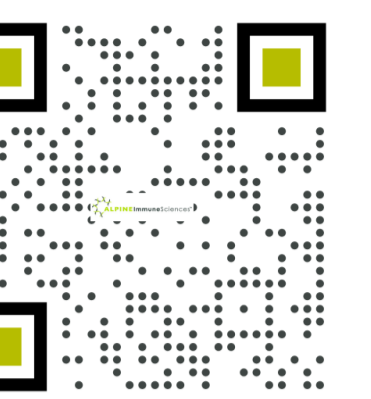


Updated results of povetacicept, an enhanced dual BAFF/APRIL antagonist, in IgA nephropathy (RUBY-3)

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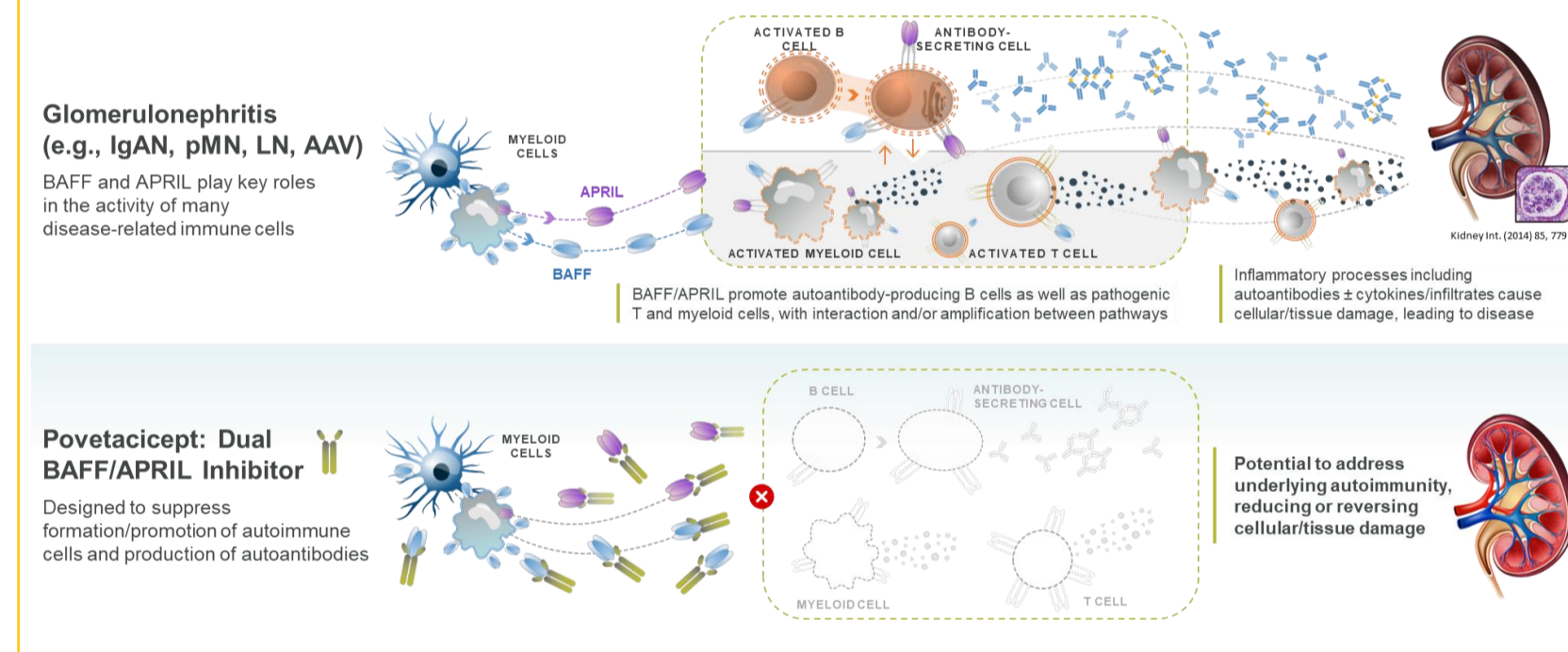
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INTRODUCTION

