Phase 1 Study in Healthy Adults of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Povetacicept (ALPN-303), a Dual BAFF/APRIL Antagonist for the Treatment of Autoimmune Glomerulonephritides

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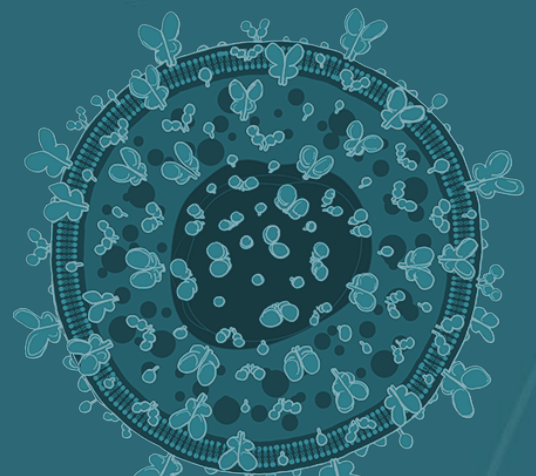
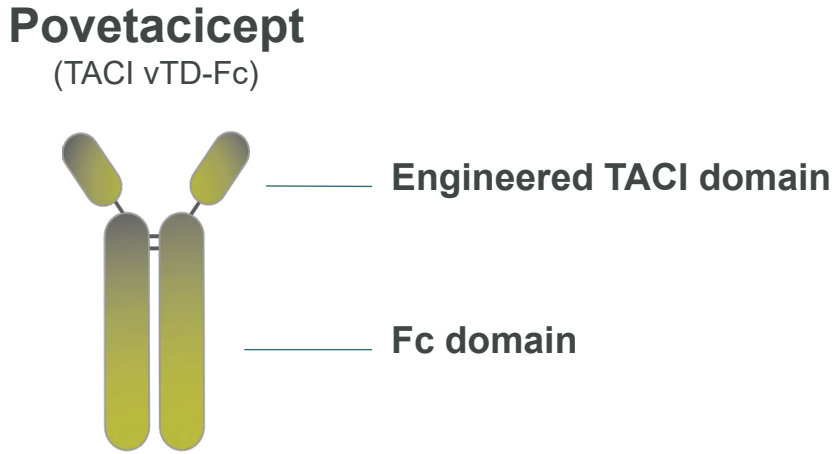


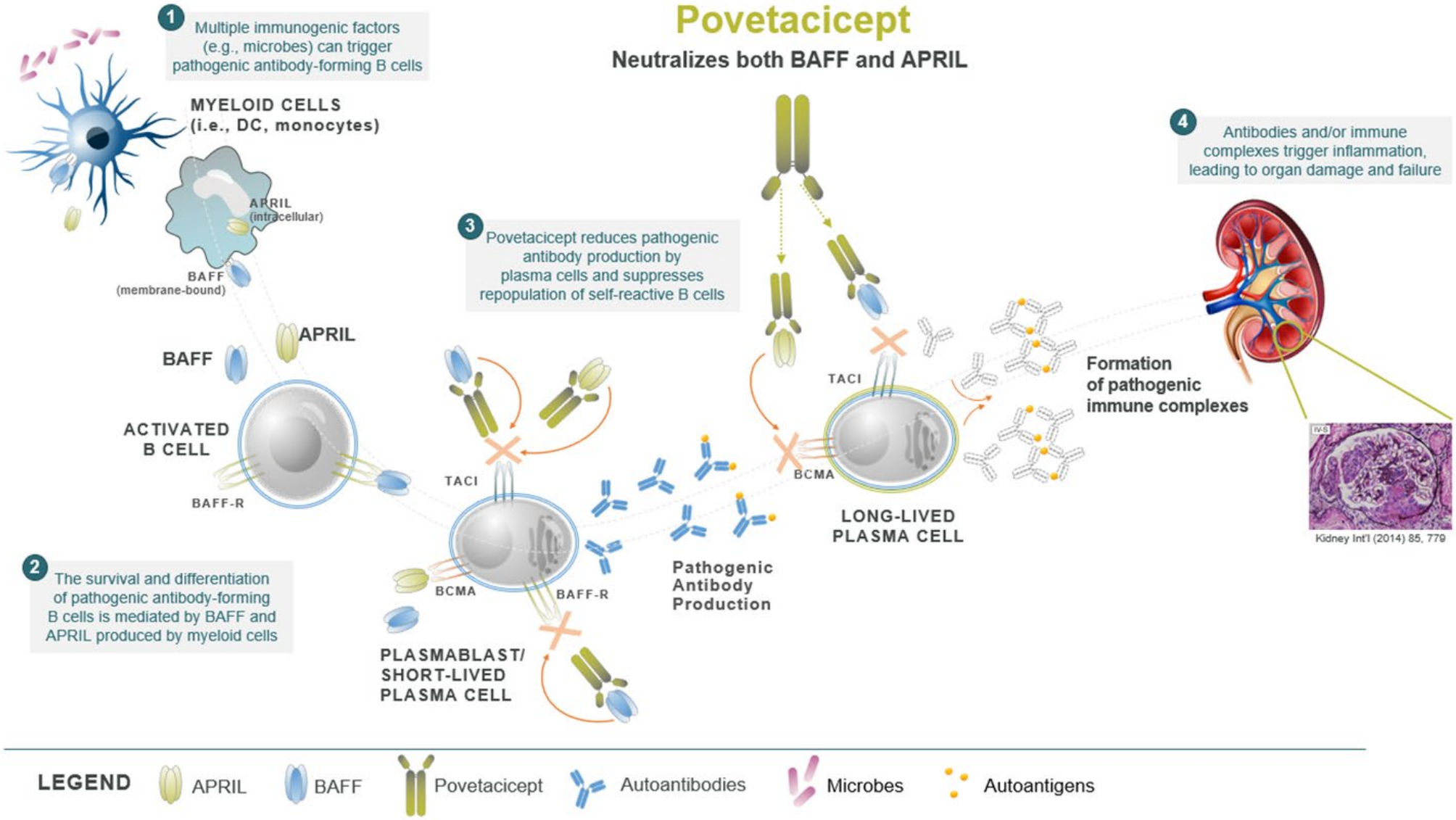
Povetacicept: An Enhanced Dual APRIL/BAFF Antagonist for GN and Other Autoantibody-Related Diseases

