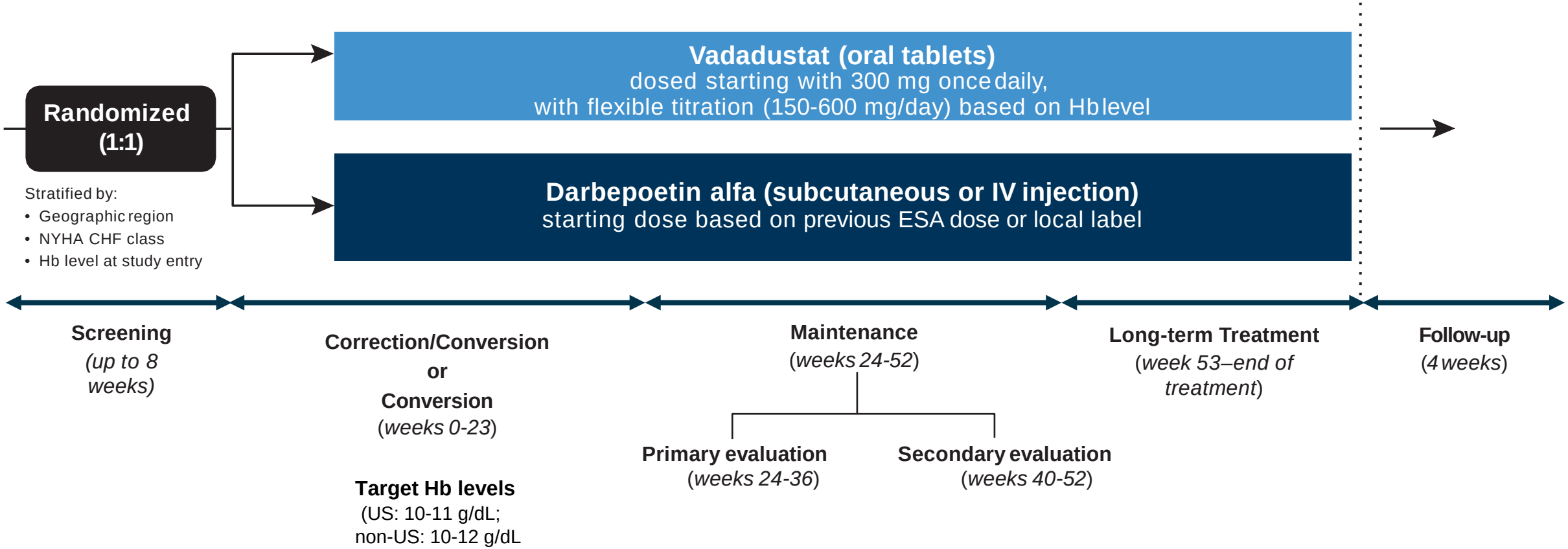
  - *prevalent* DD-CKD with established ESA treatment (baseline Hb 8-11 g/dL in US; 9-12 outside the US)

1. Maxwell PH, Eckardt KU. *Nat Rev Nephrol.* 2016;12(3):157-168. 2. Pergola PE, et al. *Kidney Int.* 2016;90(5):1115-1122. 3. Martin ER, et al. *Am J Nephrol.* 2017;45(5):380-388. 4. Haase VH, et al. *Nephrol Dial Transplant*. 2019;34(1):90-99.

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; QD, once per day; TIW, three times per week.

INNO$_2$VATE Study Design

- **Two** randomized, phase 3, global, multicenter, open-label, sponsor-blind, active-controlled noninferiority trials in *incident* DD-CKD and *prevalent* DD-CKD patients with **similar design**



CKD, chronic kidney disease; DD, dialysis dependent; ESA, erythropoiesis-stimulating agents; Hb, hemoglobin; IV, intravenous; NYHA CHF, New York Heart Association Congestive Heart Failure.

Primary Safety and Efficacy Endpoints

Safety Analysis - Combined Across Both, the *Incident* DD-CKD and the *Prevalent* DD-CKD Trial (Event Driven)

Primary Safety Endpoint

- Time to first adjudicated MACE
  (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke)
  - Noninferiority margin: Upper bound of the 95% CI of HR not exceeding **1.25***

Efficacy Analysis - Separately for Each Trial

Primary Efficacy Endpoint

- Difference in change in average Hb between baseline and the primary evaluation period (weeks 24-36)
  - Noninferiority margin: Lower bound of the 95% CI of difference in change not below **-0.75 g/dL Hb***

*Prespecified, regulatory agency–agreed upon noninferiority margins

CI, confidence interval; Hb, hemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular events; NI, noninferiority.

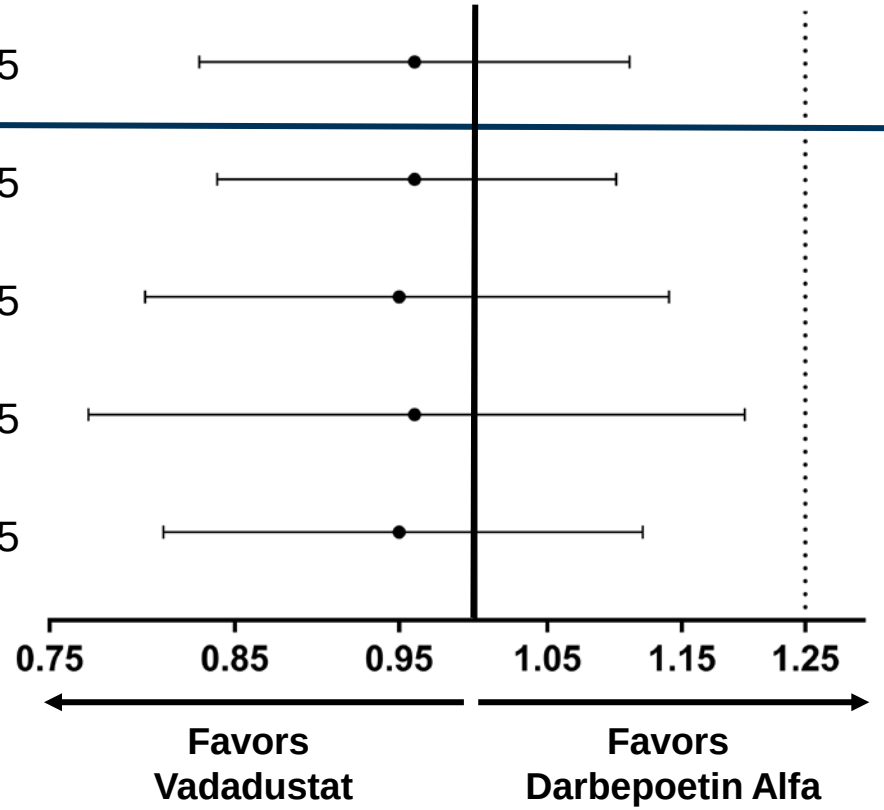
Baseline Demographics

	Incident DD-CKD (N=369)		*Prevalent* DD-CKD (N=3554)	
	Vadadustat (N=181)	Darbepoetin alfa (N=188)	Vadadustat (N=1777)	Darbepoetin alfa (N=1777)
Characteristic				
Age, y, mean (SD)	56.5 (14.8)	55.6 (14.6)	57.9 (13.9)	58.4 (13.8)
Male, no. (%)	107 (59.1)	113 (60.1)	990 (55.7)	1004 (56.5)
Time since dialysis initiated, mean (SD), y	0.14 (0.09)	0.15 (0.28)	4.00 (4.02)	3.94 (4.01)
Disease history, n (%)				
Diabetes mellitus	105 (58.0)	96 (51.1)	971 (54.6)	998 (56.2)
Cardiovascular disease	69 (38.1)	73 (38.8)	868 (48.8)	932 (52.4)
Hemoglobin				
Mean (SD), g/dL	9.4 (1.1)	9.2 (1.1)	10.3 (0.9)	10.2 (0.8)
Distribution, no. (%)				
<9.5 g/dL	94 (51.9)	99 (52.7)	N/A	N/A
≥9.5 g/dL	87 (48.1)	89 (47.3)	N/A	N/A
<10.0 g/L	N/A	N/A	620 (34.9)	619 (34.8)
≥10.0 g/dL	N/A	N/A	1157 (65.1)	1158 (65.2)
Baseline iron use, no. (%)				
Patients not receiving any iron	52 (28.7)	56 (29.8)	660 (37.1)	721 (40.6)
Patients receiving IV iron only	92 (50.8)	110 (58.5)	911 (51.3)	853 (48.0)

DD-CKD, dialysis-dependent chronic kidney disease; IV, intravenous; N/A, not available; SD, standard deviation

Primary and Key Secondary Safety Endpoints

Safety Endpoint	Vadadustat (n/N)	Darbepoetin Alfa (n/N)	HR (95% CI)
MACE	355/1947	377/1955	0.96 (0.83, 1.11)
Expanded MACE	420/1947	449/1955	0.96 (0.84, 1.10)
Cardiovascular MACE	225/1947	242/1955	0.95 (0.80, 1.14)
Cardiovascular mortality	150/1947	160/1955	0.96 (0.77, 1.20)
All-cause mortality	291/1947	310/1955	0.95 (0.81, 1.12)



