Updated Results from the RUBY-3 Study of Povetacicept, an Enhanced Dual BAFF/APRIL Antagonist, in IgA Nephropathy

Jiahua Li[1], Jonathan Barratt[2], Harmeet Singh[3], Inwhee Park[4], Arvind Madan[5], Sreedhar Mandayam[6], Hemant Kulkarni[7,8], Sang-Woong Han[9], Sung Gyun Kim[10], Rupert Davies[1], Amanda Enstrom[1], Heather Thomas[1], Stanford L. Peng[1], James Tumlin[11,12]

[1]Alpine Immune Sciences, Inc., a Vertex Company, Seattle, WA; [2]University of Leicester, Leicester, UK; [3]Western Nephrology, Arvada, CO; [4]Ajou University School of Medicine, Republic of Korea; [5]Central Florida Kidney Specialists, Orlando, FL; [6]University of Texas MD Anderson Cancer Center, Houston, TX; [7]Royal Perth Hospital, Perth, Western Australia; [8]Armadale Hospital, East Metropolitan Health Services, Perth, Western Australia; [9]Hanyang University Guri Hospital, Gyeonggi-do, Republic of Korea; [10]Hallyn University Sacred Heart Hospital, Gyeonggi-do, Republic of Korea; [11]NephroNet Clinical Trials Consortium, Atlanta, GA; [12]Emory University School of Medicine, Atlanta, GA.

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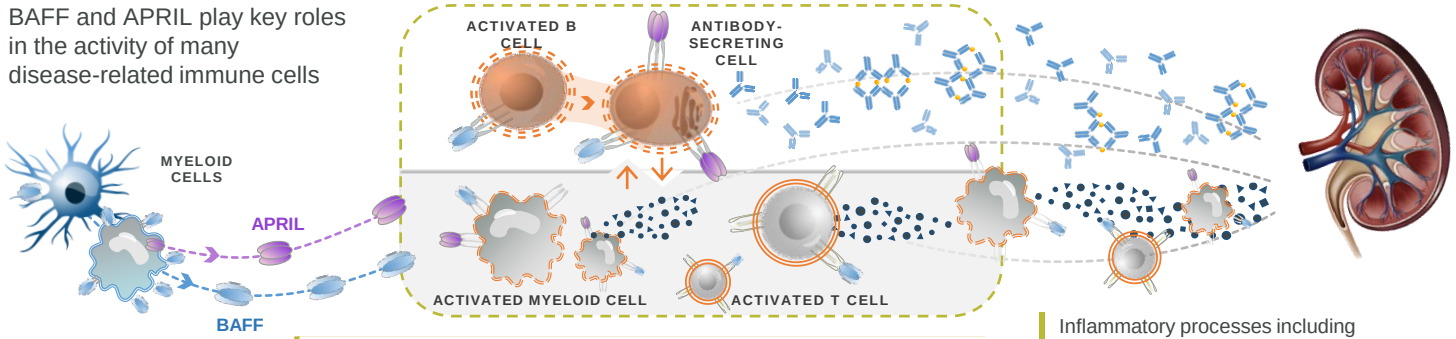
Disclosures

- **Employment** – Dr. Li is an employee of Alpine Immune Sciences, a Vertex Company

BAFF/APRIL Inhibition Potentially Modulates B Cells & Pathogenic Autoantibodies

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

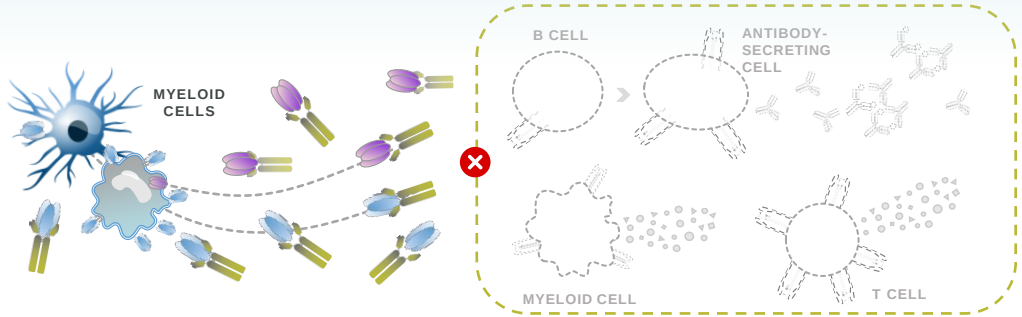
BAFF and APRIL play key roles in the activity of many disease-related immune cells



