Poster #P0500

Results of a Phase 1 Trial to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BION-1301 in Healthy Volunteers

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Background

IgA nephropathy (IgAN), the leading cause of primary glomerulonephritis, is an autoimmune disease with no approved treatments.[1] A critical step in IgAN pathogenesis is the production of galactose-deficient IgA1 (Gd-IgA1) leading to the generation of anti-Gd-IgA autoantibodies and immune complex formation that result in kidney damage.[2] A proliferation-inducing ligand (APRIL) promotes IgA class-switching and survival of IgA producing plasma cells.[3] 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.[4] BION-1301, a first-in-class humanized antagonistic antibody targeting APRIL, reduced serum IgA, IgM, and IgG levels without drug-related toxicity in nonhuman primates[5] and was well-tolerated with no dose-limiting toxicities in a Phase 1/2 first-in-human study in multiple myeloma[6]. 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.

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

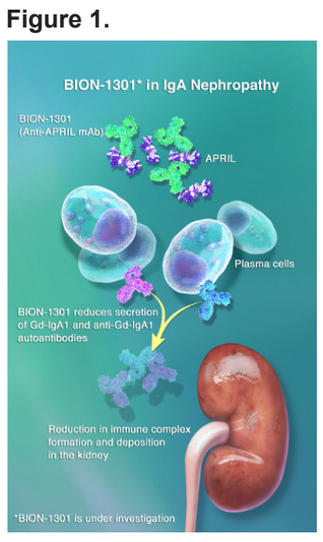
BION-1301-APRIL blockade in IgA Nephropathy

- First-in-class monoclonal antibody that blocks APRIL binding to B-cell maturation antigen (BCMA) and transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI)
- Recombinant, humanized IgG4 monoclonal antibody (mAb)
- Has been evaluated in 2 clinical studies to date *(NCT03340883, NCT03945318)*

APRIL: A PRoliferation **I**nducing **L**igand

- TNF-family ligand implicated in regulation of B-cell mediated immune responses[7]
- Soluble factor that binds to its receptors TACI and BCMA inducing B cell signaling that drives:
  - IgA class switching through TACI[7]
  - Differentiation and survival of IgA-producing plasma cells through BCMA[7]
- Patients with IgAN have higher levels of APRIL compared to healthy controls[8]
- Higher APRIL levels in IgAN patients correlate with poor prognosis[8]
- A polymorphism in the APRIL gene confers IgAN susceptibility[9]

Figure 1.



Blocking APRIL is a novel approach to address underlying pathology by reducing circulating levels of IgA, Gd-IgA1, anti-Gd-IgA1 autoantibodies and immune complex formation

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)

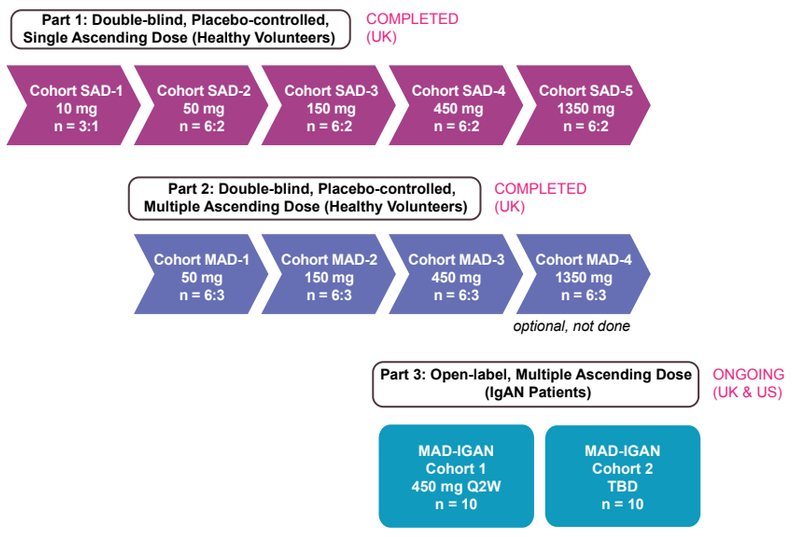


Figure 2. Data Extract: 22 April 2020

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 activity
- Assess changes in renal function in patients with IgAN

Methodology

- PK analyses performed on serum concentration data using non-compartmental analysis and nominal sampling times and fixed doses with Phoenix® WinNonlin® Version 8.1
- Serum PK concentrations that were below the lower limit of quantitation (LLOQ) were reported as BQL (below quantification limit = 0.01 µg/ml) and excluded from the PK analyses
- Levels of BION-1301 in serum were quantitated using ELISA-based immunoassays under GLP
- Immunogenicity was assessed from serum samples for presence of anti-drug antibodies (ADA) and neutralizing ADAs (Nabs) under GLP
- Serum levels of IgA, IgG, and IgM were measured using an immunoturbidimetric assay on the Roche Cobas 702 analyzer (lower limit of detection: IgA 0.05 g/L, IgG 0.30 g/L, IgM 0.05 g/L)