→ vadadustat noninferior to darbepoetin alfa

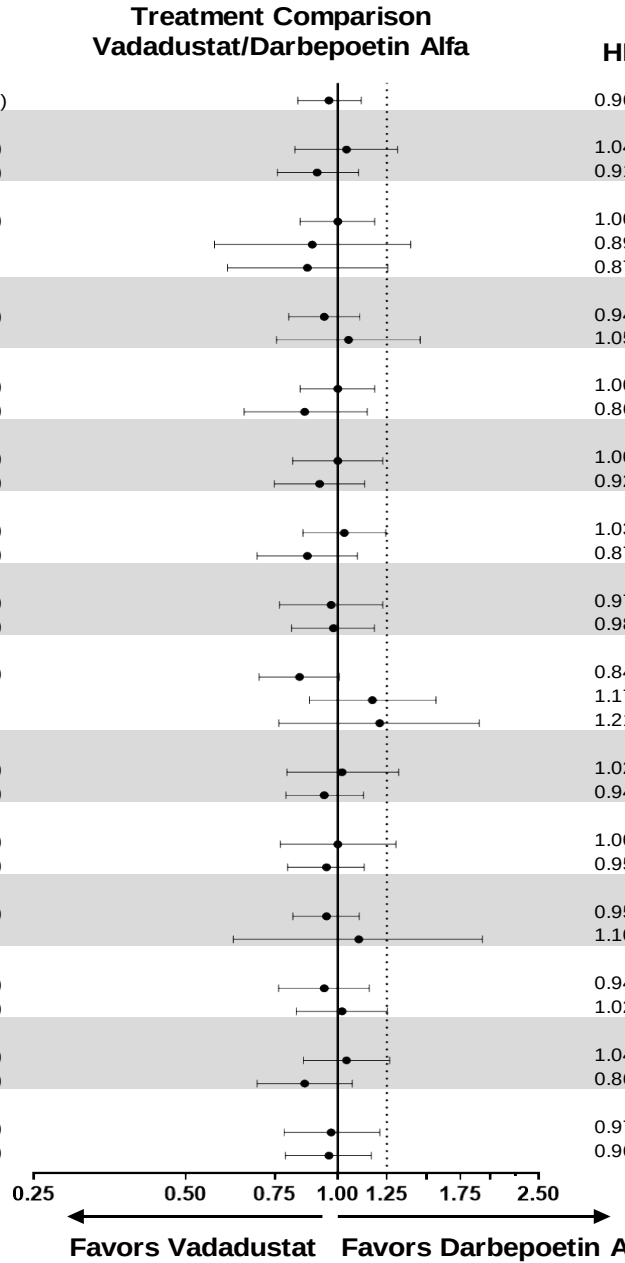
Noninferiority margin: 1.25

MACE: all cause mortality, non-fatal MI or non-fatal stroke
Expanded MACE: MACE plus hospitalisations for heart failure or thromboembolic events (excluding access failure)
Cardiovascular MACE: cardiovascular mortality, non-fatal MI or non-fatal stroke

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke).

Time to First MACE Across Pre-Specified Subgroups

Subgroup	n/N (%)	HR (95% CI)
All (n=3902)	3902/3902 (100.0%)	0.96 (0.833, 1.113)
Baseline Hb Level		
Low (n=1422)	1422/3902 (36.4%)	1.04 (0.822, 1.313)
High (n=2480)	2480/3902 (63.6%)	0.91 (0.759, 1.100)
Region		
US (n=2361)	2361/3902 (60.5%)	1.00 (0.842, 1.184)
Europe (n=572)	572/3902 (14.7%)	0.89 (0.570, 1.394)
Non-US/Europe (n=969)	969/3902 (24.8%)	0.87 (0.605, 1.256)
NYHA HF Level		
0 or I (n=3398)	3398/3902 (87.1%)	0.94 (0.799, 1.106)
II or III (n=504)	504/3902 (12.9%)	1.05 (0.756, 1.456)
Target Hb Level		
10-11 g/dL (n=2361)	2361/3902 (60.5%)	1.00 (0.842, 1.184)
10-12 g/dL (n=1541)	1541/3902 (39.5%)	0.86 (0.652, 1.143)
Age (years)		
<65 (n=2572)	2572/3902 (65.9%)	1.00 (0.814, 1.228)
>=65 (n=1330)	1330/3902 (34.1%)	0.92 (0.748, 1.131)
Sex		
Male (n=2199)	2199/3902 (56.4%)	1.03 (0.853, 1.244)
Female (n=1703)	1703/3902 (43.6%)	0.87 (0.692, 1.093)
Ethnicity		
Hispanic or Latino (n=1485)	1485/3902 (38.1%)	0.97 (0.766, 1.228)
Not Hispanic or Latino (n=2293)	2293/3902 (58.8%)	0.98 (0.809, 1.181)
Race		
White (n=2486)	2486/3902 (63.7%)	0.84 (0.698, 1.006)
Black (n=948)	948/3902 (24.3%)	1.17 (0.878, 1.564)
All others (n=468)	468/3902 (12.0%)	1.21 (0.764, 1.906)
Diabetes Mellitus		
No (n=1744)	1744/3902 (44.7%)	1.02 (0.793, 1.320)
Yes (n=2158)	2158/3902 (55.3%)	0.94 (0.789, 1.125)
History of CV Disease		
No (n=1967)	1967/3902 (50.4%)	1.00 (0.769, 1.304)
Yes (n=1935)	1935/3902 (49.6%)	0.95 (0.795, 1.127)
Type of Dialysis		
Hemodialysis (n=3590)	3590/3902 (92.0%)	0.95 (0.815, 1.102)
Peritoneal (n=309)	309/3902 (7.9%)	1.10 (0.621, 1.933)
C-reactive Protein		
<=0.6 mg/dL (n=2422)	2422/3902 (62.1%)	0.94 (0.763, 1.154)
>0.6 mg/dL (n=1423)	1423/3902 (36.5%)	1.02 (0.827, 1.253)
Baseline TSAT (%)		
<median (34.5)(n=1919)	1919/3902 (49.2%)	1.04 (0.854, 1.267)
>=median (34.5)(n=1980)	1980/3902 (50.7%)	0.86 (0.692, 1.068)
Baseline Ferritin (ng/mL)		
<median (709)(n=1952)	1952/3902 (50.0%)	0.97 (0.783, 1.212)
>=median (709)(n=1949)	1949/3902 (49.9%)	0.96 (0.787, 1.164)



CI, confidence interval; CV, cardiovascular; Hb, hemoglobin; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke); NYHA, New York Heart Association; TSAT, transferrin saturation.

Summary of TEAEs and TEAEs Occurring in >10% of Patients in Either Treatment Group

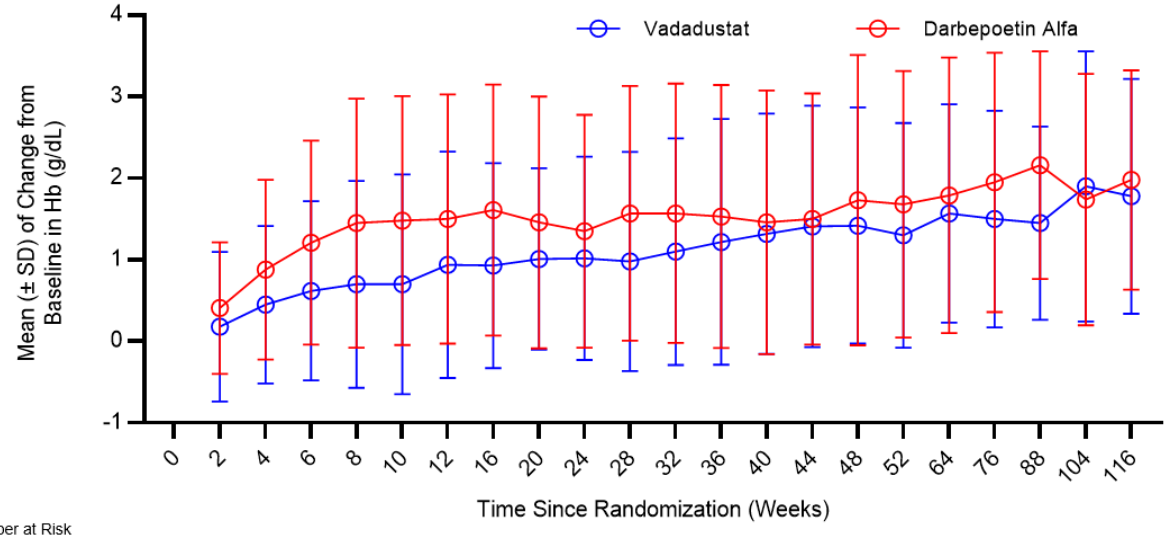
	Incident DD-CKD, No. (%)		Prevalent DD-CKD, No. (%)	
	Vadadustat (N=179)	Darbepoetin alfa (N=186)	Vadadustat (N=1768)	Darbepoetin alfa (N=1769)
Any TEAEs	150 (83.8)	159 (85.5)	1562 (88.3)	1580 (89.3)
Any TEAEs, drug-related	7 (3.9)	5 (2.7)	169 (9.6)	68 (3.8)
Any serious TEAEs	89 (49.7)	105 (56.5)	973 (55.0)	1032 (58.3)
Any serious TEAEs, drug-related	1 (0.6)	4 (2.2)	29 (1.6)	27 (1.5)
Any TEAEs leading to study treatment discontinuation	5 (2.8)	2 (1.1)	91 (5.1)	20 (1.1)
Any drug-related TEAEs leading to study treatment discontinuation	2 (1.1)	0	42 (2.4)	5 (0.3)
Any TEAE leading to death	15 (8.4)	18 (9.7)	266 (15.0)	276 (15.6)
Deaths	15 (8.4)	20 (10.8)	276 (15.6)	290 (16.4)
Common AEs (>10%)				
Hypertension	29 (16.2)	24 (12.9)	187 (10.6)	244 (13.8)
Diarrhea	18 (10.1)	18 (9.7)	230 (13.0)	178 (10.1)
Pneumonia	13 (7.3)	15 (8.1)	195 (11.0)	172 (9.7)
Hyperkalemia	8 (4.5)	10 (5.4)	160 (9.0)	191 (10.8)

AE, adverse event; DD-CKD, dialysis-dependent chronic kidney disease; TEAE, treatment-emergent adverse event.

