

Povetacicept (ALPN-303), a Potent Dual BAFF/APRIL Antagonist, for the Treatment of Myasthenia Gravis and Other Antibody-Related Neurological Diseases

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Background

B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) are cytokines that signal through transmembrane activator and CAML interactor (TACI), B cell maturation antigen (BCMA), and/or BAFF-Receptor (BAFF-R); these cytokines play important roles in the activation, differentiation and/or survival of B cells, particularly antibody-secreting cells, as well as T cells and innate immune cells. Therapeutic agents targeting B cell pathways, including BAFF and APRIL, have demonstrated promising clinical potential in the treatment of myasthenia gravis (MG), as well as other autoantibody-related neurological diseases; however, there is still need for more safe and efficacious therapies. Povetacicept (ALPN-303) is an Fc fusion protein of an engineered TACI variant TNFRSF domain (vTD) with enhanced affinity for APRIL and BAFF, which has more potent inhibitory activity than wild-type (WT) TACI-Fc or BAFF- or APRIL-specific antibodies and demonstrates superiority to anti-CD20 therapeutics in preclinical models.¹ Povetacicept may therefore significantly improve clinical outcomes in MG and other B cell-related diseases. In this first-in-human study (NCT05034484), 72 healthy adult volunteers were treated in single ascending dose cohorts of intravenous (IV) or subcutaneous (SC) povetacicept or placebo. Participants were followed to assess safety and PK, circulating immunoglobulins (Ig), and circulating lymphocyte populations by flow cytometry.

Figure 1: Povetacicept is an Enhanced APRIL/BAFF Antagonist that Potently Modulates B Cells and Pathogenic Autoantibodies

