CHINOOK THERAPEUTICS

4th Annual CKD Summit
Chronic Kidney Disease Drug Development

Neutralization of APRIL with BION-1301: A Targeted, Potentially Disease-Modifying Approach to IgA Nephropathy

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Outline

- Excess production of galactose-deficient IgA1 (**Gd-IgA1**) by IgA-secreting plasma cells is considered the initiating pathogenic event (**Hit 1**) in IgA nephropathy

- **A Pr**oliferation-**I**nducing **L**igand (**APRIL**), a TNF-family cytokine, drives IgA class-switching, survival of IgA-secreting plasma cells and stimulates Gd-IgA1 secretion

- **BION-1301**, a novel humanized monoclonal antibody, binds and blocks APRIL, and has demonstrated initial validation of this **targeted mechanism** in patients with IgA nephropathy in a Phase 1/2 clinical study

IgA Nephropathy (IgAN) Overview

A Potentially Progressive, Chronic Glomerular Disease with Limited Treatment Options

Although considered a rare disease, IgAN is the most common primary glomerulonephritis globally

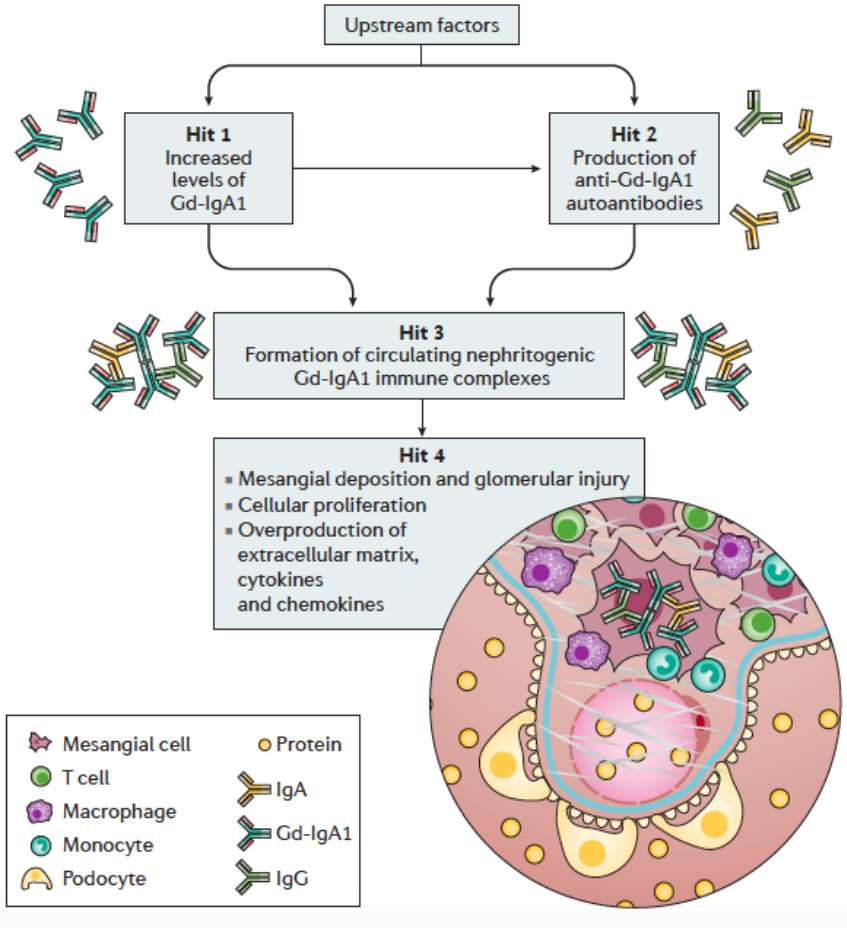
Approximately 30-45% of IgAN patients will develop end-stage kidney disease (ESKD) over a period of 20-25 years

Limited treatment options for high-risk patients and currently no targeted disease-modifying therapies are available

- RAS inhibition (ACEi/ARB) is frontline (KDIGO 1B)
- Steroids & immunosuppressive agents provide inconsistent therapeutic benefit and are accompanied by significant side effects (KDIGO 2B); Tarpeyo (budesonide) recently approved
- DAPA-CKD – suggests benefit of SGLT2i in non-diabetic CKD, including IgAN

Clear need for novel strategies to directly target the initiating molecular events in the complex pathogenesis of IgAN

Model of Multi-Hit IgAN Pathogenesis



Wyatt, R. J., & Julian, B. A. (2013). IgA nephropathy. New England Journal of Medicine, 368(25), 2402-2414.
Lai, K., Tang, S., Schena, F. et al. IgA nephropathy. Nat Rev Dis Primers 2, 16001 (2016).

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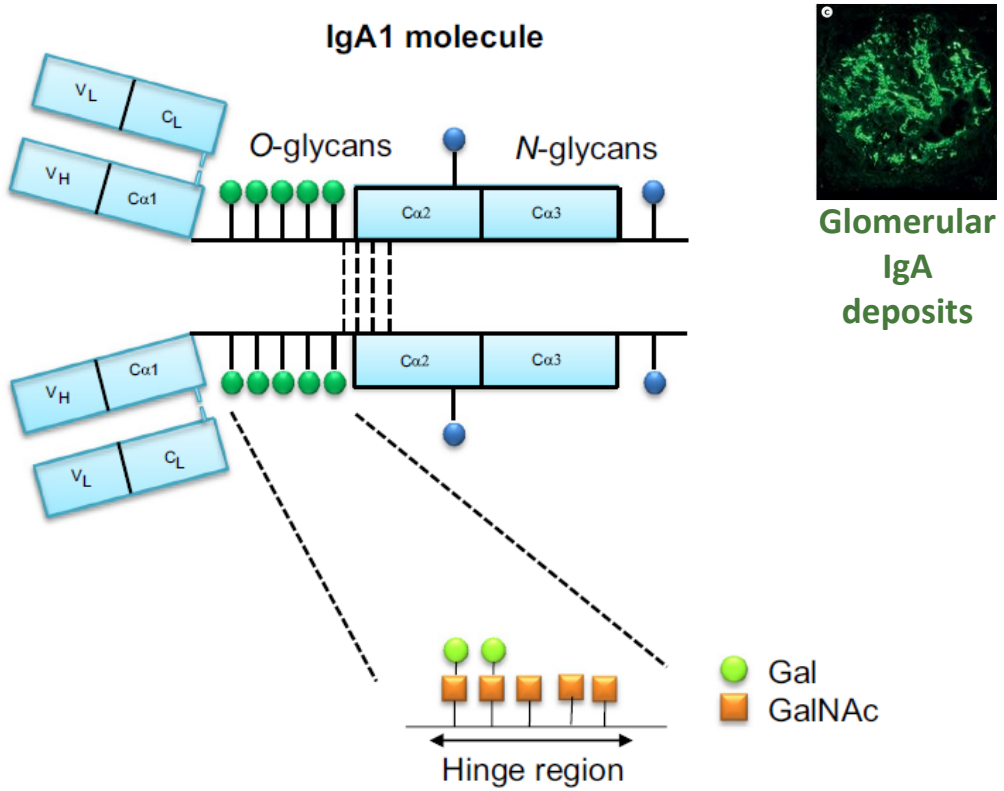
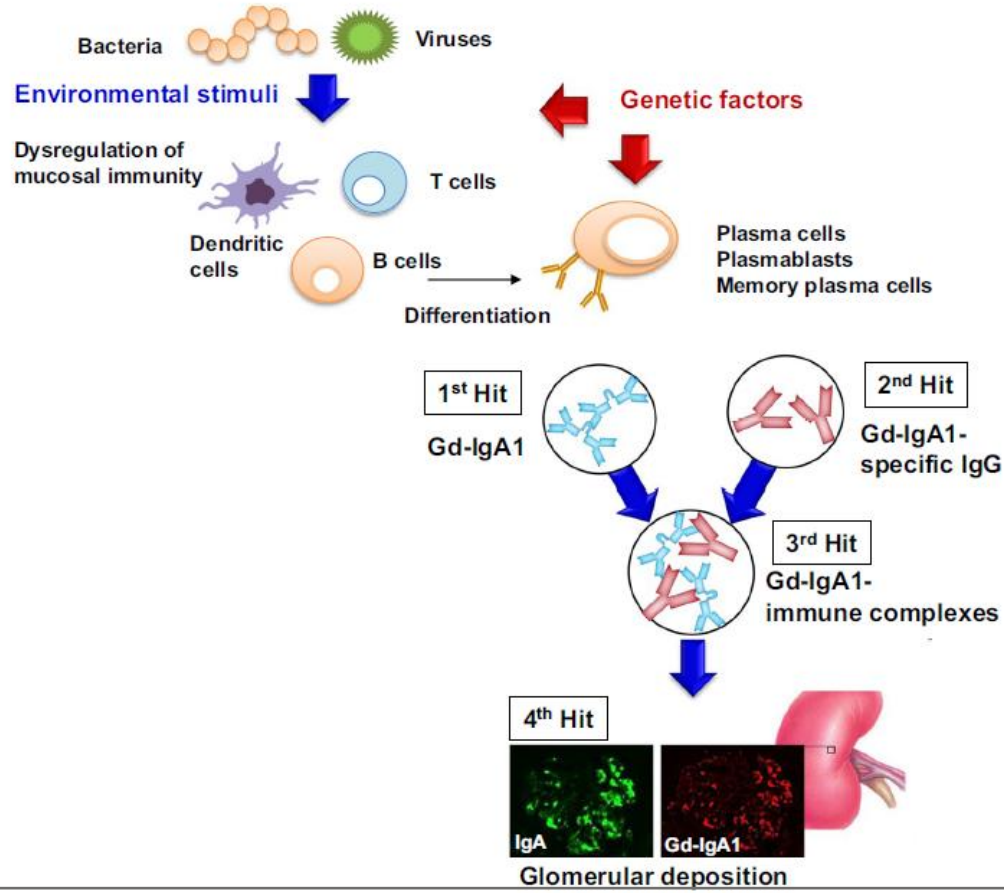
Gd-IgA1: The Target Antigen Leading to the Formation of Pathogenic Circulating Immune Complexes

