ADU-CL-19: a Phase 1/2, Multicenter Trial to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BION-1301 in Healthy Volunteers and Adults With IgA Nephropathy

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Background and Aims

IgA nephropathy (IgAN) is the most common primary glomerulonephritis globally, with up to 45% of IgAN patients at risk of progressing to ESKD. There are currently limited treatment options for IgA nephropathy, especially for patients at high risk of disease progression.[1] The initiating step in IgAN pathogenesis is the excess production of galactose-deficient IgA1 (Gd-IgA1) resulting in formation of pathogenic immune complexes that cause kidney inflammation and damage.[2] A Proliferation-Inducing Ligand (APRIL), a TNF-superfamily cytokine, is elevated in IgAN patients and correlated with higher levels of Gd-IgA1 and proteinuria, and lower eGFR.[3,4] BION-1301 is a novel monoclonal antibody which binds and blocks APRIL. The primary objective of Study ADU-CL-19 is to assess the safety and tolerability of BION-1301 in Healthy Volunteers (HV) and IgAN patients and to secondarily assess the PK, PD, immunogenicity, and preliminary clinical activity.

Introduction

Role of APRIL and BION-1301 in IgA Nephropathy (IgAN)

IgAN is a chronic, autoimmune, inflammatory glomerulopathy[1-3]

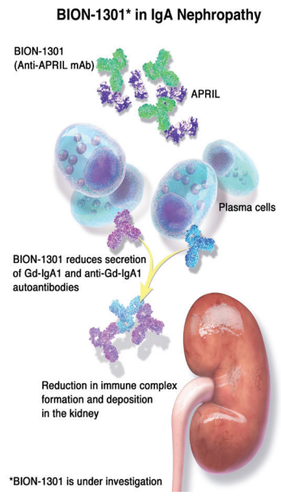
- B cells of patients with IgAN produce galactose-deficient IgA1 (Gd-IgA1)
- In patients with IgAN, Gd-IgA1 gives rise to autoantibody production
- Gd-IgA1–autoantibody complexes deposit in the kidneys, resulting in complement activation, inflammation and subsequent renal damage

A PRoliferation Inducing Ligand (APRIL) is a signaling molecule that regulates B-cell immune responses[1-3]

- APRIL binds to receptors BCMA and TACI on B cells to drive IgA class-switching and proliferation/survival of IgA-producing plasma cells
- Patients with IgAN have significantly higher levels of APRIL than normal
- Higher APRIL levels in IgAN patients correlate with poor prognosis
- A polymorphism in the APRIL gene confers IgAN susceptibility

BION-1301

- Novel humanized monoclonal antibody (mAb) that binds and blocks APRIL



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Methods

The Phase 1/2 study (NCT03945318) comprises 3 parts. Parts 1 and 2 were blinded, placebo-controlled single and multiple ascending dose designs in HV and have been completed. Part 3 is a multicenter (US, UK, South Korea), multicohort, open-label study in up to 40 patients with IgAN. Patients in Cohort 1 receive BION-1301 at 450mg IV every 2 weeks for up to 1 year. 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. Subsequent cohorts will be given BION-1301 via SC injection.

BION-1301 ADU-CL-19 Protocol Amendment 7

ADU-CL-19

- Part 1, SAD in healthy volunteers (up to 1350 mg) — Completed
- Part 2, MAD in healthy volunteers (up to 450 mg) — Completed
- Part 3, Cohort 1 in IgAN patients: 450 mg Q2W IV, up to 52 weeks — Completed
- Part 3, Cohort 2 in IgAN patients: 600 mg Q2W SC, up to 52 weeks — Enrolling
- Part 3, Optional additional cohorts in IgAN patients: Dose/schedule TBD, up to 52 weeks — Not yet enrolling

Objectives: Part 1 and 2

- Safety, pharmacokinetics, immunogenicity, and biomarker effects in healthy volunteers and IgAN patients
- Proof of mechanism (free APRIL, IgA, and Gd-IgA1)
- Explore dose/schedule (exposure) in patients necessary to achieve reduction in IgA and Gd-IgA1
- Assess changes in renal function in IgAN patients