Primary and Key Secondary Efficacy Endpoint

Mean change[a] from baseline in Hb levels in randomized populations

Incident DD-CKD Trial

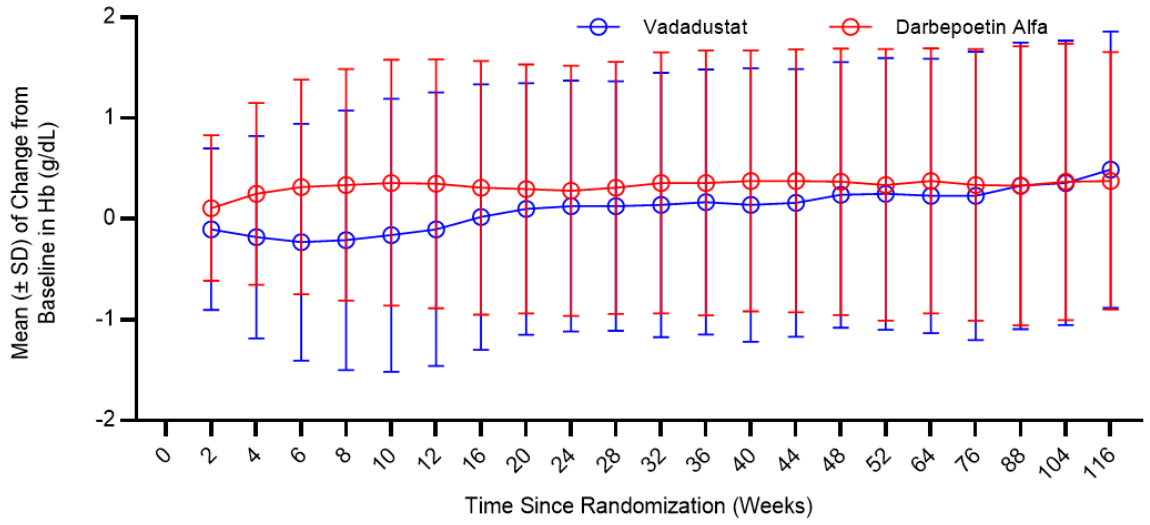


Number at Risk

Vadadustat	181	165	165	162	162	156	163	160	156	151	147	145	139	127	113	101	92	82	55	43	26	21
Darbepoetin Alfa	188	180	170	174	169	167	167	166	169	165	162	157	151	139	112	106	100	82	67	46	24	19

Mean (SEM) change from baseline, g/dL	Vadadustat	Darbepoetin alfa	Difference (vadadustat - darbepoetin alfa)
Weeks 24-36	1.26 (0.11)	1.58 (0.11)	**-0.31 (0.11) (95% CI, -0.53 to -0.10)**
Weeks 40-52	1.42 (0.13)	1.50 (0.14)	**-0.07 (0.13) (95% CI, -0.34 to 0.19)**

Prevalent DD-CKD Trial



Number at Risk

Vadadustat	1777	1663	1625	1609	1590	1582	1585	1590	1548	1510	1483	1457	1434	1391	1325	1253	1232	1066	881	628	422	286
Darbepoetin Alfa	1777	1658	1668	1654	1619	1603	1605	1625	1604	1557	1514	1511	1485	1456	1395	1323	1294	1184	1002	714	510	352

Mean (SEM) change from baseline, g/dL	Vadadustat	Darbepoetin alfa	Difference (vadadustat - darbepoetin alfa)
Weeks 24-36	0.19 (0.03)	0.36 (0.03)	**-0.17 (0.03) (95% CI, -0.23 to -0.10)**
Weeks 40-52	0.23 (0.03)	0.41 (0.03)	**-0.18 (0.03) (95% CI, -0.25 to -0.12)**

Noninferiority margin: -0.75

→ vadadustat noninferior to darbepoetin alfa

[a]Mean ± SD is presented here to show the extent of variability, given the large sample size.

DD-CKD, dialysis-dependent chronic kidney disease; Hb, hemoglobin; SD, standard deviation; SEM, standard error of the mean.

Summary and Conclusions

Outcomes: Vadadustat was noninferior to darbepoetin alfa with respect to cardiovascular safety and hematological efficacy in patients on dialysis.

Strengths

- Large sample size (N=3923); mean FU > 1.5 yrs
- Diverse patient population (by age, sex, race/ethnicity, geography and underlying causes of kidney failure)
- Broad inclusion criteria (patients new to and established on dialysis, as well as patients on peritoneal dialysis and hemodialysis)
- All MACE safety endpoints were adjudicated by a committee blinded to treatment assignment.

Limitations

- Investigators and patients not blinded for treatment assignment, which precluded a meaningful study of self-reported physical function and fatigue.
- Many patients with DD-CKD require treatment of anemia for many years, and some for decades.

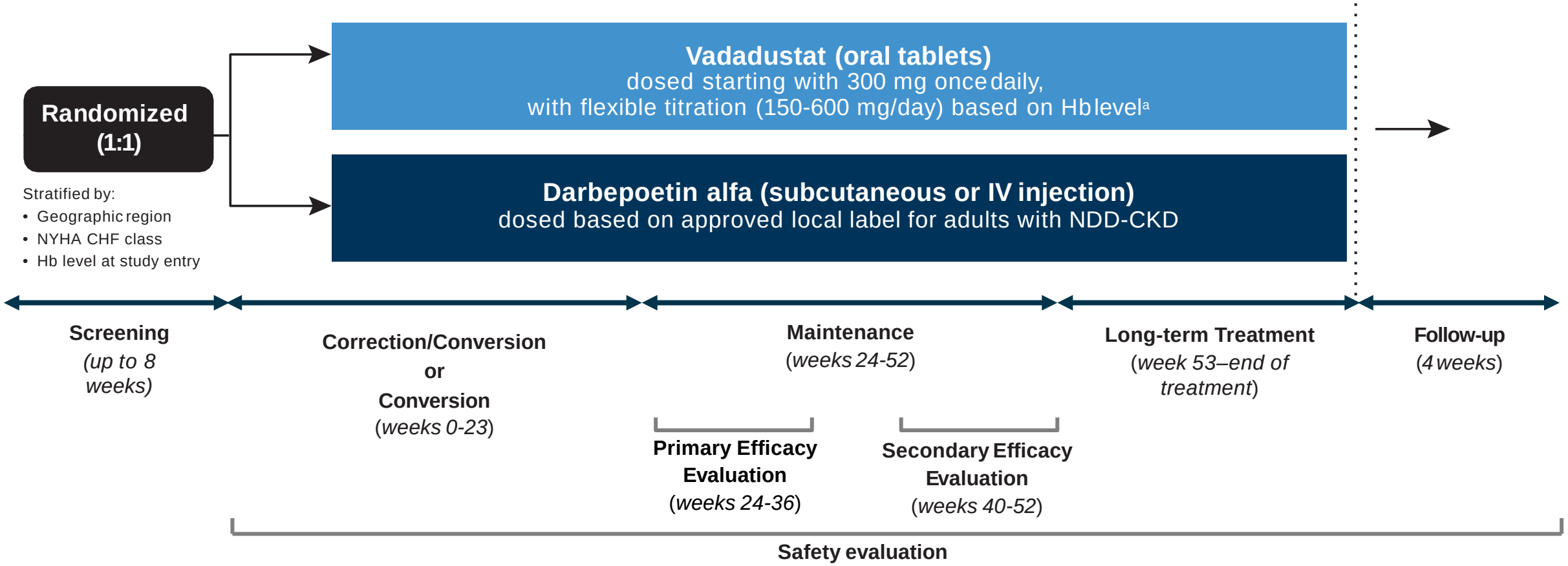
Conclusion: The INNO$_2$VATE trials show that oral vadadustat could be used in patients with DD-CKD in place of darbepoetin alfa without increasing cardiovascular risk.

PRO_2TECT Program

Global Phase 3 Clinical Trials of Vadadustat for Treatment of Anemia in Patients With Non–Dialysis-Dependent Chronic Kidney Disease

PRO$_2$TECT Study Design

- Two randomized, phase 3, global, multicenter, open-label, sponsor-blind, active-controlled noninferiority trials compared vadadustat with darbepoetin alfa in patients with NDD-CKD:
  - ESA-untreated patients (“Correction”) OR ESA-treated patients (“Conversion”)
  - Target Hb levels US: 10-11 g/dL; non-US: 10-12 g/dL



[a]Study drug is titrated to achieve target Hb levels (US: 10-11 g/dL; non-US: 10-12 g/dL).
CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agents; Hb, hemoglobin; IV, intravenous; NDD, non–dialysis dependent; NYHA CHF, New York Heart Association Congestive Heart Failure.

PRO$_2$TECT Key Eligibility Criteria

	PRO$_2$TECT: ESA-untreated NDD-CKD	PRO$_2$TECT: ESA-treated NDD-CKD
Age	≥18 years	
RBC transfusions	No RBC transfusions within 8 weeks before randomization	
Baseline Hb level	<10.0 g/dL	8.0-11.0 g/dL (inclusive) US 9.0-12.0 g/dL (inclusive) Non-US
ESA use	No ESA within 8 weeks before randomization	Currently maintained on ESA therapy, with a dose received within 6 weeks before screening
Iron parameters	Serum ferritin ≥100 ng/mL and TSAT ≥20%	

ESA, erythropoiesis-stimulating agent; EU, European Union; Hb, hemoglobin; NDD-CKD, non–dialysis-dependent chronic kidney disease; RBC, red blood cell; TSAT, transferrin saturation.

PRO$_2$TECT Primary Safety and Efficacy Endpoints

Safety Analysis - Combined Across Both, the *ESA-untreated* NDD-CKD and the *ESA-treated* NDD-CKD Trial (Event Driven)

Primary Safety Endpoint

- Time to first adjudicated MACE
  (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke)
  - Noninferiority margin: Upper bound of the 95% CI of HR not exceeding **1.25***

Efficacy Analysis - Separately for Each Trial

Primary Efficacy Endpoint

- Difference in change in average Hb between baseline and the primary evaluation period (weeks 24-36)
  - Noninferiority margin: Lower bound of the 95% CI of difference in change not below **-0.75 g/dL Hb***

*Prespecified, regulatory agency–agreed upon noninferiority margins

CI, confidence interval; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular events; NDD-CKD, non–dialysis-dependent chronic kidney disease.