Glomerular Immuno-deposits are Enriched for Aberrantly Glycosylated IgA1 Glycoforms (Gd-IgA1)



Example of a Gal-deficient hinge-region glycopeptide (altered expression and activity of key glycosyltransferases in IgAN)

Gd-IgA1 Depletion Represents a Potentially Disease Modifying Strategy to Treat IgAN



Seminars in Immunopathology (2021) 43:669–678
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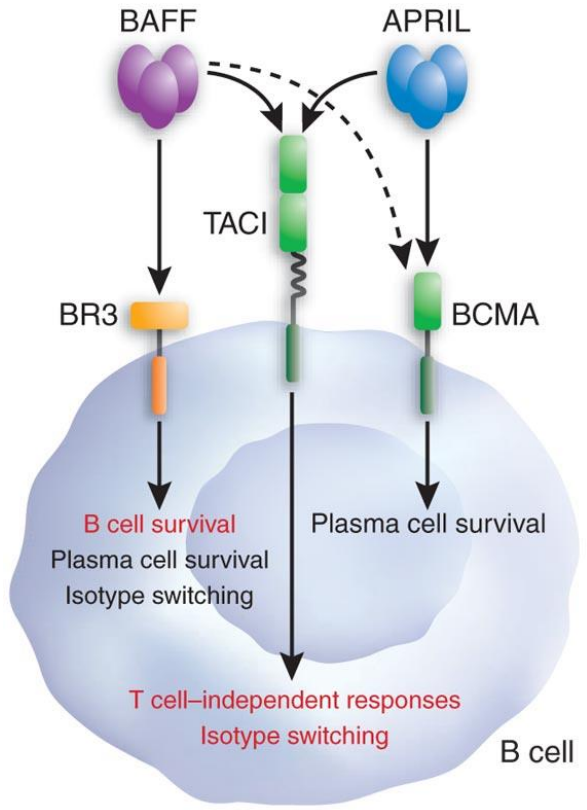
A PRoliferation Inducing Ligand (APRIL)

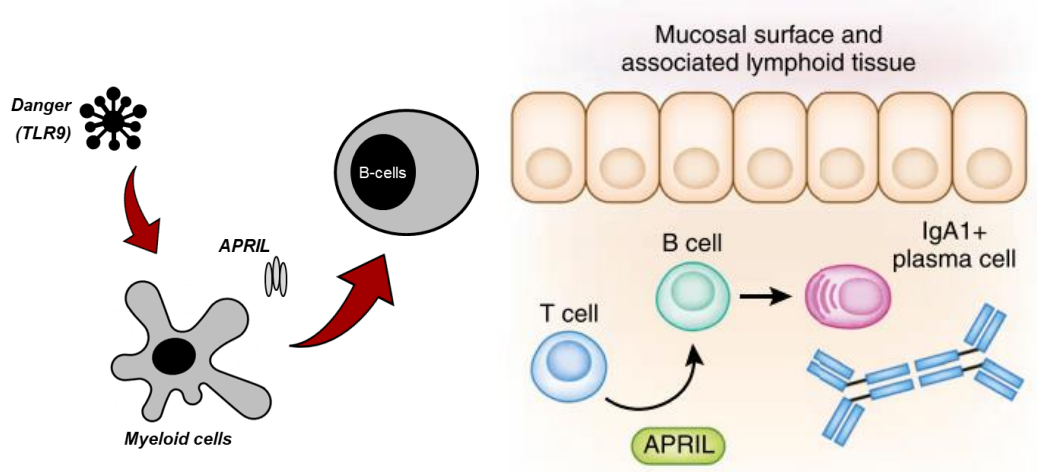
TNF-superfamily cytokine (TNFSF13) involved in B-cell signaling

APRIL drives IgA class switching and survival of IgA-secreting plasma cells, via TACI and BCMA



Strong genetic and clinical associations for APRIL in IgAN

- Higher APRIL levels in IgAN patients correlated with higher Gd-IgA1 and proteinuria and lower eGFR
- APRIL gene variants confer increased risk of IgAN
- Shown to increase Gd-IgA1 secretion from IgAN patient lymphocytes



Guadagnoli, M, et al. Blood. 2016. He B, et al. Nat Immunol. 2010; Zhai YL, et al. Medicine (Baltimore). 2016; Yu XQ, et al. Nature Genetics. 2012 Feb;44(2):178-182; Clin J Am Soc Nephrol 12: 677–686, 2017

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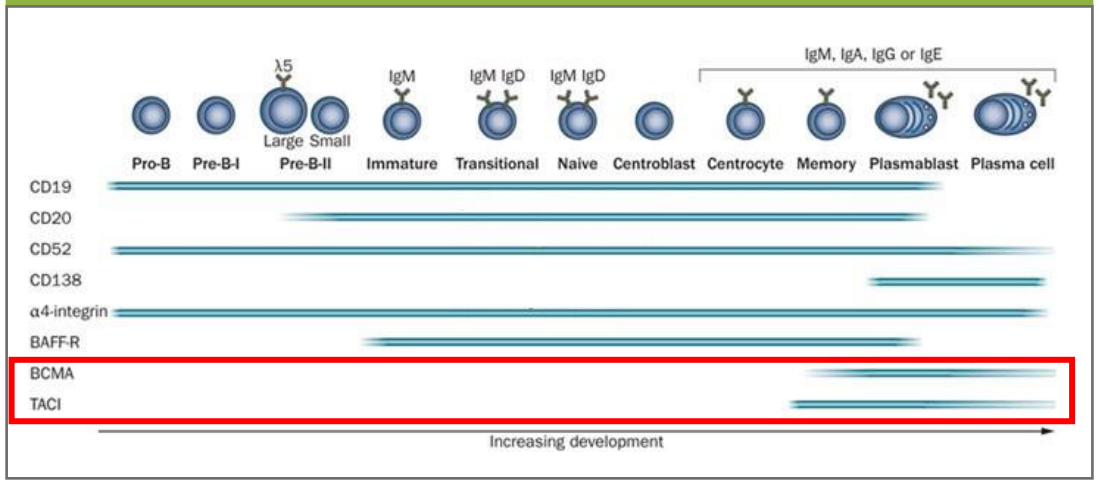
APRIL Action Primarily Targeted to Plasma-blasts/cells

