Povetacicept, an Enhanced Dual BAFF/APRIL Antagonist, in Autoantibody-Associated Glomerulonephritis

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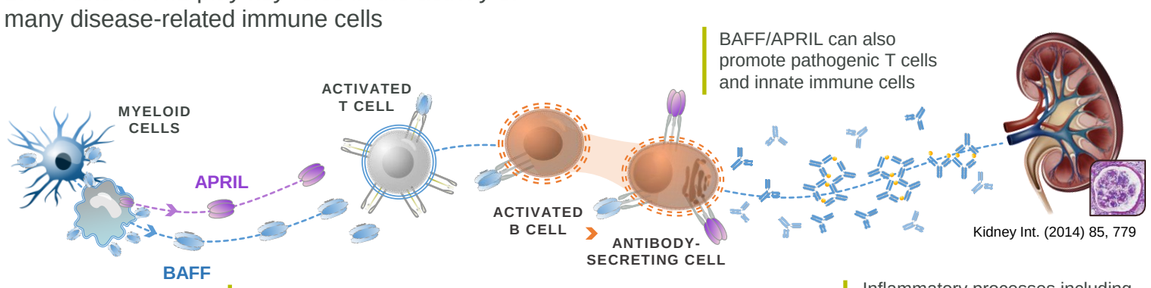
INTRODUCTION

- BAFF and APRIL play critical, overlapping, and non-redundant roles in the activation, differentiation, and/or survival of B cells (particularly antibody-secreting cells) and other immune cell types.[1,2]
- Inhibition of BAFF and/or APRIL has shown promise in multiple glomerulonephritis conditions,[3-8] with the potential to modify the underlying pathogenic autoimmunity.
- Povetacicept (ALPN-303) is an Fc fusion of a variant TACI domain engineered for more potent dual BAFF/APRIL inhibition than wild-type TACI-Ig or anti-BAFF or anti-APRIL antibodies.[9]
- In multiple preclinical disease models, povetacicept demonstrated activity superior to wild-type TACI-Ig; BAFF-, APRIL-, or FcRn-specific inhibitors; and B-cell depletion.[9-11]
- In healthy volunteers, povetacicept was well tolerated and induced on-target PD effects, including reduced circulating Ig levels (including the IgAN biomarker Gd-IgA1) and antibody-secreting cells.[12]

Povetacicept Potently Modulates B Cells and Pathogenic Autoantibodies

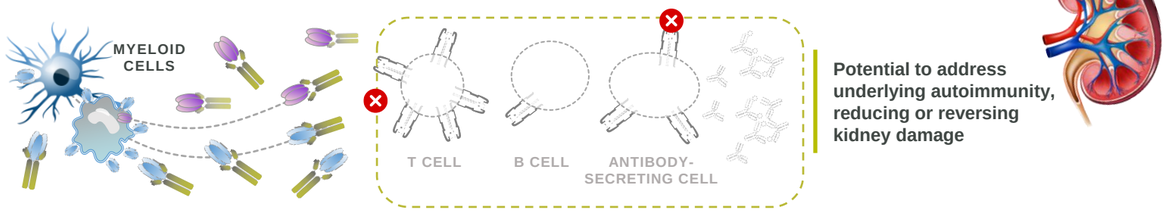
Glomerulonephritis (e.g., IgAN, pMN, LN)

BAFF and APRIL play key roles in the activity of many disease-related immune cells