Baseline Demographics

	SAD BION-1301 (N=27)	SAD Placebo (N=9)	MAD BION-1301 (N=18)	MAD Placebo (N=9)
Age (years)				
Mean (std dev)	36.66 (8.38)	35.0 (8.39)	35.4 (9.01)	36.55 (7.85)
Sex				
Male	27 (100%)	9 (100%)	18 (100%)	9 (100%)
Female	0	0	0	0
Race				
American Indian or Alaskan Native	0	0	0	0
Asian	2 (7.4%)	3 (33.3%)	0	0
Black or African American	6 (22.2%)	1 (11.1%)	3 (16.7%)	2 (22.2%)
White	18 (66.7%)	4 (44.4%)	11 (61.11%)	4 (44.4%)
Native Hawaiian or Pacific Islander	0	0	0	0
Multiple	1 (16.7%)	1 (11.1%)	4 (22.2%)	3 (33.3%)
BMI (kg/m²)				
Mean (std dev)	25.46 (2.47)	23.73 (2.94)	25.65 (3.00)	25.95 (1.56)

Table 1.

BION-1301 Is Well-Tolerated in Healthy Volunteers

Single Ascending Dose (SAD) 1 Dose (Day 1) Study Duration 13 Weeks	10 mg (N=3)	50 mg (N=6)	150 mg (N=6)	450 mg (N=6)	1350 mg (N=6)	Placebo (N=9)	Total (N=36)
Any TEAEs	2 (66.7%)	3 (50.0%)	3 (50.0%)	4 (66.7%)	3 (50.0%)	7 (77.8%)	22 (61.1%)
Grade 3 or higher TEAEs	0	0	0	0	0	0	0
Treatment-related TEAEs	2 (66.7%)	0	1 (16.7%)	1 (16.7%)	1 (16.7%)	2 (22.2%)	7 (19.4%)
≥ Grade 3 Treatment-related TEAEs	0	0	0	0	0	0	0
Treatment-emergent SAEs	0	0	0	0	0	0	0
Treatment-related treatment-emergent SAEs	0	0	0	0	0	0	0
Infusion-related reactions	0	0	0	0	0	0	0

Multiple Ascending Dose (MAD) 3 Doses (Day 1, 15, 29) Study Duration 17 Weeks	50 mg (N=6)	150 mg (N=6)	450 mg (N=6)	Placebo (N=9)	Total (N=27)
Any TEAEs	2 (33.3%)	6 (100%)	5 (83.3%)	6 (66.7%)	19 (70.4%)
Grade 3 or higher TEAEs	0	1 (16.7%)	0	0	1 (3.7%)
Treatment-related TEAEs	2 (33.3%)	2 (33.3%)	1 (16.7%)	1 (11.1%)	6 (22.2%)
≥ Grade 3 Treatment-related TEAEs	0	0	0	0	0
Treatment-emergent SAEs	0	0	0	0	0
Treatment-related treatment-emergent SAEs	0	0	0	0	0
Infusion-related reactions	0	1 (16.7%)	0	0	1 (3.7%)

Table 2. No SAEs, treatment discontinuations or events meeting stopping criteria were reported. All patients received pre-medication prior to first infusion, and 1 infusion related reaction was reported in the MAD 150 mg cohort. The most common AE occurring in ≥ 10% of subjects in the SAD cohorts was nasopharyngitis. The most common AEs occurring in ≥ 10% of subjects in the MAD cohorts were headache, pain in extremity, elevated AST and nasopharyngitis. Note: A grade 3 TEAE of AST was reported but not considered related to study drug.

BION-1301 Dosing Is Associated With a Low Incidence of Non-Neutralizing Anti-Drug Antibodies (ADA) With No Correlation to Dose

	Subjects ADA+ (Treatment Emergent)	ADA Titer Median, Maximum
Placebo (n=18)	**2 (11.1%)**	**150, 270**
SAD placebo (n=9)	N/A	N/A
MAD placebo (n=9)	2 (22.2%)	150, 270
BION-1301 (n=45)	**4 (8.9%)**	**270, 810**
SAD (n=27)	1 (3.7%)	270, 270
MAD (n=18)	3 (16.7%)	270, 810
Total (N=63)	**6 (9.5%)**	**270, 810**

Table 3. Incidence of ADA in treated groups. No NAb were detected. Potential impact on PK cannot be determined as BION-1301 concentrations were already low when ADAs were detected. Note: Treatment Emergent ADA defined as ADA+ subjects that were negative pre-dose, or subjects with pre-existing ADA and twice the dilution level increase in titer post-dose. Based on Best Available Data.