Preferential impact on IgA vs. IgG secreting cells

BCMA and TACI Expression Primarily Restricted to Ig Secreting Plasmablasts and Plasma cells#

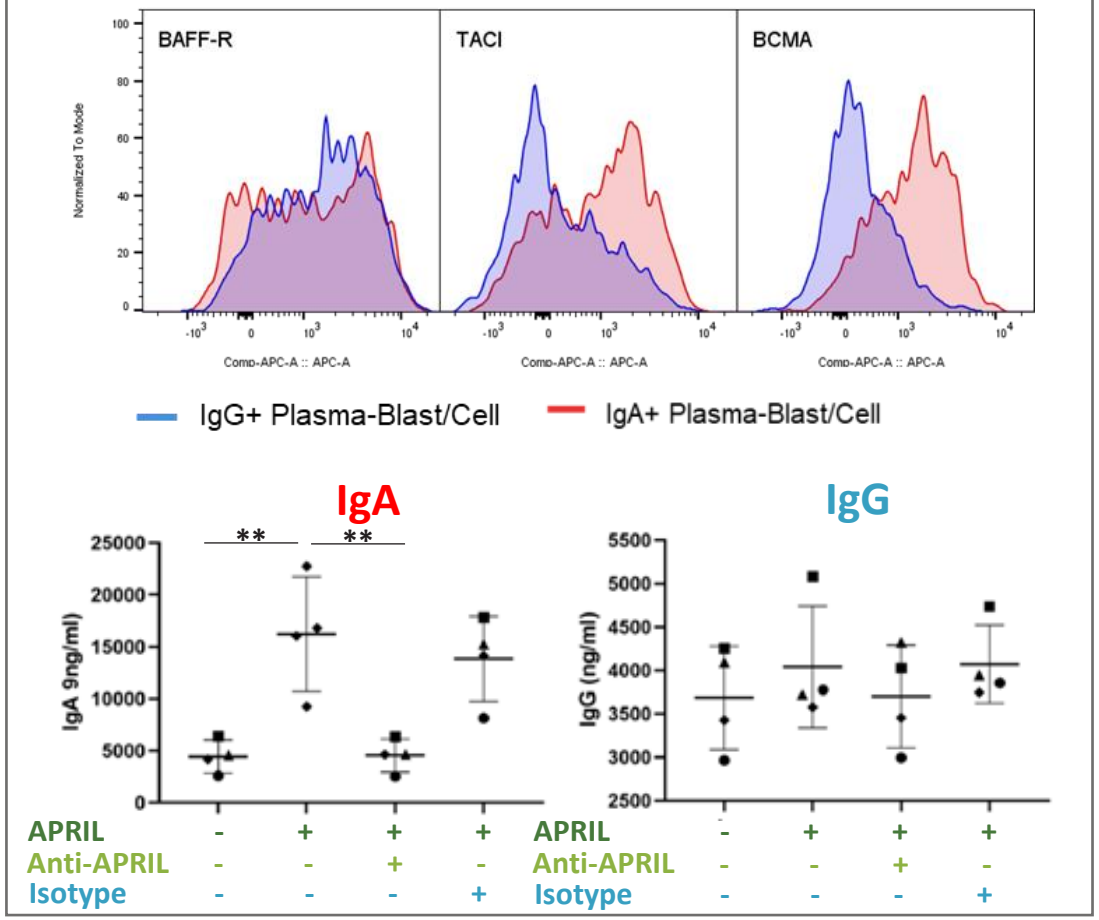


Modulation of APRIL has the potential to target IgA production while minimizing impact on IgG and immature lymphocyte populations

#Also expressed on memory B cells

* IgM secreting plasmablasts and plasma cells, have similar receptor expression profile and APRIL responsiveness as IgA secreting cells

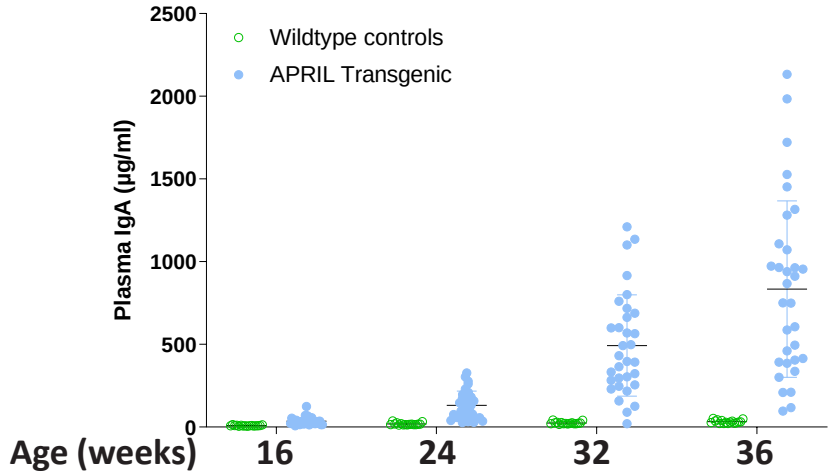
Differential Receptor Expression and APRIL Responsiveness: IgA* vs. IgG Secreting Plasma Cells



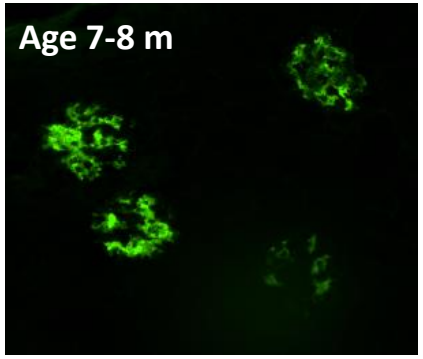
Nature Reviews Neurology volume 8, pages613–623 (2012), Paul Vink, John Dulos, Jeroen Bakker, Maurice Habraken, Lilian Driessen, David Lutje Hulsik, Joost Kreijtz, Hans van Eenennaam, Andrea van Elsas and Barratt lab

huAPRIL Transgenic Mice Demonstrate Increased Serum IgA, Kidney IgA Deposits and Increased IgA-Secreting Cells

Increased Plasma IgA Concentrations

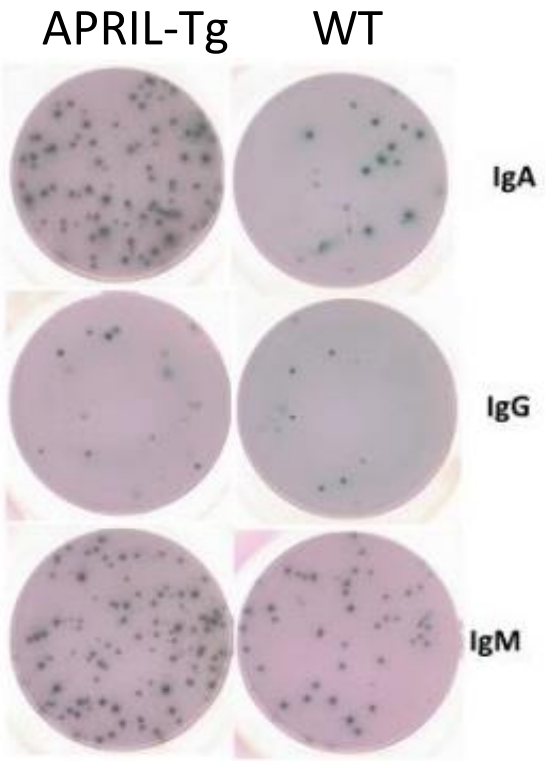


Kidney IgA Deposits



Despite IgA deposition in the kidney huAPRIL Tg mice do not develop an IgAN phenotype (**multi-hit IgAN pathogenesis**)