- Elevation of BAFF and APRIL occurs in GNs. They are clinically validated targets in IgAN, LN, SLE, and other autoantibody-related diseases.[1-8]
- BAFF and/or APRIL may mediate escape/resistance to rituximab and other B cell-depleting therapies.
- Povetacicept is a decoy receptor Fc fusion incorporating an engineered TACI domain with superior inhibitory activity against BAFF and APRIL.
- In preclinical studies, povetacicept demonstrates superior efficacy versus WT TACI-Ig or BAFF or APRIL inhibition alone.[9]



1. Huang X, Su G. Front. Pharmacol. 2021; https://doi.org/10.3389/fphar.2021.715253. 2. Sá H, et al. Int Rev Immunol. 2017;36(3):182-203. 3. Selvaskandan H, et al. Expert Opin Investig Drugs. 2022;31(12):1321-38. 4. Krustev E, et al. Expert Rev Clin Immunol. 2023;19(1):55-70. 5. Benson MJ, et al. J Immunol. 2008;180(6):3655-9. 6. Haselmayer P, et al. Eur J Immunol. 2017;47(6):1075-85. 7. Huard B, et al. PLoS One. 2012;7(2):e31837. 8. Jacob CO, et al. Arthritis Rheumatol. 2012;64(5):1610-19. 9. Evans LS, et al. Arthritis Rheumatol. 2023 Jan 27. doi: 10.1002/art.42462.

Povetacicept is an Enhanced APRIL/BAFF Antagonist that Potently Modulates B Cells and Pathogenic Autoantibodies

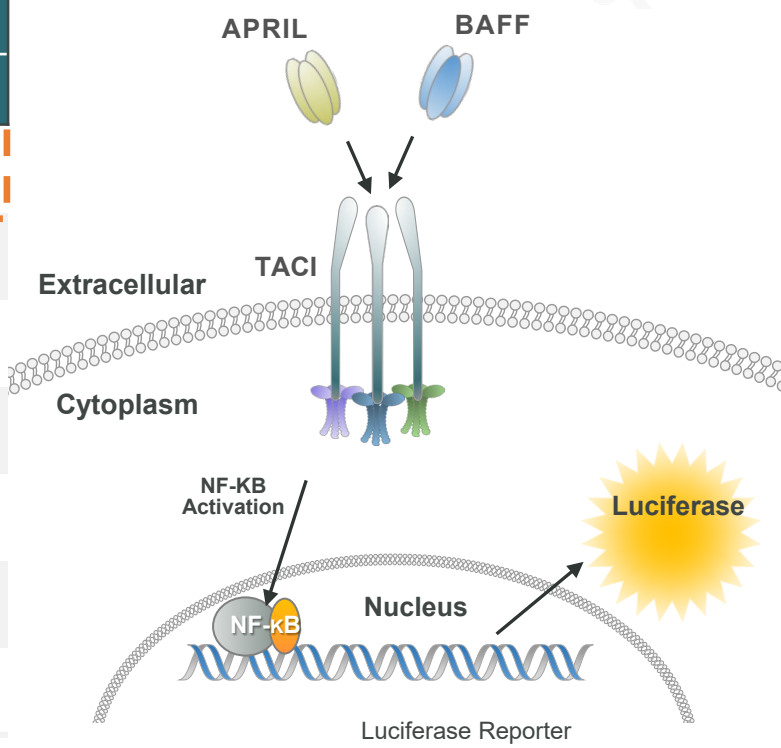


Povetacicept Demonstrates Best-In-Class Inhibitory Potential

Dual inhibitor that addresses wild-type TACI's relatively poor binding to APRIL

Reagent	IC_{50} (nM)[1]		
	APRIL	BAFF	APRIL + BAFF
Povetacicept (ALPN-303)	**3.8**	**1.4**	**3.1**
WT TACI-Fc[2]	>200	20.8	>200
Telitacicept[3]	53.9	14.5	>200
Anti-APRIL mAb[4]	21.9	CNBD	>200
Anti-APRIL mAb[5]	5.1	CNBD	CNBD
Belimumab	CNBD	4.8	CNBD
Belimumab + Anti-APRIL mAb[4]	18.9	4.8	10.8

TACI/Jurkat/NF-κB Functional Assay



1 TACI/Jurkat/NF-κB reporter assay
2 WT TACI 30-110-Fc; generated by ALPN using published atacicept sequence (SEQ ID NO: 54 of US Patent 8,815,238 B2)
3 WT TACI 13-118-Fc, as identified in WHO Drug Information, Vol. 32, No. 4, 2018 and confirmed by mass spec/peptide sequencing on Tai'ai®
4 Generated by ALPN using published BION-1301 sequence (SEQ ID NO: 50 and 52 from US Patent Appl. US 2020/0079859)
5 Generated by ALPN using published sibeprenlimab sequence (https://www.imgt.org/3Dstructure-DB/cgi/details.cgi?pdbcode=11575)
CNBD, Could not be determined