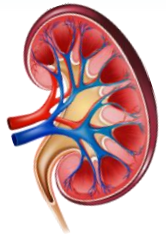
BAFF/APRIL promote autoantibody-producing B cells as well as pathogenic T and myeloid cells, with interaction and/or amplification between pathways

Inflammatory processes including autoantibodies ± cytokines/infiltrates cause cellular/tissue damage, leading to disease

Dual BAFF/APRIL Inhibition



Potential to address underlying autoimmunity reducing or reversing cellular/tissue damage



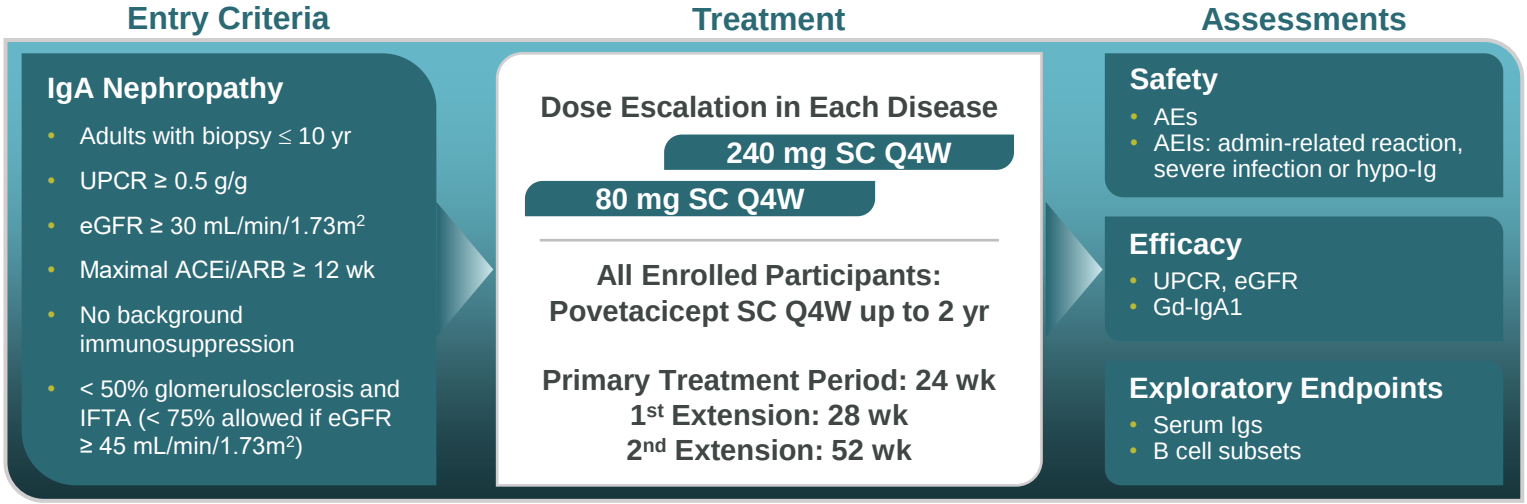
LEGEND

- APRIL
- BAFF
- BAFF-R, BCMA, TACI
- Povetacicept
- (AUTO)ANTIBODIES
- AUTOANTIGENS
- IMMUNE COMPLEX
- CYTOKINES

Adapted from Tumlin J, et al. Poster presented at the World Congress of Nephrology (WCN), Buenos Aires, Argentina, April 13-16, 2024.

RUBY-3 Study Schema: IgAN Cohorts

- 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.



- 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.

AAV, antineutrophilic cytoplasmic antibody-associated vasculitis; ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; AEI, AE of interest; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; Gd-IgA1, galactose-deficient IgA1; IFTA, interstitial fibrosis and tubular atrophy; Ig, immunoglobulin; IgAN, IgA nephropathy; LN, lupus nephritis; pMN, primary membranous nephropathy; Q4W, once every 4 weeks; SC, subcutaneous; UPCR, urine protein to creatinine ratio.