Increased Bone Marrow* IgA+ Cells



* Similar phenotype in spleen

The phenotype of huAPRIL Tg mice was reversed by an anti-huAPRIL mAb (IgA & IgM > IgG)

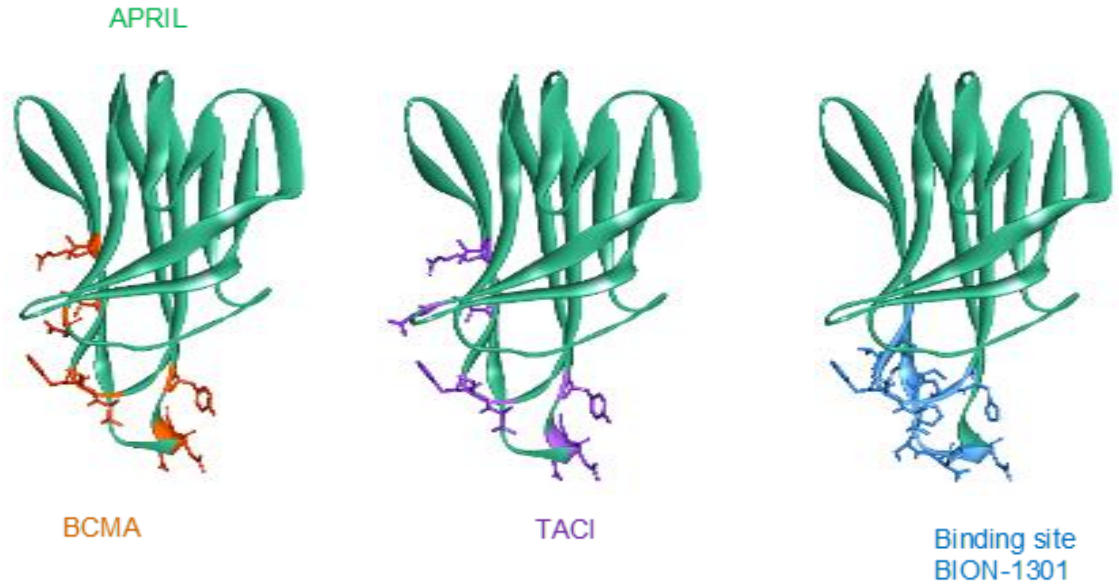
Paul Vink, John Dulos, Jeroen Bakker, Maurice Habraken, Lilian Driessen, David Lutje Hulsik, Joost Kreijtz, Hans van Eenennaam, Andrea van Elsas and Barratt lab

BION-1301: A humanized anti-APRIL mAb

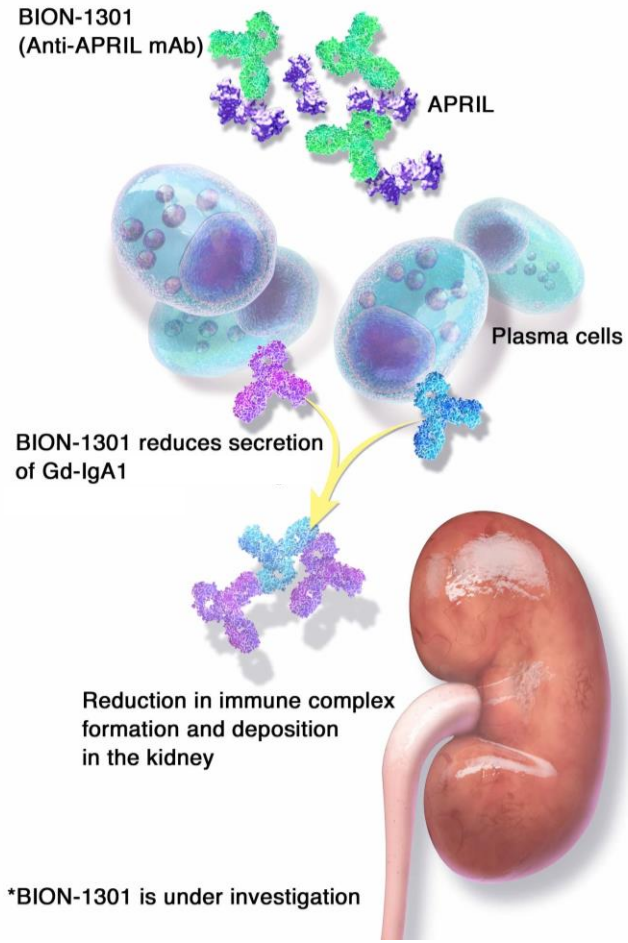
A Potentially Disease-Modifying Approach to Reduce IgA Immune Complex Formation

BION-1301: humanized IgG4 monoclonal antibody that blocks APRIL binding to its receptors (BCMA/TACI)

- Potently binds recombinant human and cynomolgus APRIL (but does not bind rodent APRIL)
- Functional blocking of APRIL at BCMA and TACI receptors
- Does not induce cytokine release in human PBMCs



Therapeutic Hypothesis BION-1301* in IgAN



1. Guadagnoli, M, et al. Blood. 2016. 2. He B, et al. Nat Immunol. 2010; 3. Zhai YL, et al. Medicine (Baltimore). 2016. 4. Yu XQ, et al. Nature Genetics. 2012 Feb;44(2):178-182.
5. Kreijtz J, et al. ERA-EDTA 2020 poster presentation: poster #P0379. 6. Bensinger W, et al. ASCO 2019 poster presentation: poster #338.

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BION-1301: Well Tolerated in NHPs and Demonstrates Anticipated Pharmacodynamic Response

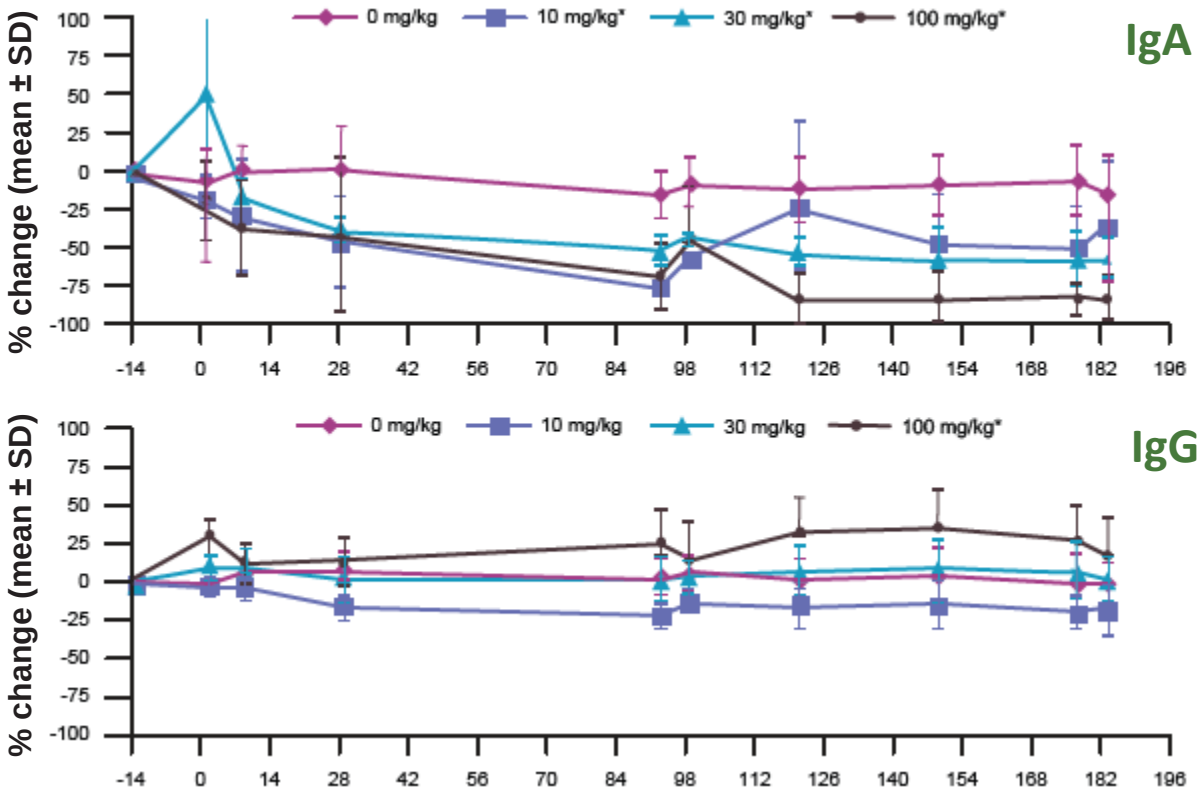
- BION-1301 was well-tolerated in NHPs when dosed biweekly (IV) up to 100mg/kg for 26 weeks or when dosed weekly (SC) up to 180 mg/kg for 4 weeks with **no BION-1301 related tox findings**

