Accelerating the Development of BION-1301 for the Treatment of IgAN

From Proof of Concept to Phase 3

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Chief Scientific Officer
March 9, 2023
The potentially disease modifying MOA of BION-1301* in IgAN

BION-1301 clinical development program to IgAN PoC

BION-1301 Phase 3 key trial design elements

*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 the use(s) under investigation.
**IgA NEPHROPATHY HAS A LARGE UNMET MEDICAL NEED**

IgAN is the most common primary glomerular disease globally and requires chronic treatment

~150,000 Biopsy-confirmed IgAN patients in the U.S.\(^1\)

~45% with >1 g/day\(^1\)

~25% with 0.5 – 1 g/day\(^1\)

Patients with persistent proteinuria despite optimized standard of care RAS inhibition (ACEi or ARB)

~100,000 Patients remain at high risk for progression (US)

Clear need for novel strategies to directly target the initiating molecular events in the complex pathogenesis of IgAN

~30-45% of IgAN patients progress to ESKD over 20-25 years\(^3-6\)

**ACHIEVING**

30% PROTEINURIA REDUCTION

**EQUATES TO**

>10 YEAR DELAY IN TIME TO ESKD\(^2\)

Greater proteinuria reductions are associated with greater clinical benefit
Complex Multi-Hit Pathogenesis of IgAN Provides Potential for Targeted Therapeutic Strategies

Mucosal Infection in Individuals with Genetic Predisposition to IgAN

- Bacteria
- Virus

Intestines

- Tonsils
- B Cell

TLR

Dysregulated Mucosal/Innate Immune Response (TLRs/APRIL)

IgA Nephropathy Disease Pathophysiology

**Hit 1**
Elevated Gd-IgA1

**Hit 2**
Anti-Gd-IgA1 autoantibodies

**Hit 3**
Increased circulating Gd-IgA1 immune complexes

**Hit 4**
Immune complexes deposit in the mesangium, causing:
- Mesangial cell activation (cellular proliferation and excess secretion of extracellular matrix and cytokines)
- Cellular cross-talk resulting in podocyte dysfunction and proteinuria
- Ultimately tubular epithelial cell injury (atrophy, inflammation and fibrosis)

IgA-secreting plasma cell

IgG-secreting plasma cell

APRIL

BCMA & TACI Receptors

IgA

Gd-IgA1

Anti-Gd-IgA1

Gd-IgA1 Immune Complexes

Podocyte

Proteins

Extracellular Matrix

Immune Cells
Complex Multi-Hit Pathogenesis of IgAN Provides Potential for Targeted Therapeutic Strategies

Mucosal Infection in Individuals with Genetic Predisposition to IgAN

- Bacteria
- Virus
- Tonsils
- Intestines
- TLR
- Dysregulated Mucosal/Innate Immune Response (TLRs/APRIL)

IgA Nephropathy Disease Pathophysiology

- IgA-secreting plasma cells
- IgG-secreting plasma cell
- APRIL
- BCMA & TACI Receptors
- IgA
- Gd-IgA1
- Anti-Gd-IgA1
- Gd-IgA1 Immune Complexes
- Podocyte
- Proteins
- Extracellular Matrix
- Immune Cells

BION-1301

Hit 1
Elevated Gd-IgA1

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Anti-Gd-IgA1 autoantibodies

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Increased circulating Gd-IgA1 immune complexes

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Immune complexes deposit in the mesangium, causing:
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Atrasentan
BION-1301: Potentially Disease-Modifying Anti-APRIL mAb in IgAN

**APRIL**

- TNF-family cytokine involved in B-cell signaling
  - Drives IgA production and survival of IgA-secreting plasma cells
  - Shown to increase Gd-IgA1 secretion
  - Higher APRIL levels in IgAN patients correlated with higher Gd-IgA1 and proteinuria and lower eGFR
  - APRIL gene variants confer increased risk of IgAN

**BION-1301** Humanized IgG4 monoclonal antibody that blocks APRIL binding to its receptors

- 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

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**BION-1301 Development Program: HV, POM and POC in IgAN**

**ADU-CL-19**  
**Phase 1/2: HV & IgAN Patients**

- **Part 1:** Single Ascending Dose, Healthy Volunteers
- **Part 2:** Multiple Ascending Dose, Healthy Volunteers
- **Part 3:** Proof of Mechanism / Proof of Concept, IgAN Patients

**Other**  
**Additional HV Studies**

- **SC Bioavailability:** Single Dose IV/SC, Healthy Volunteers
- **Japanese HV:** Single Ascending Dose, Healthy Volunteers (in progress)
- **Chinese HV:** Single Ascending Dose, Healthy Volunteers (planned)
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 (PD) 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, T½ ~ 33 days; low incidence of non-neutralizing ADAs
Phase 1 Study in Healthy Volunteers (HVs): Target Engagement

Immediate, dose-dependent and sustained neutralization of APRIL
Phase 1 Study in Healthy Volunteers (HVs): PD Responses

- Dose-dependent and durable reductions in IgA & IgM, with lesser effects on IgG
- Offers a pharmacodynamic window to exploit IgA reduction while minimizing impact on IgG
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 generally well tolerated:
  - No SAES or early terminations
  - No ISRs
  - 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.