Mean Serum BION-1301 Concentration Is Generally Dose-Proportional but Moderately Greater than Dose-Proportional at Higher Doses

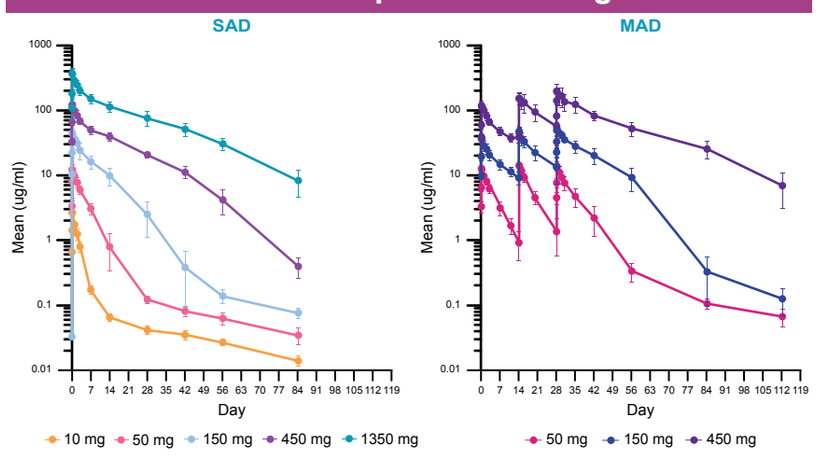


Figure 3. Mean BION-1301 serum concentrations ± SD vs nominal time. Concentrations were similar within cohorts, with individual differences likely the result of fixed dose and variable body weights affecting drug disposition.

BION-1301 Demonstrates Durable Dose-Dependent Increase in Target Engagement as Measured by Free APRIL (fAPRIL)

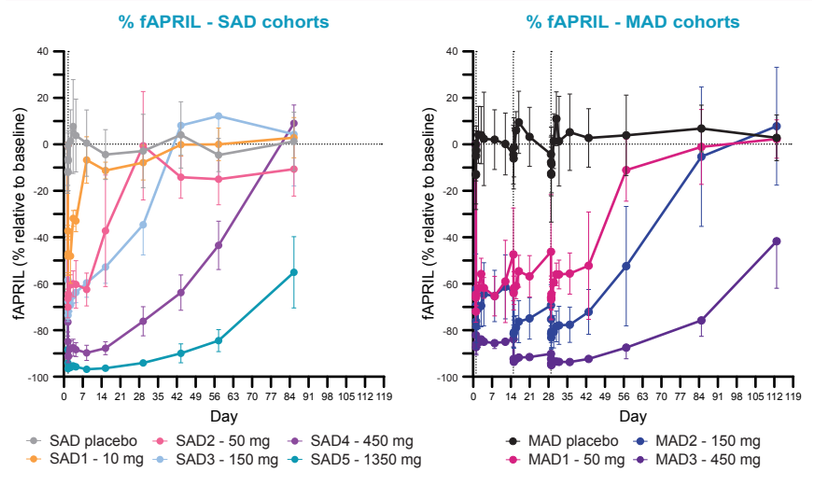


Figure 4. Percent change relative to baseline of free APRIL in serum over time (days). Target engagement is sustained for > 1 month at higher doses. Note: APRIL levels in IgAN patients are reported to be higher than in healthy volunteers.

BION-1301 PK is Well Behaved and the Estimated Half-Life Suggests the Potential for Monthly Dosing

Summary Statistics	Single Ascending Dose (mg) 10	50	150	450	1350	Multiple Ascending Dose (mg) 50	150	450
	Mean (CV%)	Mean (CV%)	Mean (CV%)	Mean (CV%)	Mean (CV%)	Mean (CV%)	Mean (CV%)	Mean (CV%)
C_{max} (µg/mL)	2.62 (5.9)	12.5 (19.5)	44.7 (18.5)	120 (9.0)	363 (18.4)	12.8 (5.8)	38.9 (12.7)	123 (18.6)
T_{max} (day)	0.11 (43.3)	0.09 (45.4)	0.13 (36.5)	0.13 (36.5)	0.11 (38.5)	0.1 (35.0)	0.08 (0.0)	0.11 (38.7)
$AUC_{0\text{-}14\ day}$ (day • µg/mL)	7.3 (12.9)	56.1 (18.8)	264 (22.0)	789 (13.2)	2340 (15.0)	58.9 (15.5)	235 (16.5)	779 (12.8)
$AUC_{0\text{-}14}$/Dose (day • µg/mL/mg)	0.73 (NC)	1.12 (NC)	1.76 (NC)	1.75 (NC)	1.73 (NC)	1.18 (NC)	1.57 (NC)	1.73 (NC)