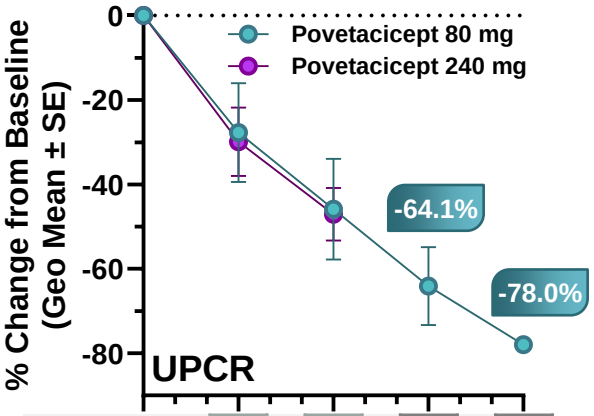
Baseline Characteristics: IgAN

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 - Eculizumab	 2 (17%) 1 (8%)	 4 (14%) 0
Current Treatments - SGLT2 Inhibitor - Endothelin Antagonist	 2 (17%) 0	 11 (38%) 0
Medical History - Hypertension - Diabetes	 7 (58%) 5 (42%)	 18 (62%) 4 (14%)

BMI, body mass index; eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy; Q4W, once every 4 weeks; SC, subcutaneous; SGLT2, sodium-glucose cotransporter 2; UPCR, urine protein to creatinine ratio.

Povetacicept Shows UPCR Reduction, Remission, and Hematuria Resolution in IgA Nephropathy

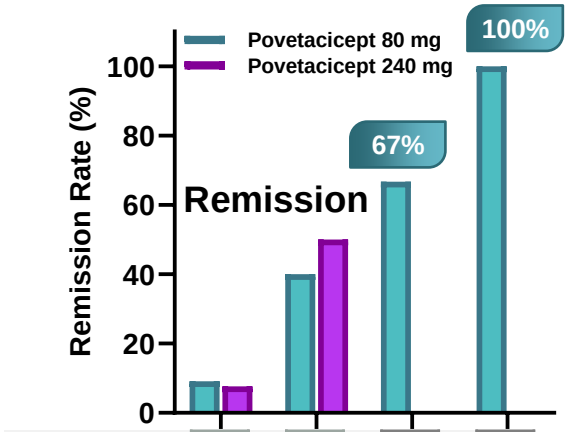
Reductions in Proteinuria (UPCR)



WEEK	12	24	36	48
80 mg N	11	10	6	1
240 mg N	13	2	–	–

Achievement of Remission

Defined as[1]: UPCR < 0.5 g/g, UPCR reduced by ≥ 50% from BL, and stable renal function (≤ 25% reduction in eGFR from BL)



WEEK	12	24	36	48
80 mg N	11	10	6	1
240 mg N	13	2	–	–

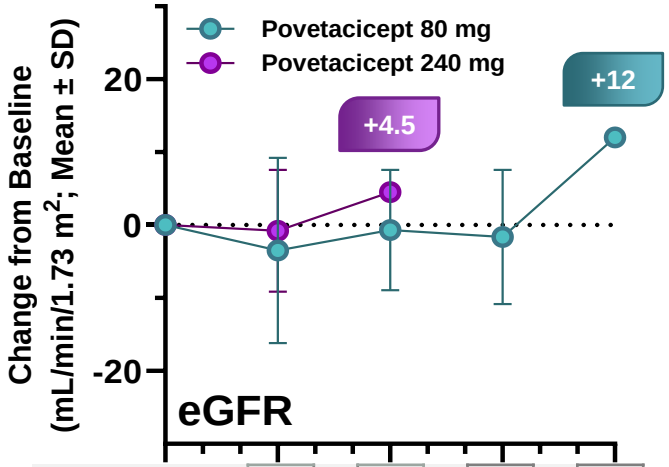
100% of IgAN participants achieved Hematuria Resolution, defined as negative/trace hematuria among those with non-negative/trace hematuria at BL, at 36 and 48 weeks (4/4 and 1/1, respectively)

BL, baseline; eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy; UPCR, urine protein to creatinine ratio.

1. Bagchi S. Kidney Int Rep. 2021;6(6):1661-1668.

Povetacicept Provides Stable eGFR in IgA Nephropathy

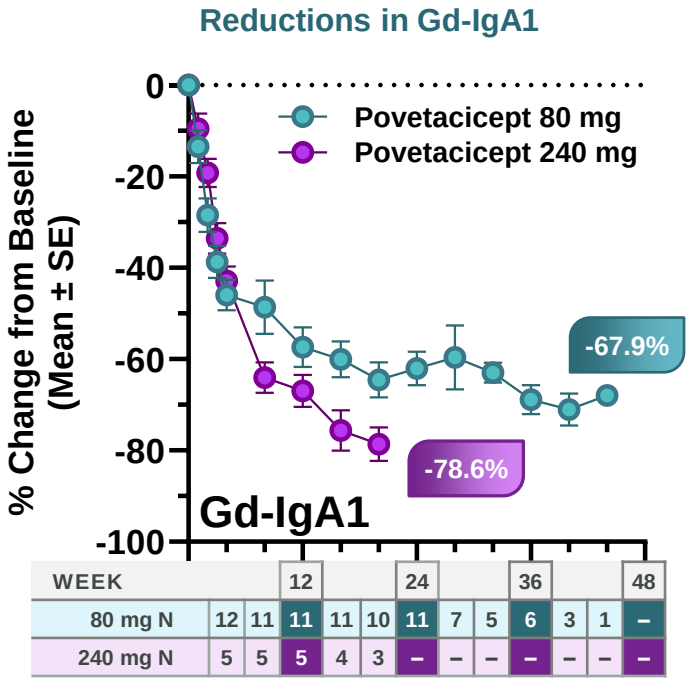
Stable Renal Function (eGFR)



