PO1632

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

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Disclosures for Presenting Author

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

Mechanism of APRIL and BION-1301 in IgA Nephropathy

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

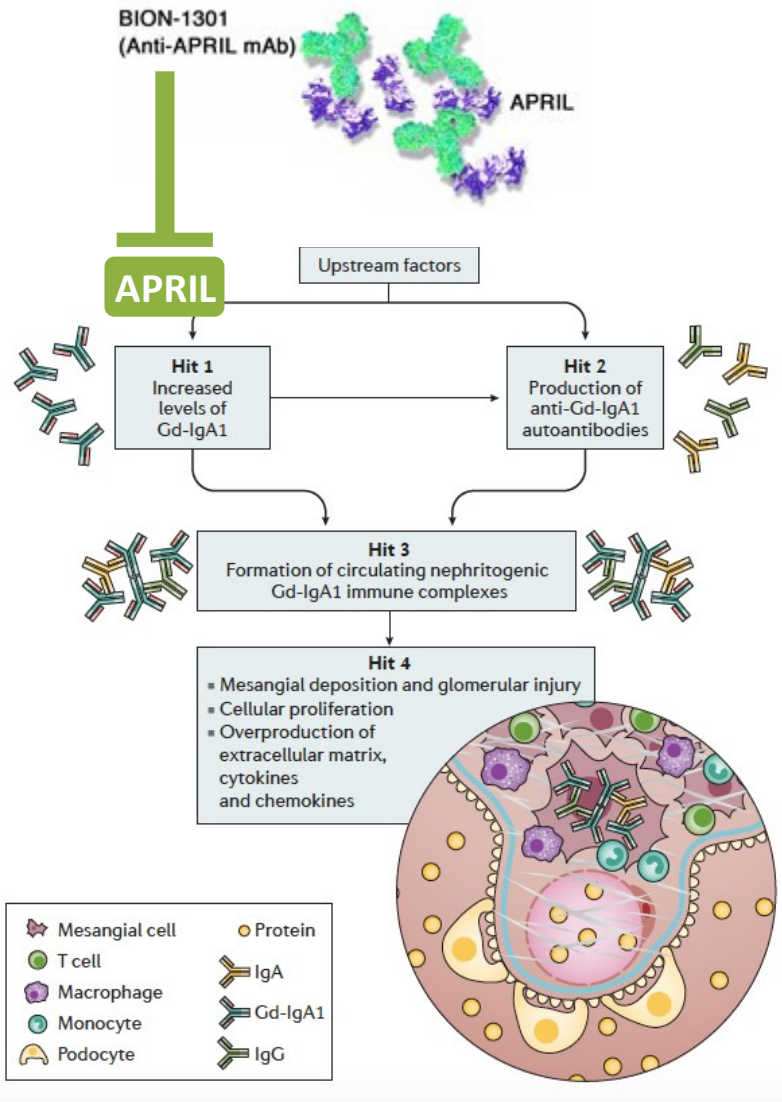
- Excess production of galactose-deficient IgA1 (**Gd-IgA1**) by IgA-secreting plasma cells is considered the initiating pathogenic event (**Hit 1**)
- Immune recognition by anti-Gd-IgA1 autoantibodies (**Hit 2**) results in the formation of nephritogenic immune complexes (**Hit 3**) that cause glomerular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



*TNF: tumor necrosis factor

1. Schena FP, Nistor I. *Semin Nephrol*. 2018;38(5):435-442 . **2.** Magistroni R et al. *Kidney Intl*. 2015;88(5):974-89. **3.** Ilyas M. Pediatric IgA Nephropathy. *Medscape*. 2017. https://emedicine.medscape.com/article/981516-overview. Accessed September 2021.

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IgAN Phase 1/2 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 ≥ 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 INFO32 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.

