BION-1301 Blocks APRIL, a Critical Factor Driving the Etiology/Pathophysiology of IgAN

**Background**

- **IgG-reliant IgA** (a leading cause of primary glomerulonephritis), is an autoimmune disease with no approved treatments.
- A critical step in IgG-reliant IgA pathogenesis is the development of anti-IgG1 autoantibodies and immune complex formation that result in a kidney damage. A polyclonal, IgG-reliant APRIL, promotes IgG class-switching and survival of IgG-producing plasma cells.2 In a study of patients with IgAN, those with high plasma APRIL levels had higher Gd-IgA1 and proteinuria and lower estimated glomerular filtration rates than those with lower plasma APRIL levels.2 In another study of patients with IgAN, APRIL targeted APRIL reduced serum IgG, IgA, and IgM levels without disrupting the normal IgM profile and did not develop antibodies to the drug.3 With no dose-limiting toxicities in a Phase 1/2 first-in-human study in multiple myeloma3, here we present healthy volunteer data from an ongoing three-part Phase 1 trial to characterize the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of BION-1301 in healthy volunteers (HV) and patients with IgAN.

**Study Design and Objectives**

**ADU-CL-19 is a Phase 1 Multicenter Trial to Evaluate the Safety, Tolerability, PK, and PD of IV Administered BION-1301. The Study Will Be Conducted in HVs (Parts 1, 2) and in Adults With IgA Nephropathy (Part 3).**

- **PK** studies of BION-1301 blocks APRIL.
- **PD** analysis of IgA-reliant IgAN.
- **Safety** and tolerability
- **Characterize effects** of BION-1301 on APRIL levels in normal and IgAN plasma.
- **Characterize select biomarkers of activity**
- **Analyze biomarkers** for IgA:nephropathy in patients with IgAN

**Methodology**

- **PK** analysis performed on serum concentration data using non-compartmental analysis and non-compartmental analysis with Phoenix® WinNonlin® Version 8.1.
- **Safety** data collected from subjects who were below the lower limit of quantification (LLQ) were reported as 0.1 pg/mL and were not included in the PK analysis.
- **Levels of BION-1301** in serum were quantitated using ELISA-based immunoassays using a microplate reader.
- **Immunogenicity** was assessed from serum samples for presence of antibodies against BION-1301 (anti-BION-1301) under GLP.
- **Levels of serum IgA, IgG, and IgM** were measured using an immunoneutralization assay on the Roche Cobas TD 700 analyzer.
- **Levels of APRIL** and IgG, IgA, and IgM were measured using an immunoneutralization assay on the Roche Cobas TD 700 analyzer.

**Baseline Demographics**

| Age (y) | Mean (SD) | Median | Minimum | Maximum | F: M | Male | Female | African American | Asian | Caucasian | Hispanic | Other | Multiple | Other
|---------|-----------|--------|---------|---------|------|------|--------|-----------------|-------|-----------|----------|-------|----------|-------
| 18-21   | 20.6 (2.4) | 20.0   | 18.0    | 21.0    | 0    | 0    | 0      | 0               | 0     | 0         | 0        | 0     | 0        | 0     |
| 22-40   | 29.4 (3.8) | 28.8   | 25.0    | 40.0    | 1    | 0    | 0      | 0               | 0     | 0         | 0        | 0     | 0        | 0     |
| 41-60   | 54.3 (5.0) | 54.0   | 45.0    | 65.0    | 0    | 0    | 0      | 0               | 0     | 0         | 0        | 0     | 0        | 0     |
| 61+     | 70.9 (6.6) | 70.8   | 61.0    | 82.0    | 0    | 0    | 0      | 0               | 0     | 0         | 0        | 0     | 0        | 0     |

**Active Treatment (n=36)**

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**BION-1301 Dose-Dependent and Durability Reduces IgA and IgM, and to a Lesser Extent IgG Data Consistent With Potential for Monthly Dosing**

- **Mean Serum BION-1301 Concentration is Generally Dose-Proportional but Moderately Greater than the Proportionality at Higher Doses**
- **BION-1301 Demonstrates Durable Dose-Dependent Increase in Target Engagement as Measured by Free APRIL (RAPRIL)**
- **BION-1301 Is Well-Tolerated in Healthy Volunteers**
- Although IgA, IgM, and to a Lesser Extent IgG are Durably Reduced, IgG Values Remain in the Normal Range

**CONCLUSIONS**

- **BION-1301** was well-tolerated in healthy volunteers with no evidence of non-neutrophilic AEs reported.
- **The PK/Immunogenicity of BION-1301** was well-balanced, generally dose-proportional and demonstrated a half-life with the potential to be administered by monthly dosing.
- **BION-1301** demonstrates a durable dose-dependent increase in target engagement as measured by RAPRIL.
- **BION-1301** dosedependently and durably reduces IgA and IgM to a lesser extent IgG, however, IgG values remain in the normal range.
- **BION-1301**-induced suppression of immunoglobulins offers a pharmacodynamic window to exploit IgA reduction while minimizing impact on IgG.

**Next Steps**

- Complete analysis of exploratory biomarkers (e.g. IgG4-IgA) from Parts 1 and 2.
- Evaluate impact of BION-1301 on IgAN patients in Part 3 (NCT03945318) and the long-term impact of BION-1301 administration in an Open-Label Extension study for these patients.
- Continue development of BION-1301 by determining SC immunogenicity.

**References**


**Click Here to See Other Poster PDFS summarizing or non-digital with data BION-1301**

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