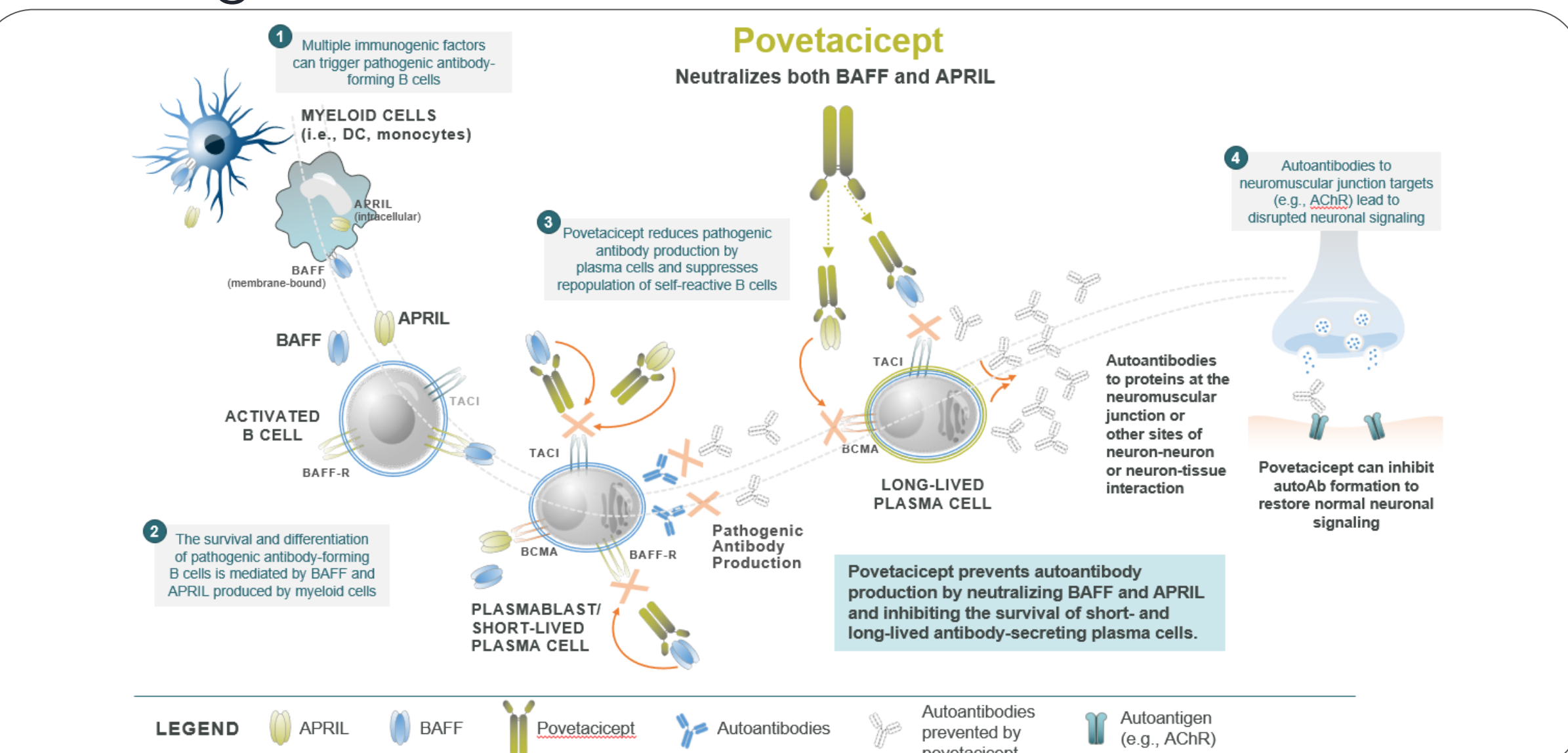


Figure 2: Povetacicept Ameliorates Experimental Autoimmune Myasthenia Gravis (EAMG)