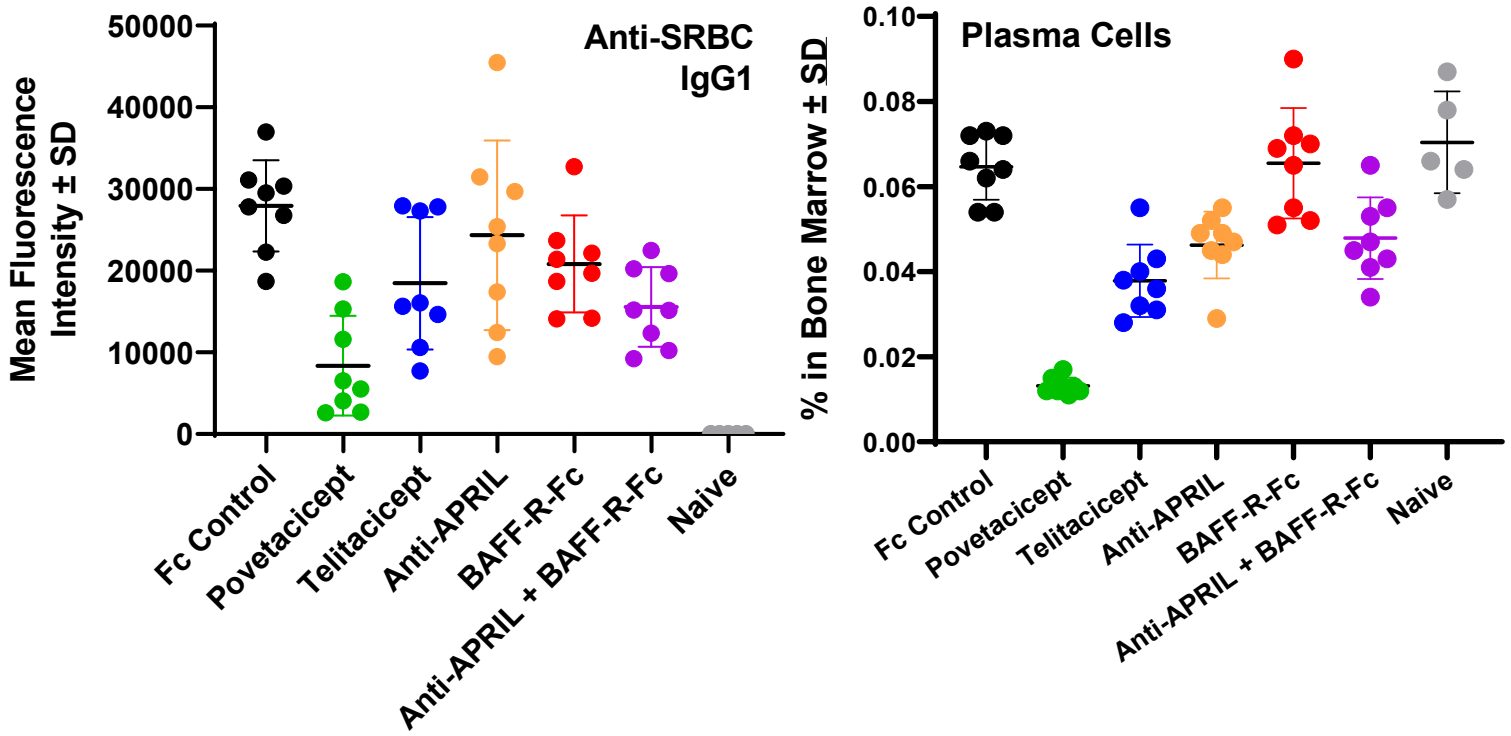
Source: ALPN generated data and
Evans LS, et al. *Arthritis Rheumatol* 2023 Jan 27; doi: 10.1002/art.42462

Dual BAFF/APRIL Inhibition Provides Superior Efficacy in Preclinical Studies

Povetacicept is Superior to Single Cytokine and to Combination Biologic Inhibition in Preclinical Studies

Povetacicept Shows Superior Efficacy in Mouse SRBC Challenge

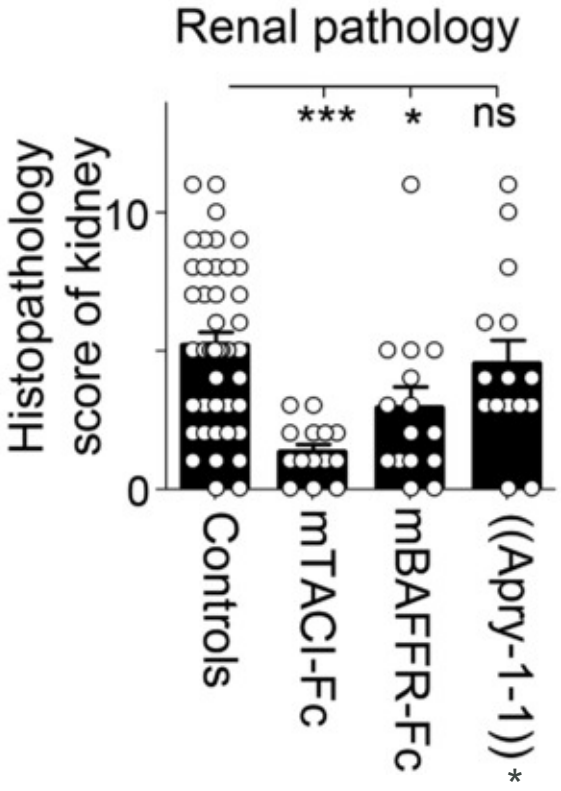
Including vs. combination of BAFF- + APRIL-specific biologics



SRBC = Sheep Red Blood Cell(s)
Alpine Immune Sciences, Data on File

Evans LS, et al. *Arthritis Rheumatol* 2023 Jan 27; doi: 10.1002/art.42462

Consistent with Superiority of Dual Inhibition in Murine Lupus (NZB/W F1)



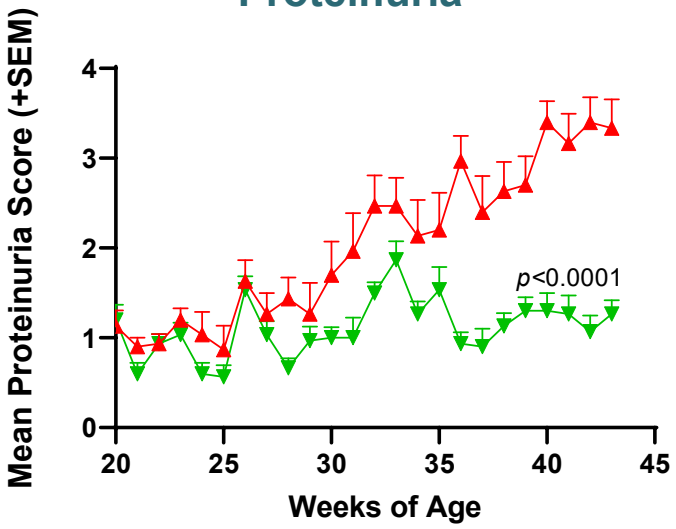
Haselmayer P, et al. Eur J Immunol. 2017;47(6):1075-85.

