generalizable to the UK and similar populations. **Conclusions:** Our findings support the use of therapeutics that increase Hb in patients with SCD to protect against deleterious organ damage. **Disclosures:** This study and its analysis were conducted by CorEvitas LLC and sponsored by Global Blood Therapeutics.

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EFFICACY AND SAFETY OF NIPOCALIMAB, AN FCRN BLOCKER, IN WARM AUTOIMMUNE HEMOLYTIC ANEMIA (WAIHA): ENERGY PHASE 2/3 STUDY DESIGN

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Objectives: Warm autoimmune hemolytic anemia (wAIHA) is characterized by the destruction of red blood cells (RBCs) by pathogenic autoantibodies which bind to RBCs and lead to their clearance in the spleen and liver. Patients with wAIHA can experience acute worsening of anemia, which can be a medical emergency, and have an increased risk of thromboembolic events and premature death. Nipocalimab is a fully human, aglycosylated, effectorless IgG1 monoclonal antibody that blocks the IgG binding site on the neonatal Fc receptor (FcRn) with high affinity. FcRn, which is expressed in endothelial cells, is responsible for recycling IgG into the circulation and for the relatively long half-life of IgG antibodies compared to other Igs. It is expected that nipocalimab, by blocking IgG binding to FcRn, will prevent IgG recycling and lower pathogenic IgG autoantibodies that cause many autoantibody diseases, including wAIHA. Nipocalimab has been studied in multiple phase 1 studies in healthy subjects and in a completed phase 2 study in subjects with Generalized Myasthenia Gravis (gMG). Treatment with nipocalimab was associated with rapid and durable total serum IgG and pathogenic IgG autoantibody reduction and meaningful clinical response. Here we share the rationale and study design for an adaptive, phase 2/3 multicenter, randomized, double-blind, placebo-controlled study in patients with wAIHA whose aim is to evaluate the efficacy, safety, tolerability, PK, and PD of nipocalimab compared with placebo (NCT04119050). **Materials and methods:** Male or female subjects ≥18 years of age who have been diagnosed with primary or secondary wAIHA and have not experienced a sufficient response or have not tolerated currently available treatments will be included in the study. Subjects with cold antibody AIHA, cold agglutinin syndrome, mixed type (i.e., warm and cold) AIHA, or paroxysmal cold hemoglobinuria will be excluded. Participants will be randomized 1:1:1 to receive nipocalimab at two different dose schedules or placebo. Following completion of 24 weeks of double-blind treatment, participants may enter an open-label extension period to receive nipocalimab. **Results:** The primary endpoint is percentage of participants achieving durable response of improvement in hemoglobin (Hgb). The main secondary endpoints are change from baseline in the total score from the FACIT-Fatigue Scale, number of participants who attain normal lactate dehydrogenase, normal haptoglobin, and normal indirect bilirubin levels at a minimum of 3 consecutive visits after baseline. **Discussion:** ENERGY is a phase 2/3 study that will evaluate the efficacy and safety of nipocalimab in wAIHA. **Conclusion:** ENERGY is currently enrolling globally. **Conflicts of interest:** IM received research support from Alexion, Annexon, Incyte, Kezar, Momenta, Rigel, and Sanofi; and served as a consultant for Apellis, Janssen, Momenta, Novartis, Rigel, and Sanofi. BF is a consultant of Alexion, Amgen, Janssen, Momenta, and Novartis. DC is an employee of Janssen Global Services, LLC, which is a wholly owned subsidiary of Johnson & Johnson, and may own stock or stock options in Johnson & Johnson; was an employee of Momenta. AMBP is an employee of Janssen Latin America, which is a wholly owned subsidiary of Johnson & Johnson, and may own stock or stock options in Johnson & Johnson. MHJ was an employee of Momenta.

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LONG-TERM EFFICACY AND SAFETY OF THE ORAL PYRUVATE KINASE ACTIVATOR MITAPIVAT IN ADULTS WITH NON −TRANSFUSION-DEPENDENT ALPHA- OR BETA-THALASSEMIA

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Objectives: Thalassemic red blood cells (RBCs) have insufficient levels of adenosine triphosphate (ATP) to meet increased energy demands associated with globin chain precipitation and oxidative stress responses. Mitapivat is a first-in-class, small molecule, oral activator of pyruvate kinase (PK), a key glycolytic enzyme regulating ATP production. In a phase 2, open-label trial of mitapivat in adults with α- or β-non−transfusion-dependent (NTD) thalassemia (NCT03692052), 80% (16/20) of patients (pts) met the primary endpoint of a hemoglobin (Hb)

