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BEYOND: A Phase 3, randomized, double-blind, placebo-controlled trial of zigakibart in adults with IgA nephropathy

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SUMMARY

- Zigakibart provides a potentially disease-modifying approach for the treatment of IgAN that directly targets the disease pathogenesis by blocking excess production of Gd-IgA1
- The Phase 3 BEYOND registrational study will evaluate the effect of zigakibart vs placebo on proteinuria, eGFR, and composite clinical endpoints as well as the key safety measures in adult patients with IgAN at risk of progressive kidney function loss

BACKGROUND

IgA nephropathy

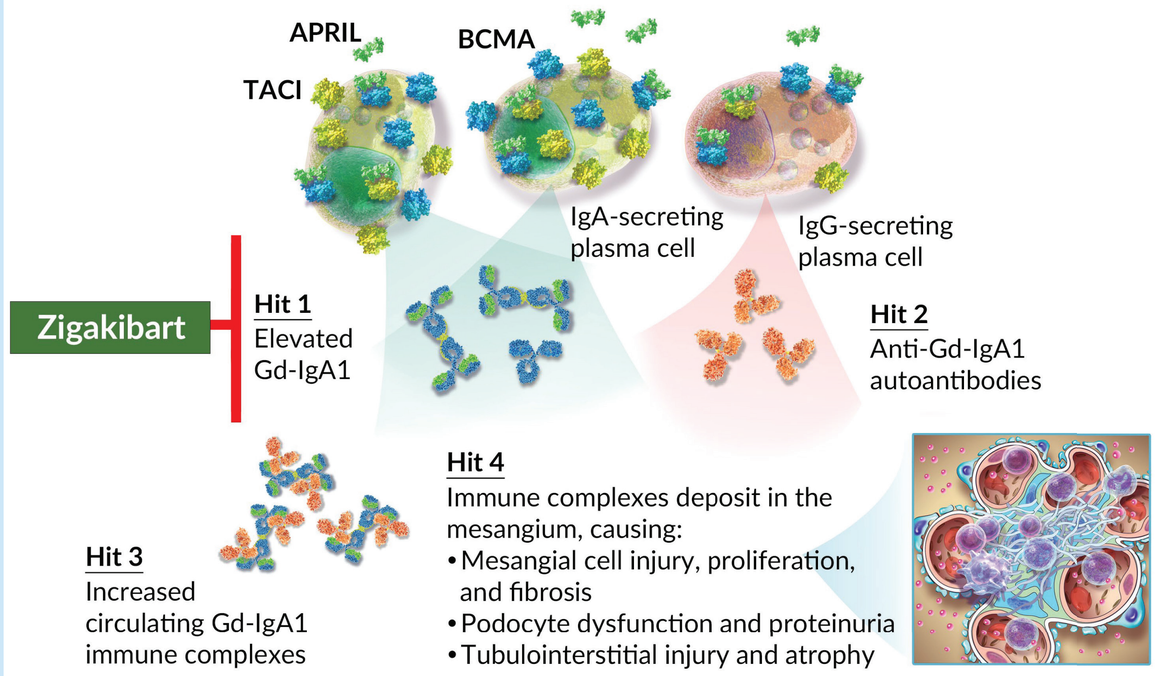
- IgAN is the leading cause of primary glomerulonephritis worldwide[1]
- Approximately 30–45% of IgAN patients progress to ESKD over a period of 20–25 years[2–5]
- Proteinuria is strongly associated with kidney disease progression in IgAN[2,6–7]; treatments that reduce proteinuria result in improved renal outcomes in IgAN[8–9]

Zigakibart* and the APRIL pathway

Zigakibart is a novel, humanized monoclonal antibody that binds and blocks APRIL (a proliferation-inducing ligand)

- APRIL is a TNF superfamily cytokine that drives IgA class switching and survival of IgA-secreting plasma cells in IgAN, leading to elevated Gd-IgA1 and immune complex deposition in the mesangium (**Figure 1**)[10–12]
- Blocking APRIL with zigakibart is a potentially disease-modifying mechanism by decreasing Gd-IgA1 and preventing pathogenic immune complex formation (**Figure 1**)
- Interim results from a Phase 1/2 trial of zigakibart in patients with IgAN (NCT03945318) demonstrate rapid and durable reductions in Gd-IgA1, along with sustained, clinically meaningful reductions in proteinuria and an acceptable safety profile[13]

Figure 1. Zigakibart is a novel, humanized monoclonal antibody that binds and blocks APRIL

