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Rationale and Design of the PRO$_2$TECT Global Phase 3 Studies of Vadadustat for the Treatment of Anemia in Patients With Non-Dialysis-Dependent Chronic Kidney Disease

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Pablo E. Pergola;[1] Bruce S. Spinowitz;[2] Matthew R. Weir;[3] James Tumlin;[4] Rajiv Agarwal;[5] Masaomi Nangaku;[6] Qing Zuraw;[7] Emil deGoma;[7] Amit Sharma;[7] Bradley J. Maroni;[7] Geoffrey A. Block[8]

[1]Renal Associates PA, San Antonio, TX, USA; [2]New York Presbyterian Queens, Flushing, NY, USA; [3]University of Maryland School of Medicine, Baltimore, MD, USA; [4]Southeast Renal Research Institute, Chattanooga, TN, USA; [5]Indiana University School of Medicine, Indianapolis, IN, USA; [6]The University of Tokyo Graduate School of Medicine, Tokyo, Japan; [7]Akebia Therapeutics, Inc., Cambridge, MA, USA; [8]Denver Nephrology Research, Denver, CO, USA

Background

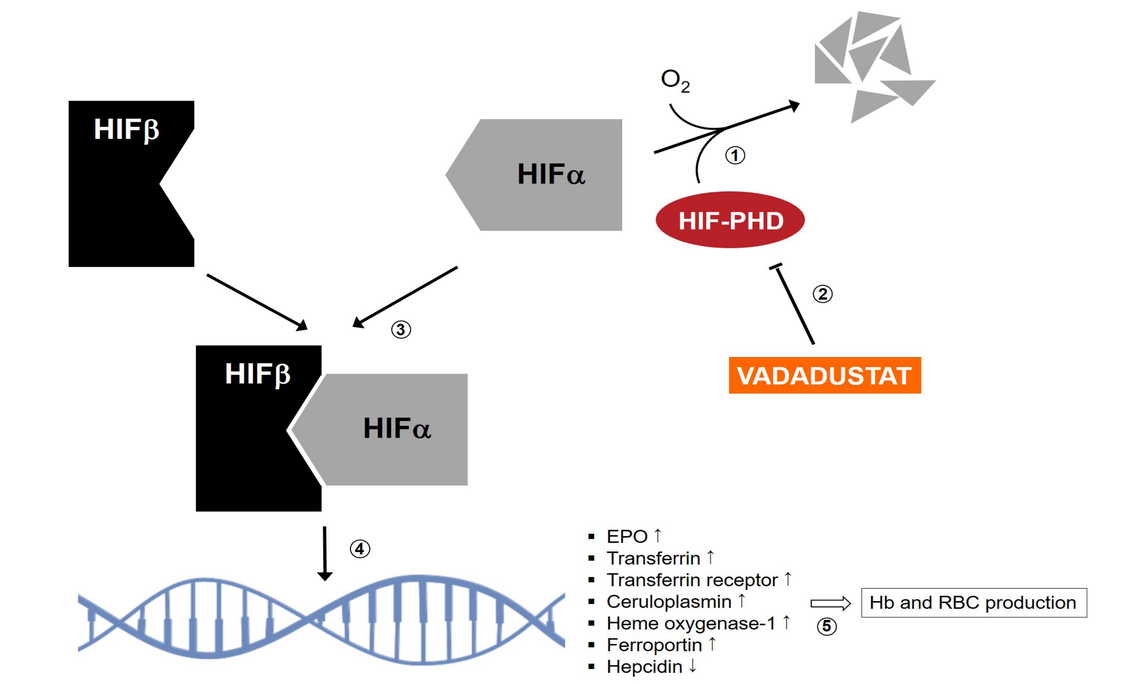
- Anemia is a common complication of chronic kidney disease (CKD), with an estimated prevalence exceeding 50% in patients with CKD stage 4 or 5.[1]
- The presence of anemia is associated with worse prognosis in CKD, including a higher risk of cardiovascular disease, hospitalization, and mortality.[2,3]
- 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.