- BAFF and APRIL play critical roles in the activation, differentiation, and/or survival of B cells (particularly antibody-secreting cells) as well as other immune cells including T cells and innate immune cells.^{1,2}
- Inhibition of BAFF and/or APRIL has shown promise in multiple glomerulonephritis conditions,³⁻¹¹ with the potential to modify the underlying pathogenic autoimmunity. Due to their overlapping but non-redundant roles,¹² dual BAFF/APRIL inhibition is likely required for optimal efficacy.
- Povetacicept (ALPN-303) is an Fc fusion of a variant TACI domain engineered for enhanced dual BAFF/APRIL inhibition.¹³ Povetacicept has demonstrated activity superior to WT TACI-Ig; BAFF-, APRIL-, or FcRn-specific inhibitors; and B-cell depletion in multiple preclinical disease models.¹³⁻¹⁵
- Povetacicept was well tolerated in healthy volunteers and induced on-target PD effects, including reduced circulating Ig levels (including the IgAN biomarker Gd-IgA1) and antibody-secreting cells.¹⁶
- Initial results with povetacicept 80 mg SC Q4W in participants with IgAN enrolled in the ongoing RUBY-3 study (NCT05732402) showed good tolerability with multiple dosing and promising reductions in UPCR and Gd-IgA1.¹⁷

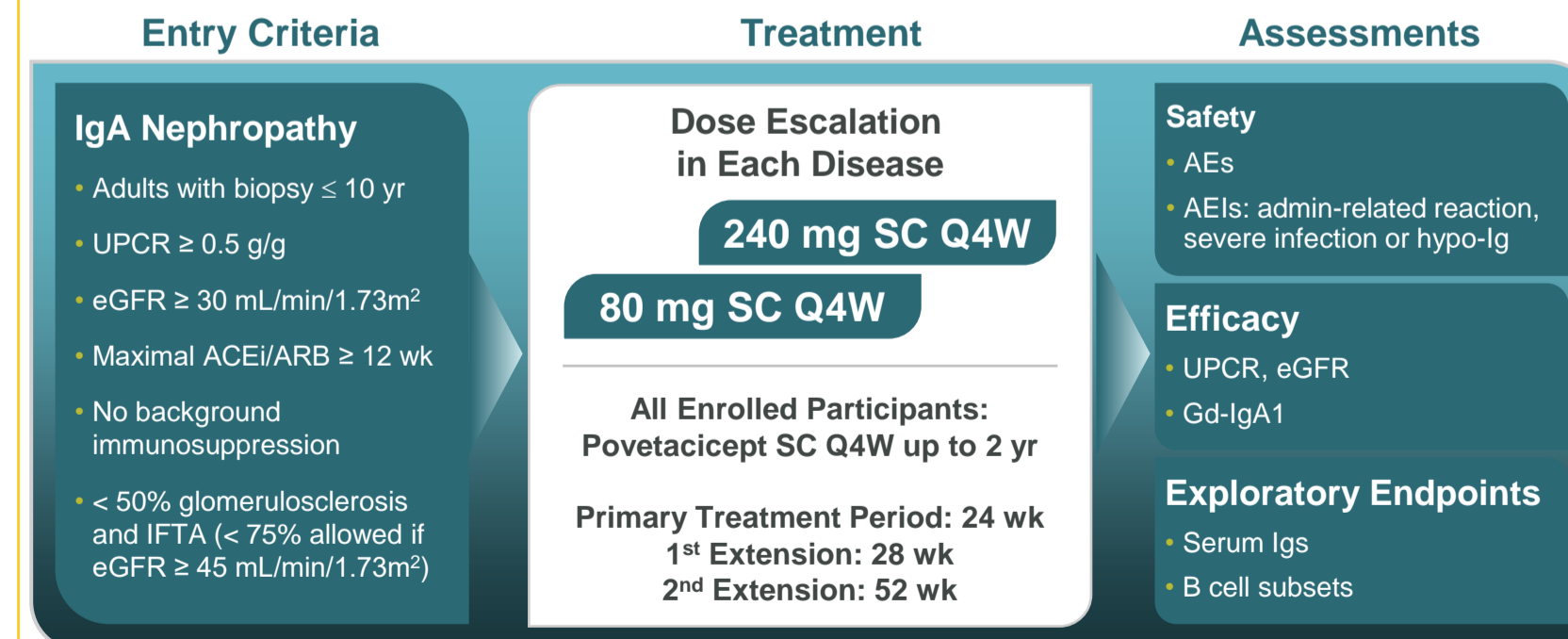
Povetacicept Potently Modulates B Cells and Pathogenic Autoantibodies