Comparable reductions in serum fAPRIL

A single 300mg SC or IV dose of BION-1301 provides similar reductions in immunoglobulins
ADU-CL-19 (Part 3) is an ongoing phase 1/2 trial investigating BION-1301 in patients with IgAN (NCT03945318)

**Objectives**
- Safety, tolerability, PK, immunogenicity, biomarker effects, and preliminary effect on proteinuria in patients with IgAN
- Proof of mechanism
- Proof of concept
- Explore dose/schedule, IV and SC administration

**Key Eligibility Criteria, Cohort 2**
- Biopsy-proven IgAN diagnosis within past 10 years
- Total protein excretion ≥ 0.5 g/24h OR UPCR ≥ 0.5 g/g based on 24-hour urine collection at screening
- eGFR ≥ 30 mL/min per 1.73 m²
- Stable/optimized dose of RASi for ≥ 3 months prior to screening (or intolerant to RASi)

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Cohort 1 (n=10)

- 450 mg Q2W IV → 600 mg Q2W SC, up to 104 weeks
- Ongoing

Cohort 2 (n=30)

- 600 mg Q2W de novo SC, up to 104 weeks
- Ongoing

† Patients transitioned to SC at ≥24 weeks

|| An optional 1-year treatment extension is available to both cohorts
### Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Cohort 1 (n=10\ **) 450 mg IV → 600 mg SC</th>
<th>Cohort 2 (n=24) 600 mg de novo SC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean (min, max)</strong></td>
<td>42 (27, 59)</td>
<td>40 (21, 74)</td>
</tr>
<tr>
<td><strong>Sex, male, n (%)</strong></td>
<td>9 (90)</td>
<td>15 (63)</td>
</tr>
<tr>
<td><strong>Race, White, n (%)</strong></td>
<td>10 (100)</td>
<td>11 (46)</td>
</tr>
<tr>
<td><strong>Asian, n (%)</strong></td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>Black, n (%)</strong></td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>Missing, n (%)</strong></td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>Ethnicity, Hispanic, n (%)</strong></td>
<td>2 (20)</td>
<td>2 (8)</td>
</tr>
<tr>
<td><strong>Country, US, n (%)</strong></td>
<td>10 (100)</td>
<td>16 (67)</td>
</tr>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td><strong>Median (min, max)</strong></td>
<td><strong>Median (min, max)</strong></td>
</tr>
<tr>
<td>Time from biopsy, years</td>
<td>2.1 (0.3, 7.7)</td>
<td>3.3 (0.1, 7.6)</td>
</tr>
<tr>
<td>Blood pressure (mmHg), Systolic</td>
<td>127 (113, 133)</td>
<td>127 (110, 147)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83 (69, 88)</td>
<td>79 (57, 88)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m$^2$)[6]</td>
<td>69 (30, 122)</td>
<td>75 (37, 131)</td>
</tr>
<tr>
<td>24-hour urine protein excretion (g/day)</td>
<td>1.2 (0.7, 6.5)</td>
<td>1.0 (0.6, 2.7)</td>
</tr>
<tr>
<td>24-hour UPCR (g/g)</td>
<td>0.5 (0.4, 4.6)</td>
<td>0.8 (0.2, 3.2)</td>
</tr>
<tr>
<td>Renin-angiotensin system inhibitor use (%)</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*\[6\] eGFR by CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration

**Two patients withdrew from study for reasons unrelated to study drug

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**Cohort 1 enrollment and treatment duration:**
- 10 patients enrolled; 8 patients continued to SC
- Mean treatment duration of 64 weeks (range 0.1 to 106 weeks)
  - Mean treatment duration of 450 mg IV prior to transition to SC was 37 weeks
  - Mean treatment duration after transition to 600 mg SC was 40 weeks

**Cohort 2 enrollment and treatment duration:**
- 24 patients enrolled (enrolling up to 30 patients)
- Mean treatment duration of 17 weeks (range 2 to 30 weeks)
Safety and Tolerability

In Cohort 1 and Cohort 2:

- BION-1301 is generally well tolerated in IgAN patients, with no reported deaths, SAEs, or AEs leading to discontinuation of study drug to date.
- All infections in patients with IgAN have been Grade 1 or 2 in severity and only one infection, which was Grade 1 in severity, was assessed as treatment-related.
- Injection site reactions have all been Grade 1 or Grade 2 in severity.
- IgG level below the study defined threshold (< 3 g/L) occurred in one patient in Cohort 1, requiring protocol-mandated withholding of study drug. There have been no infections reported in this patient.