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

Safety and Tolerability

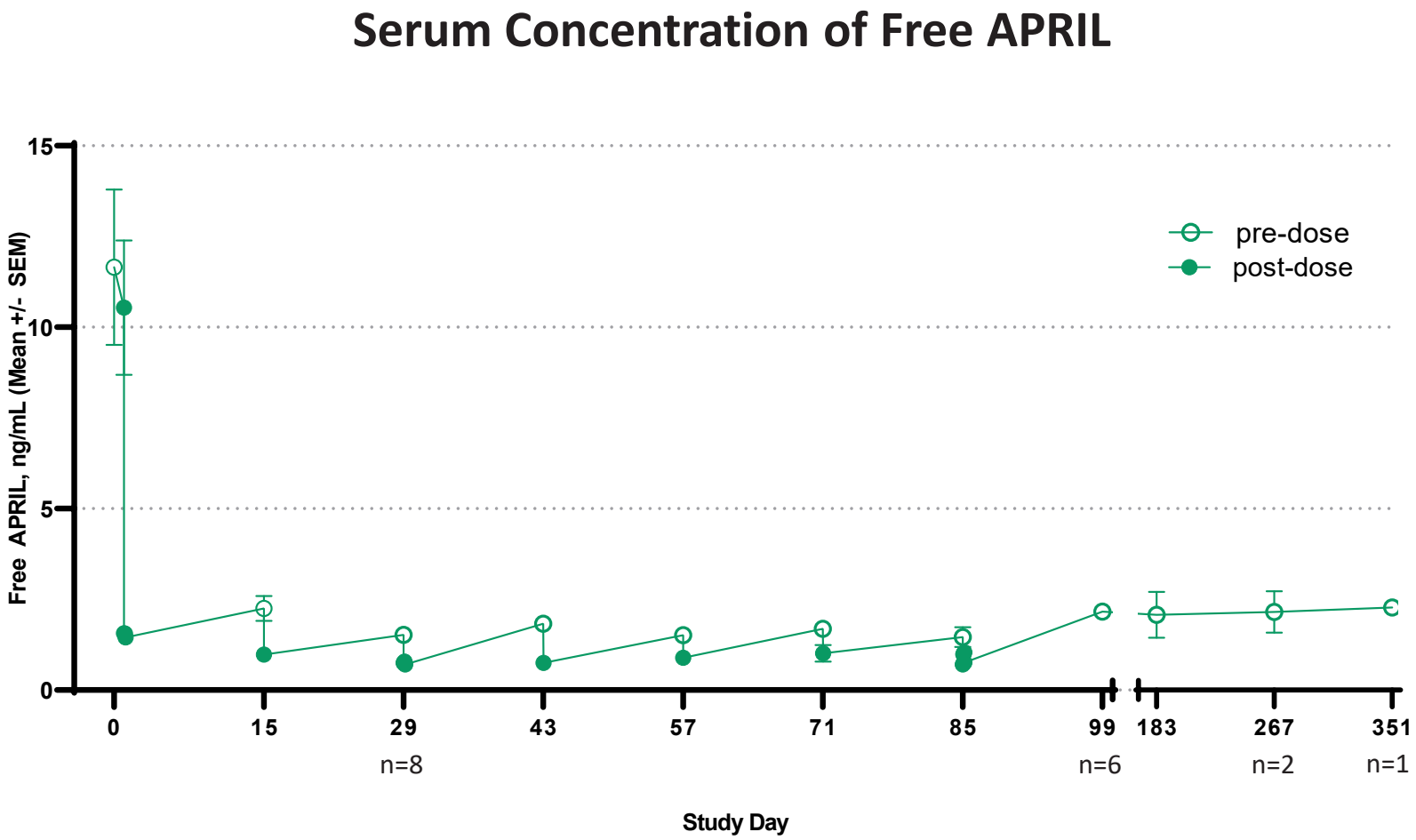
- To date, BION-1301 has been well-tolerated in IgAN patients (n=10)