Table 4. Summary statistics of PK parameters by dose cohort. Exposures were similar within cohorts, with individual differences likely the result of fixed dose and variable body weights affecting drug disposition. Half-life ($t_{1/2}$) was estimated for SAD 1 and SAD 2 cohorts as 31.8 days and 34.0 days, respectively. Clearance was estimated for SAD 1 and SAD 2 cohorts as 1000 ml/day and 765 ml/day, respectively. Note: Multiple dose cohorts only include data from the 1st dose.

BION-1301 Dose-Dependently and Durably Reduces IgA and IgM, and to a Lesser Extent IgG; Data Consistent With Potential for Monthly Dosing

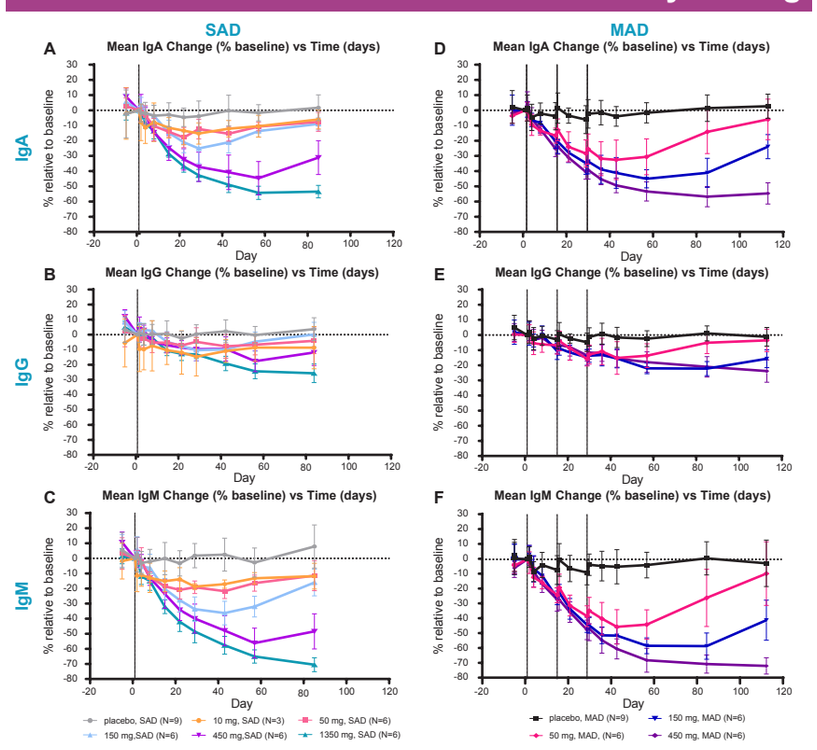


Figure 5. Mean % change ± SD of immunoglobulin levels in serum relative to baseline. (A-C) Single dose cohorts and (D-F) multiple dose cohorts relative to baseline over time (days). Baseline sample taken on Day 1 pre-dose.

Although IgA, IgM and to a Lesser Extent IgG are Durably Reduced, IgG Values Remain in the Normal Lab Range