Povetacicept: Dual BAFF/APRIL Inhibitor

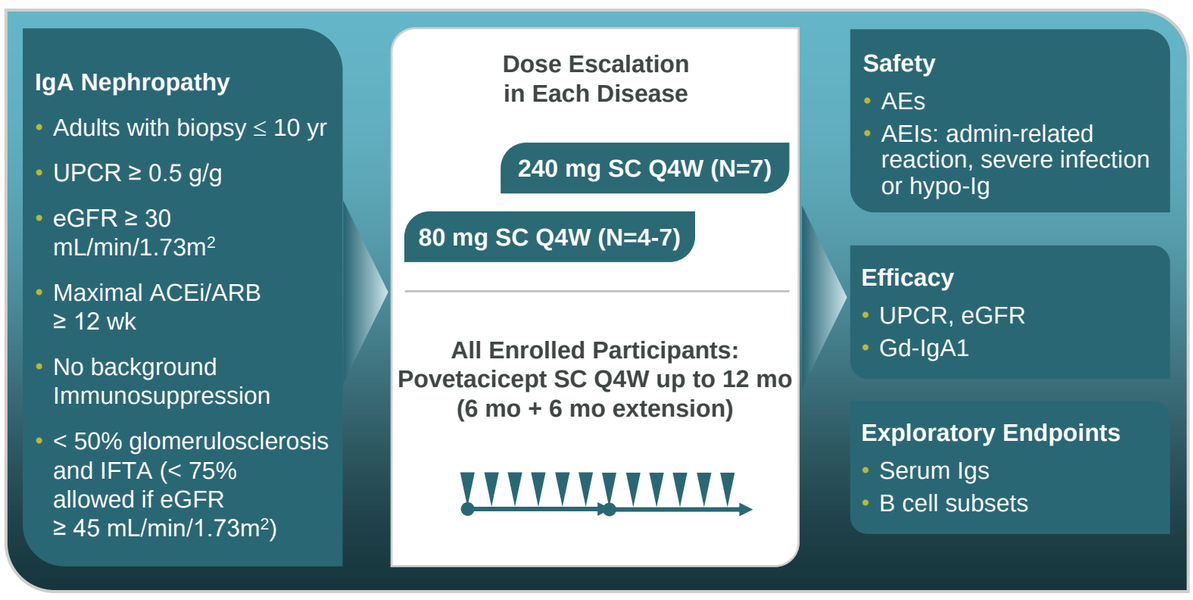
Designed to suppress the formation and/or promotion of autoimmune cells and autoantibodies

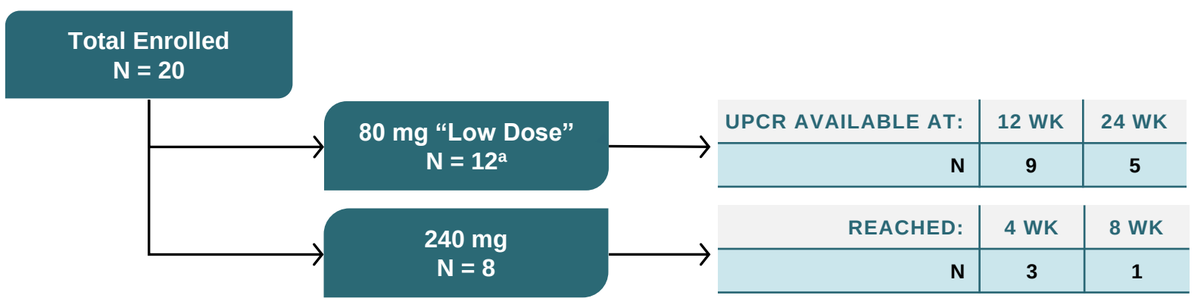


STUDY DESIGN & STATUS

RUBY-3 (NCT05732402) is an ongoing, first-in-disease, open-label, multiple ascending dose, phase 1b/2a study of povetacicept in adults with glomerulonephritis, including IgAN, pMN, and LN.

RUBY-3 Study Schema and Disposition and Analysis Status: IgAN Cohorts





UPCR AVAILABLE AT:	12 WK	24 WK
N	9	5

REACHED:	4 WK	8 WK
N	3	1

[a] One participant was withdrawn from the study at the investigator's discretion.

