Poster P0379

BION-1301, a Fully Blocking Antibody Targeting APRIL for the Treatment of IgA Nephropathy: Assessment of Safety, Toxicokinetics and Pharmacodynamics in Long-Term Nonclinical Studies

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Introduction

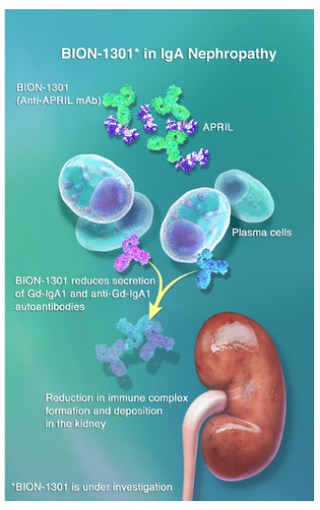
IgA nephropathy (IgAN), the leading cause of primary glomerulonephritis, is an autoimmune disease with no approved treatments.[1] A critical step in IgAN pathogenesis is the production of galactose-deficient IgA1 (Gd-IgA1) leading to the generation of Anti-Gd-IgA1 autoantibodies and immune complex formation that results 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, was developed for the treatment of IgA nephropathy. Here we describe the safety, toxicokinetics (TK) and pharmacodynamics (PD) of BION-1301 after repeated intravenous (IV) and subcutaneous (SC) dosing in non-human primates (cynomolgus monkeys).

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)*

Figure 1.



APRIL: A PRoliferation Inducing Ligand

- TNF-family ligand implicated in regulation of B-cell mediated immune responses[5]
- Soluble factor that binds to its receptors TACI and BCMA inducing B cell signaling that drives:
  - IgA class switching through TACI[5]
  - Differentiation and survival of IgA-producing plasma cells through BCMA[5]
- Patients with IgAN have higher levels of APRIL compared to healthy controls[6]
- Higher APRIL levels in IgAN patients correlate with poor prognosis[6]
- A polymorphism in the APRIL gene confers IgAN susceptibility[7]

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

The objectives of the nonclinical studies were to evaluate the toxicity and determine the toxicokinetics of BION-1301 upon repeat dosing via the intravenous or subcutaneous routes of administration, and to provide a no-observed adverse-effect level (NOAEL) for BION-1301 in each study.

Male and female cynomolgus monkeys were assigned to 4 groups and administered BION-1301 or vehicle control article by intravenous (IV) (bolus) injection at a dose volume of 5 ml/kg or subcutaneous (SC) injection at a dose volume of 2 mL/kg.

Assessment of toxicity was based on mortality, clinical observations, bodyweights, bodyweightchange, qualitativefoodconsumption, dose site dermal observations, ECGs and neurobehavioral assessments and clinical and anatomic pathology (including immunophenotyping [IPT]). Blood samples were collected for immunogenicity testing and toxicokinetic (TK) and pharmacodynamic (PD) analyses.

4-Week Study with Weekly Subcutaneous Dosing (5 doses)

Group	Treatment	No. of Animals		Dose Level (mg/kg/dose)
		Male	Female	
1	Control	5	5	0
2	BION-1301	3	3	20
3	BION-1301	3	3	60
4	BION-1301	5	5	180

For the 4 week recovery period 2 animals per sex were included in Group 1 and Group 4

14-Week Study with Bi-weekly Intravenous dosing (8 doses)

Group	Treatment	No. of Animals		Dose Level (mg/kg/dose)
		Male	Female	
1	Control	3	3	0
2	BION-1301	3	3	10
3	BION-1301	3	3	30
4	BION-1301	3	3	100

26-Week Study with Bi-weekly Intravenous Dosing (14 doses)

Group	Treatment	No. of Animals		Dose Level (mg/kg/dose)
		Male	Female	
1	Control	6	6	0
2	BION-1301	4	4	10
3	BION-1301	4	4	30
4	BION-1301	6	6	100

For the 13 week recovery period 2 animals per sex were included in Group 1 and Group 4

