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

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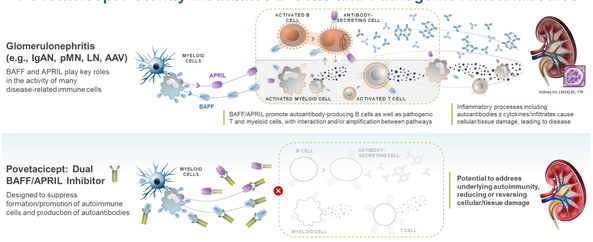
Poster 401
Abstract NKF-SUB-14448

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]

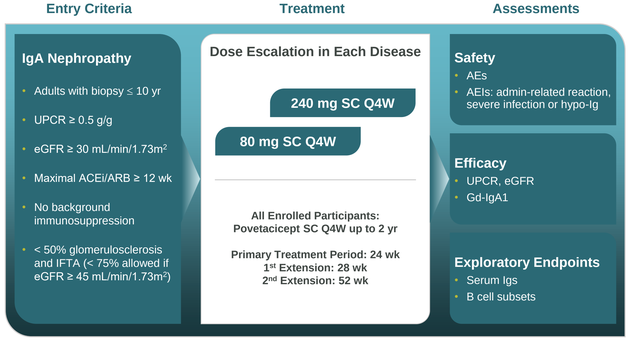
Povetacicept Potently Modulates B Cells and Pathogenic Autoantibodies



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

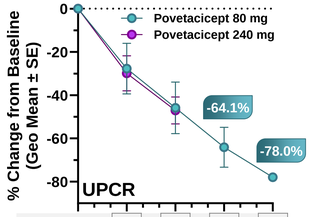


- As of 01 Mar 2024, a total of 41 participants with IgAN had enrolled (80 mg, N=12; 240 mg, N=29).
- All data reported are from 01 Mar 2024 except Gd-IgA1 data, which are from 11 Mar 2024.

RESULTS

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

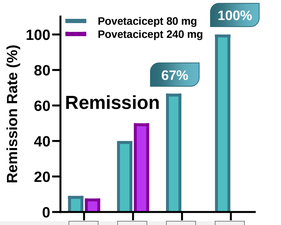
Reductions in Proteinuria (UPCR)



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

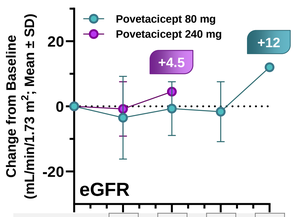
Achievement of Remission

Defined as[18]: UPCR < 0.5 g/g, UPCR reduced by ≥ 50% from BL, and stable renal function (≤ 25% reduction in eGFR from BL)



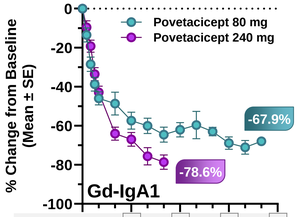
WEEK	12	24	36	48
80 mg N	11	10	6	1
240 mg N	13	2	–	–

Stable Renal Function (eGFR)



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

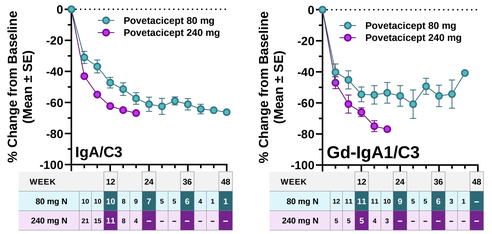
Reductions in Gd-IgA1



WEEK	12	24	36	48
80 mg N	12	11	11	11	10	11	7	5	6	3	1	–
240 mg N	5	5	5	4	3	–	–	–	–	–	–	–

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)

Reductions in 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	–	–	–	–	–	–	–

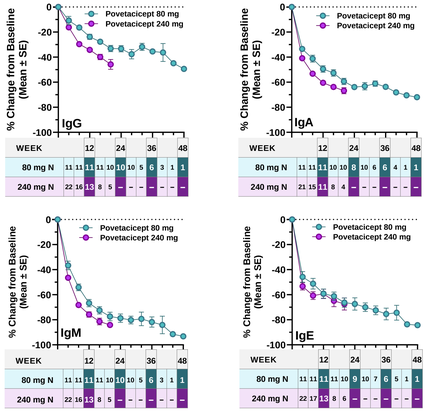
WEEK	12	24	36	48
80 mg N	12	11	11	10	9	5	5	6	3	1	–
240 mg N	5	5	5	4	3	–	–	–	–	–	–

[a] Biomarkers of IgAN disease severity and progression.[19-21]

Other Results

- Reductions in IgA1/C3 were similar to IgA/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]

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	11	10	10	10	5	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	–	–	–	–	–	–	–

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 IgA/C3 and Gd-IgA1/C3 ratios.
- Further development of povetacicept in glomerulonephritis, particularly IgAN, remains strongly supported. A pivotal trial in IgAN (RAINIER) is in preparation and planned to initiate later this year.

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SCAN ME

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/m²	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 m²	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%)

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, %)	7 (58%)	10 (34%)	17 (41%)
- Grade 1	5 (42%)	5 (17%)	10 (24%)
- Grade 2	1 (8%)	5 (17%)	6 (15%)
- Grade 3	1 (8%)[a]	0	1 (2%)
- Grade ≥ 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%)
- Grade 1	1 (8%)	5 (17%)	6 (15%)
- Grade 2	1 (8%)	3 (10%)	4 (10%)
- Grade ≥ 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.

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; 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.

REFERENCES

1. Samy E. Int Rev Immunol. 2017;36(1):3-19. 2. Benson MJ. J Immunol. 2008;180(6):3655-3659. 3. Anthera 10-K 05Mar2018: Anthera Press Release 28Aug2017. 4. Furie R. N Engl J Med. 2020;383(12):1117-1128. 5. Kooienga L. J Am Soc Nephrol. 2022;33:TH-PO991 [ASN22]. 6. Barratt J. Nephrol Dial Transplant. 2023;38:4337 [ERA23]. 7. Barratt J. Kidney Int Rep. 2022;7(8):1831-1841. 8. Lv J. Kidney Int Rep. 2023;8(3):499-506. 9. Isenberg D. Abs 1291016 [ACR22]. 10. Chen J-W. Int J Rheum Dis. 2023;26(7):1417-1421. 11. Lenert A. Drug Des Devel Ther. 2015;9:333-347. 12. Krumbholz M. Nat Rev Neurol. 2012;8(11):613-623. 13. Evans LS. Arthritis Rheumatol. 2023;75(7):1187-1202. 14. Lewis KE. Abs P104 [SLEuro24]. 15. Lewis KE. Abs 3614 [AAN24]. 16. Dillon SR. Abs ide078 [IIgANN23]. 17. Tumlin JA. J Am Soc Nephrol. 2023;34:TH-PO1125 [ASN23]. 18. Bagchi S. Kidney Int Rep. 2021;6(6):1661-1668. 19. Chen P. Clin J Am Soc Nephrol. 2019;14(10):1458-1465. 20. Mizerska-Wasiak M. Pediatr Nephrol. 2015;30(7):1113-1120. 21. Stefan G. Iran J Kidney Dis. 2020;14(6):470-477.

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