- NHP a relevant translational model, due to BION-1301 cross-reactivity
  - Significant APRIL reductions
  - Robust IgA (& IgM) reductions with fairly modest IgG reductions, even at toxicological doses

Modulation of APRIL has the potential to target IgA production while minimizing impact on IgG

BION-1301 Reduces Serum IgA (and IgM) levels in NHPs, With Less Impact on IgG

BION-1301 IV administration



Kreijtz J, et al. ERA-EDTA 2020 poster presentation: poster #P0379

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Phase 1 Study in Healthy Volunteers (HVs)

Study Design, Safety and Pharmacokinetics (PK)

Primary Objective

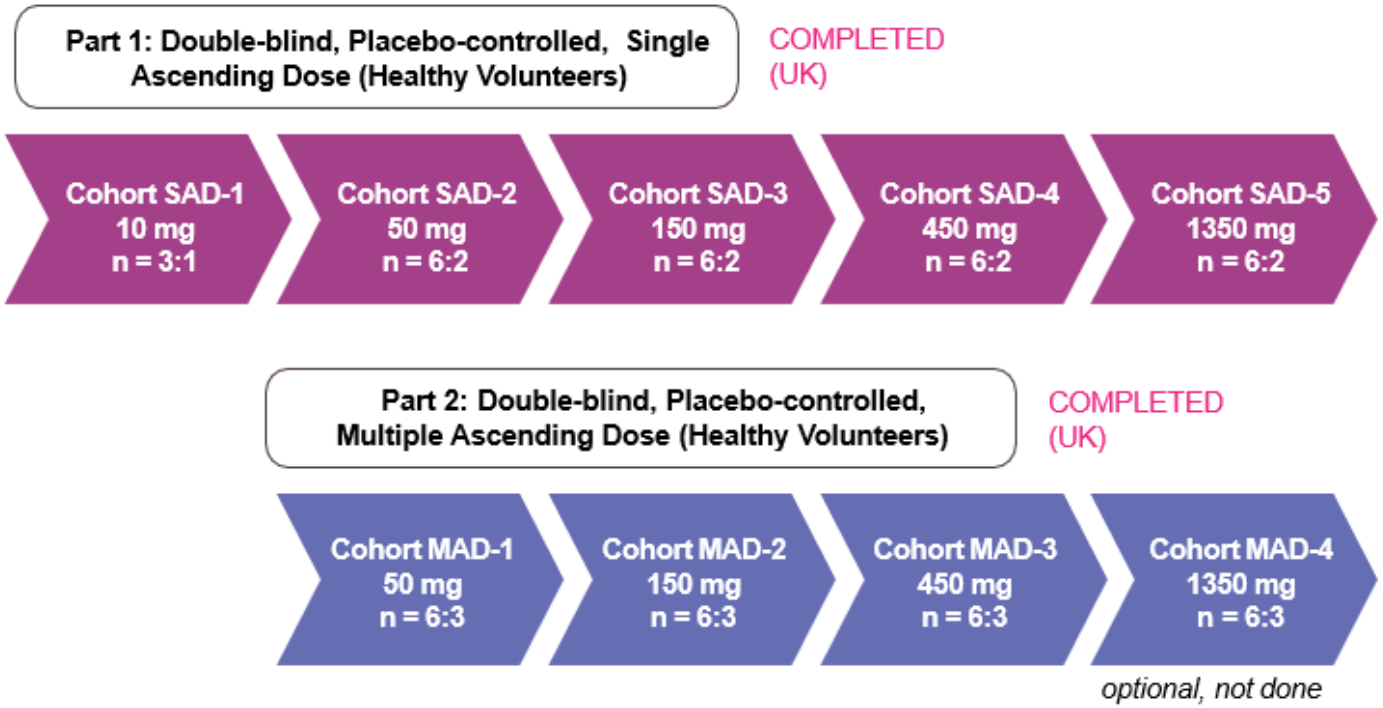
- Assess safety and tolerability

Secondary Objective

- Characterize PK/PD and immunogenicity of BION-1301 administered by IV infusion

Exploratory Objectives

- Characterize select biomarkers of pharmacodynamic activity



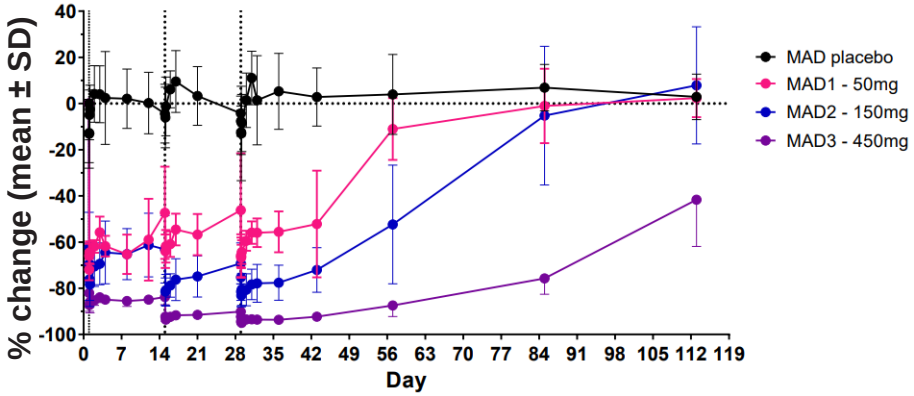
- BION-1301 was well-tolerated in HVs; no SAEs, treatment discontinuations or events meeting stopping criteria
- PK of BION-1301 was well behaved, generally dose-proportional, T ½ ~ 33 days; low incidence of non-neutralizing ADAs (no difference in incidence of ADA between placebo and BION-1301 group)

Lo J, et al. ERA-EDTA 2020 poster presentation: poster #P0500

Phase 1 Study in Healthy Volunteers (HVs)

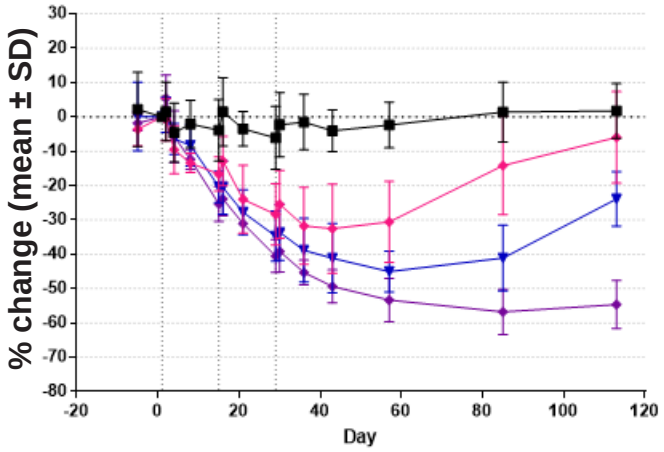
Pharmacodynamic Biomarker Responses (MAD)