TK/PD Methodology

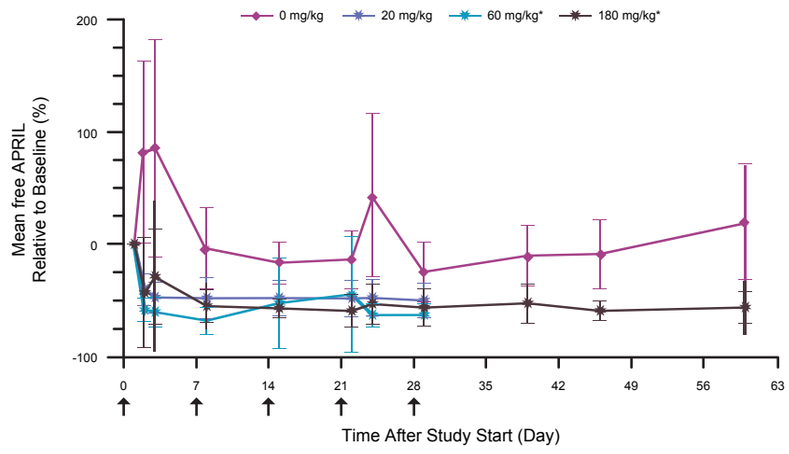
- TK analyses performed on serum concentration data using non-compartmental analysis, nominal sampling times, and weight normalized doses with Phoenix® WinNonlin® Version 8.1
- Serum BION-1301 concentrations that were below the lower limit of quantification (LLOQ) were reported as BQL (below quantification limit = 0.0750 µg/ml) and excluded from the TK analysis
- Levels of BION-1301 and free APRIL (fAPRIL) in serum were quantitated using ELISA methods under GLP
- Immunogenicity was assessed from serum samples for presence of anti-drug antibodies (ADA) and neutralizing ADAs (Nabs) using validated methods
- Serum levels of IgA, IgG and IgM were measured using an Electrochemiluminescence immunoassay

BION-1301 was Well-Tolerated and Markedly Reduced fAPRIL in 4-Week SC Toxicity Study

Study summary

- BION-1301 was well-tolerated when dosed SC weekly for 4 weeks (5 doses) to cynomolgus monkeys
- No BION-1301-related clinical observations, changes in body weight and food consumption, neurobehavioral findings, changes in ECGs, or clinical and anatomic pathology findings were reported
- No anti-drug antibodies (ADA) were detected
- The NOAEL was 180 mg/kg/dose, corresponding to sex-combined C_{max} and AUC values of 5040 µg/mL and 513,000 µg•hr/mL, respectively on Day 22 (dosing phase)
- Maximum measured reduction of fAPRIL of –50% to –68% was observed 8-29 days after study start

Figure 2. Changes in Serum APRIL Levels Upon Repeated SC Dosing of BION-1301 to Cynomolgus Monkeys for 4 Weeks (5 doses)



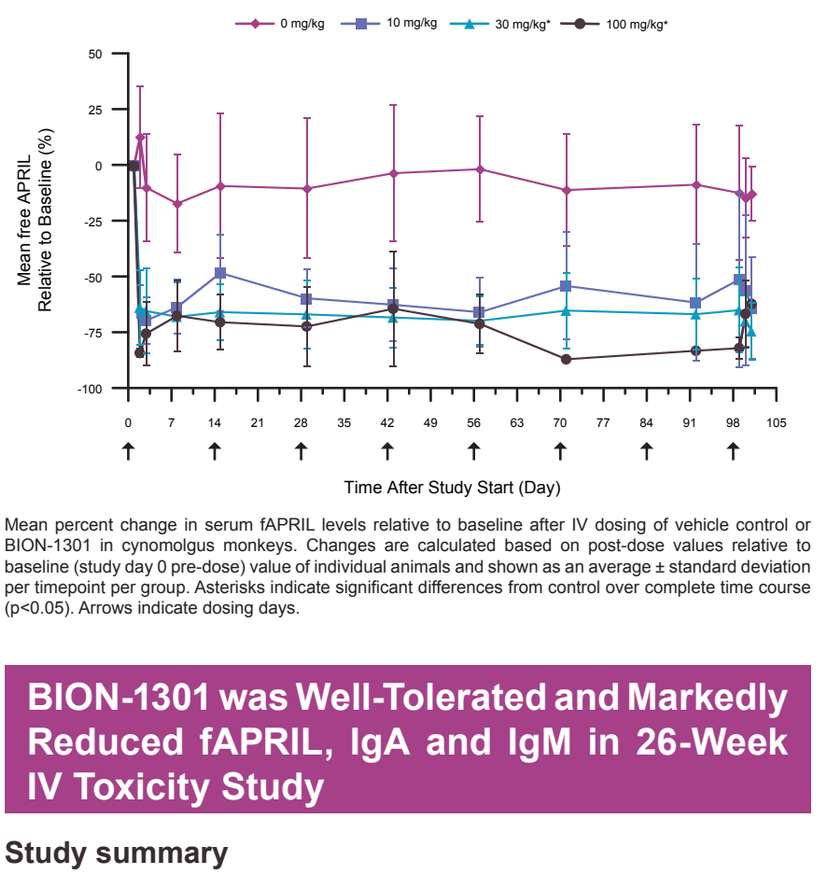
Mean percent change in serum fAPRIL levels relative to baseline after SC dosing of vehicle control or BION-1301 in cynomolgus monkeys. Changes are calculated based on post-dose values relative to baseline (study day 0 pre-dose) value of individual animals and shown as an average ± standard deviation per timepoint per group. Asterisks indicate significant differences from control over complete time course (p<0.05). Arrows indicate dosing days.

