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ASCEND-ND: STUDY DESIGN AND BASELINE CHARACTERISTICS

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BACKGROUND AND AIMS: The Anemia Study in Chronic kidney disease (CKD): Erythropoiesis via a Novel prolyl hydroxylase inhibitor (PHI) Daprodustat-Non-Dialysis (ASCEND-ND; NCT02876835) trial is evaluating the efficacy and safety of daprodustat when compared with darbepoetin alfa in CKD patients with anaemia not requiring dialysis. We report the trial design as well as key baseline characteristics of participants.

METHOD: Eligible patients from 39 countries were adults with CKD stages 3–5 who were able to provide informed consent and demonstrated adherence to daprodustat placebo tablets and study procedures during the run-in period. Patients were eligible if (1) they were not using erythropoiesis stimulating agents (ESAs) and had a screening haemoglobin (Hb) 8 to 10 g/dL or if (2) they were receiving ESAs with screening Hb of 8 to 12 g/dL. Patients were required to be iron replete [transferrin saturation (TSAT) >20% and serum ferritin >100 ng/mL] at screening. Participants were randomised to daprodustat or darbepoetin alfa (1:1) in an open-label (sponsor-blind) trial design with blinded endpoint assessment. An IDMC conducts regular reviews of unblinded safety and efficacy data and makes recommendations for additions or adjustments. An external, independent and blinded Clinical Events Classification (CEC) group, led by the Duke Clinical Research Institute, in collaboration with George Clinical, adjudicate predefined events.

During the study, both groups had randomised treatment adjusted using a protocol-defined algorithm targeting a Hb range of 10 to 11 g/dL. Participants also followed protocol-defined iron management criteria to ensure they remained iron replete. Additionally, an anaemia rescue algorithm was in place to minimise the risk of

extended periods of inadequate Hb response and to ensure consistent application of rescue therapy across the study.
The co-primary endpoints are mean change in Hb between baseline and Evaluation Period (EP; Weeks 28 to 52, inclusive) and time to first adjudicated major adverse cardiovascular event (MACE; composite of all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke). The study has more than 99% power for the Hb non-inferiority (NI) test with an NI margin of -0.75 g/dL for the treatment difference of mean change in Hb between baseline and EP, and approximately 90% power to exclude the NI margin of 1.25 for time to first adjudicated MACE, for daprodustat compared with darbepoetin alfa. Conditional on both co-primary endpoints achieving NI at the one-sided 2.5% level, statistical testing will progress to evaluate MACE and the principal secondary endpoint of CKD progression for superiority. These tests will be multiplicity adjusted.
RESULTS: A total of 3872 patients were randomised (median age 67 years, 56% female; 55% white, 28% Asian, and 10% black). The median baseline Hb was 9.8 g/dL, serum ferritin was 274 ng/mL, TSAT 30%, and eGFR 18 mL/min/1.73 m^2. Among randomised patients, 54% were ESA non-users, 57% reported a history of diabetes mellitus and 36% a history of cardiovascular disease. Median blood pressure was 135/74 mmHg. Sixty percent of participants were taking angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, while 57% were taking lipid modifying agents at baseline. The trial is expected to complete during 2021.
CONCLUSION: ASCEND-ND will define the efficacy and safety of daprodustat compared with darbepoetin alfa in the treatment of patients with anaemia associated with CKD not requiring dialysis.