Pharmacodynamic and Clinical Responses to BION-1301 in Patients with IgA Nephropathy: Initial Results of a Phase 1/2 Trial

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Disclosures for Presenting Author

• Current Employer: University of Leicester
• Consultancy: Chinook, EMD Serono, Omeros, Calliditas, Novartis, Retrophin, Visterra, Alnylam, Dimerix, George Clinical, and Astellas
• Research Funding: Novartis, GlaxoSmithKline, Calliditas, Visterra, Chinook, and Retrophin
• Honoraria: AstraZeneca
• Scientific Advisor or Membership: Editorial Board of Kidney International, Clinical Journal of the American Society of Nephrology, and Clinical Science
Mechanism of APRIL and BION-1301 in IgA Nephropathy

**Multi-hit pathogenesis of IgAN, an immune-mediated primary glomerular disease**

1. Excess production of galactose-deficient IgA1 (Gd-IgA1) by IgA-secreting plasma cells is considered the initiating pathogenic event (Hit 1).
2. Immune recognition by anti-Gd-IgA1 autoantibodies (Hit 2) results in the formation of nephritogenic immune complexes (Hit 3) that cause glomerular injury following mesangial deposition (Hit 4).

**A PRoliferation Inducing Ligand (APRIL) is a TNF*-family cytokine involved in B-cell signaling via TACI and BCMA receptor activation**

1. Drives IgA class-switching and survival of IgA-secreting plasma cells.
2. Stimulates Gd-IgA1 secretion.
3. Higher APRIL levels in IgAN patients is correlated with higher Gd-IgA1 and proteinuria and lower eGFR.
4. APRIL gene variants confer increased risk of IgAN.

**BION-1301, a novel humanized monoclonal antibody that binds and blocks APRIL**

- Potentially disease-modifying mechanism to deplete Gd-IgA1 (Hit 1) and prevent pathogenic immune complex formation (Hit 3).

*TNF: tumor necrosis factor


IgAN Phase 1/2 Study Design

Objectives
• Safety, tolerability, PK, biomarker effects and preliminary proteinuria
  – Proof of mechanism
  – Proof of concept
• Explore dose/schedule, intravenous (IV) and subcutaneous (SC) administration

Key Eligibility Criteria
• Biopsy-proven IgAN within past 10 years
• Urine protein ≥ 0.5 g/24h OR UPCR ≥ 0.5 g/g
• eGFR over 45 mL/min per 1.73 m²*
• Stable on an optimized dose of RASi for ≥ 3 months prior to screening (or intolerant to RASi)

Cohort 1
450 mg Q2W IV, up to 52 wks
n=10

Cohort 2
600 mg Q2W SC, up to 52 wks
n=10

Optional Additional Cohorts
SC Dose/Schedule TBD, up to 52 wks

Visit INFO32 for further details about the Phase 1/2 trial

RASi, renin-angiotensin system inhibitors; eGFR, estimated glomerular filtration rate; PK, pharmacokinetics; Q2W, every 2 weeks; UPCR, urine protein/creatinine ratio.