BION-1301 was Well-Tolerated and Markedly Reduced fAPRIL in 14-Week IV Toxicity Study

Study summary

- BION-1301 was well-tolerated when dosed IV bi-weekly for 14 weeks (8 doses) to cynomolgus monkeys
- No BION-1301-related clinical observations, changes in body weight and food consumption, changes in ECGs, or clinical and anatomic pathology findings were reported
- No impact of ADA on PK was observed
- The NOAEL was 100 mg/kg/dose, corresponding to sex-combined C_{max} and AUC values of 5920 µg/mL and 934,000 µg•hr/mL, respectively on Day 85 (dosing phase)
- Maximum measured reduction of fAPRIL of –69% to –75% was observed, with 1/6, 1/6, and 5/6 animals dropping BQL by end of study in low, mid, high dose groups, respectively

Figure 3. Changes in Serum APRIL Levels After Repeated IV Dosing of BION-1301 to Cynomolgus Monkeys for 14 Weeks (8 doses)



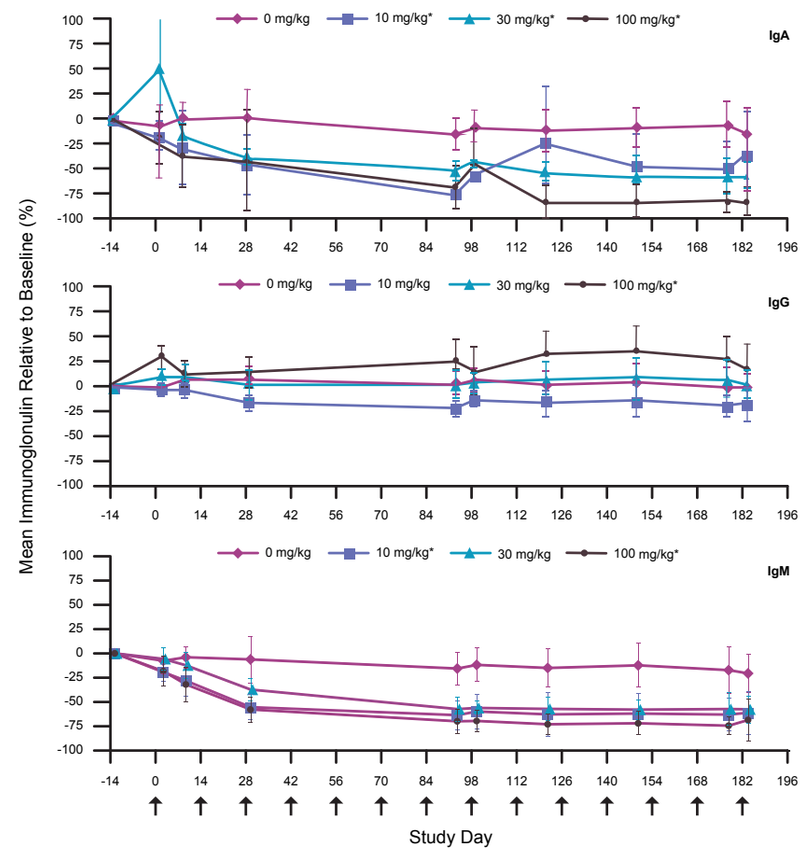
Mean percent change in serum fAPRIL levels relative to baseline after IV dosing of vehicle control or BION-1301 in cynomolgus monkeys. Changes are calculated based on post-dose values relative to baseline (study day 0 pre-dose) value of individual animals and shown as an average ± standard deviation per timepoint per group. Asterisks indicate significant differences from control over complete time course (p<0.05). Arrows indicate dosing days.

BION-1301 was Well-Tolerated and Markedly Reduced fAPRIL, IgA and IgM in 26-Week IV Toxicity Study

