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

Dana V. Rizk, MD
University of Alabama at Birmingham, USA

17th International Symposium on IgA Nephropathy
September 30, 2023

Initially presented at ERA, Milan, June 16, 2023

*Zigakibart (BION-1301) is an investigational drug that has not been approved by regulatory authorities.
I have the following relationships to disclose any COI for this research presentation within the period of 36 months:

**Employment/Leadership position/Advisory role:** Novartis, Otsuka, Chinook, Vera

**Stock ownership or options:** Reliant Glycosciences, LLC

**Honoraria (e.g. lecture fees):** Novartis, GSK, George Clinical, Eledon Pharmaceuticals, Otsuka Pharmaceuticals (Visterra), Calliditas Therapeutics (Pharmalink), Chinook Pharmaceuticals, LaRoche, Vera Therapeutics

**Research funding:** Reata Pharmaceuticals, Travere Therapeutics (Retrophin), Pfizer Pharmaceuticals, Calliditas Therapeutics (Pharmalink), Otsuka Pharmaceuticals (Visterra), Vertex Pharmaceuticals, Chinook Pharmaceuticals, Vera Therapeutics

**Travel fees, gifts, and others:** Otsuka

**Patent royalties/licensing fees, Manuscript fees, Subsidies or Donations, Endowed departments by commercial entities:** None
IgAN is a Progressive Kidney Disease and the Most Common Form of Primary Glomerulonephritis\(^1\)

- Among 667 patients with IgAN/IgA vasculitis (76% IgAN) from the CureGN cohort, which includes study sites across the USA, Canada, Italy, and Poland.
  8. Hastings, M. C., et al. KI Reports, 2018

- Global Incidence
  ~2.5/100,000 adults per year\(^1,2\)

- Gender Breakdown\(^3,a\)
  - 60% of patients are male

- More severe clinical presentation and higher risk of disease progression has been reported in Asians than Europeans\(^4\)

- Progresses to ESRD in 30-45% of patients in 20-25 years\(^5-8\)

---

\(\text{a. Among 667 patients with IgAN/IgA vasculitis (76% IgAN) from the CureGN cohort, which includes study sites across the USA, Canada, Italy, and Poland.}
Proteinuria is Strongly Associated with Kidney Disease Progression and Renal Failure in IgAN\textsuperscript{1-4}

- Proteinuria $> 1\text{ g/day}$ is associated with a 9.4-fold increased risk of ESKD compared to patients with proteinuria $< 1\text{ g/day}$\textsuperscript{3}

Each gram above 1 g/day (reference group) was associated with worse renal survival (defined as time from onset to ESKD)

Reproduced from Figure 1: Reich HN, et al. JASN. 2007;18(12):3177-3183.

APRIL (A PRoliferation Inducing Ligand) is a Key Molecule Involved in Hit 1 of IgAN Pathogenesis\textsuperscript{1,2}

Zigakibart\* and the APRIL Pathway

- Zigakibart is a novel, humanized monoclonal antibody that blocks APRIL\textsuperscript{3,4}
- Blocking APRIL with zigakibart is a potentially disease-modifying mechanism to deplete Gd-IgA1 and prevent pathogenic immune complex formation\textsuperscript{4}

APRIL promotes plasma cell survival and IgA production leading to increased production of Gd-IgA1

APRIL, A PRoliferation Inducing Ligand; Gd-IgA1, galactose-deficient immunoglobulin A; IgA, immunoglobulin A; IgAN, IgA nephropathy; IgG, immunoglobulin G; mAb, monoclonal antibody.


\*Zigakibart (BION-1301) is an investigational agent and has not been approved for any use in patients.
Zigakibart treatment results in sustained, clinically meaningful proteinuria reduction in patients with IgAN

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 (Barratt, et al. 2023, ERA).

**Immunoglobulins, Combined Cohorts**

<table>
<thead>
<tr>
<th>Week</th>
<th>IgA</th>
<th>Gd-IgA1</th>
<th>IgG</th>
<th>IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>35</td>
<td>34</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>34</td>
<td>26</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>24</td>
<td>30</td>
<td>26</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>52</td>
<td>16</td>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>76</td>
<td></td>
<td></td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

**UPCR, Combined Cohorts**

<table>
<thead>
<tr>
<th>Week</th>
<th>% Reduction</th>
<th>Data cut-off May 8, 2023</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>-20%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>-39%</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>-67%</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>-67%</td>
<td></td>
</tr>
<tr>
<td>76</td>
<td>-72%</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median (range) baseline protein excretion: 1.1 (0.3, 7.0) g/day
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.

**Study Objective**

Approximately 272 patients will be enrolled across North America, South America, Europe and Asia-Pacific.

**Randomize**

Randomize 1:1 (N=272)*

- **Zigakibart 600 mg SC Q2W (n=136)**
- **Placebo SC Q2W (n=136)**

**Screening**

6 weeks

**Treatment Period**

104 weeks

**Safety Follow-up**

24 weeks

**Primary Analysis**

UPCR @ Week 40

**Secondary Analysis**

eGFR @ Week 104
BEYOND Key Inclusion Criteria

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Adults with biopsy-proven IgAN within the past 10 years (not due to secondary causes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR</td>
<td>eGFR ≥ 30 ml/min/1.73m$^2$ (CKD-EPI)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Total urine protein ≥ 1.0 g/day and UPCR ≥ 0.7 g/g at screening</td>
</tr>
<tr>
<td>RAS inhibitor</td>
<td>Receiving stable, maximally tolerated ACEi/ARB ≥ 12 weeks prior to screening or intolerant</td>
</tr>
<tr>
<td>Concomitant meds</td>
<td>May be on a stable dose of SGLT2i, mineralocorticoid receptor antagonist, and/or endothelin receptor antagonist ≥ 12 weeks prior to screening</td>
</tr>
<tr>
<td>BEYOND Study Endpoints</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Primary</strong></td>
<td>Change in proteinuria (UPCR from a 24-hour urine collection) from baseline to week 40</td>
</tr>
<tr>
<td><strong>Key secondary</strong></td>
<td>Change in eGFR from baseline to week 104</td>
</tr>
</tbody>
</table>
| **Additional secondary**| Composite clinical outcome, including at least one of the following:  
• 30% or 40% reduction in eGFR  
• eGFR < 15 mL/min/1.73m²  
• Dialysis, kidney transplantation or all-cause mortality |
| **Safety**              | Type, incidence, severity and relatedness of adverse events (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 |
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 key safety measures in adult patients with IgAN at risk of progressive kidney function loss.

For more information, scan QR or visit https://clinicaltrials.gov/ct2/show/NCT05834738