THE INNO$_2$VATE PHASE 3 PROGRAM OF VADADUSTAT FOR TREATMENT OF ANEMIA IN DIALYSIS-DEPENDENT CKD: RATIONALE AND STUDY DESIGN

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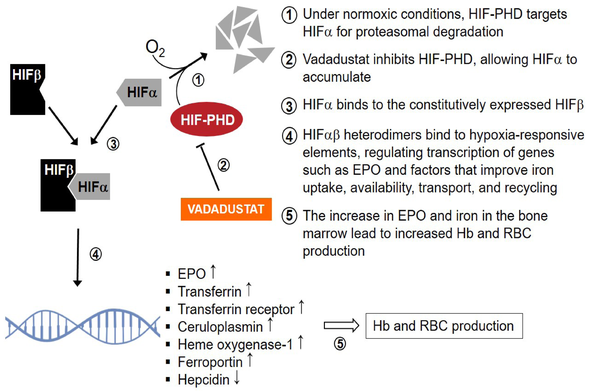
Background

- Anemia is a common complication of chronic kidney disease (CKD), with an estimated prevalence exceeding 50% in patients with CKD stage 4 or 5.[1]
- The presence of anemia is associated with worse prognosis in CKD, including a higher risk of cardiovascular disease, hospitalization, and mortality.[2,3]
- The current mainstay of treatment of CKD-associated anemia are erythropoiesis-stimulating agents (ESAs) and oral and intravenous iron.[4,5]
- Several clinical studies in patients with CKD reported that the use of ESAs, although effective in treating anemia, was associated with worse cardiovascular outcomes.[6-8]
- Despite the decline in ESA use following these trial results,[9] patients with CKD and anemia continue to suffer from a substantial burden of cardiovascular morbidity and mortality.[10] Thus, there is an unmet need for alternative therapies that present an improvement on the existing standard of care for CKD-associated anemia.

Vadadustat, a Hypoxia-Inducible Factor Prolyl-Hydroxylase Domain (HIF-PHD) Inhibitor

- Vadadustat is an orally bioavailable, HIF-PHD inhibitor under clinical development for the treatment of anemia in patients with dialysis-dependent and non-dialysis-dependent CKD (DD-CKD and NDD-CKD, respectively; **Figure 1**).
- Because it mimics the body's natural adaptive response to hypoxia,[11] HIF-PHD inhibition by vadadustat is being studied to determine if it raises and maintains hemoglobin (Hb) levels in the target range.

Figure 1. Mechanism of Action of Vadadustat



EPO, erythropoietin; Hb, hemoglobin; HIF, hypoxia-inducible factor; HIF-PHD, HIF prolyl-hydroxylase domain; RBC, red blood cell