STUDY DESIGN & STATUS

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

RUBY-3 Study Schema: IgAN Cohorts

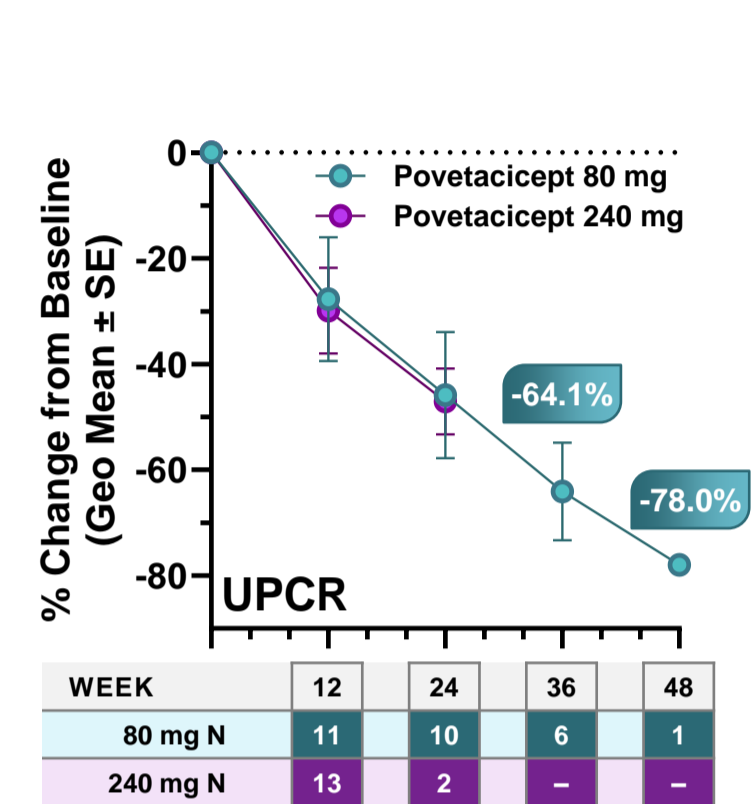


- As of 01 Mar 2024, a total of 41 participants with IgAN had enrolled (80 mg, N=12; 240 mg, N=29).
- All data reported are from 01 Mar 2024 except Gd-IgA1 data, which are from 11 Mar 2024.

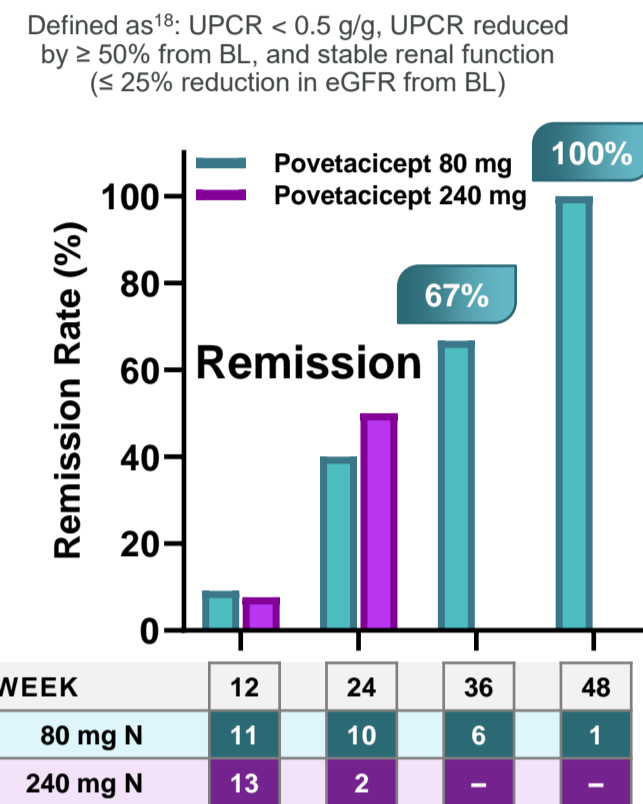
RESULTS

Povetacicept Provides Clinically Meaningful UPCR Reduction, Remission, Hematuria Resolution, and Stable eGFR in IgA Nephropathy, Associated with Reductions in Gd-IgA1

