Neutralization of APRIL with BION-1301: A Targeted, Potentially Disease-Modifying Approach to IgA Nephropathy

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• Excess production of galactose-deficient IgA1 (Gd-IgA1) by IgA-secreting plasma cells is considered the initiating pathogenic event (Hit 1) in IgA nephropathy

• A proliferation-inducing ligand (APRIL), a TNF-family cytokine, drives IgA class-switching, survival of IgA-secreting plasma cells and stimulates Gd-IgA1 secretion

• BION-1301, a novel humanized monoclonal antibody, binds and blocks APRIL, and has demonstrated initial validation of this targeted mechanism in patients with IgA nephropathy in a Phase 1/2 clinical study
IgA Nephropathy (IgAN) Overview

A Potentially Progressive, Chronic Glomerular Disease with Limited Treatment Options

Although considered a rare disease, IgAN is the most common primary glomerulonephritis globally.

Approximately 30-45% of IgAN patients will develop end-stage kidney disease (ESKD) over a period of 20-25 years.

Limited treatment options for high-risk patients and currently no targeted disease-modifying therapies are available:
- RAS inhibition (ACEi/ARB) is frontline (KDIGO 1B)
- Steroids & immunosuppressive agents provide inconsistent therapeutic benefit and are accompanied by significant side effects (KDIGO 2B); Tarpeyo (budesonide) recently approved
- DAPA-CKD – suggests benefit of SGLT2i in non-diabetic CKD, including IgAN

Clear need for novel strategies to directly target the initiating molecular events in the complex pathogenesis of IgAN.
Gd-IgA1: The Target Antigen Leading to the Formation of Pathogenic Circulating Immune Complexes

Glomerular Immuno-deposits are Enriched for Aberrantly Glycosylated IgA1 Glycoforms (Gd-IgA1)

Example of a Gal-deficient hinge-region glycopeptide (altered expression and activity of key glycosyltransferases in IgAN)

Gd-IgA1 Depletion Represents a Potentially Disease Modifying Strategy to Treat IgAN
A PRoliferation Inducing Ligand (APRIL)

TNF-superfamily cytokine (TNFSF13) involved in B-cell signaling

**APRIL drives IgA class switching and survival of IgA-secreting plasma cells, via TACI and BCMA**

**Strong genetic and clinical associations for APRIL in IgAN**

- Higher APRIL levels in IgAN patients correlated with higher Gd-IgA1 and proteinuria and lower eGFR
- APRIL gene variants confer increased risk of IgAN
- Shown to increase Gd-IgA1 secretion from IgAN patient lymphocytes

APRIL Action Primarily Targeted to Plasma-blasts/cells

**Preferential impact on IgA vs. IgG secreting cells**

BCMA and TACI Expression Primarily Restricted to Ig Secreting Plasmablasts and Plasma cells

![Cell cycle diagram](image)

Differential Receptor Expression and APRIL Responsiveness: IgA* vs. IgG Secreting Plasma Cells

Modulation of APRIL has the potential to target IgA production while minimizing impact on IgG and immature lymphocyte populations

# Also expressed on memory B cells

* IgM secreting plasmablasts and plasma cells, have similar receptor expression profile and APRIL responsiveness as IgA secreting cells

![Graphs showing IgA and IgG secretion](image)
huAPRIL Transgenic Mice Demonstrate Increased Serum IgA, Kidney IgA Deposits and Increased IgA-Secreting Cells

**Increased Plasma IgA Concentrations**

![Graph showing increased plasma IgA concentrations over age (weeks)]

**Kidney IgA Deposits**

Despite IgA deposition in the kidney huAPRIL Tg mice do not develop an IgAN phenotype *(multi-hit IgAN pathogenesis)*

**Increased Bone Marrow* IgA+ Cells**

![Images showing bone marrow samples: APRIL-Tg vs WT] * Similar phenotype in spleen

The phenotype of huAPRIL Tg mice was reversed by an anti-huAPRIL mAb (IgA & IgM > IgG)
BION-1301: A humanized anti-APRIL mAb
A Potentially Disease-Modifying Approach to Reduce IgA Immune Complex Formation

**BION-1301**: humanized IgG4 monoclonal antibody that blocks APRIL binding to its receptors (BCMA/TACI)

- Potently binds recombinant human and cynomolgus APRIL (but does not bind rodent APRIL)
- Functional blocking of APRIL at BCMA and TACI receptors
- Does not induce cytokine release in human PBMCs

**Therapeutic Hypothesis BION-1301** in IgAN

BION-1301: Well Tolerated in NHPs and Demonstrates Anticipated Pharmacodynamic Response

- BION-1301 was well-tolerated in NHPs when dosed biweekly (IV) up to 100mg/kg for 26 weeks or when dosed weekly (SC) up to 180 mg/kg for 4 weeks with no BION-1301 related tox findings.

