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

admissions. Pts who complete the double-blind period will be eligible to receive mitapivat in the open-label extension period in each ph. **Results:** Pending. **Discussion:** N/A. **Conclusion:** This ph 2/3 study will investigate the efficacy and safety of mitapivat in pts with SCD. Enrollment is currently ongoing.

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SELECTIVE TARGETING OF FCRN AND IGG CLEARANCE BY NIPOCALIMAB PRESERVES KEY IMMUNE FUNCTIONS

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Objectives: Autoantibody disorders are caused by immune-system-produced antibodies that can damage the body's tissues or organs. In the case of warm autoimmune hemolytic anemia (wAIHA), pathogenic autoantibodies lead to the destruction of red blood cells. There is an unmet need for innovative targeted therapies that address the underlying pathogenesis of wAIHA in a safe and efficacious way. Nipocalimab is a fully human, aglycosylated, effectorless IgG1 monoclonal antibody that blocks the IgG binding site on the neonatal Fc receptor (FcRn) which prevents IgG recycling, leading to reduced serum levels of total IgGs, including pathogenic IgG autoantibodies. Nipocalimab is in clinical development for the treatment of multiple IgG-mediated autoantibody diseases, including wAIHA (NCT04119050). Rapid, sustained lowering of IgG was observed in the phase 2 VIVACITY study in generalized myasthenia gravis (gMG) and in phase 1 healthy volunteers. In gMG patients, nipocalimab induced rapid and sustained lowering of anti-AChR autoantibodies and MG-ADL scores, but no serious adverse events including clinically significant infections. Here, we characterize the effect of nipocalimab on immune function. **Materials and methods:** Nipocalimab was evaluated extensively *in vitro* and in nonhuman primate-based chronic toxicology studies to evaluate selectivity, tolerability, safety and immunopharmacology. Safety, tolerability and immune-focused assessments in clinical phase 1 and Phase 2 MG studies were also completed (NCT02828046, NCT03772587). **Results:** Nipocalimab binds specifically *in vitro* to FcRn without activation of effector function or inhibition of antigen presentation. In nonhuman primates administered up to 300 mg/kg nipocalimab QW for up to 6 months, sustained lowering of IgG was observed without adverse effects. Immunotoxicology identified no effect on immune cell phenotypes; CD8 T cell, NK or innate cell functions; T-dependent neoantigen IgM responses. Neoantigen IgG production was observed, but with lowered peak IgG titers consistent with the anticipated increase in IgG clearance with nipocalimab. In clinical studies, nipocalimab demonstrated a reproducible selective decrease in total serum IgG, including all subclasses of IgG, with no effect on IgM, IgA, IgE, CH50, C3, C4, inflammatory cytokines or acute phase proteins including, C-reactive protein (CRP). **Discussion:** These data suggest that nipocalimab can selectively lower IgG and IgG autoantibodies while preserving cellular immunity, complete IgM response and IgG production after neoantigen challenge. **Conclusions:** Overall, nipocalimab's selective effect on IgG recycling provides a mechanistic rationale for potentially decreased infection risk despite substantial IgG lowering. **Conflicts of interest:** LEL *, FY *, CJB *, JB *, RX *, AMBP are employed by the Janssen Pharmaceutical Companies of Johnson & Johnson and may hold stock or stock options in Johnson & Johnson; ST * is an employee of Orna Therapeutics; SK * is an employee of Checkmate Pharmaceuticals; JD * is an employee of Faze Medicines; WA * is an employee of Kisbee Therapeutics. *Former employees of Momenta Pharmaceuticals which was acquired by Janssen Pharmaceutical Companies of Johnson & Johnson.

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A PHASE 1 PLACEBO-CONTROLLED SINGLE-DOSE STUDY OF NIPOCALIMAB ADMINISTERED AT DIFFERENT RATES OF INTRAVENOUS INFUSION IN HEALTHY ADULTS

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Objectives: Warm autoimmune hemolytic anemia (wAIHA) is a rare, life-threatening disorder characterized by the destruction of red blood cells by pathogenic IgG autoantibodies. There is currently no approved treatment for wAIHA. 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, which is in clinical development for the treatment of wAIHA. In a prior phase 1 study in healthy adults receiving single and multiple ascending doses infused intravenously (IV) over 2 hours, nipocalimab was well-tolerated with an adverse event profile comparable to placebo. However, shorter durations of nipocalimab infusion may be more convenient for patients. Here we assess the safety and tolerability of single doses of nipocalimab administered at different IV infusion rates in healthy adults to support the potential use of shortened infusions in future studies. **Materials and methods:** The trial was a single dose, sequential, randomized, double-blind, placebo-controlled, escalating dose and infusion rate study. Eligible