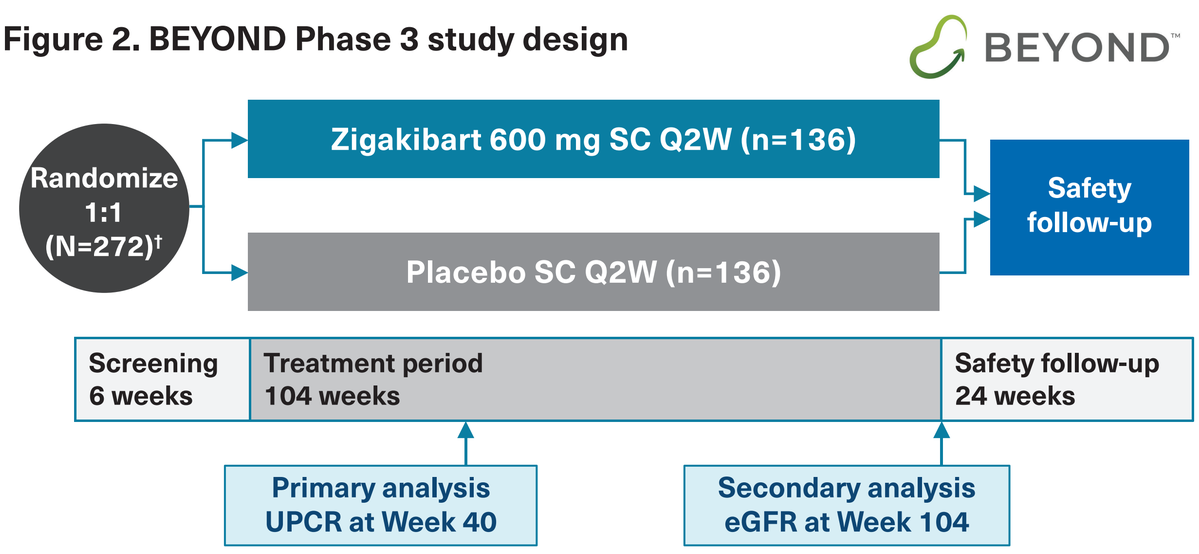


METHODS

Study objective

- BEYOND (NCT05852938) is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the effect of zigakibart in adults with primary IgAN at risk of progressive kidney function loss (**Figure 2**)
- Approximately 272 patients will be enrolled across North America, South America, Europe, and Asia Pacific

Figure 2. BEYOND Phase 3 study design



†Up to 20 additional patients with eGFR ≥20 to <30 mL/min/1.73 m² will be enrolled in an exploratory cohort (not included in the primary analysis) for a total N=292

Key inclusion criteria

- Biopsy-proven IgAN within the past 10 years (not due to secondary causes)
- eGFR ≥30 mL/min/1.73 m² (CKD-EPI)
- Total urine protein ≥1.0 g/day and UPCR ≥0.7 g/g at screening
- Receiving stable, maximally tolerated ACEi/ARB ≥12 weeks prior to screening or intolerant
- May be on a stable dose of SGLT2i, mineralocorticoid receptor antagonist, and/or endothelin receptor antagonist ≥12 weeks prior to screening

Study endpoints

Primary	Change in proteinuria (UPCR from a 24-hour urine collection) from baseline to Week 40
Key secondary	Change in eGFR from baseline to Week 104
Additional secondary	Composite clinical outcome, including at least one of the following: • 30% or 40% reduction in eGFR • eGFR <15 mL/min/1.73 m² • Dialysis, kidney transplantation or all-cause mortality
Safety	Type, incidence, severity, and relatedness of AEs and serious AEs
Exploratory	Impact of zigakibart on disease biomarkers and health-related quality of life as well as analysis of zigakibart pharmacokinetics and immunogenicity

Disclaimer

*Zigakibart (BION-1301) is an investigational drug that has not been approved by regulatory authorities. Efficacy and safety have not been established. There is no guarantee that it will become commercially available for use(s) under investigation.

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; **APRIL**, a proliferation-inducing ligand; **ARB**, angiotensin II receptor blockers; **BMI**, body mass index; **BP**, blood pressure; **CKD**, chronic kidney disease; **CKD-EPI**, Chronic Kidney Disease Epidemiology Collaboration; **eGFR**, estimated glomerular filtration rate; **ERAs**, endothelin receptor antagonists; **ESKD**, end-stage kidney disease; **Gd-IgA1**, galactose-deficient immunoglobulin A1; **HbA1c**, hemoglobin A1c; **IgAN**, immunoglobulin A nephropathy; **KDIGO**, Kidney Disease Improving Global Outcomes; **MRAs**, mineralocorticoid receptor antagonists; **Q2W**, administered every 2 weeks; **RPGN**, rapidly progressive glomerulonephritis; **SC**, subcutaneous; **SGLT2i**, sodium-glucose cotransporter-2 inhibitor; **TNF**, tumor necrosis factor; **UPCR**, urine protein–creatinine ratio.

References

1. Mcgrogan et al, 2011, *NDT.* **2.** Reich et al, 2007, *JASN.* **3.** Moriyama et al, 2014, *PLOS ONE.* **4.** Rauen et al, 2020, *Kidney Int.* **5.** Hastings et al, 2018, *Kidney Int Rep.* **6.** Thompson et al, 2019, *CJASN.* **7.** Barbour et al, 2019, *JAMA Int Med.* **8.** Inker et al, 2016, *AJKD.* **9.** Inker et al, 2019, *CJASN.* **10.** Suzuki et al, 2021, *Sem Immunol.* **11.** Zhai et al, 2016, *Medicine.* **12.** McCarthy et al, 2011, *JClin Invest.* **13.** J Barratt et al, ASN Kidney Week 2022; FR-PO659.

For more information, visit

https://clinicaltrials.gov/study/NCT05852938