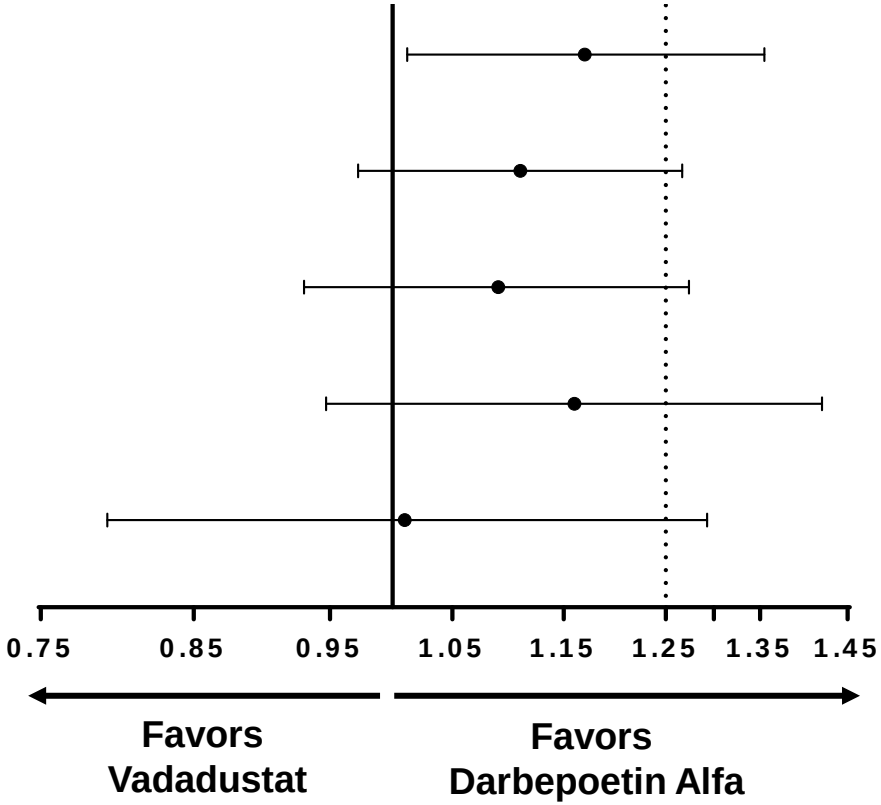
PRO_2TECT Baseline Characteristics

Characteristic	PRO_2TECT: ESA-untreated NDD-CKD			PRO_2TECT: ESA-treated NDD-CKD		
	Vadadustat (N=879)	Darbepoetin alfa (N=872)	Total (N=1751)	Vadadustat (N=862)	Darbepoetin alfa (N=863)	Total (N=1725)
Age, y, mean (SD)	65.2 (14.3)	64.9 (13.7)	65.0 (14)	67.3 (13.1)	66.5 (13.5)	66.9 (13.3)
Female, n (%)	475 (54.0)	506 (58.0)	981 (56.0)	468 (54.3)	488 (56.5)	956 (55.4)
Race, n (%)						
White	546 (62.1)	571 (65.5)	1117 (63.8)	631 (73.2)	603 (69.9)	1234 (71.5)
Black	188 (21.4)	172 (19.97)	360 (20.6)	93 (10.8)	131 (15.2)	224 (13.0)
Asian	48 (5.5)	37 (4.2)	85 (4.9)	62 (7.2)	55 (6.4)	117 (6.8)
American Indian	22 (2.5)	23 (2.6)	45 (2.6)	32 (3.7)	26 (3.0)	58 (3.4)
Other	75 (8.5)	69 (7.9)	144 (8.2)	44 (5.1)	48 (5.6)	92 (5.3)
eGFR, mL/min/1.73m^2, mean (SD)	21.2 (12.0)	21.9 (12.6)	21.5 (12.3)	22.6 (11.6)	22.8 (12.0)	22.7 (11.8)
Disease history, n (%)						
Diabetes mellitus	581 (66.1)	599 (68.7)	1180 (67.4)	517 (60.0)	518 (60.0)	1035 (60.0)
Cardiovascular disease	406 (46.2)	412 (47.2)	818 (46.7)	375 (43.5)	402 (46.6)	777 (45.0)
Mean Hemoglobin at baseline (SD), g/dL	9.1 (0.8)	9.1 (0.8)	9.1 (0.8)	10.4 (0.9)	10.4 (0.9)	10.4 (0.9)
Baseline iron use, n (%)						
Patients not receiving any iron	483 (54.9)	467 (53.6)	950 (54.3)	418 (48.5)	459 (53.2)	877 (50.8)
Patients receiving IV iron only	22 (2.5)	20 (2.3)	42 (2.4)	43 (5.0)	49 (5.7)	92 (5.3)

ESA, erythropoiesis-stimulating agent; NDD-CKD, non–dialysis-dependent chronic kidney disease; IV, intravenous; N/A, not available; SD, standard deviation

PRO$_2$TECT MACE, Expanded MACE, and Other Safety Endpoints

Safety Endpoint	Vadadustat (n/N)	Darbepoetin Alfa (n/N)	HR (95% CI)
MACE	382/1739	344/1732	1.17 (1.01, 1.36)
Expanded MACE[a]	451/1739	424/1732	1.11 (0.97, 1.27)
All-cause mortality	319/1739	307/1732	1.09 (0.93, 1.27)
Cardiovascular MACE[b]	198/1739	178/1732	1.16 (0.95, 1.42)
Cardiovascular mortality	127/1739	131/1732	1.01 (0.79, 1.29)



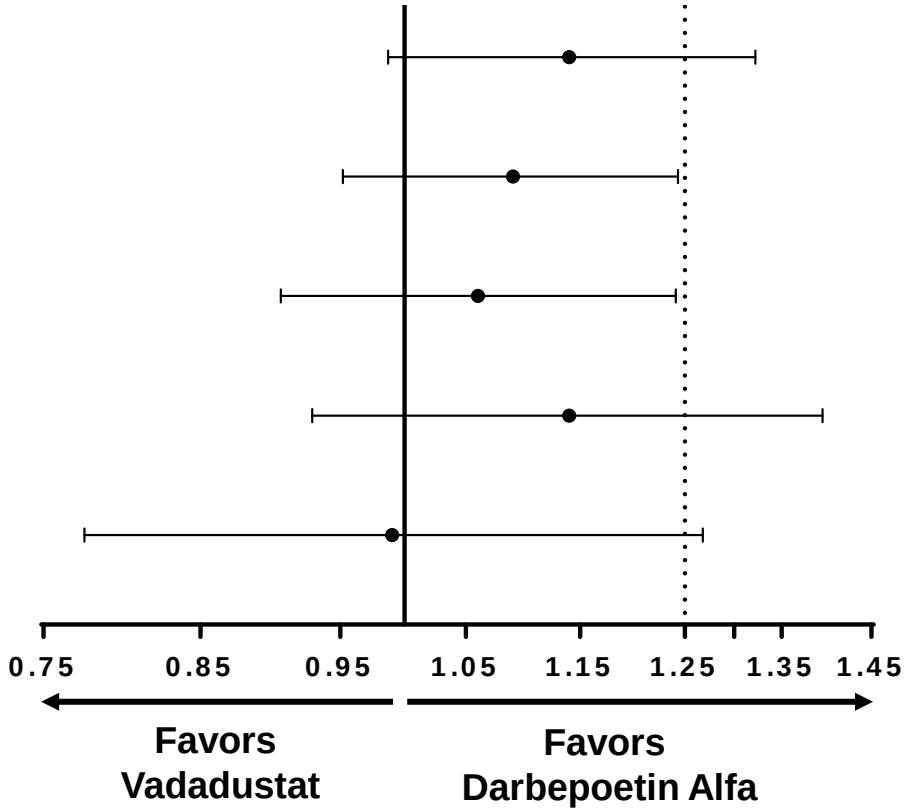
Age as a dichotomous variable in the Cox model

Variables in prespecified Cox model included: age (>65; ≤65), baseline Hb (continuous); randomization strata of region (US; Ex-US), NYHA (0 or I; II or III), sex (male; female), race (white or non-white), preexisting cardiovascular disease (yes/no), diabetes mellitus (yes/no)

[a]Expanded MACE: MACE plus hospitalization for heart failure or thromboembolic events, excluding vascular access failure.
[b]Cardiovascular MACE: Adjudicated cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke.
CI, confidence interval; Hb, hemoglobin; NYHA, New York Heart Association; HR, hazard ratio; MACE, major adverse cardiovascular event (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke).