Reductions in Proteinuria (UPCR)

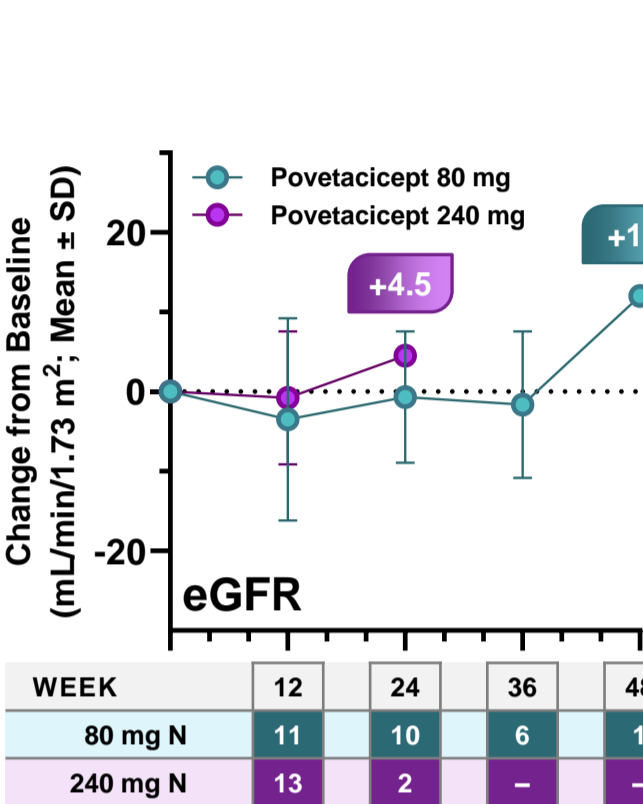


Achievement of Remission

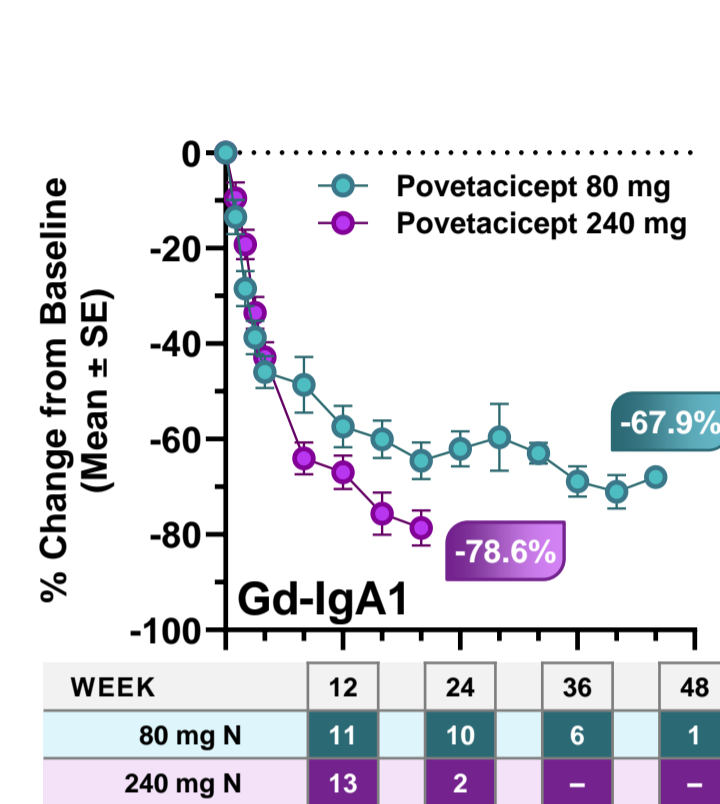


100% of IgAN participants achieved Hematuria Resolution, defined as negative/trace hematuria among those with non-negative/trace hematuria at BL, at 36 and 48 weeks (4/4 and 1/1, respectively)

Stable Renal Function (eGFR)