*Anti-APRIL mAb

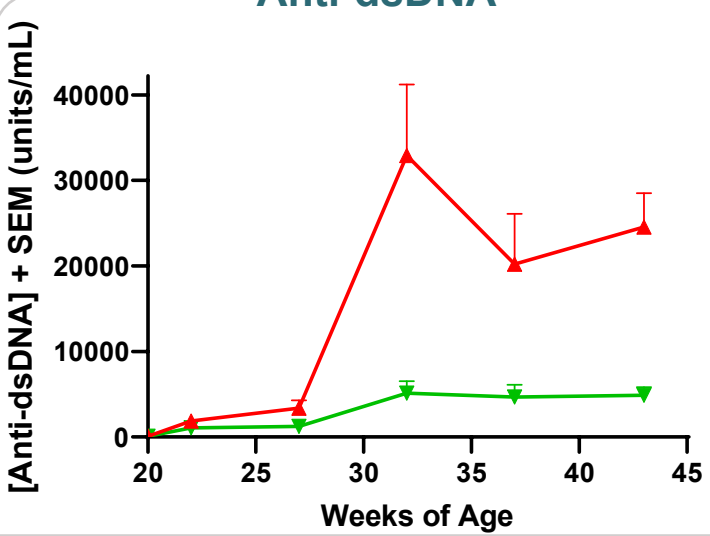
Povetacicept Suppresses Systemic Autoimmunity, incl. Glomerulonephritis

NZB/W F1 – a Model for SLE, LN and Other GNs, Sjögren's, and Other Autoantibody-Related Diseases