Free APRIL

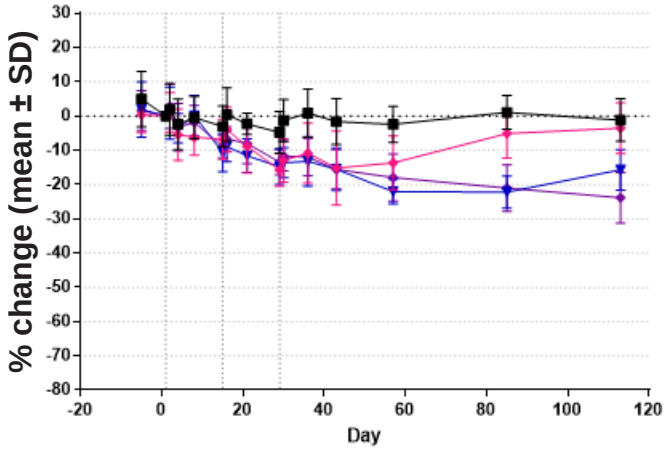


- Immediate, dose-dependent and sustained neutralization of APRIL
- Dose-dependent and durable reductions in IgA & IgM, with lesser effects on IgG (remaining in normal range)
- Offers a pharmacodynamic window to exploit IgA reduction while minimizing impact on IgG

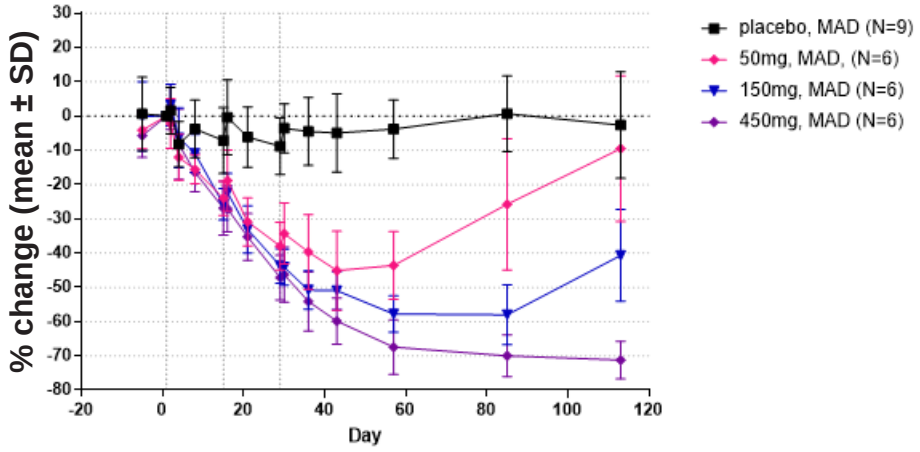
IgA



IgG



IgM



Lo J, et al. ERA-EDTA 2020 poster presentation: poster #P0500

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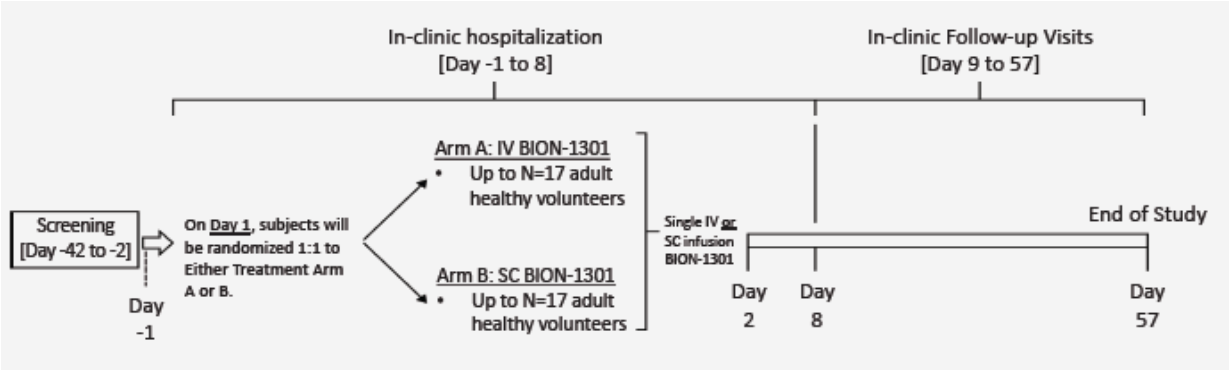
Phase 1 Subcutaneous Bioavailability Study in HVs: Supports Transition to SC Administration of BION-1301

A Phase 1, Open Label, Randomized, Single Dose, Parallel Group Safety and Bioavailability Study of BION-1301 Administered by Intravenous (IV) and Subcutaneous (SC) Routes



- BION-1301 was well tolerated:
  - No SAES or early terminations due to a TRAE
  - No ISRs or IRRs
  - No ADAs in the SC cohort

Comparable reductions in serum fAPRIL

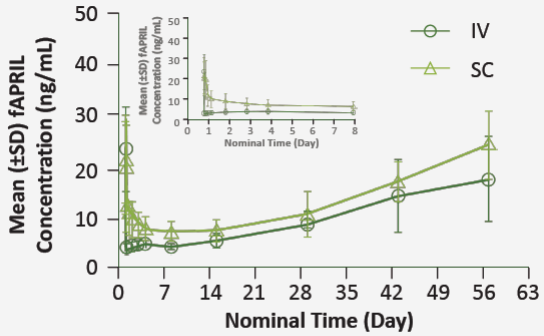


Figure 5: Mean (±SD) fAPRIL Concentrations After Single-Dose IV or SC Administration

The PK profile of BION-1301 was consistent with previous clinical studies and minimal differences in drug concentration were observed between administration routes after 1 week

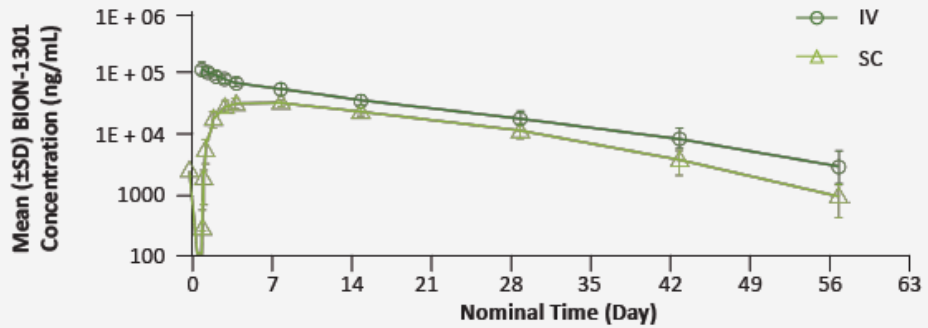


Figure 4: Mean (±SD) Serum Concentrations of BION-1301 in Healthy Volunteers After Single-Dose IV or SC Administration

A single 300mg SC or IV dose of BION-1301 provides similar reductions in immunoglobulins

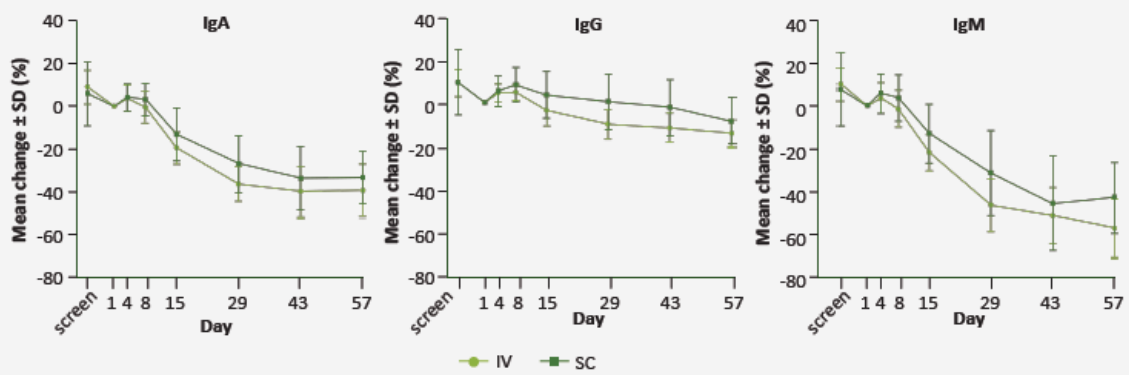


Figure 7. Mean % Change ± SD (Relative to Baseline) in Serum Immunoglobulin Levels Over Time (Days)

