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

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Background and Aims

IgA nephropathy (IgAN) is an autoimmune disease with limited treatment options, especially for high-risk patients.[1] A critical step in IgAN pathogenesis is the production of galactose-deficient IgA1 (Gd-IgA1) leading to the generation of anti-Gd-IgA1 autoantibodies and the formation of immune complexes that result in kidney inflammation and damage.[2] A Proliferation-Inducing Ligand (APRIL), a soluble factor that regulates B cell differentiation, proliferation and survival of plasma cells, and IgA class-switching is elevated in patients with IgAN. IgAN patients with high plasma APRIL levels are reported as having higher levels of Gd-IgA1 and proteinuria and lower estimated glomerular filtration rates compared to those with lower plasma APRIL levels.[3,4] BION-1301 is a novel humanized blocking antibody targeting APRIL that has been evaluated in a Phase 1 study of healthy volunteers (HV). In that study, BION-1301 was well-tolerated with no serious adverse events (SAEs), a pharmacokinetic (PK) half life >30 days and demonstrated dose-dependent pharmacodynamic (PD) effects characterized by durable reductions in serum levels of free April (fAPRIL), IgA and Gd-IgA1, IgM, and to a lesser extent IgG.[5] Here we present interim results from Part 3 of the Phase 1 and the Phase 2 Open-Label Extension (OLE) trials that characterize the safety, PK and PD profile, and preliminary efficacy of BION-1301 in patients with IgAN. Data from this cohort was initially presented at the ASN Kidney Week 2021 Congress.[6]

Introduction

Mechanism of APRIL and BION-1301 in IgA Nephropathy

Multi-hit pathogenesis of IgAN, an immune-mediated primary glomerular disease[1-3]

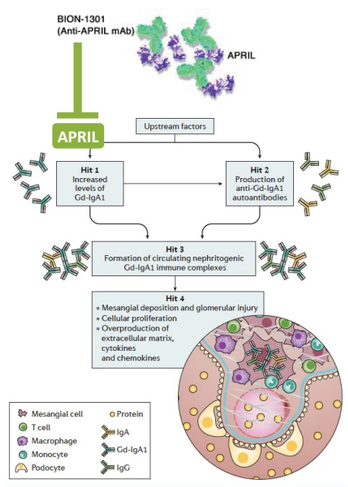
- Excess production of galactose-deficient IgA1 (**Gd-IgA1**) by IgA-secreting plasma cells is considered the initiating pathogenic event (**Hit 1**)
- Immune recognition by anti-Gd-IgA1 autoantibodies (**Hit 2**) results in the formation of nephritogenic immune complexes (**Hit 3**) that cause glomerular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

- Drives **IgA class-switching** and **survival of IgA-secreting plasma cells**
- Stimulates **Gd-IgA1** secretion
- **Higher APRIL** levels in IgAN patients is correlated with higher Gd-IgA1 and proteinuria and lower eGFR
- 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**)



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*TNF: tumor necrosis factor

Methods

The Phase 1 study (NCT03945318) comprises 3 parts. Parts 1 and 2 assessed single- and multiple ascending doses of BION-1301 in HV. Part 3 is an ongoing, open-label design in approximately 40 IgAN patients. Cohort 1 enrolled 10 patients to receive BION-1301 at 450mg once every 2 weeks for up to 52 weeks intravenously. Patients in Cohort 1 will transition from IV to receive 600 mg of BION-1301 SC biweekly after completing at least 24 weeks of IV dosing. Cohort 2 is currently enrolling patients to receive BION-1301 at 600mg once every 2 weeks for up to 52 weeks via subcutaneous administration. Key eligibility criteria for Part 3 include: (1) biopsy-verified diagnosis of IgAN within the past 10 years,(2) urine protein excretion ≥0.5 g/24h or baseline UPCR ≥0.5 g/g, and (3) stable/optimized dose of ACE-I/ARB (or intolerant). To evaluate PK and PD effects of BION-1301, serum levels of BION-1301, fAPRIL, antidrug antibodies (ADA), neutralizing antibodies (NAbs), and Gd-IgA1 were quantitated using ELISA-based immunoassays. Serum levels of IgA, IgG, and IgM were measured by immunoturbidimetry. UPCR was assessed from 24-hour urine collections.

IgAN Phase 1/2 Part 3 Study Design

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

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

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

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 excretion ≥ 0.5 g/24h OR UPCR ≥ 0.5 g/g
- eGFR over 45 mL/min per 1.73 m^2*
- Stable on an optimized dose of RASi for ≥ 3 months prior to screening (or intolerant to RASi)

RASi, renin-angiotensin system inhibitors; eGFR, estimated glomerular filtration rate; PK, pharmacokinetics; Q2W, every 2 weeks; UPCR, urine protein/creatinine ratio. Visit Abstract # WCN22-0483 for further details about the Phase 1/2 trial.
*Or 30 to 45 mL/min/1.73m^2 if kidney biopsy performed within 2 years prior to Day 1 does not provide evidence of glomerular fibrosis, eGFR determined by CKD-EPI.

Results

BION-1301 has been well tolerated in IgAN patients receiving a 450mg IV dose every two weeks for 12+ weeks with no SAEs or treatment related AE's. Consistent with PD responses previously reported in HVs, durable reductions in serum levels of fAPRIL and immunoglobulins were observed in IgAN patients. Clinically meaningful reductions in proteinuria were seen as early as 12 weeks and were associated with the reduction in Gd-IgA1 levels.