Proteinuria

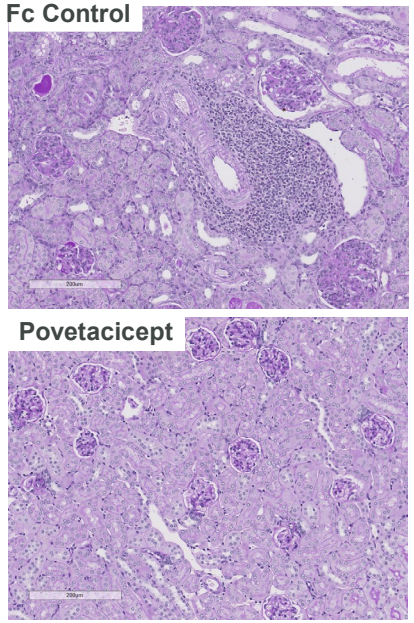


Anti-dsDNA

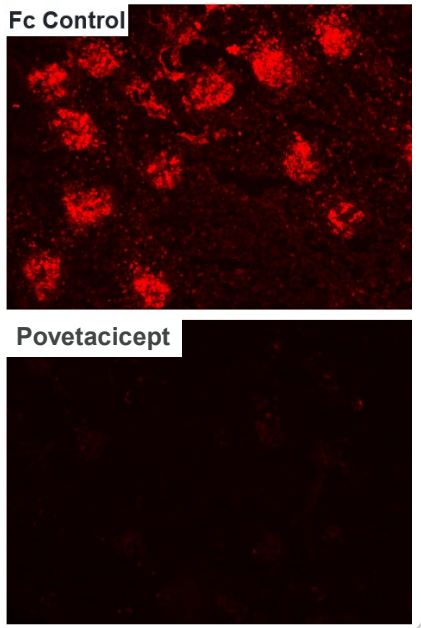


Renal Disease

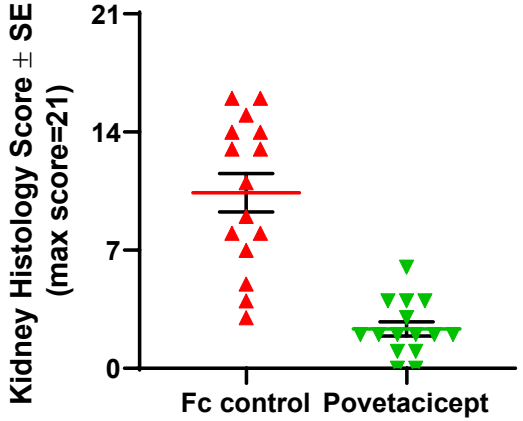
Histopathology



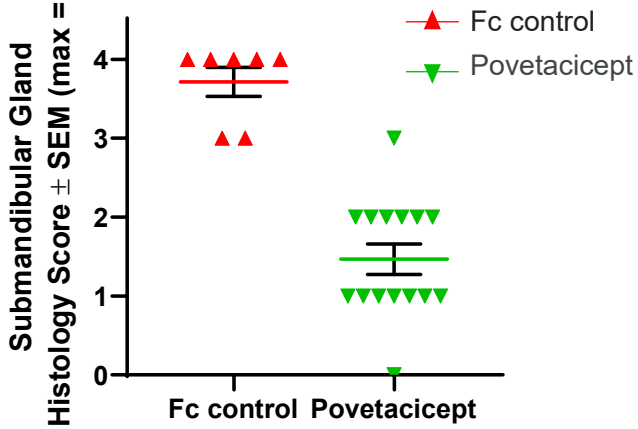
Immune Deposits



Nephritis



Sialadenitis



GN	Glomerulonephritis
LN	Lupus nephritis
SLE	Systemic lupus erythematosus

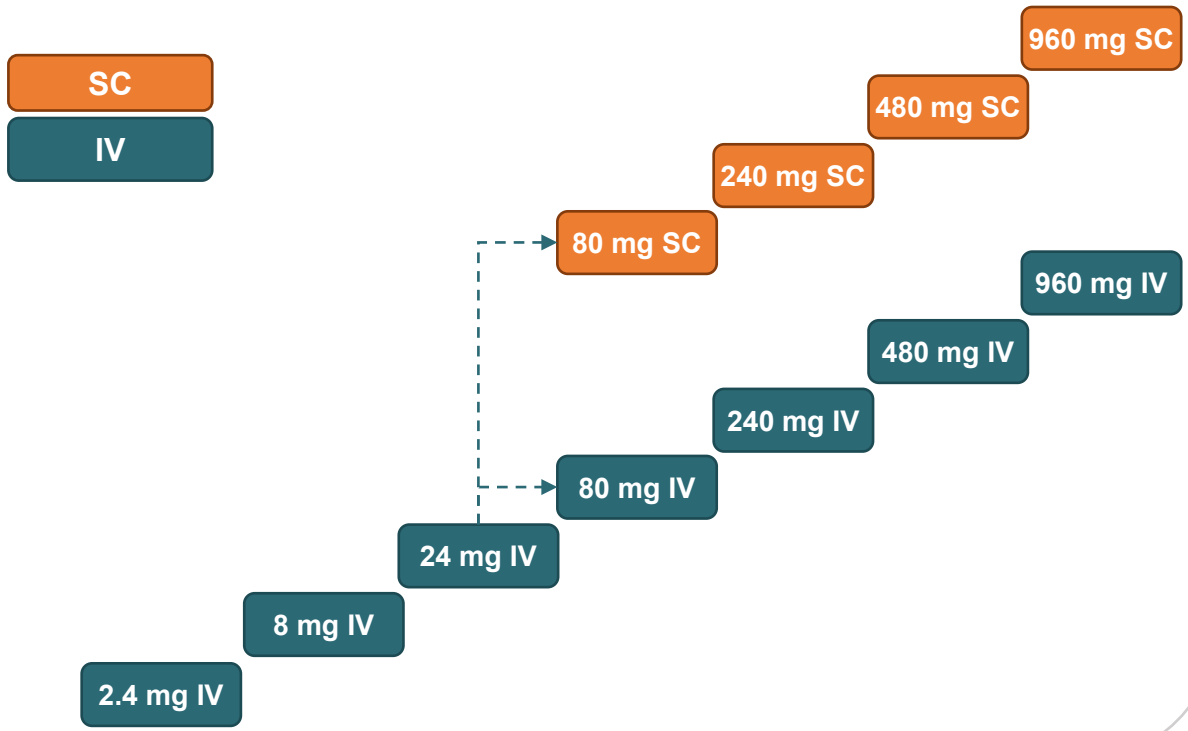
Evans LS, et al. Arthritis Rheumatol 2023 Jan 27; doi: 10.1002/art.42462

Povetacicept dosed at 17mg/kg IP 3x/week from 22-42 weeks of age

RUBY-1: Povetacicept Phase 1 in Adult Healthy Volunteers*

Single Ascending Dose

- 2.4 - 960 mg, IV and SC
- NCT05034484



*Data extract 14 MAR 2023
AE=Adverse Events; IV=Intravenous; SC=Subcutaneous; PoC=Proof of concept

Endpoints

- **Safety:** AE's, immunogenicity, EKGs
- **Pharmacokinetics**
- **Pharmacodynamics**
  - Serum immunoglobulins
  - Circulating B cells and subsets

Desired Outcomes

vs. WT TACI-Ig + BAFF/APRIL mAbs:[1-4]

- Equivalent or superior PD changes
  - Circulating Igs (IgM, IgA, IgG)
  - B cells (esp. antibody-secreting cells)
- Competitive SC dosing interval (≥ 4 weeks)

1. Willen D, et al. Eur J Drug Metab Pharmacokinet. 2020;45:27-40.
2. Xie J, et al. Clin Pharmacol Drug Dev. 2022;11(11):1273-1283.
3. Lo J, et al. 2020. Kidney Week Abstract PO1843 (JASN 31: 2020).
4. Mathur M, et al. Kidney Int Rep. 2022;7:993-1003.

Povetacicept is Well Tolerated in Adult Healthy Volunteers

Treatment-Emergent Adverse Event Summary (Preliminary)

Treatment-Emergent Adverse Event (TEAE)	All Placebo (N=22)	All Povetacicept (N=50)
Any TEAE	**12 (55%)**	**40 (80%)**
Grade 1	7 (32%)	24 (48%)
Grade 2	4 (18%)[1]	15 (30%)[2]
Grade 3	1 (5%)[3]	1 (2%)[3]
AE of Interest	**1 (5%)**	**1 (2%)**
Administration-Related Reaction[4]	1 (5%)	1 (2%)
Injection Site Pain (Grade 1)	1 (5%)	1 (2%)
Severe or Serious Infection	0	0
Severe Hypogammaglobulinemia	0	0
Cytokine Release Syndrome[5]	0	0

[1] Dyspepsia, iron deficiency anemia, lipase increased, URTI, COVID-19 (n=1 each; 1 participant had 2 different Grade 2 events).
[2] Back pain, COVID-19, headache, migraine, nausea, Staphylococcal infection, urinary tract infection (URTI), or Varicella zoster virus infection (n=1 each); lipase increased (n=2); presyncope (n=3); URTI (n=4). 2 participants had 2 different Grade 2 events.
[3] Blood creatine phosphokinase increased, attributed to strenuous exercise.
[4] Infusion-related reaction, injection-related reaction, injection site pain, or injection site reaction.