Data: 25 Oct 2023

RESULTS

Baseline Characteristics for IgAN Cohort Treated with Low Dose Povetacicept (80 mg SC Q4W)

Characteristic (Mean ± SD or N [%])	80 mg SC Q4W N=12
Age, yr	51 ± 12
Female / Male	7 (58%) / 5 (42%)
Caucasian / Asian	7 (58%) / 5 (42%)
BMI, kg/m²	28 ± 6.5
Duration of Disease, yr	4.4 ± 6.5
24-hr UPCR, g/g	1.3 ± 0.8
eGFR, mL/min/1.73 m²	70 ± 35
Prior Treatments	
- Corticosteroids	2 (17%)
- Eculizumab	1 (8%)
Current SGLT2 Inhibitor Use	2 (17%)
Medical History	
- Hypertension	7 (58%)
- Diabetes	4 (33%)

Data: 20 Oct 2023

Low Dose Povetacicept (80 mg SC Q4W) Has Been Well Tolerated in IgAN

- Treatment-emergent AEs during treatment with povetacicept 80 mg SC Q4W have been low grade to date, with none considered treatment-related.
- No administration-related reactions, severe infections or severe hypogammaglobulinemia (IgG < 3 g/L).

Status	80 mg SC Q4W N=12
Treatment-Emergent AEs (n, %)	4 (33%)
- Grade 1	3 (25%)
- Grade 2	1 (8%)
- Grade ≥ 3	0
- Treatment-related	0
AEs of Interest (n, %)	
- Administration-related reaction	0
- Hypogammaglobulinemia (IgG < 3 g/L)	0
- Grade ≥ 3 infection	0
Any Infection (n, %)	2 (17%)[a]

[a] Grade 1 nasopharyngitis, n=1; grade 2 upper respiratory tract infection, n=1. Data: 20 Oct 2023

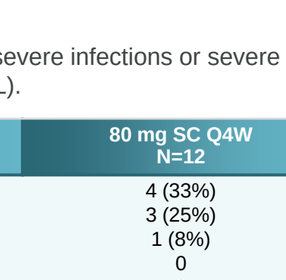
Low-Dose Povetacicept in pMN: A Case of Immunological Remission (Ongoing)

Primary Membranous Nephropathy[14]

- PLA2R1 is the major target antigen (up to 80%)
- Anti-PLA2R1 is highly correlated with clinical outcome
- Resolution of proteinuria lags behind immunological remission by months

First and only participant with pMN enrolled to date:

- 70-yr-old African-American male
- Duration of disease: 0.4 yr
- Current treatment: lisinopril



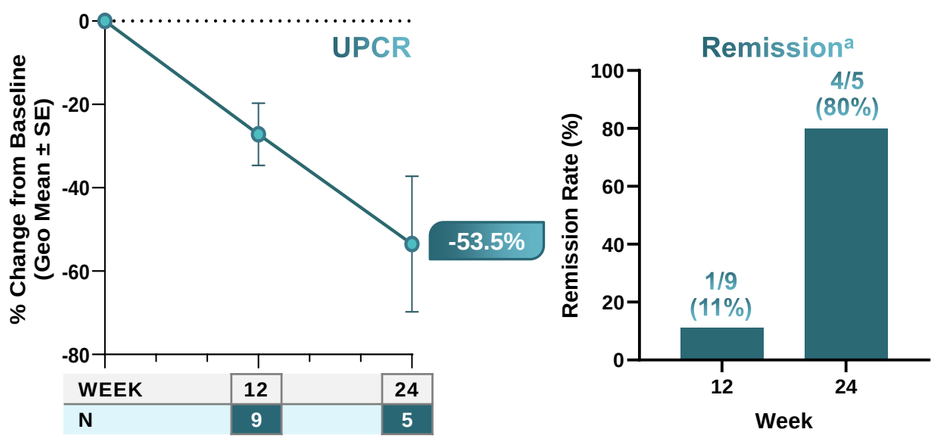
Data: 25 Oct 2023

Immunological remission (anti-PLA2R1 reduced to below the limit of detection) at wk 22

To obtain a copy of this poster, please scan the QR code. **SCAN ME**

KEY RESULTS: Low Dose Povetacicept (80 mg SC Q4W) in IgA Nephropathy

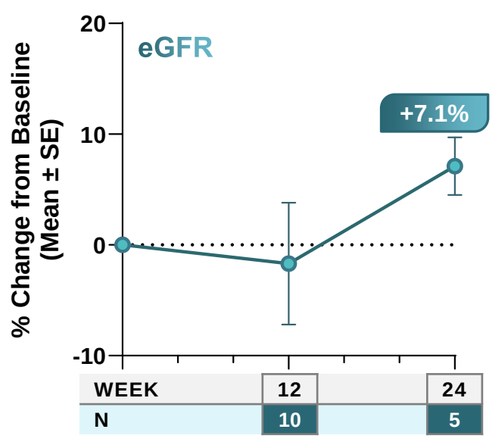
Clinically Meaningful Improvements in Proteinuria, Suggesting Remission



[a] Remission criteria based on Bagchi S, et al.[13]: UPCR < 0.5 g/g, UPCR reduced by ≥ 50% from baseline, and stable renal function (≤ 25% reduction in eGFR from baseline).