Additional Objectives: Part 3

√ Incorporate initial SC dosing, starting with Cohort 2

Modifications to Part 3:

√ Simplify operational complexity by combining ADU-CL-19 and ADU-CL-24 total duration to 52 weeks

√ Add optional additional cohorts of IgAN patients

√ Increase sample size (up to 40 patients)

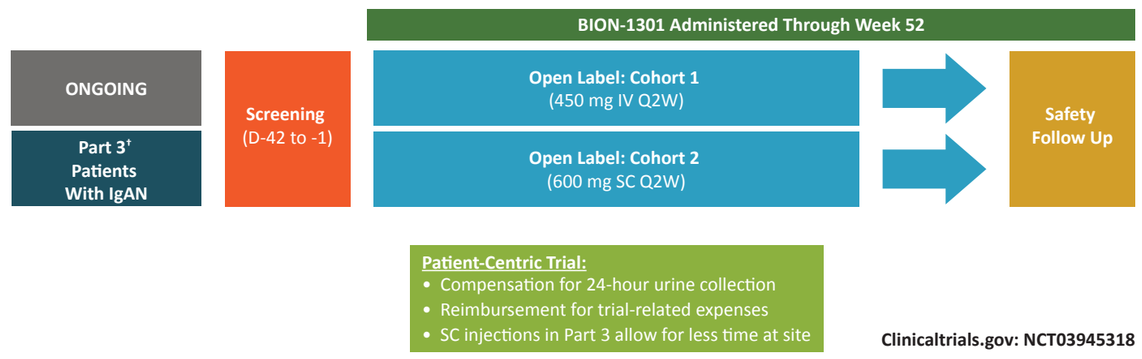
√ ***Now enrolling patients in the US; soon to be enrolling in the United Kingdom and South Korea***

SAD, single ascending dose; MAD, multiple ascending dose; IV, intravenous; Q2W, every 2 weeks; SC, subcutaneous; TBD, to be determined.

Key Eligibility Criteria

√ Age 18 years and older
√ Biopsy-proven IgAN within the past 10 years
√ Urine protein excretion ≥0.5 g/24h OR UPCR ≥0.5 g/g
√ eGFR over 45 mL/min/1.73 m^2*
√ Stable on an optimized dose of ACE/ARB for ≥3 months prior to screening (or intolerant to ACE/ARB)
√ No history of other chronic kidney disease or any transplantation
√ No history of secondary forms of IgAN
√ No Type 1 or 2 diabetes

BION-1301 Study Eligibility and Schema



Patient-Centric Trial:

- Compensation for 24-hour urine collection
- Reimbursement for trial-related expenses
- SC injections in Part 3 allow for less time at site

Clinicaltrials.gov: NCT03945318

ACE/ARB, angiotensin converting enzyme inhibitors/ angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; UPCR, urine protein to creatinine ratio.
*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; †Part 3 is capped at N=40

Results

Final HV data from Parts 1 and 2 have been presented at earlier conferences.[5] Part 3 is ongoing, and interim data from Cohort 1 with IV dosing are being presented at the WCN 2022 (Abstract # WCN22-0485).

Conclusions

The current design of the Phase 1/2 study, incorporating SC dosing, provides for an improved patient experience, and will enable the generation of long-term safety, PK, PD, immunogenicity, and preliminary activity data for use of BION-1301 in IgAN patients.

Disclosures for Presenting Author

- Current Employer: University of Leicester
- Consultancy: Chinook, EMD Serono, Omeros, Calliditas, Novartis, Retrophin, Visterra, Alnylam, Dimerix, George Clinical, and Astellas
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- Honoraria: AstraZeneca
- Scientific Advisor or Membership: Editorial Board of Kidney International, Clinical Journal of the American Society of Nephrology, and Clinical Science

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