<table>
<thead>
<tr>
<th>AE Category (N=34)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment emergent AEs (TEAEs)</td>
<td></td>
</tr>
<tr>
<td>Patients with any TEAE</td>
<td>23 (67.6)</td>
</tr>
<tr>
<td>Patients with Infection TEAE (Grades 1 or 2)</td>
<td>17 (50.0)</td>
</tr>
<tr>
<td>Infection TEAE occurring in N&gt;1 patient</td>
<td></td>
</tr>
<tr>
<td>COVID-19</td>
<td>8 (23.5)</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Asymptomatic COVID-19</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td></td>
</tr>
<tr>
<td>Patients with any treatment-related AE</td>
<td>8 (23.5)</td>
</tr>
<tr>
<td>Related AEs occurring in N&gt;1 patient</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>3 (8.8)</td>
</tr>
</tbody>
</table>
Pharmacokinetics

- Low inter-individual variability in BION-1301 serum concentrations following IV and SC administrations

- Trough concentrations of BION-1301 following 600 mg SC Q2W (Cohort 2) are consistent with trough concentrations observed following 450 mg IV Q2W (Cohort 1)

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

Mean (± SD) BION-1301 serum concentrations following IV (Cohort 1) or SC (Cohort 2) administration Q2W†. Data points after Day 7 are trough concentrations.

Data cut-off Sep 30, 2022
BION-1301 Results in Rapid and Durable Reduction in IgA and Gd-IgA1

IgA % Change from Baseline (Mean ± SE)

Data cut-off Oct. 13, 2022

<table>
<thead>
<tr>
<th>Wk</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
<th>40</th>
<th>52</th>
<th>64</th>
<th>76</th>
<th>88</th>
<th>100</th>
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</thead>
<tbody>
<tr>
<td>Co 1, n=</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>5</td>
<td>6</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Co 2, n=</td>
<td>2318151010</td>
<td>9</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Gd-IgA1 % Change from Baseline (Mean ± SE)

Data cut-off Aug. 31, 2022

<table>
<thead>
<tr>
<th>Wk</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
<th>40</th>
<th>52</th>
<th>64</th>
<th>76</th>
<th>88</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co 1, n=</td>
<td>8</td>
<td>0</td>
<td>8</td>
<td>8</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Co 2, n=</td>
<td>2013</td>
<td>910</td>
<td>8</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Mean Gd-IgA1 are not available at week 100
Reductions in IgM, and to a Lesser Extent IgG, Were Also Observed

**IgM % Change from Baseline (Mean ± SE)**

<table>
<thead>
<tr>
<th>Wk</th>
<th>Co 1, n=</th>
<th>Co 2, n=</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>8 8 8 8 2 5 6 8 7 7</td>
<td>2318151010 9 3</td>
</tr>
<tr>
<td>8</td>
<td>40 52 64 76 88 100</td>
<td></td>
</tr>
</tbody>
</table>

**IgG % Change from Baseline (Mean ± SE)**

<table>
<thead>
<tr>
<th>Wk</th>
<th>Co 1, n=</th>
<th>Co 2, n=</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>8 8 8 8 2 5 6 8 7 7</td>
<td>2318151010 9 3</td>
</tr>
<tr>
<td>8</td>
<td>40 52 64 76 88 100</td>
<td></td>
</tr>
</tbody>
</table>

Mean IgM are not available at week 100
BION-1301 Treatment Results in Sustained, Clinically Meaningful Proteinuria Reductions

COHORT 1 (IV → SC)
- Clinically meaningful reductions in UPCR were seen in patients with IgAN across a wide range of baseline proteinuria levels
- UPCR continued to decline through one year and was maintained through two years, providing evidence of sustained efficacy
- At Week 52, 7/8 evaluable patients demonstrated >50% reductions in UPCR

COHORT 2 (de novo SC)
- Mean reduction in UPCR of >50% at 24 weeks in Cohort 2 with de novo SC administration is consistent with Cohort 1