PRO$_2$TECT MACE, Expanded MACE, and Other Safety Endpoints

Safety Endpoint	Vadadustat (n/N)	Darbepoetin Alfa (n/N)	HR (95% CI)
MACE	382/1739	344/1732	1.14 (0.99, 1.32)
Expanded MACE[a]	451/1739	424/1732	1.09 (0.95, 1.24)
All-cause mortality	319/1739	307/1732	1.06 (0.91, 1.24)
Cardiovascular MACE[b]	198/1739	178/1732	1.14 (0.93, 1.39)
Cardiovascular mortality	127/1739	131/1732	0.99 (0.77, 1.27)



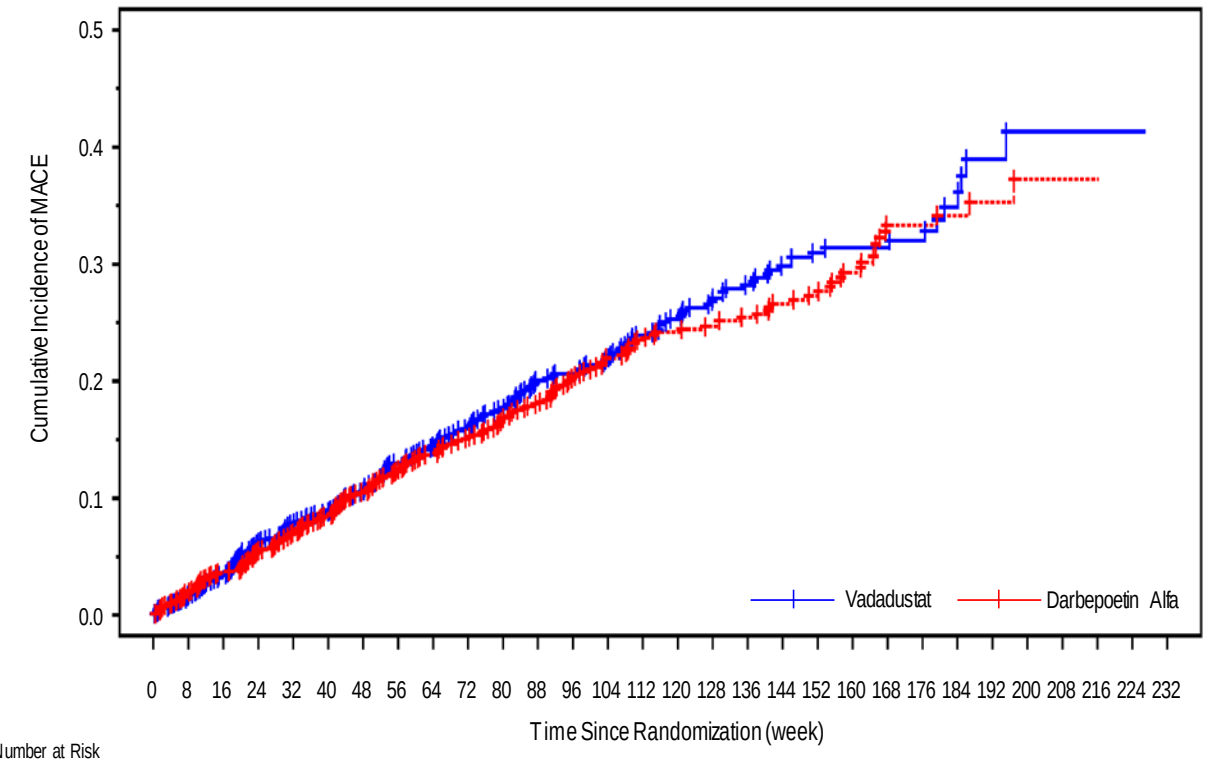
Age as a continuous variable in the Cox model

Variables in Cox model included: **age (continuous variable)**, baseline Hb (continuous); randomization strata of region (US; Ex-US), NYHA (0 or I; II or III), sex (male; female), race (white or non-white), preexisting cardiovascular disease (yes/no), diabetes mellitus (yes/no)

[a]Expanded MACE: MACE plus hospitalization for heart failure or thromboembolic events, excluding vascular access failure.
[b]Cardiovascular MACE: Adjudicated cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke.
CI, confidence interval; Hb, hemoglobin; NYHA, New York Heart Association; HR, hazard ratio; MACE, major adverse cardiovascular event (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke).

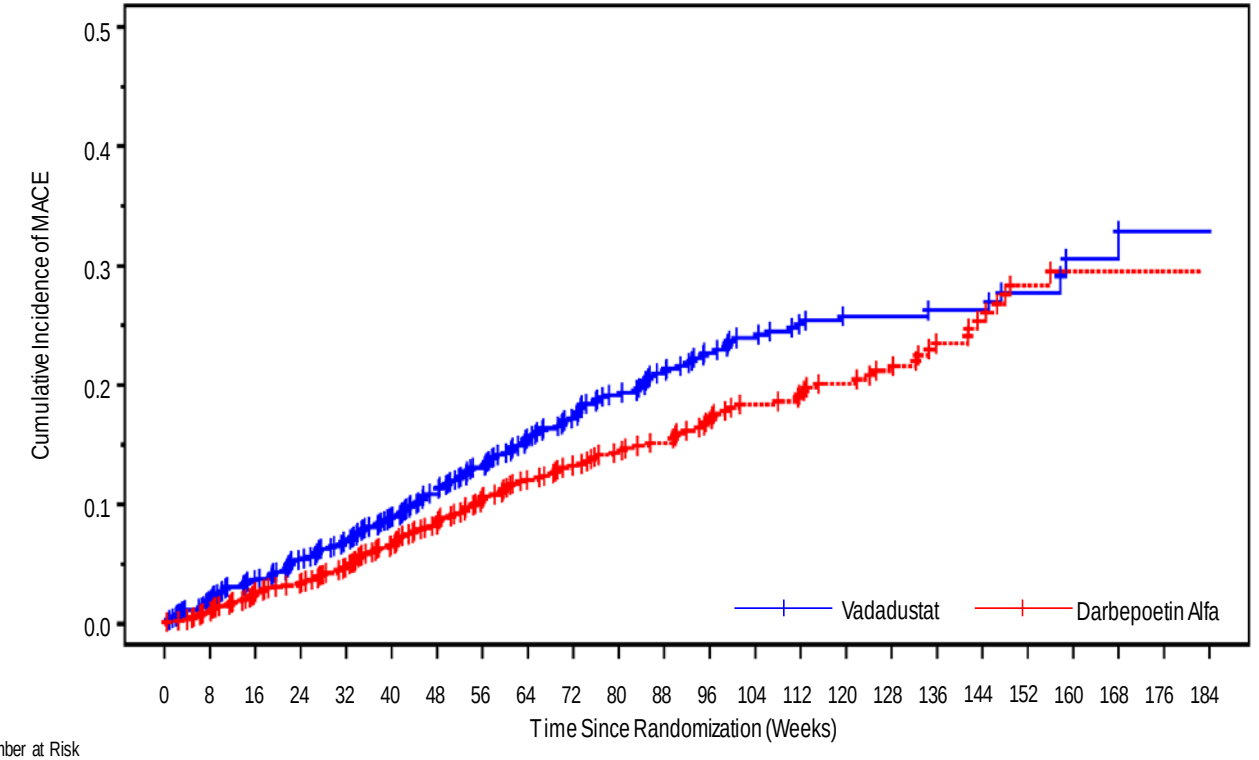
PRO$_2$TECT MACE by Region

Prespecified Subgroup Analysis: US (N=1723)



Number at Risk																												
Vadadustat	861	846	824	796	778	739	677	614	575	538	505	457	421	380	342	312	276	238	203	171	139	107	87	51	30	14	4	3	1	0
Darbepoetin Alfa	862	842	826	808	792	747	674	621	583	543	510	464	424	387	346	326	302	272	235	201	168	121	96	65	43	26	6	1	0	

Prespecified Subgroup Analysis: Non-US (N=1748)



Number at Risk																												
Vadadustat	878	860	844	827	809	745	624	574	533	479	426	378	338	289	246	218	183	142	108	68	46	30	10	1				
Darbepoetin Alfa	870	862	848	839	826	758	655	604	546	502	451	406	350	305	275	241	203	154	111	75	45	21	7	0				

[a]Expanded MACE: MACE plus hospitalization for heart failure or thromboembolic event, excluding vascular access failure.
[b]Cardiovascular MACE: Adjudicated cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke.
CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke).

PRO$_2$TECT MACE by Region

	MACE HR (95% CI)	
	US (N=1723)	**Non-US** (N=1748)
MACE	1.01 (0.83, 1.23)	1.29 (1.03, 1.60)
Expanded MACE[a]	0.99 (0.83, 1.17)	1.23 (1.00, 1.51)
All-cause mortality	0.86 (0.69, 1.07)	1.27 (1.01, 1.60)
Cardiovascular MACE[b]	1.16 (0.89, 1.52)	1.08 (0.78, 1.49)
Cardiovascular mortality	0.92 (0.65, 1.29)	1.04 (0.72, 1.48)

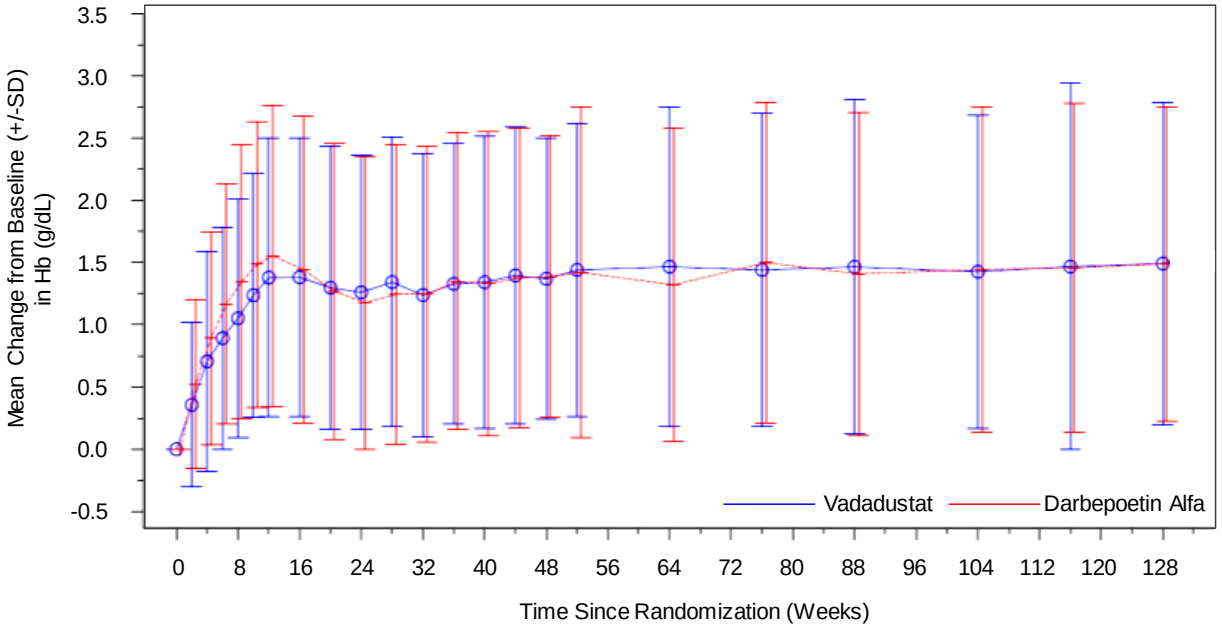
Age as a continuous variable in the Cox model

[a]Expanded MACE: MACE plus hospitalization for heart failure or thromboembolic event, excluding vascular access failure.
[b]Cardiovascular MACE: Adjudicated cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke.
CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke).