WEEK	12	24	36	48
80 mg N	11	10	6	1
240 mg N	13	2	–	–

eGFR, estimated glomerular filtration rate.

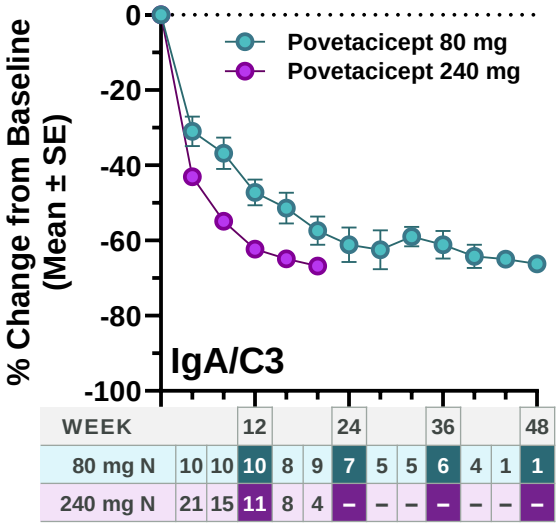
Povetacicept Reduces Plasma Gd-IgA1 Levels



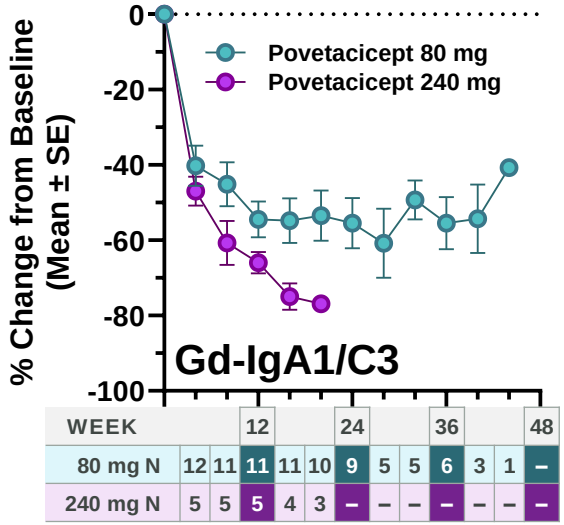
Gd-IgA1, galactose-deficient IgA1 (a key biomarker in IgAN[1])

1. Zhang K, et al. Kidney Blood Press Res. 2019;44(5):1196-1206.

Povetacicept Reduces IgA/C3 and Gd-IgA1/C3 Ratios[a]



WEEK			12			24			36			48
80 mg N	10	10	10	8	9	7	5	5	6	4	1	1
240 mg N	21	15	11	8	4	–	–	–	–	–	–	–



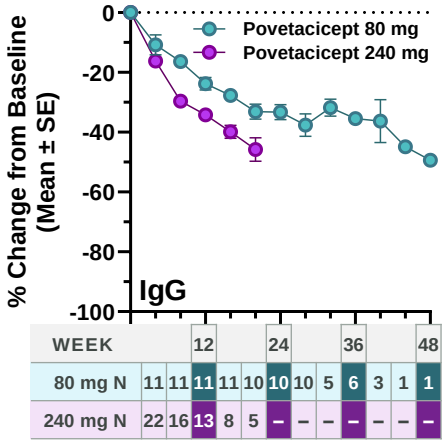
WEEK			12			24			36			48
80 mg N	12	11	11	11	10	9	5	5	6	3	1	–
240 mg N	5	5	5	4	3	–	–	–	–	–	–	–

Reductions in IgA1/C3 were similar to IgA/C3 and Gd-IgA1/C3 (not shown).