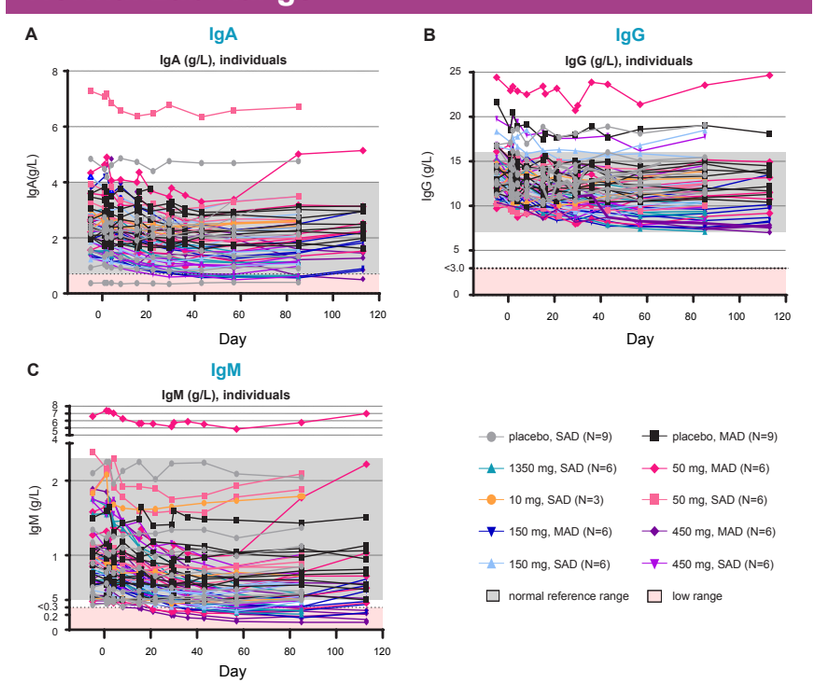


Figure 6. Serum levels (g/L) of (A) IgA, (B) IgG, and (C) IgM of individual subjects over time. BION-1301 at the 1350 mg single or 450 mg multiple dose levels results in suppression of IgM into low laboratory value range; however, there was no increase in infections associated with treatment. BION-1301-mediated immunoglobulin reduction has the potential to disrupt the stoichiometry of IgA:IgG immune complexes.

Effective Suppression of Immunoglobulins Offers a Pharmacodynamic Window to Exploit IgA Reduction While Tempering Impact on IgG

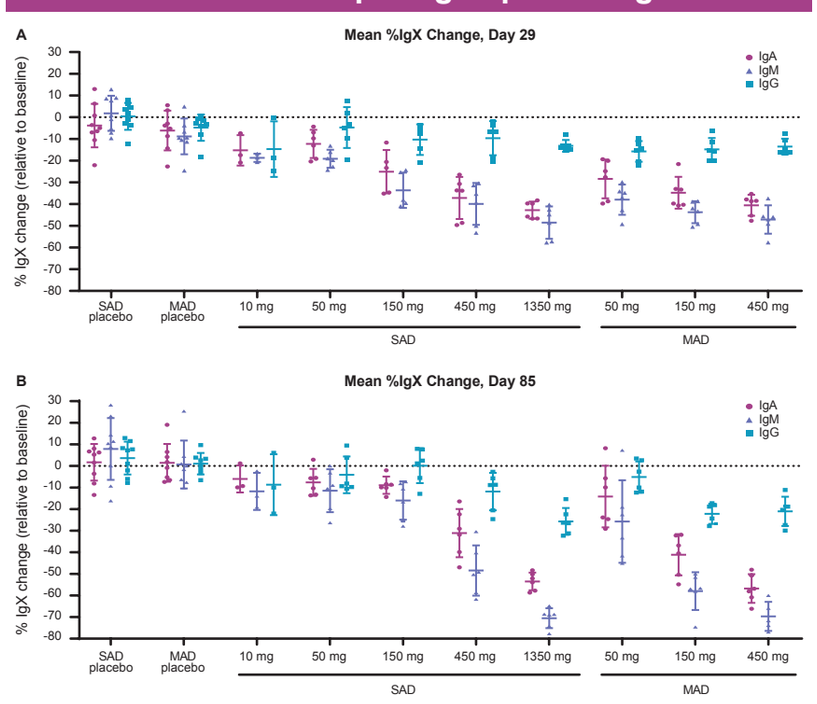


Figure 7. Comparison of mean % change across immunoglobulins at (A) Day 29 and (B) Day 85, relative to baseline. Note: Data from multiple dose cohorts at Day 29 (A) reflect % changes following only 2 doses.

CONCLUSIONS

- BION-1301 was well-tolerated in healthy volunteers with low incidence of non-neutralizing ADAs reported
- The PK profile of BION-1301 was well behaved, 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 fAPRIL
- BION-130 dose-dependently and durably reduces IgA and IgM, and to a lesser extent IgG; however, IgG values remain in the normal lab 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. Gd-IgA1) from Parts 1 and 2
- Enroll and 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 bioavailability

References

1. Berthelot L, et al. *Kidney Int.* 2015. **2.** Reily C, et al. *Biotechniques.* 2018. **3.** He B, et al. *Nat Immunol.* 2010. **4.** Zhai YL, et al. *Medicine (Baltimore).* 2016. **5.** Dulos J, et al. *ASN Annual Meeting.* 2018. **6.** Bensinger W, et al. A*SCO Annual Meeting.* 2019. **7.** Guadagnoli, M, et al. *Blood.* 2016. **8.** Han, SS, et.al. *JASN.* 2016. **9.** Xie, J, et.al. *Contribu Nephrol.* 2013.

Please see our other Poster P0379 summarizing our nonclinical data with BION-1301

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