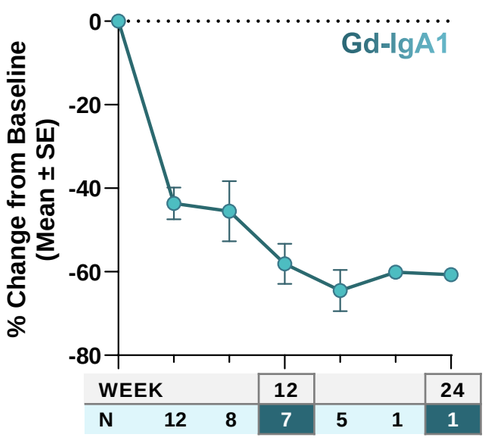
Data: 25 Oct 2023

Associated with Stable Renal Function (eGFR)



Data: 25 Oct 2023

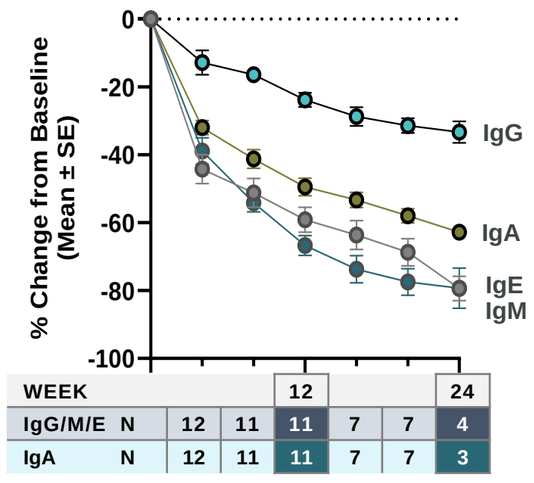
Reduces the Key IgAN-Specific Biomarker, Gd-IgA1



Data: 13 Oct 2023

Reduces Serum Ig Levels

- Pharmacodynamically-expected reductions in serum IgG, IgA, and IgM have been observed.
- Similar reductions in IgE were also noted.



Data: 25 Oct 2023

SUMMARY/CONCLUSIONS

- Povetacicept 80 mg SC Q4W has been well tolerated with multiple dosing.
- In participants with IgAN, povetacicept 80 mg demonstrates very promising activity at 6 months, with > 50% reduction in UPCR, > 60% reduction in Gd-IgA1, and consideration of clinical remission.
- In a first and ongoing case of pMN, immunological remission was observed at 22 wk.
- A higher dose of povetacicept (240 mg SC Q4W) is currently being evaluated.
- These findings suggest a highly promising clinical profile for povetacicept (based on initial clinical and biomarker activity and dose schedule) and strongly support further development in glomerulonephritis, particularly IgAN.

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ABBREVIATIONS

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; AEI, AE of interest; APRIL, a proliferation-inducing ligand; ARB, angiotensin receptor blocker; BAFF, B cell activating factor; BMI, body mass index; eGFR, estimated glomerular filtration rate; FcRn, neonatal Fc receptor; Gd-IgA1, galactose-deficient IgA1; IFTA, interstitial fibrosis and tubular atrophy; Ig, immunoglobulin; IgAN, IgA nephropathy; LN, lupus nephritis; PD, pharmacodynamics; pMN, primary membranous nephropathy; Q4W, once every 4 weeks; SC, subcutaneous; SGLT2, sodium-glucose cotransporter 2; TACI, transmembrane activator and CAML interactor; UPCR, urine protein to creatinine ratio.

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