UPCR % Reduction (Geometric Mean ± SE)

Data cut-off Oct. 13, 2022

-30.4% -48.8% -66.9% -67.4% -71.0%

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Wk 4 12 24 52 76 100

Cohort 1 n= 8 7 8 8 4 2
Cohort 2 n= 23 15 9

Median (range) baseline protein excretion: Cohort 1, 1.2 (0.7, 6.5) g/day ; Cohort 2, 1.0 (0.6, 2.7) g/day
BION-1301 MOVING FORWARD

Plan to advance cohort 2 dose/schedule in pivotal trial, given strong clinical data

STATUS

Cohort 1 in IgAN
- 450 mg IV → 600 mg SC q2w
- Enrollment of 10 Patients Completed

Cohort 2 in IgAN
- 600 mg SC q2w
- Enrollment of 30 Patients Completed

NEXT STEPS

- Align with global health authorities (ongoing)
- Conduct site and country feasibility (ongoing)
- Initiate pivotal trial in mid-2023
Leveraging Population PK/PD Modeling and Simulations to Support Phase 3

**PopPK/PD Model Framework and Modules**

- Preliminary IV PopPK Model
- HV IV
- Final IV + CC PopPK model
- IgAN

**Simulations**

- Test Patient Status on IV PopPK model
- IgAN
- IV + SC PoPK
- HV SC
- DOSE
  - Concentration
  - Time
  - PK
  - PD
  - Efficacy (IgA)
  - Safety (IgG)
  - Exposure Variability
  - Response Variability

**Phase 3 Dose and Schedule**

- Virtual Patient Populations
- Simulations of 1000 Subjects

**Target optimal IgA reduction for max UPCR effect**
BION-1301 600 mg SC Q2W: Simulations

600 mg SC Q2W provides broad coverage IgA > EC\textsubscript{95} accounting for simulated PK variability
Simulations support Phase 3 dose selection to optimize IgA reduction accompanied by only modest IgG reductions and support I/E criteria as an added safety measure.
A Phase 3, Randomized, Double-blind, Placebo-controlled Study of BION-1301 in Adults with IgAN

Phase 3 Targeting IgAN Patients at Risk for Disease Progression

Key Inclusion Criteria
- Biopsy-proven IgAN
- Patients on maximally-tolerated, optimized and stable dose of RASi (≥12w), or RASi intolerant
- Background optimized and stable dose (≥12w), of SGLT2i or ERA (if approved) allowed
- Proteinuria >1 g/day; eGFR >30 ml/min/1.73m²

Key Exclusion Criteria
- Secondary IgAN, IgA vasculitis, other CKD, RPGN
- Recent immunosuppressant use, immune-deficient state, current severe infection, IgG < 6g/L

Exploratory cohort eGFR 20 to < 30 mL/min/1.73m² (n=20)

Stratification Factors
- Proteinuria (≥ 2 g/day vs. < 2 g/day), eGFR (≤ 45 v > 45 mL/min , Region (Asia v ROW))

Primary Endpoint
UPCR @ 9 mos (40wks), n= 204

Key Secondary Endpoint
eGFR (change from baseline) @ 2 yrs (104 wks), n=272

Additional Secondary Endpoints
Composite 30% or 40% reduction in eGFR, eGFR < 15 mL, dialysis, kidney transplantation or all-cause mortality
Percent of subjects achieving a ≥ 25% reduction of UPCR to < 1.0 g/day at week 40

Safety Endpoints
Type, incidence and severity of AEs and AESIs

Exploratory Endpoints
Characterize PK, exposure response, immunogenicity, QOL, MOA
Summary: BION-1301 From Proof of Concept to Phase 3

**Disease Modifying Potential of APRIL Neutralization in IgAN**

- APRIL is a cytokine that drives IgA class switching, survival of IgA-secreting plasma cells and the excess secretion of GdIgA1
  - Potential for APRIL blockade to directly target the events initiating IgAN and prevent immune complex formation

**Proof-of-concept for BION-1301 in IgAN to:**

- deplete pathogenic Gd-IgA1 in patients with IgAN
- reduce proteinuria in patients with IgAN who remain at risk for progression with residual proteinuria despite optimized standard-of-care treatment

**Efficient advancement of BION-1301 from POC to Phase 3 enabled by:**

- biomarker rich Phase 1 HV SAD/MAD study enabling PopPK/PD modelling and simulations to support Phase 3 dose selection
- open label Phase 1/2 POC study in IgAN allowing interim data cuts with disease specific biomarkers assessments and demonstration of clinically meaningful reduction in proteinuria