Data Extract: 14 Mar 2023

Povetacicept is Well Tolerated in Adult Healthy Volunteers

Most Common Treatment-Emergent Adverse Event Summary (Preliminary)

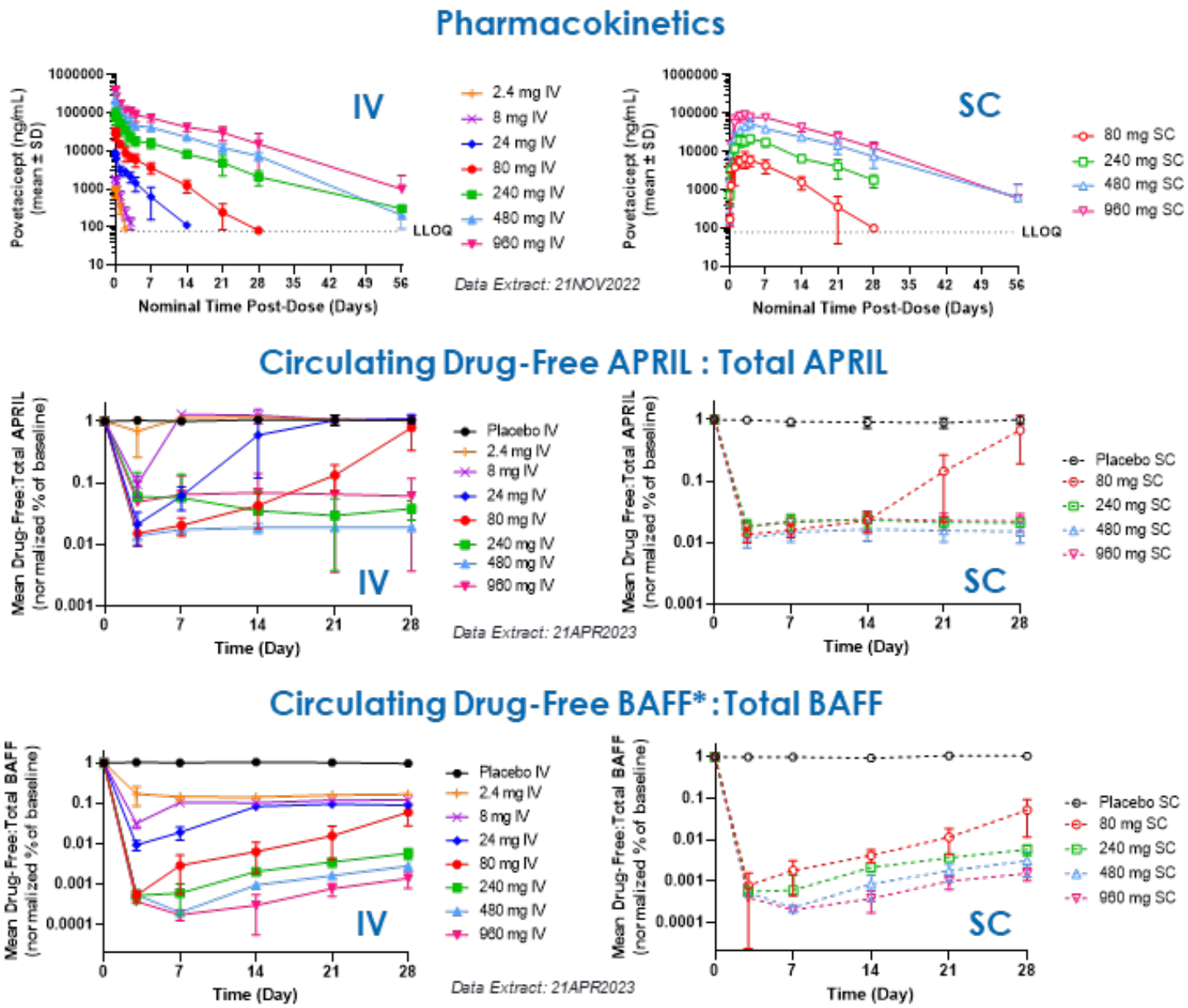
Most Common[1] TEAEs

Preferred Term[1] (Any Grade)	All Placebo (N=22)	All Povetacicept (N=50)
Headache or Migraine	**4 (18%)**	**12 (24%)**
Grade 1	4 (18%)	10 (20%)
Grade 2	0	2 (4%)
Infections	**6 (27%)**	**12 (24%)**
Grade 1	4 (18%)[2]	4 (8%)[3]
Grade 2	2 (9%)[4]	8 (16%)[5]
Dizziness[6]	**1 (5%)**	**6 (12%)**
Grade 1	1 (5%)	3 (6%)
Grade 2	0	3 (6%)

N = Number of subjects in the safety population; TEAE = Treatment-emergent adverse events
[1] Non-Ig TEAEs observed in > 10% of povetacicept-treated participants.
[2] COVID-19 (n=2) or URTI (n=2).
[3] Furuncle (n=1), or COVID-19 (n=3).
[4] URTI or COVID-19 (n=1) each.
[5] COVID-19, Staphylococcal infection, urinary tract infection, Varicella zoster virus infection (n=1) each; URTI (n=4).
[6] Dizziness, dizziness postural, presyncope, or vertigo