response (≥1.0 g/dL increase from baseline [BL] at ≥1 assessments between Weeks (Wk) 4–12, inclusive). Improvements in markers of hemolysis and ineffective erythropoiesis were also observed and mitapivat was generally well tolerated. Here we report data from the ongoing long-term extension (LTE) period (≤Wk 72; data cutoff 27Mar2021). **Material and methods:** Pts aged ≥18 years (y) with α- or β-thalassemia, Hb concentration ≤10.0 g/dL, and ≤5 RBC units transfused in prior 24 wk and none in 8 wk prior to study drug were eligible. All pts started mitapivat 50 mg twice daily (BID), escalating to 100 mg BID based on individual safety and Hb assessments. Pts with a Hb response or a delayed Hb response (after Wk 12), with no ongoing study drug-related grade ≥3 treatment-emergent adverse events (AE), could continue on mitapivat in the LTE at the Wk 24 visit dose. LTE study visits occur every 12 wk. **Results:** Twenty patients started treatment; 19 pts completed the core period, 17 entered the LTE. As of the data cutoff, 1 pt discontinued (pt decision). Median treatment duration for pts in the LTE was 70.9 wk (range 54.7, 105.6); 8 pts received ≥72 wk of treatment as of data cutoff. Baseline values for patients who continued in LTE were: median age 44 y (range 29, 67), mean (standard deviation [SD]) Hb 8.1 (1.2) g/dL, total bilirubin 40.1 (26.2) μmol/L, lactate dehydrogenase (LDH), 272.4 (121.7) U/L, and median erythropoietin (EPO) 70.5 (range 15, 11191) IU/L. Hb improvements achieved in the core period were sustained in the LTE. Mean (SD) Hb increase from BL to Wk 60 (α-thalassemia, n = 4; β-thalassemia, n = 9) and Wk 72 (β-thalassemia, n = 8) were 1.5 (0.4) and 1.7 (0.5) g/dL, respectively. Improvements in markers of hemolysis and ineffective erythropoiesis observed in the core period were maintained in the LTE up to Wk 72 (change in mean [SD] bilirubin and LDH, −15.8 [16.6] μmol/L and −63.6 [216.0] U/L, respectively; change in median [range] EPO, −33.0 [−72.0, −16.0] IU/L). The safety profile was consistent with that observed in the core period. AEs in ≥15% of pts were headache (5/17) and back pain (3/17), 0 were grade ≥3. No treatment-related serious AEs or trends for decreases in bone mineral density were observed. **Discussion:** In pts with either α- or β-thalassemia, a favorable efficacy-safety profile was observed with long-term mitapivat treatment. Data show sustained improvements in Hb, hemolysis, and ineffective erythropoiesis across a spectrum of globin genotypes, and no new safety findings. **Conclusions:** Mitapivat's mechanism of action may represent a novel therapeutic approach for thalassemia. Two phase 3 trials of mitapivat in α- and β-thalassemia for both NTD (ENERGIZE, NCT04770753) and transfusion-dependent (ENERGIZE-T, NCT04770779) pts are enrolling.

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A PHASE 2/3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF MITAPIVAT IN PATIENTS WITH SICKLE CELL DISEASE

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Objectives: The key pathology in sickle cell disease (SCD), a life-threatening, hereditary hemoglobin (Hb) disorder, is red blood cell (RBC) sickling due to polymerization of deoxygenated sickle Hb (HbS), which can be exacerbated by increased levels of the glycolytic metabolite 2,3-diphosphoglycerate (2,3-DPG) and decreased ATP. Sickled RBCs are rigid, nondeformable, and fragile, resulting in vaso-occlusive pain and chronic hemolysis. Current SCD treatment options are limited; therefore, there is an unmet need for safe, effective therapies that alleviate both anemia and pain. Activation of the key RBC glycolytic enzyme pyruvate kinase (PKR) by oral mitapivat decreases 2,3-DPG and increases ATP, which may reduce HbS polymerization, RBC sickling, and hemolysis in SCD. Data from the phase (ph) 1 National Institutes of Health multiple ascending dose study of up to 100 mg mitapivat twice daily (BID) in patients with SCD (NCT04000165) showed that mitapivat was safe and tolerable, increased ATP and decreased 2,3-DPG in a dose-dependent manner, and improved anemia and hemolysis. Here we report the study design of RISE UP (NCT05031780, EudraCT: 2021-001674-34), a ph 2/3, double-blind, randomized, placebo (PBO)-controlled, multicenter study evaluating the efficacy and safety of mitapivat in patients (pts) with SCD. **Materials and methods:** Eligible: pts aged ≥16 yrs (≥18 yrs [France and Germany]) with documented SCD (HbSS, HbSC, HbSβ^0/HbSβ^+ thalassemia, other variants), 2–10 sickle cell pain crises (SCPCs; acute pain requiring intervention, acute chest syndrome, priapism, hepatic or splenic sequestration) in the prior 12 months, and Hb 5.5–10.5 g/dL. If on hydroxyurea (HU), the dose must be stable for ≥ 90 days before starting study drug. Ineligible: pts receiving regular blood transfusions, with severe kidney or hepatobiliary disease, current SCD therapies except HU, or prior gene therapy, bone marrow or stem cell transplantation. In the double-blind ph 2 part, 69 pts will be randomized (1:1:1) to 50 mg or 100 mg mitapivat, or PBO BID for 12 weeks (wk). The primary objective is to determine the recommended ph 3 mitapivat dose by evaluating anemia and safety vs PBO via the following endpoints: Hb response (≥ 1.0 g/dL increase in average (avg) Hb concentration over Wk 10–12 vs baseline [BL]), and type, severity, and relationship of adverse events (AEs) and serious AEs. In the double-blind ph 3 part, 198 pts who did not participate in ph 2 will be randomized (2:1) to the selected ph 3 mitapivat dose or PBO BID for 52 wk. The primary objectives are to determine the effect of mitapivat vs PBO on anemia, measured by Hb response (≥ 1.0 g/dL increase in avg Hb concentration over Wk 24–52 vs BL), and the effect of mitapivat vs PBO on SCPC, measured by annualized rate of SCPCs. Key secondary endpoints: avg change from BL in Hb concentration, indirect bilirubin, percent reticulocyte, and Pt-Reported Outcomes Measurement Information System® Fatigue 13a Short Form score over Wk 24–52; and annualized frequency of SCPC