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

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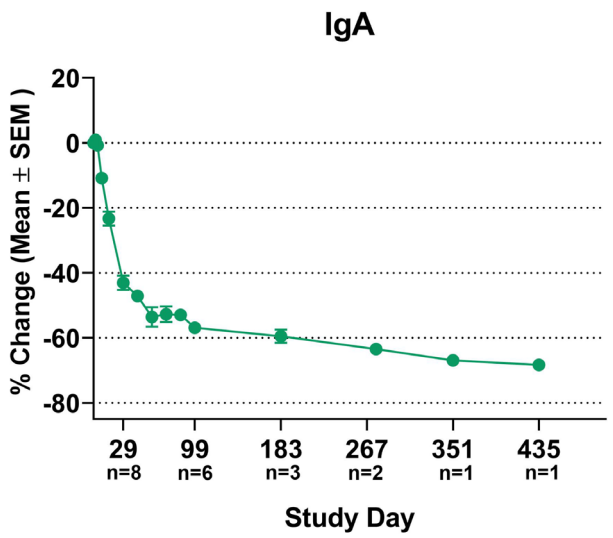
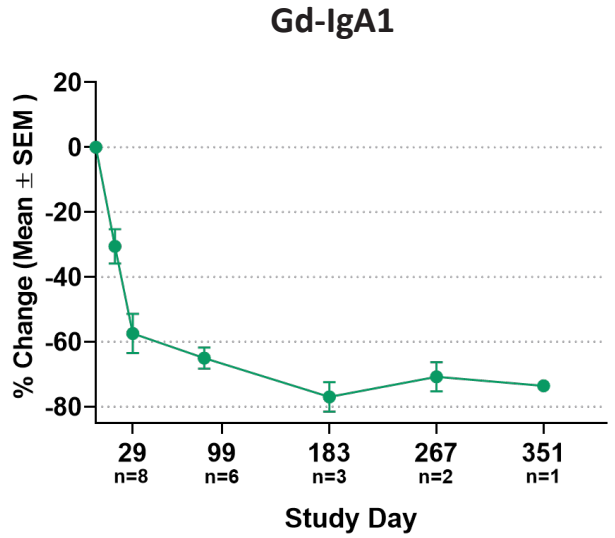
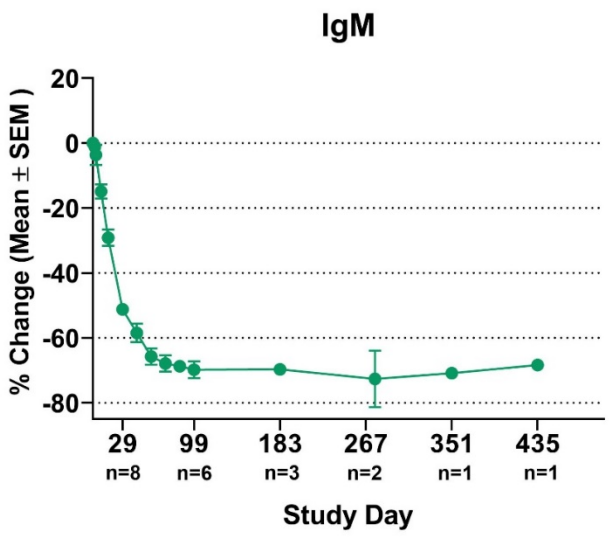
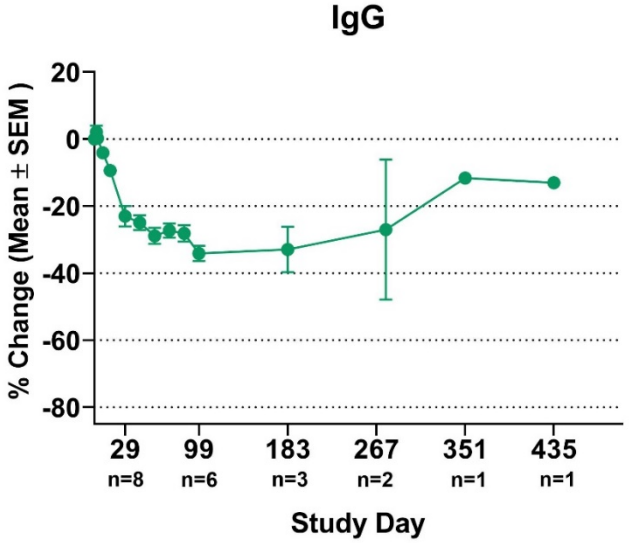
Changes in Serum Ig Concentrations from Baseline