Data Extract: 14 Mar 2023

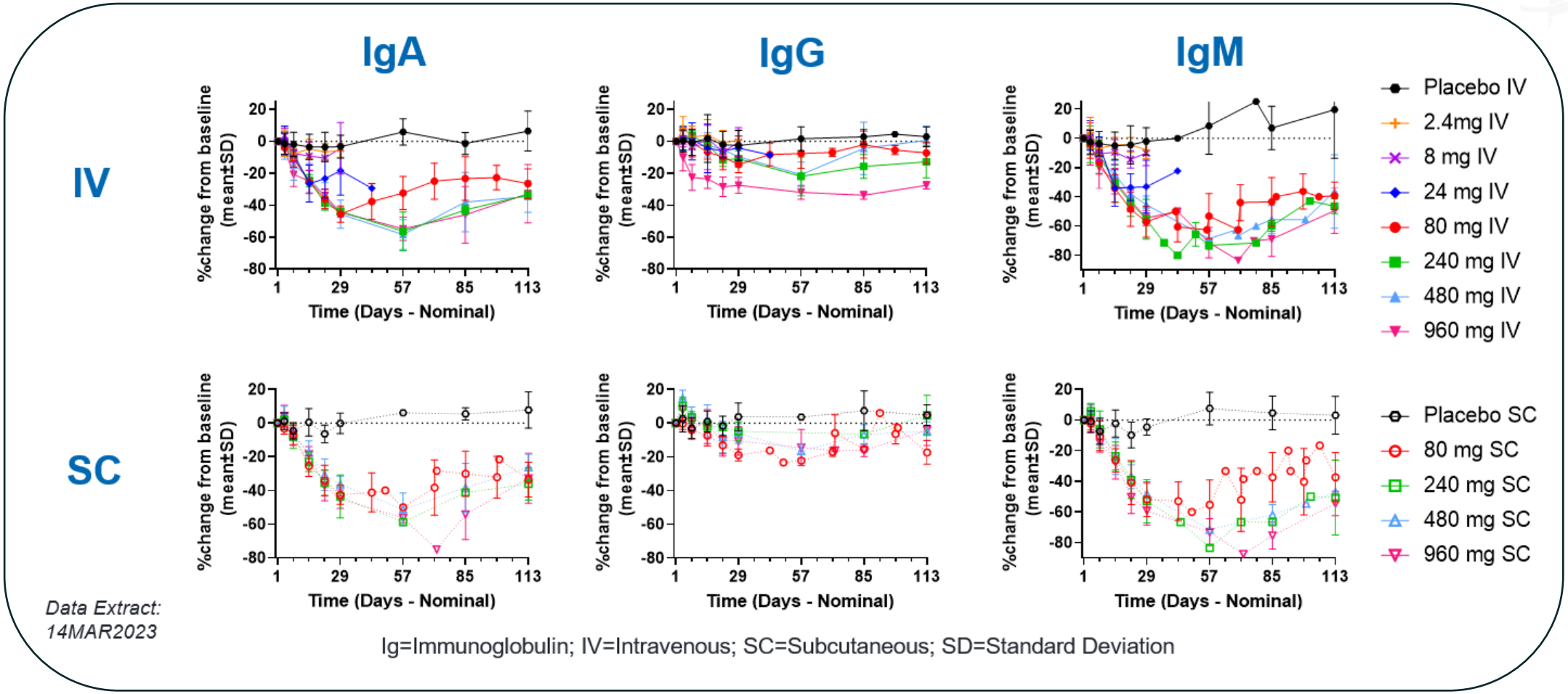
Povetacicept Exhibits Dose-Dependent Pharmacokinetics and Target Engagement



- Dose-dependent PK is observed with good bioavailability (70 to 81% at 80 to 960 mg).
- Estimated half-life ($t_{1/2}$) at 80 or 240 mg SC is 3.7 to 7.4 days, respectively.
- Preliminarily, apparent coverage of APRIL and BAFF was maintained for 2–3 and ≥4 wks after dosing with 80 and 240 mg, respectively.

*Coverage of the target cytokines BAFF and APRIL were estimated using first-generation bioassays which we refer to as "drug-free" APRIL or BAFF since they detect each respective cytokine only in the absence of bound povetacicept.

Povetacicept Dose-Dependently Reduces Circulating Immunoglobulins in Adult Healthy Volunteers (RUBY-1)