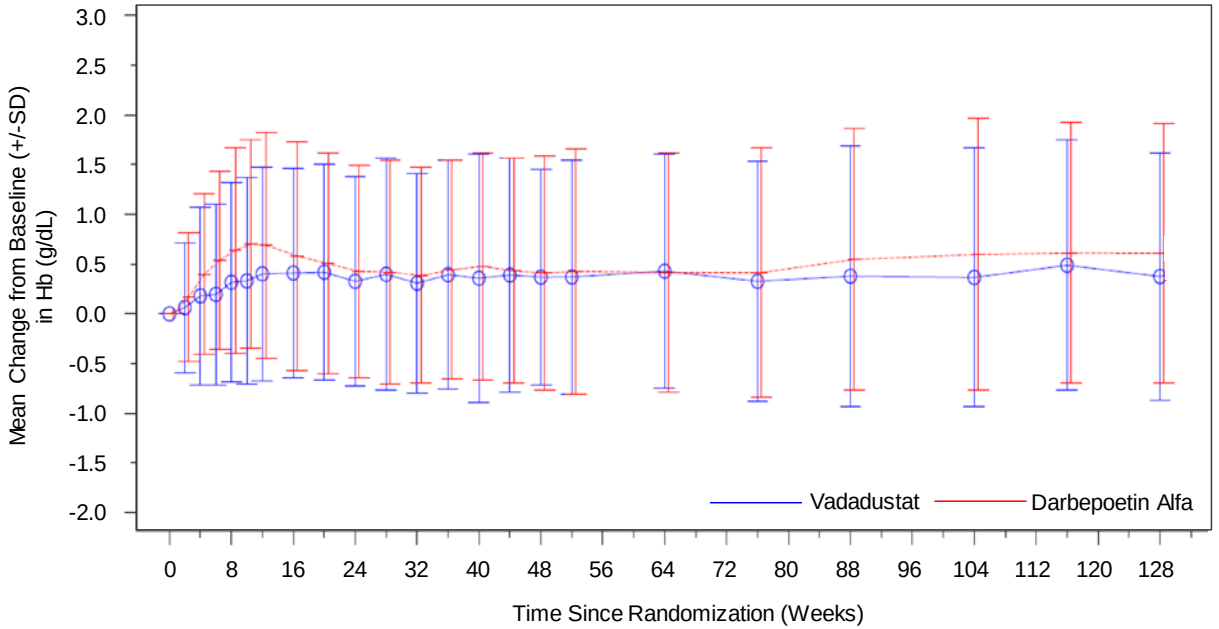
PRO$_2$TECT Hemoglobin Change From Baseline

Mean change from baseline in Hb levels in randomized populations

ESA-untreated NDD-CKD



ESA-treated NDD-CKD



Mean change from baseline, g/dL	Vadadustat	Darbepoetin alfa	Difference (vadadustat - darbepoetin alfa)
Weeks 24-36	1.43	1.38	0.05 (95% CI, -0.04 to 0.15)
Weeks 40-52	1.52	1.48	0.04 (95% CI, -0.06 to 0.14)

Mean change from baseline, g/dL	Vadadustat	Darbepoetin alfa	Difference (vadadustat - darbepoetin alfa)
Weeks 24-36	0.41	0.42	-0.01 (95% CI, -0.09 to 0.07)
Weeks 40-52	0.43	0.44	0.00 (95% CI, -0.10 to 0.09)

ESA, erythropoiesis-stimulating agent; NDD-CKD, non–dialysis-dependent chronic kidney disease; Hb, hemoglobin; SD, standard deviation; SEM, standard error of the mean.

PRO$_2$TECT Treatment-Emergent Adverse Events

	ESA-untreated NDD-CKD, No. of subjects (%)		ESA-treated NDD-CKD, No. of subjects (%)	
	Vadadustat (N=878)	Darbepoetin alfa (N=870)	Vadadustat (N=861)	Darbepoetin alfa (N=862)
Any TEAE	798 (90.0)	797 (91.6)	767 (89.1)	756 (87.7)
Any TEAE, drug-related	95 (10.8)	57 (6.6)	100 (11.6)	44 (5.1)
Any serious TEAE	573 (65.3)	561 (64.5)	504 (58.5)	488 (56.6)
Any serious TEAE, drug-related	23 (2.6)	15 (1.7)	13 (1.5)	9 (1.0)
Any TEAE leading to study treatment discontinuation	84 (9.6)	60 (6.9)	79 (9.2)	44 (5.1)
Any drug-related TEAE leading to study treatment discontinuation	13 (1.5)	4 (0.5)	16 (1.9)	2 (0.2)
Any TEAE leading to death	177 (20.2)	165 (19.0)	135 (15.7)	137 (15.9)
Deaths	180 (20.5)	168 (19.3)	139 (16.1)	139 (16.1)
Common AEs (≥10%)				
Diarrhea	122 (13.8)	87 (10.0)	119 (13.8)	76 (8.8)
End-stage renal disease	305 (34.7)	306 (35.2)	237 (27.5)	245 (28.4)
Fall	84 (9.6)	87 (10.0)	69 (8.0)	65 (7.5)
Hyperkalemia	108 (12.3)	136 (15.6)	81 (9.4)	85 (9.9)
Hypertension	155 (17.7)	192 (22.1)	124 (14.4)	128 (14.8)
Peripheral edema	110 (12.5)	91 (10.5)	85 (9.9)	87 (10.1)
Pneumonia	86 (9.8)	75 (8.6)	86 (10.0)	84 (9.7)
Urinary tract infection	113 (12.9)	104 (12.0)	105 (12.2)	125 (14.5)

AE, adverse event; NDD-CKD, non–dialysis-dependent chronic kidney disease; TEAE, treatment-emergent adverse event.

PRO_2TECT Conclusions

Cardiovascular Safety:

- Vadadustat did not meet the prespecified noninferiority criterion compared to darbepoetin alfa with respect to cardiovascular safety in patients with anemia and NDD-CKD
- Adjusting for age as a continuous variable, the hazard ratio and the upper bound of the confidence interval were attenuated
- Cardiovascular risk was similar between the two treatment arms in the US (hemoglobin target of 10-11 g/dL) but was higher in patients randomized to vadadustat in regions using a hemoglobin target of 10-12 g/dL

Efficacy:

- Vadadustat was noninferior to darbepoetin alfa in maintaining target-range hemoglobin concentrations among patients who were new to, or established on, ESA who were not on dialysis during the primary (weeks 24-36) and secondary (weeks 40-52) evaluation periods

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INNO$_2$VATE and PRO$_2$TECT Global Phase 3 Safety Data

Steven Burke, MD
Senior Vice President, R&D
Chief Medical Officer

First Major Adverse Cardiovascular Events (MACE) by Program

	INNO$_2$VATE Global Events N (%)		PRO$_2$TECT Global Events N (%)	
	Vadadustat	Darbepoetin	Vadadustat	Darbepoetin
MACE	**355 (18.2)**	**377 (19.3)**	**382 (22.0)**	**344 (19.9)**
Death (all-cause mortality)	**253 (13.0)**	**253 (12.9)**	**284 (16.3)**	**274 (15.8)**
Non-fatal MI	**76 (3.9)**	**87 (4.5)**	**66 (3.8)**	**44 (2.5)**
Non-fatal stroke	**26 (1.3)**	**37 (1.9)**	**32 (1.8)**	**26 (1.5)**

MACE is a composite of all-cause mortality, nonfatal myocardial infarction, and non-fatal stroke. Events were independently and blindly assessed by the Brigham and Women's Hospital's Clinical Endpoint Center (BWH CEC) in Boston, MA.
INNO$_2$VATE is the dialysis-dependent chronic kidney disease (DD-CKD) program
PRO$_2$TECT is the non-dialysis-dependent chronic kidney disease (NDD-CKD) program
MI is myocardial infarction

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Cardiovascular Safety: PRO$_2$TECT – Global, US and Ex-US

Region was a randomization stratification variable and a prespecified subgroup analysis
Age as a dichotomous variable (<65, ≥65) in the prespecified Cox model

	Global (N=3471) Event N HR (95% CI)	US (N=1723) (Hb target 10-11 g/dL) Event N HR (95% CI)	Ex-US (N=1748) (Hb target 10-12 g/dL) Event N HR (95% CI)
MACE	726 1.17 (1.01, 1.36)	400 1.06 (0.87, 1.29)	326 1.30 (1.05, 1.62)
Expanded MACE	875 1.11 (0.97, 1.27)	511 1.02 (0.86, 1.21)	364 1.24 (1.01, 1.52)
All-Cause Mortality	626 1.09 (0.93, 1.27)	325 0.92 (0.74, 1.15)	301 1.28 (1.02, 1.61)
CV MACE	376 1.16 (0.95, 1.42)	224 1.20 (0.92, 1.55)	152 1.09 (0.79, 1.50)
CV Mortality	258 1.01 (0.79, 1.29)	136 0.96 (0.68, 1.34)	122 1.05 (0.73, 1.50)