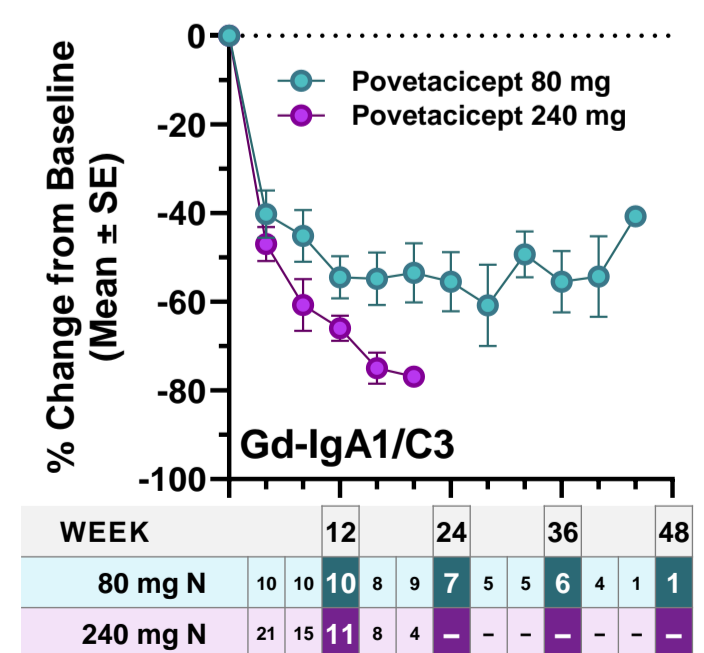
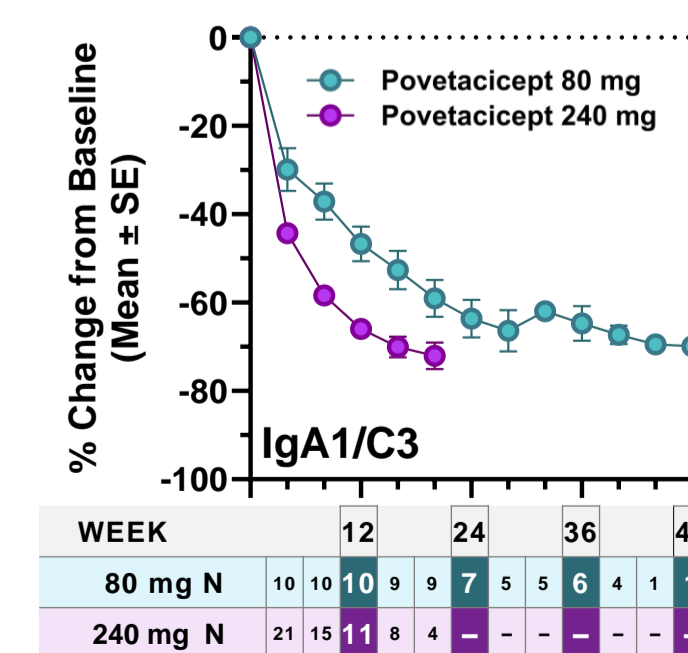
Reductions in Gd-IgA1