Lo J, et al. ISN WCN 21 poster presentation: poster #P0500

Phase 1/2 Study in Patients with IgAN

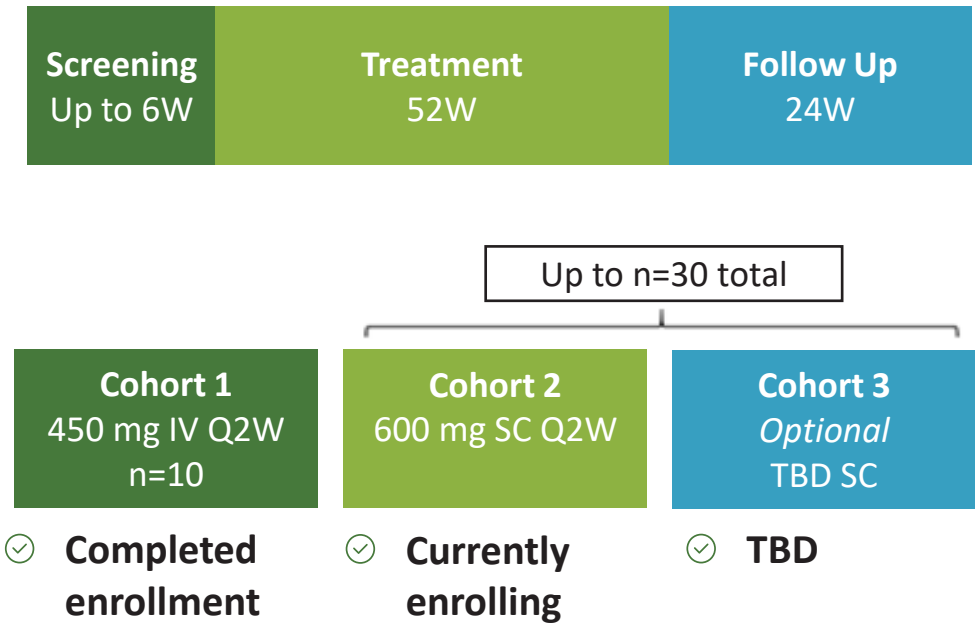
Objectives

- 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)

Open-label, multicenter, multiple-dose study in patients with IgAN



RASi, renin-angiotensin system inhibitors; eGFR, estimated glomerular filtration rate; PK, pharmacokinetics; Q2W, every 2 weeks; UPCR, urine protein/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, 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

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Safety and Tolerability

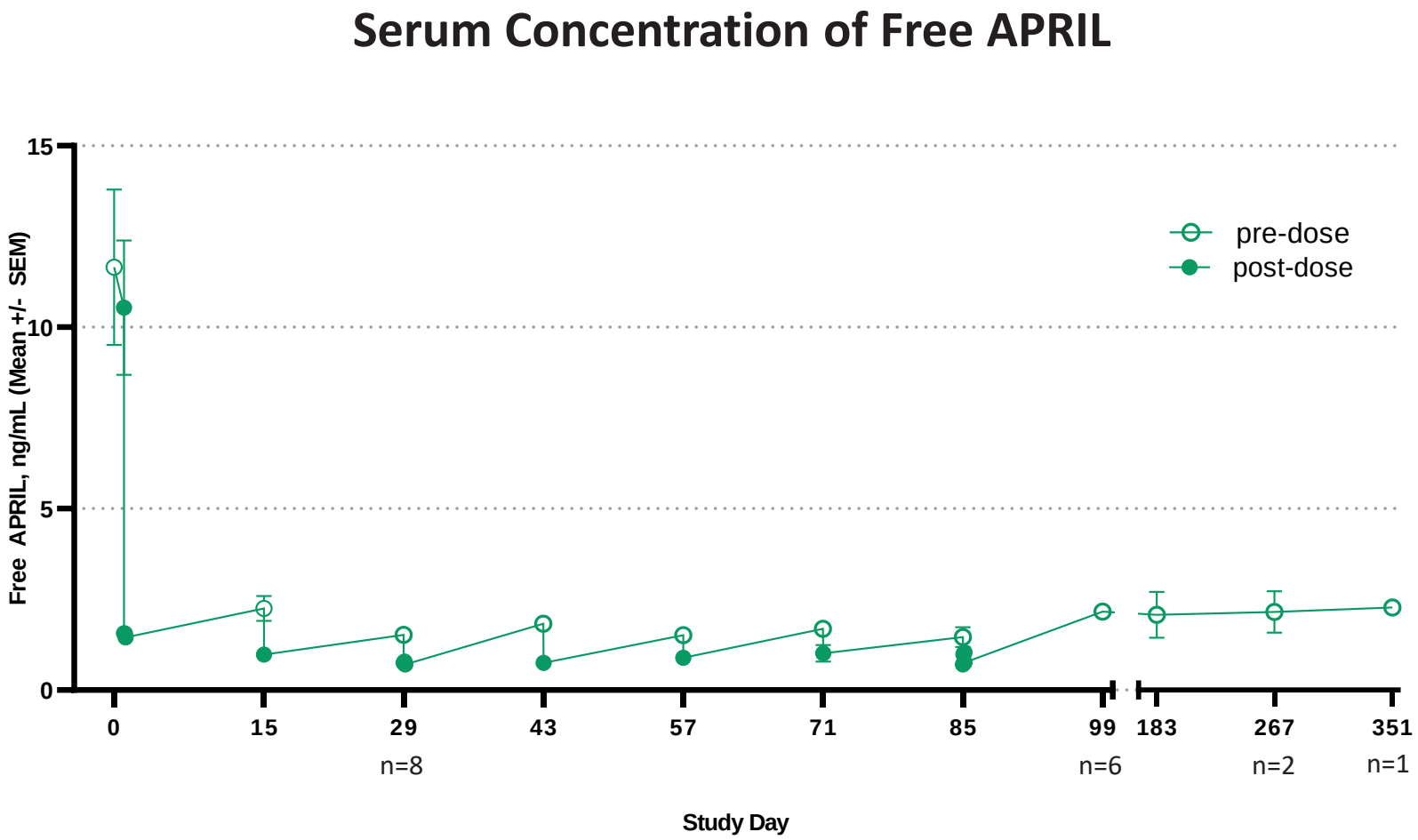
- To date, BION-1301 has been well-tolerated in IgAN patients (n=10)

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. Barratt, J, et al. ASN Kidney Week 2021 poster presentation: poster #PO1632.