631 MACE events yields ~80% power to show non-inferiority assuming a true hazard ratio of 1.0.
Expanded MACE is composite of MACE plus hospitalization for heart failure or thromboembolic event excluding vascular access failure
CV MACE is composite of cardiovascular mortality, nonfatal myocardial infarction, and non-fatal stroke
Hb is hemoglobin; HR is hazard ratio; CI is confidence interval

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Cardiovascular Safety: PRO$_2$TECT – Global, US and Ex-US

Region was a randomization stratification variable and a prespecified subgroup analysis
Age rescaled as a continuous variable in the prespecified Cox model

	Global (N=3471) Event N HR (95% CI)	US (N=1723) (Hb target 10-11 g/dL) Event N HR (95% CI)	Ex-US (N=1748) (Hb target 10-12 g/dL) Event N HR (95% CI)
MACE	726 1.14 (0.99, 1.32)	400 1.01 (0.83, 1.23)	326 1.29 (1.03, 1.60)
Expanded MACE	875 1.09 (0.95, 1.24)	511 0.99 (0.83, 1.18)	364 1.23 (1.00, 1.51)
All-Cause Mortality	626 1.06 (0.91, 1.24)	325 0.86 (0.69, 1.07)	301 1.27 (1.01, 1.60)
CV MACE	376 1.14 (0.93, 1.40)	224 1.16 (0.89, 1.52)	152 1.08 (0.78, 1.49)
CV Mortality	258 0.99 (0.78, 1.27)	136 0.92 (0.65, 1.29)	122 1.04 (0.72, 1.48)

Expanded MACE is composite of MACE plus hospitalization for heart failure or thromboembolic event excluding vascular access failure
CV MACE is composite of cardiovascular mortality, nonfatal myocardial infarction, and non-fatal stroke
Hb is hemoglobin; HR is hazard ratio; CI is confidence interval

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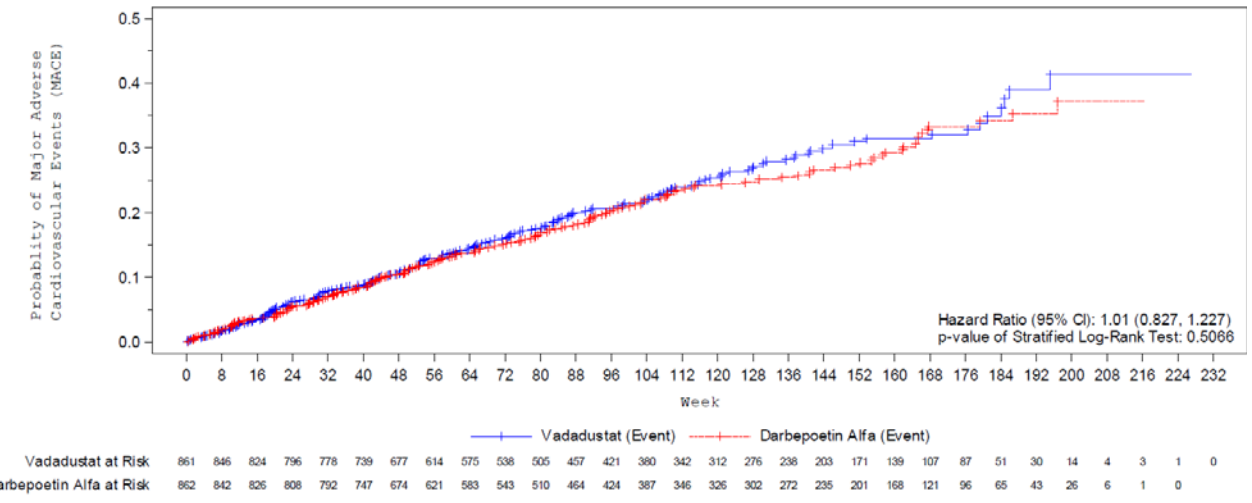
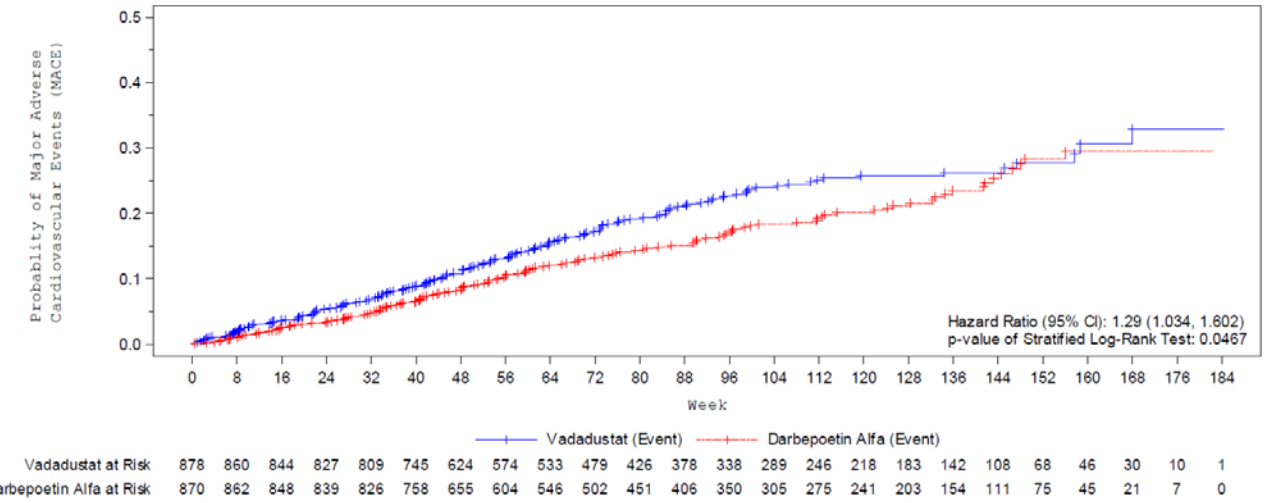
Cardiovascular Safety: PRO$_2$TECT MACE by Region (US and Ex-US)

Region was a randomization stratification variable and a prespecified subgroup analysis

Prespecified Subgroup Analysis: US (N=1723)
Hb target 10-11 g/dL



Prespecified Subgroup Analysis: Ex-US (N=1748)
Hb target 10-12 g/dL



MACE is a composite of all-cause mortality, nonfatal myocardial infarction, and non-fatal stroke
Hb is hemoglobin; HR is hazard ratio; CI is confidence interval

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Cardiovascular Safety: INNO$_2$VATE, PRO$_2$TECT and Combined in US

Region was a randomization stratification variable and a prespecified subgroup analysis
Hb target in US was 10-11 g/dL
Age rescaled as a continuous variable in the prespecified Cox model

	US INNO$_2$VATE – DD-CKD (N=2361) Event N HR (95% CI)	US PRO$_2$TECT – NDD-CKD (N=1723) Event N HR (95% CI)	US INNO$_2$VATE + US PRO$_2$TECT (N=4084) Event N HR (95% CI)
MACE	534 1.01 (0.85, 1.19)	400 1.01 (0.83, 1.23)	934 1.01 (0.89, 1.15)
Expanded MACE	651 0.99 (0.85, 1.16)	511 0.99 (0.83, 1.18)	1162 1.00 (0.89, 1.12)
All-Cause Mortality	430 0.98 (0.81, 1.18)	325 0.86 (0.69, 1.07)	755 0.94 (0.81, 1.08)
CV MACE	354 0.99 (0.80, 1.22)	224 1.16 (0.89, 1.52)	578 1.06 (0.90. 1.25)
CV Mortality	229 0.96 (0.75, 1.25)	136 0.92 (0.65, 1.29)	365 0.96 (0.78, 1.18)

Hb is hemoglobin; HR is hazard ratio; CI is confidence interval

Cardiovascular Safety: INNO$_2$VATE, PRO$_2$TECT and Combined in Ex-US

Region was a randomization stratification variable and was prespecified subgroup analysis
Hb target in Ex-US was 10-12 g/dL
Age rescaled as a continuous variable in the prespecified Cox model

	Ex-US INNO$_2$VATE – DD-CKD (N=1541) Event N HR (95% CI)	Ex-US PRO$_2$TECT – NDD-CKD (N=1748) Event N HR (95% CI)	Ex-US INNO$_2$VATE + Ex-US PRO$_2$TECT (N=3289) Event N HR (95% CI)
MACE	198 0.88 (0.67, 1.17)	326 1.29 (1.03, 1.60)	524 1.12 (0.94, 1.33)
Expanded MACE	218 0.89 (0.68, 1.16)	364 1.23 (1.00, 1.51)	582 1.09 (0.92, 1.28)
All-Cause Mortality	171 0.91 (0.68, 1.23)	301 1.27 (1.01, 1.60)	472 1.13 (0.94, 1.36)
CV MACE	113 0.87 (0.60, 1.27)	152 1.08 (0.78, 1.49)	265 0.98 (0.77, 1.25)
CV Mortality	81 0.94 (0.61, 1.47)	122 1.04 (0.72, 1.48)	203 0.99 (0.75, 1.31)