Baseline Characteristics: IgAN

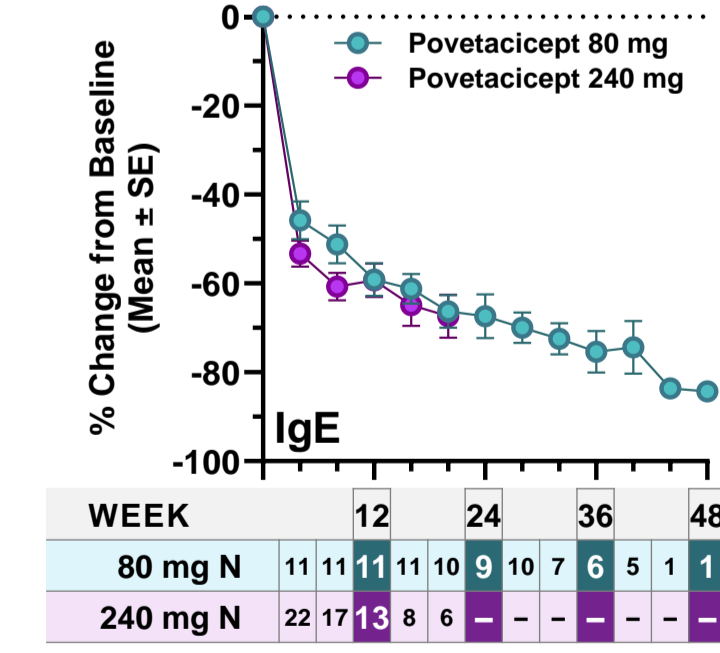
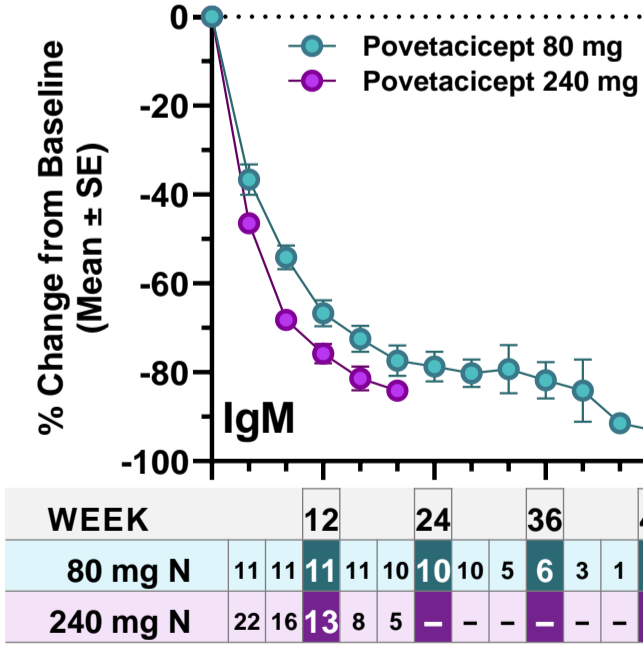
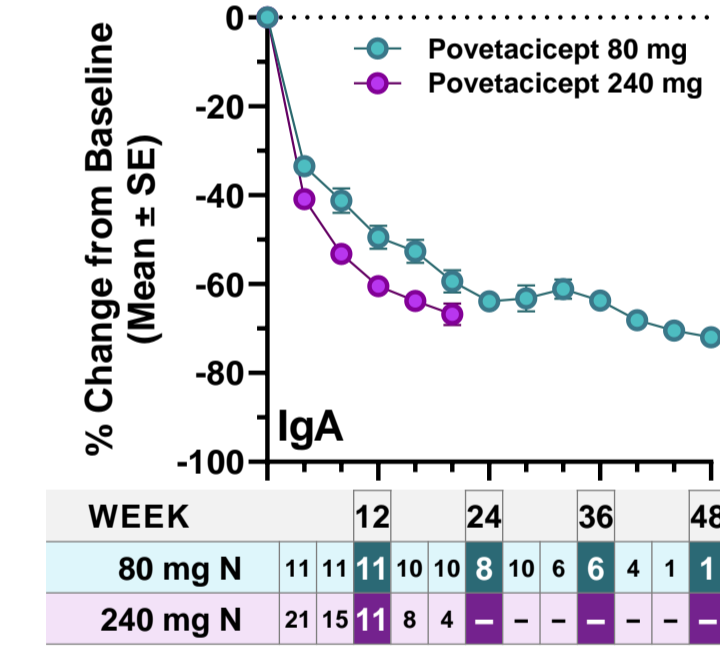
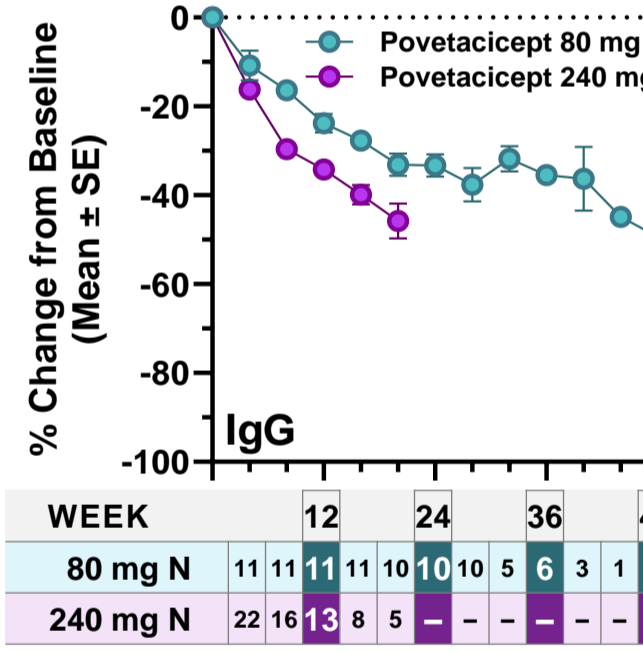
Characteristic (Mean ± SD or N [%])	80 mg SC Q4W N=12	240 mg SC Q4W N=29
Age, yr	51 ± 12	47 ± 11
Female / Male	7 (58%) / 5 (42%)	14 (48%) / 15 (52%)
Caucasian / Asian	7 (58%) / 5 (42%)	13 (45%) / 16 (55%)
BMI, kg/m ²	28 ± 6.5	25 ± 5.4
Duration of Disease, yr	4.4 ± 6.4	6.1 ± 5.5
24-hr UPCR, g/g	1.3 ± 0.8	1.2 ± 0.8
eGFR, mL/min/1.73 m ²	70 ± 35	59 ± 28
Prior Treatments		
- Corticosteroids	2 (17%)	4 (14%)
- Eculizumab	1 (8%)	0
Current Treatments		
- SGLT2 Inhibitor	2 (17%)	11 (38%)
- Endothelin Antagonist	0	0
Medical History		
- Hypertension	7 (58%)	18 (62%)
- Diabetes	5 (42%)	4 (14%)