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 (ADAs)** observed in patients with IgAN to date

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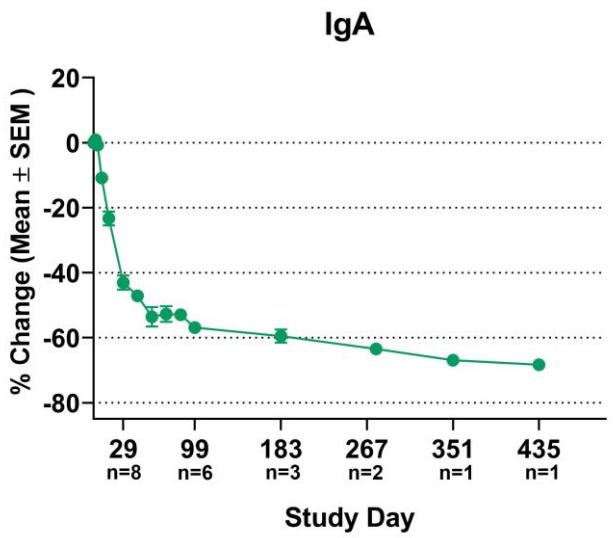
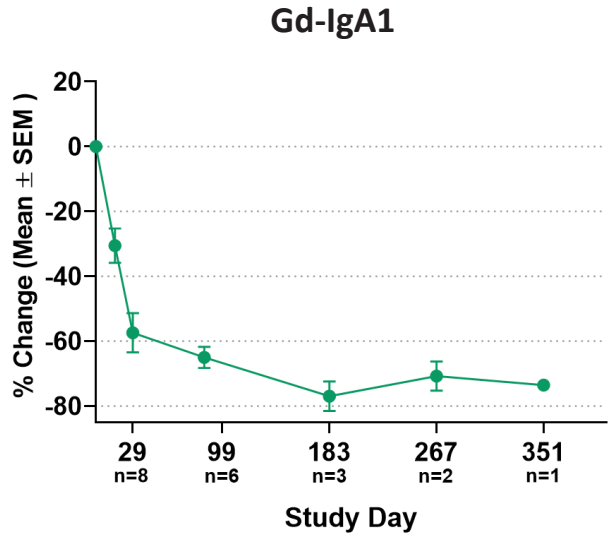
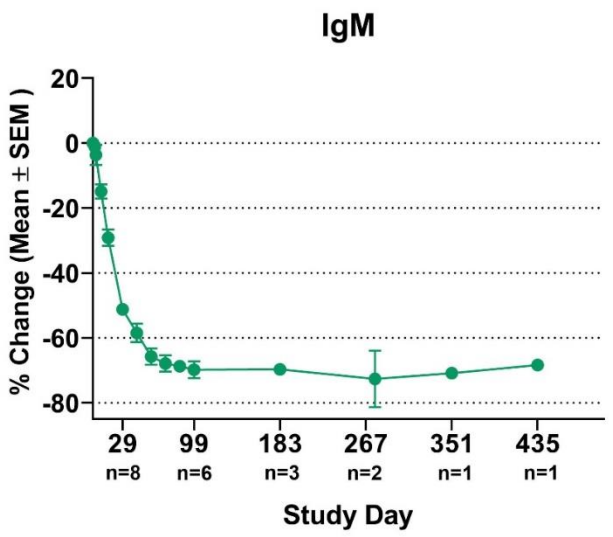
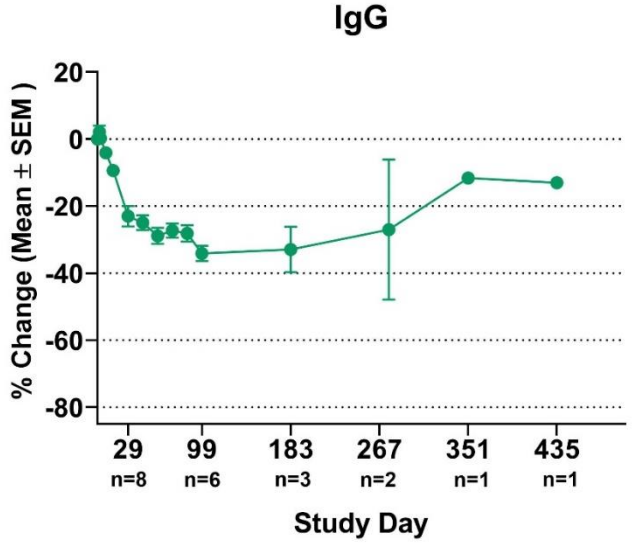
Changes in Serum Ig Concentrations from Baseline









- 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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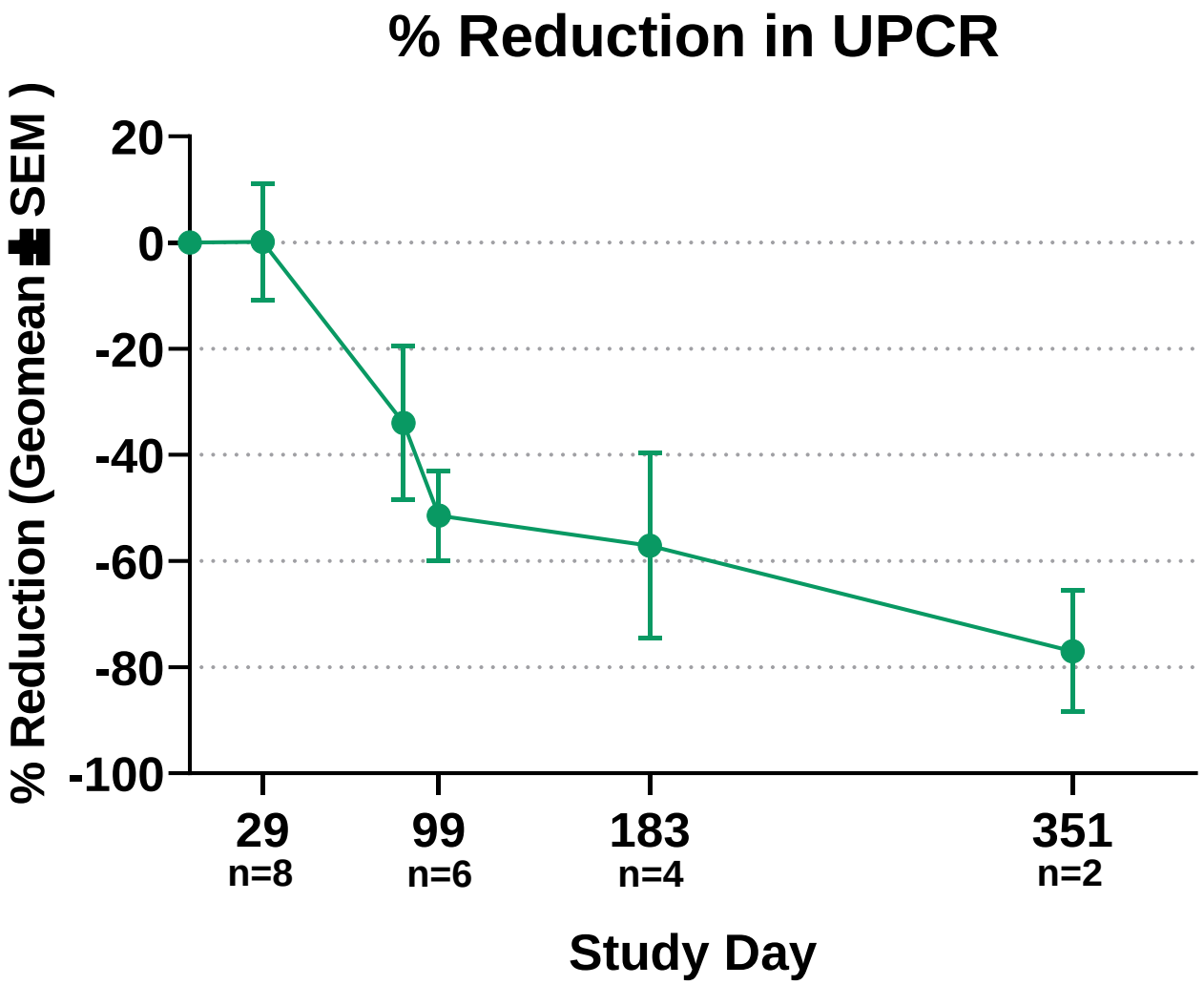
Effects on Proteinuria



- 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. Barratt, J, et al. ASN Kidney Week 2021 poster presentation: poster #PO1632.

Summary

- **A PR**oliferation **I**nducing **L**igand (**APRIL**), a TNF-family cytokine, drives IgA class-switching, survival of IgA-secreting plasma cells and stimulates Gd-IgA1 secretion (**Hit 1**)
- **BION-1301**, a novel humanized monoclonal antibody, binds and blocks APRIL, and has demonstrated initial validation of this **targeted mechanism** in patients with IgAN in a Phase 1/2 clinical study
  - ✓ **Well-tolerated**, with no early terminations due to AEs and no SAEs
  - ✓ 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

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