- NHP a relevant translational model, due to BION-1301 cross-reactivity
  - Significant APRIL reductions
  - Robust IgA (& IgM) reductions with fairly modest IgG reductions, even at toxicological doses

Modulation of APRIL has the potential to target IgA production while minimizing impact on IgG.
Phase 1 Study in Healthy Volunteers (HVs)

Study Design, Safety and Pharmacokinetics (PK)

**Primary Objective**
- Assess safety and tolerability

**Secondary Objective**
- Characterize PK/PD and immunogenicity of BION-1301 administered by IV infusion

**Exploratory Objectives**
- Characterize select biomarkers of pharmacodynamic activity

- BION-1301 was well-tolerated in HVs; no SAEs, treatment discontinuations or events meeting stopping criteria
- PK of BION-1301 was well behaved, generally dose-proportional, $T\frac{1}{2} \approx 33$ days; low incidence of non-neutralizing ADAs (no difference in incidence of ADA between placebo and BION-1301 group)
Phase 1 Study in Healthy Volunteers (HVs)

Pharmacodynamic Biomarker Responses (MAD)

- Immediate, dose-dependent and sustained neutralization of APRIL
- Dose-dependent and durable reductions in IgA & IgM, with lesser effects on IgG (remaining in normal range)
- Offers a pharmacodynamic window to exploit IgA reduction while minimizing impact on IgG

**Free APRIL**

**IgA**

**IgG**

**IgM**
Phase 1 Subcutaneous Bioavailability Study in HVs: Supports Transition to SC Administration of BION-1301

A Phase 1, Open Label, Randomized, Single Dose, Parallel Group Safety and Bioavailability Study of BION-1301 Administered by Intravenous (IV) and Subcutaneous (SC) Routes

- BION-1301 was well tolerated:
  - No SAES or early terminations due to a TRAE
  - No ISRs or IRRs
  - No ADAs in the SC cohort

The PK profile of BION-1301 was consistent with previous clinical studies and minimal differences in drug concentration were observed between administration routes after 1 week

Figure 4: Mean (±SD) Serum Concentrations of BION-1301 in Healthy Volunteers After Single-Dose IV or SC Administration

Comparative reductions in serum fAPRIL

Figure 5: Mean (±SD) fAPRIL Concentrations After Single-Dose IV or SC Administration

A single 300mg SC or IV dose of BION-1301 provides similar reductions in immunoglobulins

Figure 7. Mean % Change ± SD (Relative to Baseline) in Serum Immunoglobulin Levels Over Time (Days)
Phase 1/2 Study in Patients with IgAN

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)

Open-label, multicenter, multiple-dose study in patients with IgAN

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
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<tbody>
<tr>
<td>450 mg IV Q2W n=10</td>
<td>600 mg SC Q2W</td>
<td>Optional TBD SC</td>
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Screening
Up to 6W
Treatment
52W
Follow Up
24W

Completed
enrollment
Currently
enrolling
TBD

Up to n=30 total

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

### Demographics (n=10)

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>Median (27, 59)</td>
</tr>
<tr>
<td>Renin-angiotensin system inhibitor use</td>
<td>100 %</td>
</tr>
<tr>
<td>Sex, male</td>
<td>9 (90)</td>
</tr>
<tr>
<td>Race, white</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Ethnicity, Hispanic</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Country, US</td>
<td>10 (100)</td>
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### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Renin-angiotensin system inhibitor use</td>
<td>100 %</td>
</tr>
<tr>
<td>Time from biopsy, years</td>
<td>2.0 (0.2, 3.4)</td>
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<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
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<tr>
<td>Systolic</td>
<td>127 (113, 133)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83 (69, 88)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)*</td>
<td>69 (30, 122)</td>
</tr>
<tr>
<td>24-hour urine protein excretion (g/day)</td>
<td>1.22 (0.74, 6.47)</td>
</tr>
<tr>
<td>24-hour UPCR (g/g)</td>
<td>0.64 (0.41, 4.55)</td>
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* 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>
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<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>
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• 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
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 (ADAs) observed in patients with IgAN to date

Serum Concentration of Free APRIL

![Graph showing changes in free APRIL concentrations over study days.](chart.png)
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

Summary

- **A P**roliferation Inducing **L**igand (**APRIL**), a TNF-family cytokine, drives IgA class-switching, survival of IgA-secreting plasma cells and stimulates Gd-IgA1 secretion (**Hit 1**)
- **BION-1301**, a novel humanized monoclonal antibody, binds and blocks APRIL, and has demonstrated initial validation of this **targeted mechanism** in patients with IgAN in a Phase 1/2 clinical study
  - **Well-tolerated**, with no early terminations due to AEs and no SAEs
  - 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

These data provide early proof-of-concept for the disease-modifying potential of BION-1301 to deplete pathogenic Gd-IgA1 and reduce proteinuria in patients with IgAN who remain at risk for progression with residual proteinuria despite optimized standard-of-care treatment.