Reductions in IgA1/C3 and Gd-IgA1/C3 Ratios^a



^a Biomarkers of IgAN disease severity and progression.¹⁹⁻²¹

Pharmacodynamic Serum Ig Reductions



OTHER RESULTS

- Reductions in IgA/C3 were similar to IgA1/C3 and Gd-IgA1/C3 (not shown).
- Of note, in preclinical studies, povetacicept achieved a 19-, 7-, and 6-fold greater distribution after dosing than WT TACI-Ig to kidney, lymph node, and ileum, respectively, suggesting that increased tissue distribution may contribute to its clinical activity.¹⁴

Safety: Povetacicept Has Been Well Tolerated in IgAN

Adverse Event (AE) Type	80 mg N=12	240 mg N=29	All IgAN N=41
Treatment-Emergent AEs (n, %)			
- Gr 1	7 (58%)	10 (34%)	17 (41%)
- Gr 2	5 (42%)	5 (17%)	10 (24%)
- Gr 3	1 (8%) ^a	5 (17%)	6 (15%)
- Gr ≥ 4	0	0	1 (2%)
- Treatment-related	1 (8%) ^b	1 (3%) ^c	2 (5%)
AEs of Interest (AEI; n, %)			
- Administration-related reaction	0	1 (3%) ^d	1 (2%)
- Severe hypogammaglobulinemia (IgG < 3 g/L)	0	0	0
- Malignancy	1 (8%) ^a	0	1 (2%)
Any Infection AE (n, %)			
- Gr 1	2 (17%)	8 (28%)	10 (24%)
- Gr 2	1 (8%)	5 (17%)	6 (15%)
- Gr ≥ 3	1 (8%)	3 (10%)	4 (10%)
	0	0	0

^a Gr 3 breast ductal carcinoma in situ, considered treatment unrelated by investigator (medical history of breast lobular carcinoma in situ and melanoma in situ). ^b Gr 2 viral upper respiratory tract infection. ^c Gr 1 viral upper respiratory tract infection and blood IgM decreased in 1 participant. ^d Gr 2 rash.

SUMMARY/CONCLUSIONS

- Povetacicept is well tolerated at both 80 and 240 mg SC Q4W in IgAN.
- Povetacicept treatment continues to be associated with clinically meaningful reductions in disease activity, including a > 60% reduction in UPCR at 9 mo, stable renal function, resolution of hematuria, and remission.
- Povetacicept is also associated with significant reductions in the key disease-related biomarker Gd-IgA1 as well as prognostic IgA1/C3 and Gd-IgA1/C3 ratios.
- Further development of povetacicept in GN, particularly IgAN, remains strongly supported. A pivotal trial in IgAN (RAINIER) is in preparation and planned to initiate later this year.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

AAV, antineutrophilic cytoplasmic antibody-associated vasculitis; 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; BL, baseline; BMI, body mass index; eGFR, estimated glomerular filtration rate; FcRn, neonatal Fc receptor; Gd-IgA1, galactose-deficient IgA1; GN, glomerulonephritis; 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; WT, wild-type.