*Or 30 to 45 mL/min/1.73m² if kidney biopsy performed within 2 years prior to Day 1 does not provide evidence of glomerular fibrosis, eGFR determined by CKD-EPI.
Demographics & Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographics (n=10)</th>
<th>Baseline Characteristics</th>
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<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td><strong>Renin-angiotensin system inhibitor use</strong></td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td><strong>Time from biopsy, years</strong></td>
</tr>
<tr>
<td></td>
<td>2.0 (0.2, 3.4)</td>
</tr>
<tr>
<td><strong>Sex, male</strong></td>
<td><strong>Blood pressure (mmHg)</strong></td>
</tr>
<tr>
<td>n (%)</td>
<td>Systolic - Median (min, max)</td>
</tr>
<tr>
<td></td>
<td>127 (113, 133)</td>
</tr>
<tr>
<td>9 (90)</td>
<td>Diastolic - Median (min, max)</td>
</tr>
<tr>
<td></td>
<td>83 (69, 88)</td>
</tr>
<tr>
<td><strong>Race, white</strong></td>
<td><strong>eGFR (mL/min/1.73 m²)</strong></td>
</tr>
<tr>
<td>n (%)</td>
<td>69 (30, 122)</td>
</tr>
<tr>
<td>10 (100)</td>
<td><strong>24-hour urine protein excretion (g/day)</strong></td>
</tr>
<tr>
<td><strong>Ethnicity, Hispanic</strong></td>
<td>Median (min, max)</td>
</tr>
<tr>
<td>n (%)</td>
<td>1.22 (0.74, 6.47)</td>
</tr>
<tr>
<td>2 (20)</td>
<td><strong>24-hour UPCR (g/g)</strong></td>
</tr>
<tr>
<td><strong>Country, US</strong></td>
<td>Median (min, max)</td>
</tr>
<tr>
<td>n (%)</td>
<td>0.64 (0.41, 4.55)</td>
</tr>
<tr>
<td>10 (100)</td>
<td></td>
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</tbody>
</table>

* eGFR by CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration
Safety and Tolerability

• To date, BION-1301 has been well-tolerated in IgAN patients (n=10)

<table>
<thead>
<tr>
<th>AE Category</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any TEAE</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Any TEAE occurring in N&gt;1 subjects</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SAE</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

• Data cutoff: October 6, 2021
  – IgG concentrations remained above study-defined threshold in all patients
  – No notable changes in frequency of circulating naïve and memory B-cell subsets
  – 8/10 patients remain on treatment, with time on treatment ranging from <1 month to >14 months

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Changes in Free APRIL Concentrations

- Rapid and durable reductions in free APRIL confirm effective target neutralization sustained through 1 year.

- BION-1301 pharmacokinetics in patients with IgAN is consistent with previous experience in healthy volunteers.

- No anti-drug antibodies observed in patients with IgAN to date.

Serum Concentration of Free APRIL

- Pre-dose vs. post-dose concentrations over study days.

- Mean ± SEM for each time point is shown.

- Sample sizes (n) are indicated at each time point.
BION-1301 durably reduces IgA, IgM, and to a lesser extent, IgG in patients with IgAN.

BION-1301 produces sustained reductions in serum Gd-IgA1.

- The depletion of this pathogenic IgA isoform (Hit 1) in patients with IgAN demonstrates the potential disease-modifying mechanism of BION-1301.

IgG concentrations remained above the study-defined threshold in all patients, providing a pharmacodynamic window to deplete IgA while minimizing impact on IgG.
**Effects on Proteinuria**

- Median baseline 24-h urine protein excretion*: 1.22 g/day (range: 0.74 - 6.47 g/day)
- BION-1301 treatment results in clinically meaningful proteinuria reductions within 3 months in patients across a range of disease severities

![Graph showing % Reduction in UPCR](image)

**Study Day**

<table>
<thead>
<tr>
<th>Study Day</th>
<th>% Reduction (Geomean ± SEM)</th>
</tr>
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<tbody>
<tr>
<td>29</td>
<td>n=8</td>
</tr>
<tr>
<td>99</td>
<td>n=6</td>
</tr>
<tr>
<td>183</td>
<td>n=4</td>
</tr>
<tr>
<td>351</td>
<td>n=2</td>
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</table>
Conclusions

Interim BION-1301 IgAN patient data:

- Well-tolerated, with no early terminations due to AEs and no SAEs
- No anti-drug antibodies have been observed
- Rapid and sustained free APRIL reductions
- Durable reductions in Gd-IgA1, IgA and IgM, with smaller reductions in IgG
- Clinically meaningful reductions in proteinuria (24-hour UPCR) within 3 months

Next Steps:

- Complete enrollment of patients with IgAN in Cohort 2 utilizing subcutaneous injection of BION-1301

Acknowledgments:

Chinook Therapeutics would like to thank Karen Molyneux, Victoria Cotton, and Nadia Nawaz of University of Leicester for their contributions to the Gd-IgA1 data for this study.