Demographics & Baseline Characteristics

Demographics (n=10)	
Age, years Median (min, max)	39 (27, 59)
Sex, male n (%)	9 (90)
Race, white n (%)	10 (100)
Ethnicity, Hispanic n (%)	2 (20)
Country, US n (%)	10 (100)

Baseline Characteristics	
Renin-angiotensin system inhibitor use %	100
Time from biopsy, years Median (min, max)	2.0 (0.2, 3.4)
Blood pressure (mmHg) Systolic - Median (min, max) Diastolic - Median (min, max)	127 (113, 133) 83 (69, 88)
eGFR (mL/min/1.73 m^2)* Median (min, max)	69 (30, 122)
24-hour urine protein excretion (g/day) Median (min, max)	1.22 (0.74, 6.47)
24-hour UPCR (g/g) Median (min, max)	0.64 (0.41, 4.55)

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

Results (continued)

Safety and Tolerability

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

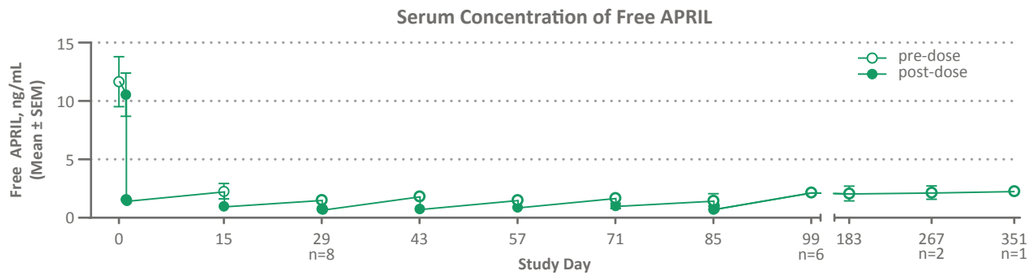
AE Category	n (%)
Subjects with any TEAE	5 (50)
Any TEAE occurring in N>1 subjects	0 (0)
Treatment-related AE	0 (0)
AE leading to discontinuation	0 (0)
SAE	0 (0)
Infusion-related reactions	0 (0)

- 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.

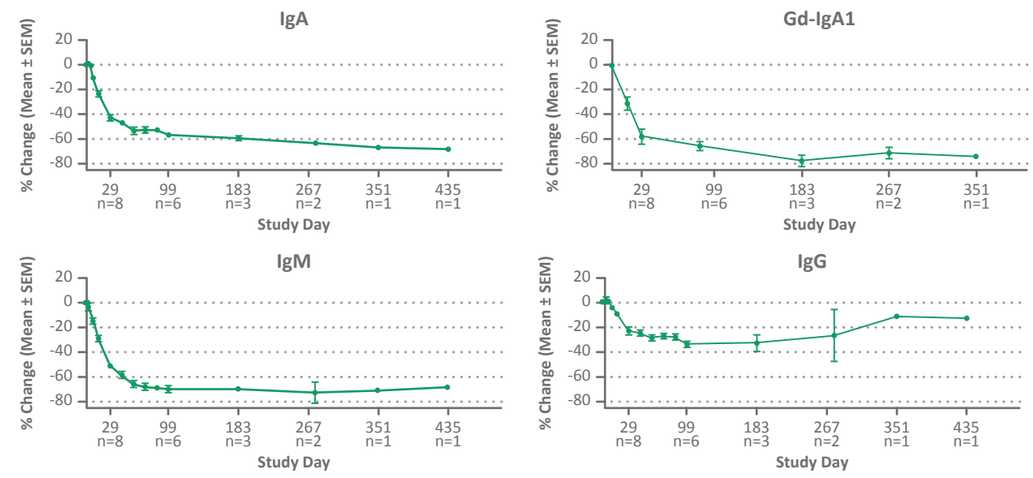
Changes in Free APRIL Concentrations

- 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



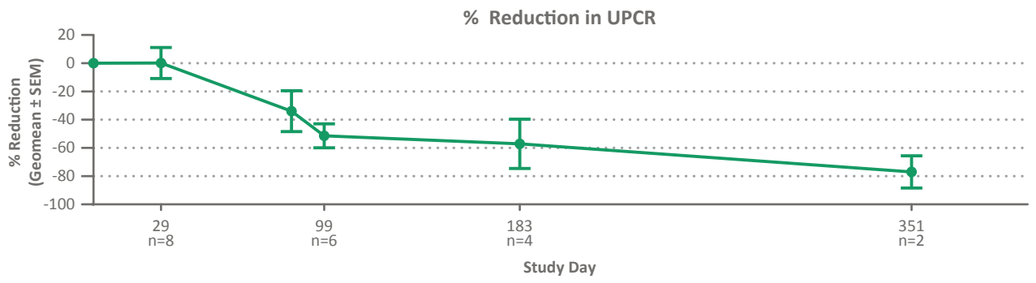
Changes in Serum Ig Concentrations from Baseline

- 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



*1/10 patients missed 24-hour collection; morning void used.

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

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

Next Steps:

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

Disclosures for Presenting Author

- Current Employer: University of Leicester
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