Hb is hemoglobin; HR is hazard ratio; CI is confidence interval

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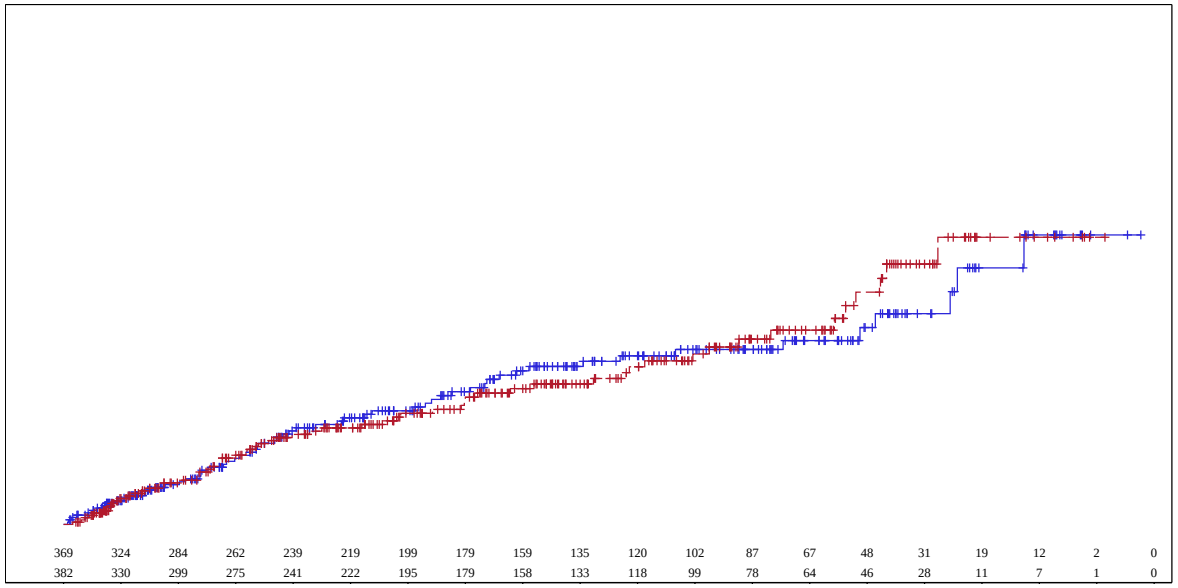
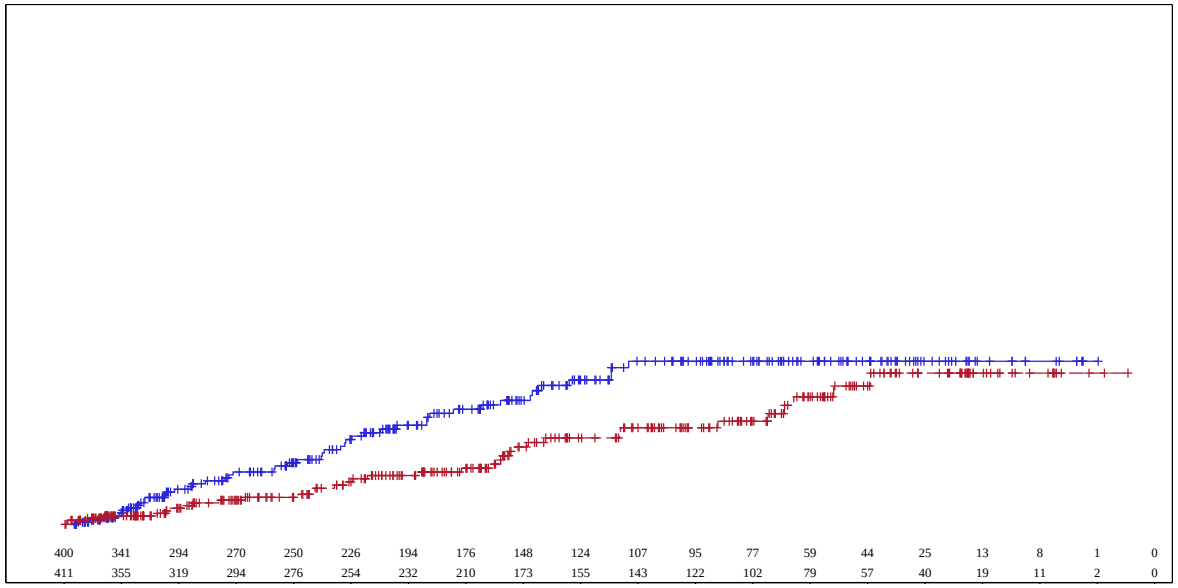
Cardiovascular Safety: PRO$_2$TECT in Ex-US by Average Hb Achieved during Primary Evaluation Period*

Achieved Hb ≤ 11 g/dL during PEP (N=751)
Hb target 10-12 g/dL



Achieved Hb > 11 g/dL during PEP (N=811)
Hb target 10-12 g/dL



*Post-hoc analysis
Time entry in this analysis starts at end of PEP + 1 day

PEP is primary evaluation period (weeks 24-36)
Hb is hemoglobin; HR is hazard ratio; CI is confidence interval

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Cardiovascular Safety: PRO$_2$TECT in Ex-US by Average Hb Achieved during Primary Evaluation Period*

Age rescaled as a continuous variable in the prespecified Cox model

	Ex-US PRO$_2$TECT (Hb Target 10-12 g/dL)	
	Achieved Hb ≤ 11 g/dL during PEP (N=751) Event N HR (95% CI)	Achieved Hb > 11 g/dL during PEP (N=811) Event N HR (95% CI)
MACE	121 1.07 (0.75, 1.53)	82 1.68 (1.07, 2.63)
Expanded MACE	132 1.00 (0.71, 1.41)	93 1.47 (0.97, 2.24)
All-Cause Mortality	110 1.08 (0.74, 1.58)	76 1.72 (1.08, 2.74)

*Post-hoc analysis
Time entry in this analysis starts at end of PEP + 1 day

PEP is primary evaluation period (weeks 24-36)
Hb is hemoglobin; HR is hazard ratio; CI is confidence interval

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Thank You!

We would like to extend our sincerest appreciation to our investigators and their staff for participating in the $INNO_2VATE$ and PRO_2TECT programs.

Most importantly, thank you to our patients who participated in these programs. Because of their commitment, we are a step closer to fulfilling our purpose to better the life of each person impacted by kidney disease.

Appendix

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†Bradley J. Maroni was an employee of Akebia Therapeutics, Inc., at the time the study was conducted.

INNO$_2$VATE Program

Global Phase 3 Clinical Trials of Vadadustat for Treatment of Anemia in Patients With Dialysis-Dependent Chronic Kidney Disease

Disclosures

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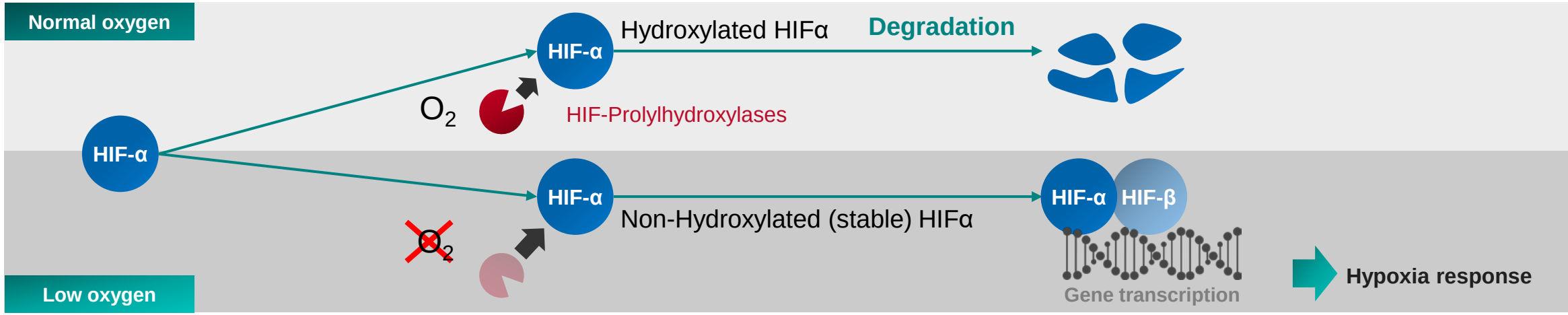
Potential conflicts of interest

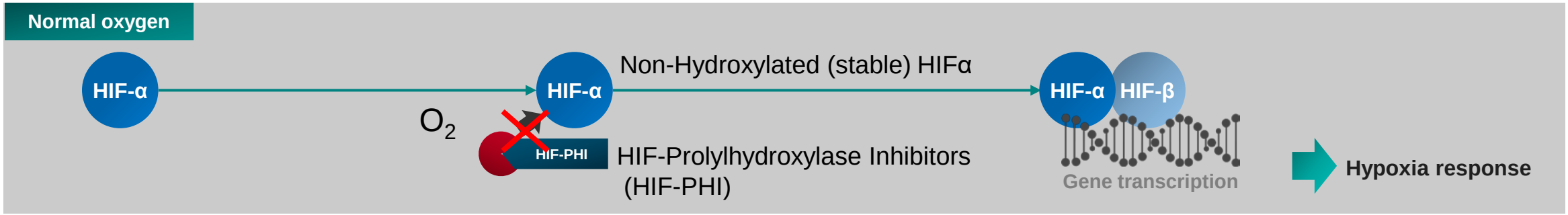
- Dr. Eckardt reports grants from Amgen, AstraZeneca, Bayer, Fresenius, Genzyme, and Vifor and personal fees from Akebia Therapeutics, Inc., Bayer, and Boehringer Ingelheim

The HIF Pathway (Nobel-Prize 2019)

The body's response to low-oxygen environments is to increase cellular HIF protein levels to induce an orchestrated response to hypoxia, including enhanced EPO production and iron utilization



Pharmacological inhibition of HIF-PH enzymes mimicks the body's physiological response to hypoxia



Maxwell PH, Eckardt KU. *Nat Rev Nephrol.* 2016;12(3):157-168.

EPO, erythropoietin; HIF, hypoxia-inducible factor; HIF-PHI, HIF-Prolylhydroxylase inhibitor; RBC, red blood cell.

Acknowledgments

The authors would like to thank the study investigators and staff for the conduct of this study and the patients for volunteering to participate in the two trials.

PRO_2TECT Program

Global Phase 3 Clinical Trials of Vadadustat for Treatment of Anemia in Patients With Non–Dialysis-Dependent Chronic Kidney Disease

Disclosures

Funding

- Funding for this study was provided by Akebia Therapeutics, Inc., and Otsuka Pharmaceutical Development & Commercialization, Inc.

Potential conflicts of interest

- Dr. Chertow reports personal fees from Akebia during the conduct of the study

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