WCN 2024- BEYOND TiP

BEYOND: A Phase 3, Randomized, Double-blind, Placebo-controlled Trial of Zigakibart in Adults with IgA Nephropathy

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Introduction:
IgA nephropathy (IgAN) is the leading cause of primary glomerulonephritis and has limited treatment options. Zigakibart (BION-1301) is a novel, humanized monoclonal antibody that blocks APRIL (a proliferation-inducing ligand), a cytokine that is elevated in patients with IgAN. APRIL promotes the production of pathogenic galactose-deficient IgA1 (Gd-IgA1), resulting in immune complex formation and glomerular deposition, causing inflammation and kidney injury. Blocking APRIL with zigakibart is a potential disease-modifying approach to treating IgAN. Interim results from a Phase 1/2 trial of zigakibart in patients with IgAN (NCT03945318) demonstrate rapid and durable reductions in Gd-IgA1 and sustained, clinically meaningful reductions in proteinuria with an acceptable safety profile.

Methods:
BEYOND is an ongoing Phase 3, randomized, double-blind, placebo-controlled trial to evaluate the effect of zigakibart in adults with primary IgAN at risk of progressive kidney function loss. Approximately 272 patients will be enrolled across North America, South America, Europe and Asia-Pacific. Key eligibility criteria include biopsy-proven IgAN within the past 10 years (not due to secondary causes), eGFR ≥ 30 ml/min/1.73m^2 (CKD-EPI) and total urine protein ≥ 1.0 g/day at screening and UPCR ≥ 0.7 g/g. Patients must be stable on a maximally tolerated dose of RAS inhibitor (RASi) for at least 12 weeks prior to screening or intolerant to RASi. Patients may also be on a stable dose of SGLT2i, mineralocorticoid receptor antagonists and/or endothelin receptor antagonists for at least 12 weeks prior to screening.

The study is comprised of a 6-week screening period, a 104-week double-blind treatment, and a 24-week safety follow-up period. Patients will be randomized 1:1 to receive subcutaneous 600 mg zigakibart Q2W or placebo for 104 weeks. Randomization will be stratified by region (Asia vs. Rest of World), baseline proteinuria (≥ 2 g/day vs. < 2 g/day) and eGFR (≤ 45 ml/min/1.73m^2 vs. > 45 ml/min/1.73m^2). An additional

~20 patients with eGFR 20 to < 30 mL/min/1.73m^2 will be enrolled into an exploratory cohort not included in the primary or secondary analyses.

Results:
The primary endpoint is change in proteinuria (UPCR from a 24-hour urine collection) from baseline to week 40. The key secondary endpoint is change in eGFR from baseline to week 104. Additional secondary endpoints will evaluate the effect of zigakibart vs. placebo on composite clinical outcomes including patients experiencing at least one of the following: 30% or 40% reduction in eGFR, eGFR < 15 mL/min/1.73m^2, dialysis, kidney transplantation or all-cause mortality. Safety endpoints include type, incidence, severity, and relatedness of adverse events (AEs) and serious AEs. Exploratory endpoints include impact of zigakibart on disease biomarkers and health-related quality of life as well as analysis of zigakibart pharmacokinetics and immunogenicity.

Conclusion:
Zigakibart provides a potentially disease-modifying approach for the treatment of IgAN by directly targeting the disease pathogenesis. The Phase 3 trial will evaluate the effect of zigakibart vs. placebo on proteinuria, eGFR and composite clinical endpoints and key safety measures in adult patients with IgAN at risk of progressive kidney function loss. This trial design has been previously presented at ERA 2023, Milan, and ASN 2023, Philadelphia.

Category: The Smart Kidney: Genetics, precision medicine, machine learning/AI, rare/orphan kidney diseases

Subcategory: Clinical glomerulonephritis

Keywords: IgA nephropathy, glomerulonephritis, clinical trial