Study summary

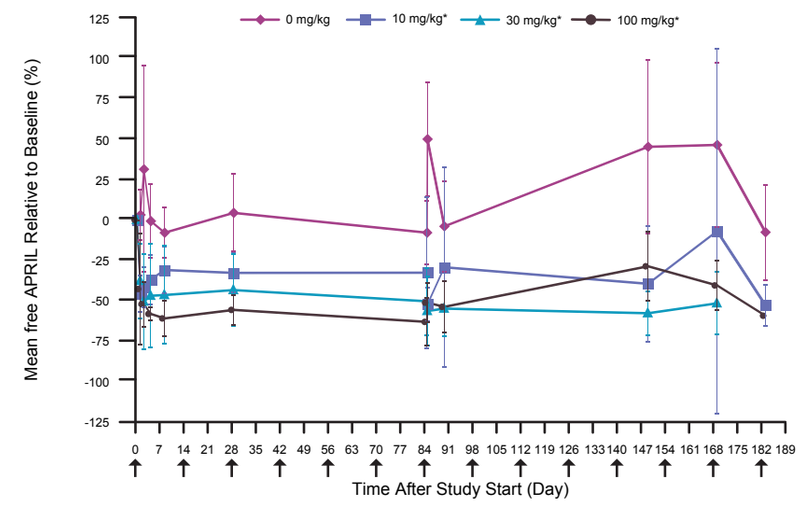
- BION-1301 was well-tolerated when dosed IV bi-weekly for 26 weeks (14 doses) to cynomolgus monkeys
- No BION-1301-related clinical observations, changes in body weight and food consumption, neurobehavioral findings, changes in ECGs, or clinical and anatomic pathology findings were reported
- Sexually mature animals were used in this study and no BION-1301-related effects on reproductive parameters (sperm count; density, motility, or morphology; and number or duration of menstrual cycles) and reproductive organs were reported
- Four animals dosed with BION-1301 tested positive for ADAs; with the exception of one animal, exposure to BION-1301 was generally lower in animals that were positive for ADAs
- The NOAEL was 100 mg/kg/dose, which corresponded to sex-combined C_{max} and AUC values of 7990 µg/mL and 927,000 µg•hr/mL, respectively on Day 169 (dosing phase)
- Maximum measured reduction of fAPRIL of –63% was observed, with 5/8, 8/8, and 11/12 animals dropping BQL by end of study in low, mid, high dose groups, respectively
- Maximum measured reduction of IgA of –92% was observed, with 5/8, 6/8, and 10/12 animals dropping BQL by end of study in low, mid, high dose groups, respectively
- Maximum measured reduction of IgG of –23% was observed, with no animals dropping BQL by end of study
- Maximum measured reduction of IgM of –77% was observed, with 1/8, 0/8, and 0/12 animals dropping BQL by end of study in low, mid, high dose groups, respectively

Figure 4. Changes in Total IgA, IgG and IgM Upon Repeated IV Dosing of BION-1301 to Cynomolgus Monkeys for 26 Weeks (14 doses)



Mean percent change in serum IgA, IgG, and IgM levels relative to baseline after IV dosing of vehicle control or BION-1301 in cynomolgus monkeys. Changes are calculated based on post-dose values relative to baseline (study day -13 pre-dose) value of individual animals and shown as an average ± standard deviation per timepoint per group. Asterisks indicate significant differences from control over complete time course (p<0.05). Arrows indicate dosing days.

Figure 5. Changes of Serum APRIL After Repeated IV Dosing of BION-1301 to Cynomolgus Monkeys for 26 Weeks (14 doses)



Mean percent change in serum fAPRIL levels relative to baseline after IV dosing of vehicle control or BION-1301 in cynomolgus monkeys. Changes are calculated based on post-dose values relative to baseline (study day 0 pre-dose) value of individual animals and shown as an average ± standard deviation per timepoint per group. Asterisks indicate significant differences from control over complete time course (p<0.05). Arrows indicated dosing days

CONCLUSIONS

- BION-1301 was well-tolerated in cynomolgus monkeys when dosed weekly (SC) up to 180mg/kg/dose and biweekly (IV) up to 100mg/kg/dose for up to 26 weeks with no BION-1301 related tox findings
- In the 26-week IV study, sexually mature animals were used and there were no BION-1301-related effects on reproductive parameters (sperm count; density, motility, or morphology; and number or duration of menstrual cycles) and reproductive organs
- Administration of BION-1301 led to marked reductions in fAPRIL levels in serum after repeated dosing via the IV route (up to 14 doses of 100 mg/kg/dose) and the SC route (up to 5 doses of 180 mg/kg/dose)
- Total IgA and IgM were also markedly reduced upon repeated dosing via the IV route (up to 14 doses of 100 mg/kg/dose). Reductions in IgG were observed to a lesser extent. Serum sample analysis for immunoglobulin levels are ongoing for the 4-Week SC study and the 14-Week IV study.
- Overall, a strong dose-dependent PD response to BION-1301 was observed on serum fAPRIL and, at somewhat higher doses, on serum IgA and IgM; a lesser PD response was demonstrated on serum IgG levels
- These PD data are consistent with modulation of the target in blood
- **These studies support the clinical development of BION-1301 in adult patients with IgAN**

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.** Guadagnoli, M, et al. *Blood.* 2016. **6.** Han, SS, et.al. *JASN.* 2016. **7.** Xie, J, et.al. *Contribu Nephrol.* 2013.

Please also view our other Poster P0500 summarizing our Phase I clinical data with BION-1301

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