- 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

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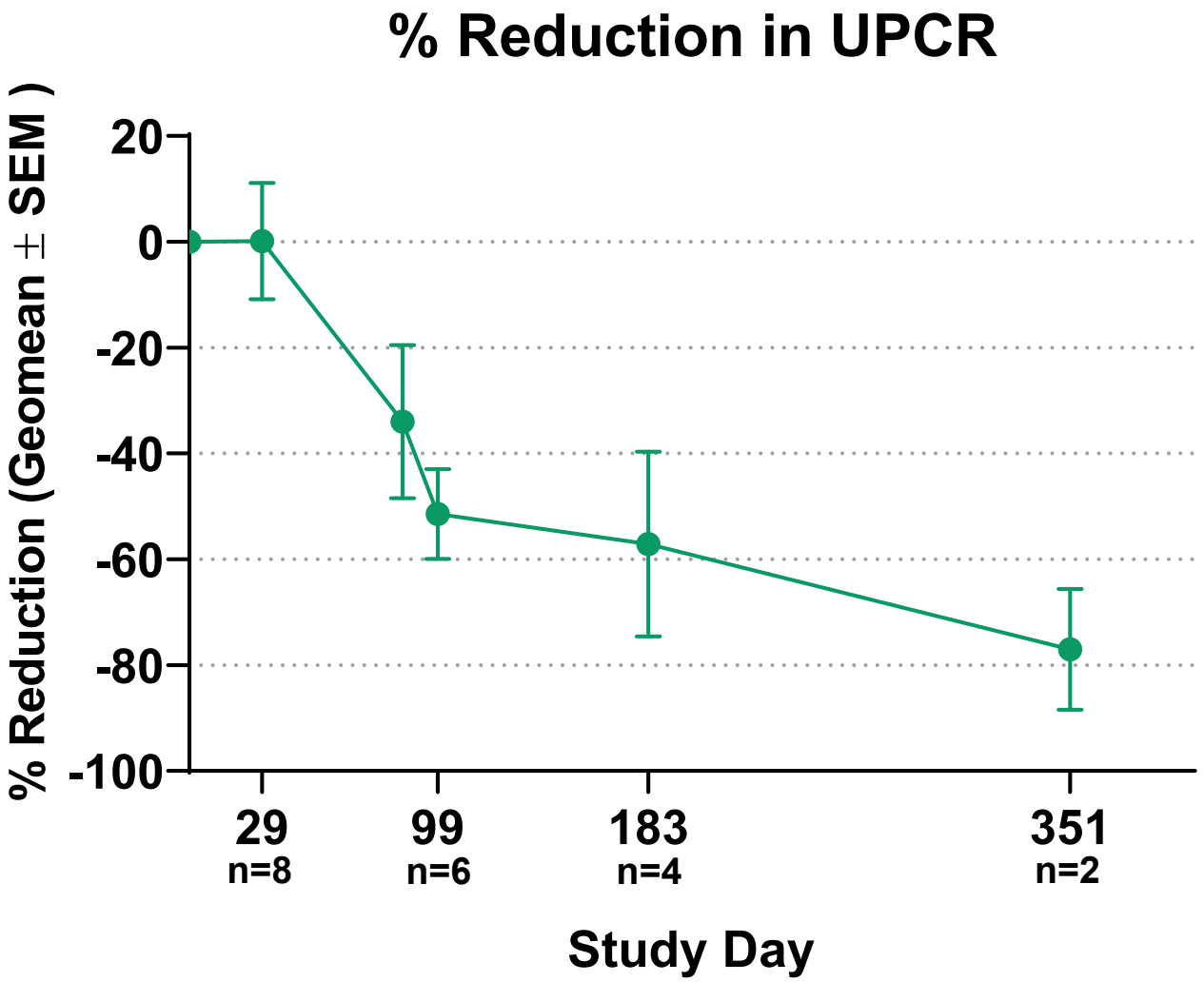
Effects on Proteinuria



- 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

Acknowledgments:
Chinook Therapeutics would like to thank Karen Molyneux, Victoria Cotton, and Nadia Nawaz of University of Leicester for their contributions to the Gd-IgA1 data for this study.

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