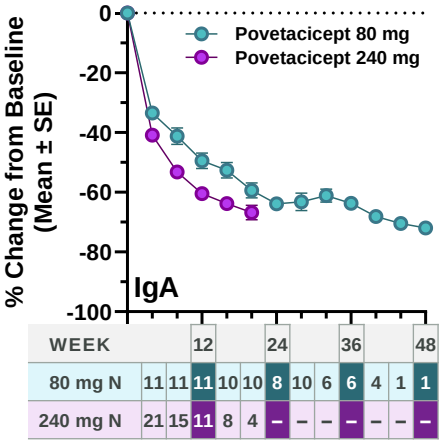
[a]Biomarkers of IgAN disease severity and progression.[1-3]
Gd-IgA1, galactose-deficient IgA1.

1. Chen P. Clin J Am Soc Nephrol. 2019;14(10):1458-1465; 2. Mizerska-Wasiak M. Pediatr Nephrol. 2015;30(7):1113-1120; 3. Stefan G. Iran J Kidney Dis. 2020;14(6):470-477.

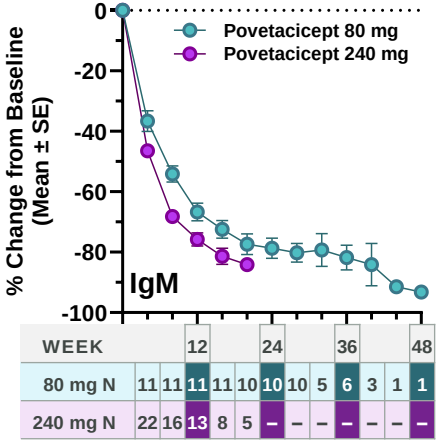
Povetacicept Produces Pharmacodynamic Serum Ig Reductions



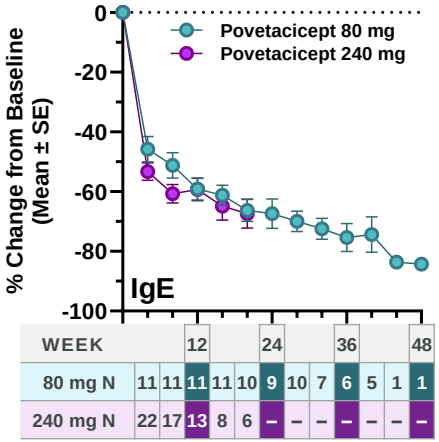
WEEK			12			24			36			48
80 mg N	11	11	11	11	10	10	10	5	6	3	1	1
240 mg N	22	16	13	8	5	–	–	–	–	–	–	–



WEEK			12			24			36			48
80 mg N	11	11	11	10	10	8	10	6	6	4	1	1
240 mg N	21	15	11	8	4	–	–	–	–	–	–	–



WEEK			12			24			36			48
80 mg N	11	11	11	11	10	10	10	5	6	3	1	1
240 mg N	22	16	13	8	5	–	–	–	–	–	–	–



WEEK			12			24			36			48
80 mg N	11	11	11	11	10	9	10	7	6	5	1	1
240 mg N	22	17	13	8	6	–	–	–	–	–	–	–

Ig, immunoglobulin.

Safety Data: Povetacicept in IgAN

Adverse Event (AE) Type	80 mg N=12	240 mg N=29	All IgAN N=41
Treatment-Emergent AEs (n, %)	7 (58%)	10 (34%)	17 (41%)
- Gr 1	5 (42%)	5 (17%)	10 (24%)
- Gr 2	1 (8%)	5 (17%)	6 (15%)
- Gr 3	1 (8%)[a]	0	1 (2%)
- Gr ≥ 4	0	0	0
- 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, %)	2 (17%)	8 (28%)	10 (24%)
- Gr 1	1 (8%)	5 (17%)	6 (15%)
- Gr 2	1 (8%)	3 (10%)	4 (10%)
- Gr ≥ 3	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.
IgAN, IgA nephropathy.

Summary/Conclusions

- Data from RUBY-3 show reductions in disease activity, including a > 60% reduction in UPCR at 9 months, stable renal function, resolution of hematuria, and remission among patients with IgAN who received povetacicept.
- Treatment was also associated with reductions in the disease-related biomarker Gd-IgA1, as well as prognostic IgA/C3 and Gd-IgA1/C3 ratios.
- Povetacicept 80 mg and 240 mg SC Q4W was generally well tolerated, with most AEs mild or moderate in severity.
- Further development of povetacicept in glomerulonephritis, particularly IgAN, is warranted; a pivotal trial in IgAN (RAINIER) is in preparation and planned to initiate later this year.

Gd-IgA1, galactose-deficient IgA1; IgAN, IgA nephropathy; Q4W, once every 4 weeks; SC, subcutaneous; UPCR, urine protein to creatinine ratio.