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.

https://doi.org/10.1016/j.htct.2022.09.021

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

LE Ling [a], S Tyler [b], CJ Beneduce [a], F Yu [a], J Brown [a], S Kumar [c], R Xu [a], J Duffner [d], AB Perdomo [e], W Avery [f]

[a] *Janssen Research and Development, LLC*
[b] *Orna Therapeutics*
[c] *Checkmate Pharmaceuticals*
[d] *Faze Medicines, Cambridge, United States*
[e] *Immunology Medical Affairs, Janssen Latin America*
[f] *Kisbee Therapeutics*

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.

https://doi.org/10.1016/j.htct.2022.09.022

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

JH Leu [a], A Vermeulen [b], AB Perdomo [c], LE Ling [d]

[a] *Janssen Research & Development, LLC, Spring House, United States*
[b] *Janssen Research & Development, a division of Janssen Pharmaceutica NV, Beerse, Belgium*
[c] *Immunology Medical Affairs, Janssen Latin America, Bogotá, Colombia*
[d] *Janssen Research & Development, LLC, Cambridge, United States*

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