Design of INNO$_2$VATE: Vadadustat Global Phase 3 DD-CKD Program

Table 1: Key Eligibility Criteria

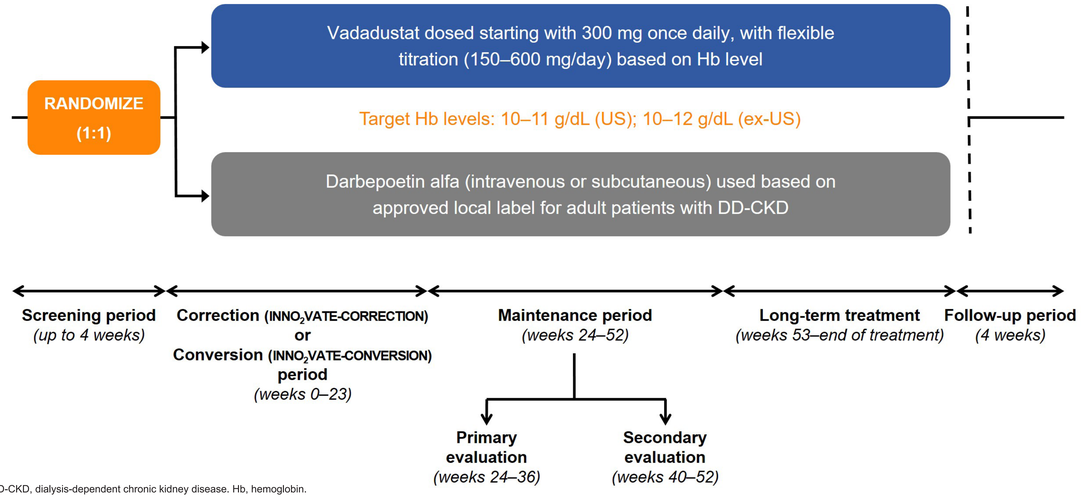
INNO$_2$VATE-CORRECTION (NCT02865850; target N = 400)	INNO$_2$VATE-CONVERSION (NCT02892149; target N = 2200)
• Adults (≥18 years) who initiated chronic maintenance dialysis (peritoneal or hemodialysis) for end-stage renal disease within 16 weeks prior to screening	• Adults (≥18 years) who initiated chronic maintenance dialysis (peritoneal or hemodialysis) for end-stage renal disease within 12 weeks prior to screening
• Anemia – Hb <10 g/dL	• Anemia – US: Hb 8–11 g/dL – Ex-US: Hb 9–12 g/dL
• No ESA (1 dose of long-acting or 2 doses of short-acting) within 8 weeks prior to or during screening	• Currently maintained on ESA therapy, with the last dose received within 8 weeks prior to screening
• Ferritin ≥100 ng/mL and transferrin saturation ≥20%	
Exclusion of patients with any of the following:	
• Anemia due to a cause other than CKD or patients with active bleeding or recent blood loss	
• Red blood cell transfusion during screening (or within 4 weeks prior to screening for INNO$_2$VATE-CONVERSION)	
• Uncontrolled hypertension at or during screening	
• Severe heart failure (New York Heart Association Class IV) at or during screening	
• Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction); sustained ventricular tachycardia, hospitalization for heart failure, or stroke within 12 weeks prior to or during screening	

Table 2. Key Efficacy and Safety Endpoints

Primary Endpoints	• Mean change in Hb from baseline to the primary evaluation period (weeks 24–36) • Time to the first occurrence of a major adverse cardiovascular event (MACE), defined as all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke.* Event-driven data from the 2 studies to be pooled
Secondary Endpoints	• Mean change in Hb from baseline to the secondary evaluation period (weeks 40–52) • Proportion of patients with mean Hb within the target range during the primary evaluation period • Proportion of patients receiving red blood cell transfusion(s) from baseline to week 52 • Arterial and venous thromboembolic events • Hospitalization for heart failure • AEs and serious AEs

*Cardiovascular safety endpoints are adjudicated by a central clinical endpoint committee blinded to treatment allocation

Figure 2. Study Design (INNO$_2$VATE-CORRECTION and INNO$_2$VATE-CONVERSION)



DD-CKD, dialysis-dependent chronic kidney disease. Hb, hemoglobin.

- INNO$_2$VATE comprises 2 global, randomized, open-label, active-controlled, noninferiority, Phase 3 studies to evaluate the efficacy and safety of oral vadadustat for the correction of anemia (INNO$_2$VATE-CORRECTION) or maintenance treatment of anemia (INNO$_2$VATE-CONVERSION) in patients with DD-CKD (**Tables 1 and 2**).
- Following the screening period, eligible patients are randomized to vadadustat or darbepoetin alfa and enter 4 sequential study periods (**Figure 2**). Study drug is titrated to achieve target Hb levels (US: 10–11 g/dL; Ex-US: 10–12 g/dL).

Summary

INNO$_2$VATE-CORRECTION and INNO$_2$VATE-CONVERSION are ongoing global Phase 3 studies evaluating the efficacy and safety of vadadustat in patients with anemia secondary to DD-CKD.

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Acknowledgments

The study was funded by Akebia Therapeutics, Inc. Editorial assistance was provided by AlphaBioCom, LLC, King of Prussia, PA, and funded by Akebia Therapeutics, Inc.

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Presented at the National Kidney Foundation 2017 Spring Clinical Meetings, Orlando, FL, April 18–22, 2017