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

Figure 1: Mechanism of Action of Vadadustat



① Under normoxic conditions, HIF-PHD targets HIFα for proteasomal degradation
② Vadadustat inhibits HIF-PHD, allowing HIFα to accumulate
③ HIFα binds to the constitutively expressed HIFβ
④ HIFαβ heterodimers bind to hypoxia-responsive elements, regulating transcription of genes such as EPO and factors that improve iron uptake, availability, transport, and recycling
⑤ The increase in EPO and iron in the bone marrow lead to increased Hb and RBC production

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

Design of PRO$_2$TECT: Vadadustat Global Phase 3 NDD-CKD Program

- PRO$_2$TECT 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 (PRO$_2$TECT-CORRECTION) or maintenance treatment of anemia (PRO$_2$TECT-CONVERSION) in patients with NDD-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).

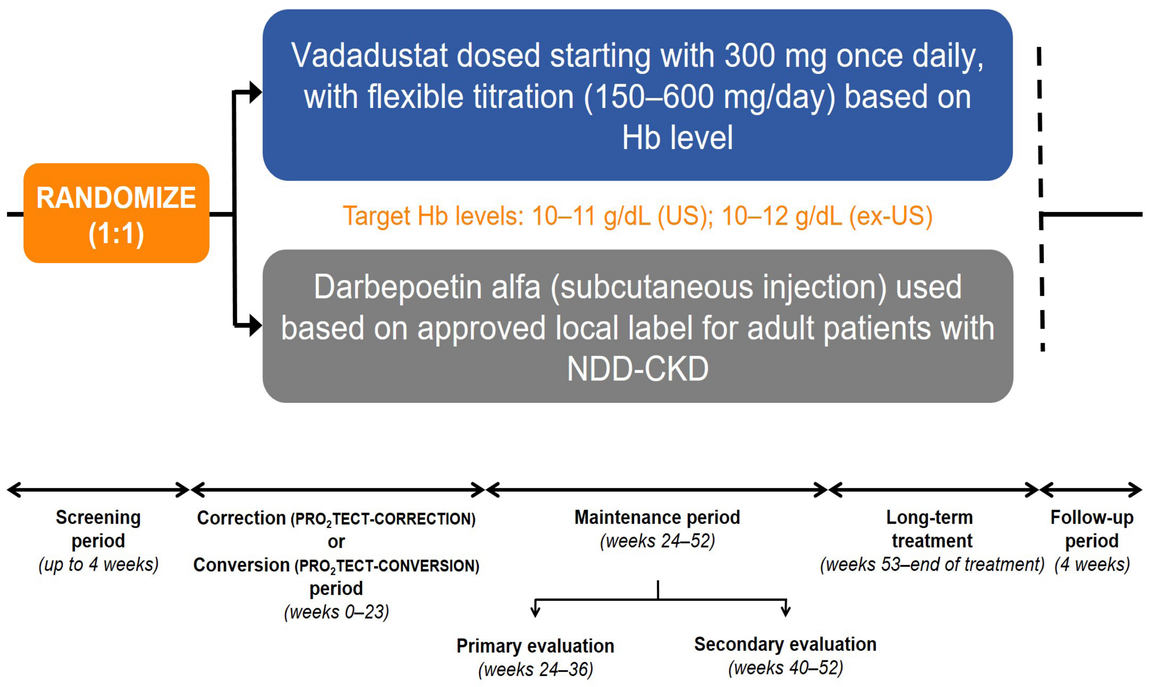
Table 1: Key Eligibility Criteria

PRO$_2$TECT-CORRECTION (NCT02648347; target N = 1000)	PRO$_2$TECT-CONVERSION (NCT02680574; target N = 2100)
• Adults (≥18 years) with CKD (eGFR ≤60 mL/min/1.73 m^2) at screening • Not expected to start dialysis within 6 months of screening • Ferritin ≥100 ng/mL and transferrin saturation ≥20%	
• Anemia – Hb <10 g/dL	• Anemia – US: Hb 8–11 g/dL – Ex-US: Hb 9–12 g/dL
• No ESA within 6 weeks prior to screening	• Currently maintained on ESA therapy, with the last dose received within 8 weeks prior to screening

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 within 4 weeks of screening
- Uncontrolled hypertension at screening
- Severe heart failure (New York Heart Association Class IV) at screening
- Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction), urgent coronary revascularization, hospitalization for heart failure, or stroke within 12 weeks prior to screening

Figure 2: Study Design (PRO$_2$TECT-CORRECTION and PRO$_2$TECT-CONVERSION)



Hb, hemoglobin; NDD-CKD, non-dialysis-dependent chronic kidney disease.

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 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

Summary

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

References

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Acknowledgments

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Contact Dr. Pergola at ppergola@raparesearch.com with any questions