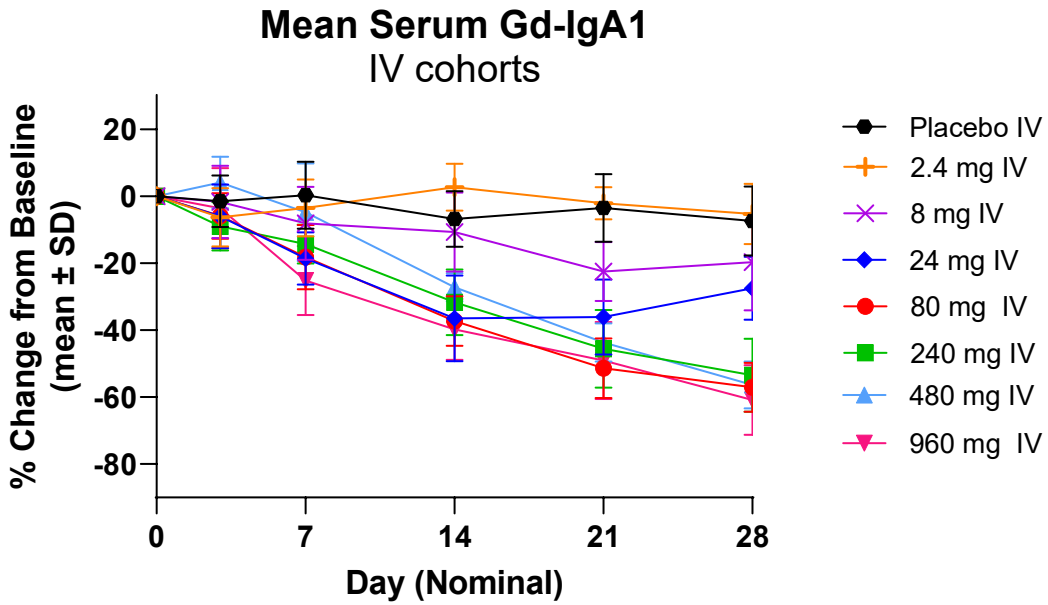


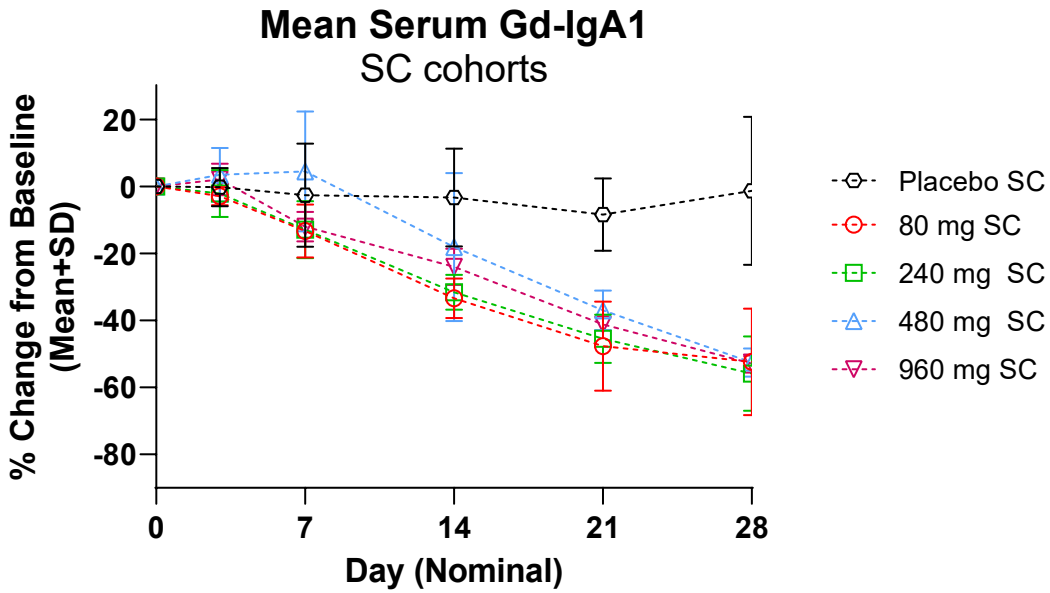
Effects generally appear saturated ≥ 80 mg for ≥ 4 weeks

Note: average serum half-life in healthy adults is 4-7 days for IgM and IgA, and >21 days for IgG.

Povetacicept Reduces IgAN-Relevant Galactose-Deficient IgA1 (Gd-IgA1)

Single Pivotal Doses in HVs (Preliminary)



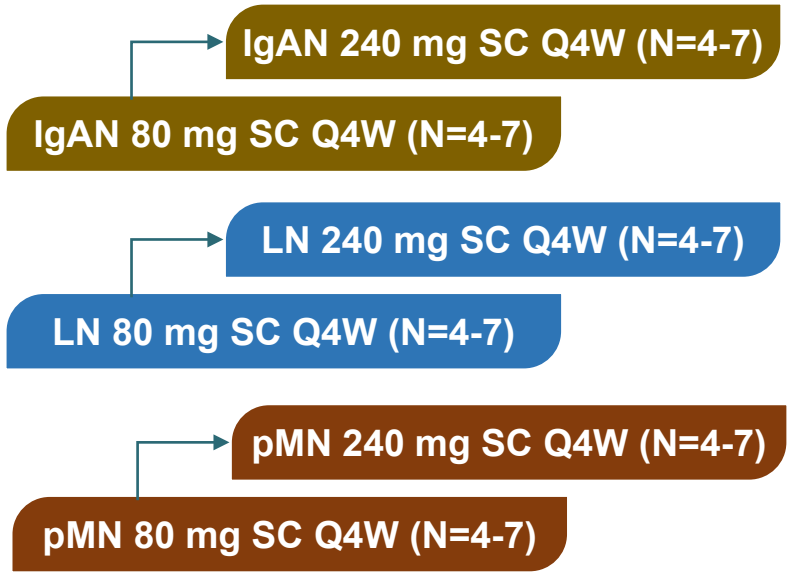


Serum galactose-deficient IgA1 (Gd-IgA1) levels were measured using an ELISA kit (Immuno-Biological Laboratories/IBL) per the manufacturer's protocol.

Data Extract: September 8, 2022

RUBY-3

Title	An Open-Label, Multiple-Ascending Dose Study to Assess the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Different Dose Levels of Povetacicept in Subjects with Autoantibody-Associated Glomerular Diseases (RUBY-3)
Design	Multiple ascending dose, parallel cohort, open-label
Patients	Biopsy-proven: • IgA Nephropathy (IgAN) • Lupus Nephritis (LN) • Primary Membranous Nephropathy (pMN)
Study drug	Povetacicept 80 or 240 mg SC Q4W (no placebo)
Duration	6 months plus optional 6-month extension
Key outcomes	UPCR, eGFR, renal response Exploratory: Autoantibodies (e.g., Gd-IgA1, dsDNA, PLA2R1)
Goal	Enable phase 3, including safety and dose rationale



ClinicalTrials.gov identifier: NCT05732402

Summary and Conclusions

- In this first-in-human study, povetacicept was well-tolerated as single IV or SC doses of up to 960 mg in adult healthy volunteers. The most frequent adverse event was mild headache. No severe infections, severe IgG hypogammaglobulinemia (IgG<3 g/L), or cytokine release were observed.
- Povetacicept demonstrates dose-dependent PK/PD. Preliminarily, apparent coverage of APRIL and BAFF was maintained for 2–3 and ≥4 wks after dosing with 80 and 240 mg, respectively, corresponding to anticipated reductions in serum Ig and supporting dose regimens of 80–240 mg SC every 4 wks in future studies.
- Future clinical study of povetacicept in autoimmune GN and other autoantibody-related disease is strongly supported. A clinical study in autoimmune GN (RUBY-3, NCT05732402), including IgAN, LN, and pMN, is actively enrolling. Other studies, including a study in autoimmune cytopenias (RUBY-4; NCT05757570) and in SLE are open for enrollment or in preparation.