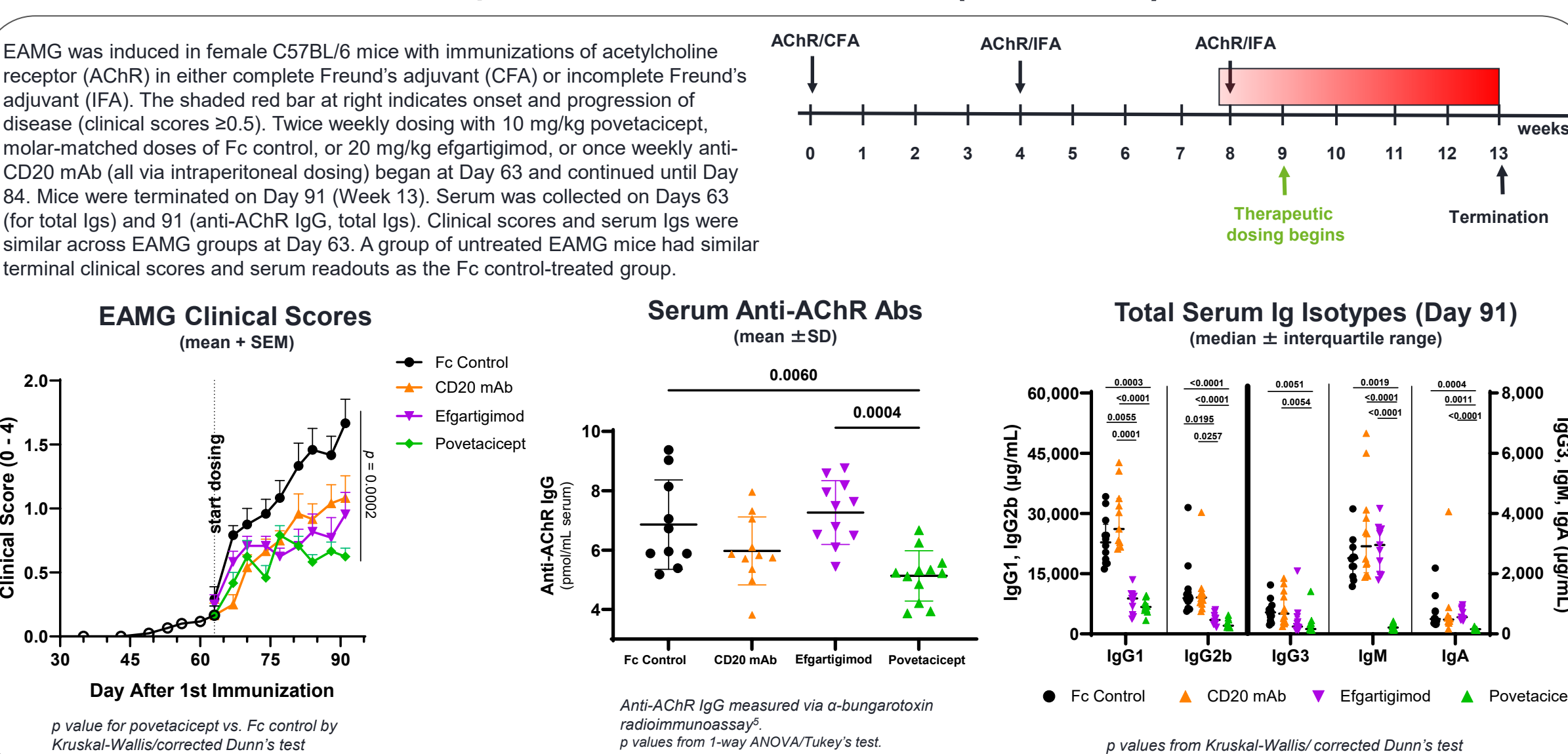


Figure 3: RUBY-1 Study Design

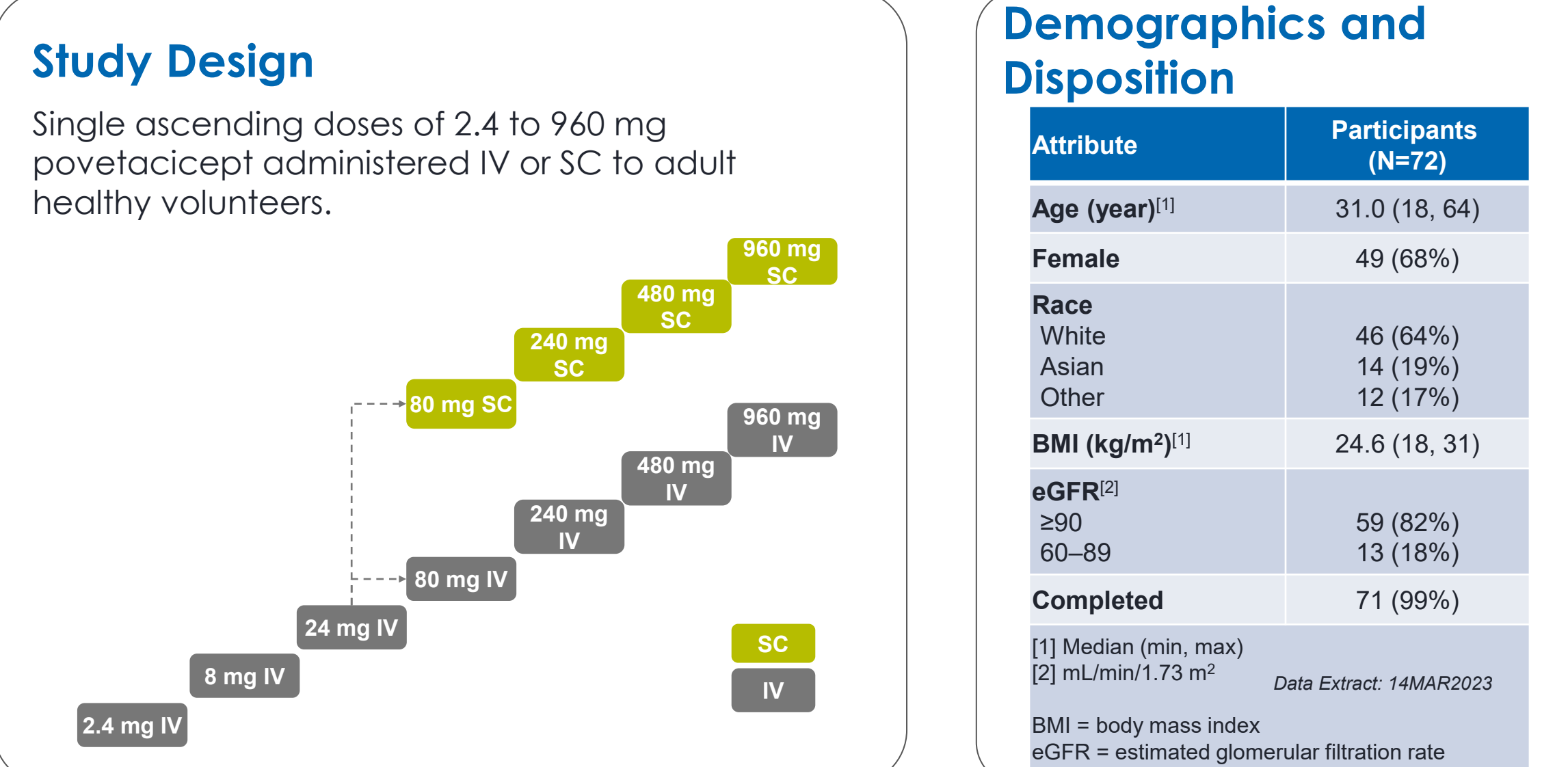


Figure 4: Povetacicept is Well-Tolerated Overall

- The most common non-laboratory adverse events (AEs) have included mild (grade 1) headache and dizziness.
- No serious or severe infections, IgG < 3g/L, or cytokine release syndrome were observed.

Povetacicept is Well-Tolerated Overall Data Extract: 14MAR2023

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]
Adverse Event of Interest	1 (5%)	1 (2%)
Administration-Related Reaction ^[4]	1 (5%)	1 (2%)
Injection Site Pain (G1)	1 (5%)	1 (2%)
Serious or Severe Infection	0	0
IgG < 3 g/L	0	0
Cytokine Release Syndrome	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.

Most Common^[1] TEAEs Data Extract: 14MAR2023

Preferred Term (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%)

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

Figure 5: 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 and 7.4 days, respectively.
- Ratios of drug-free to total APRIL and BAFF* rapidly diminished and remained low for 2–3 and ≥4 wks after dosing with 80 and 240 mg, respectively.

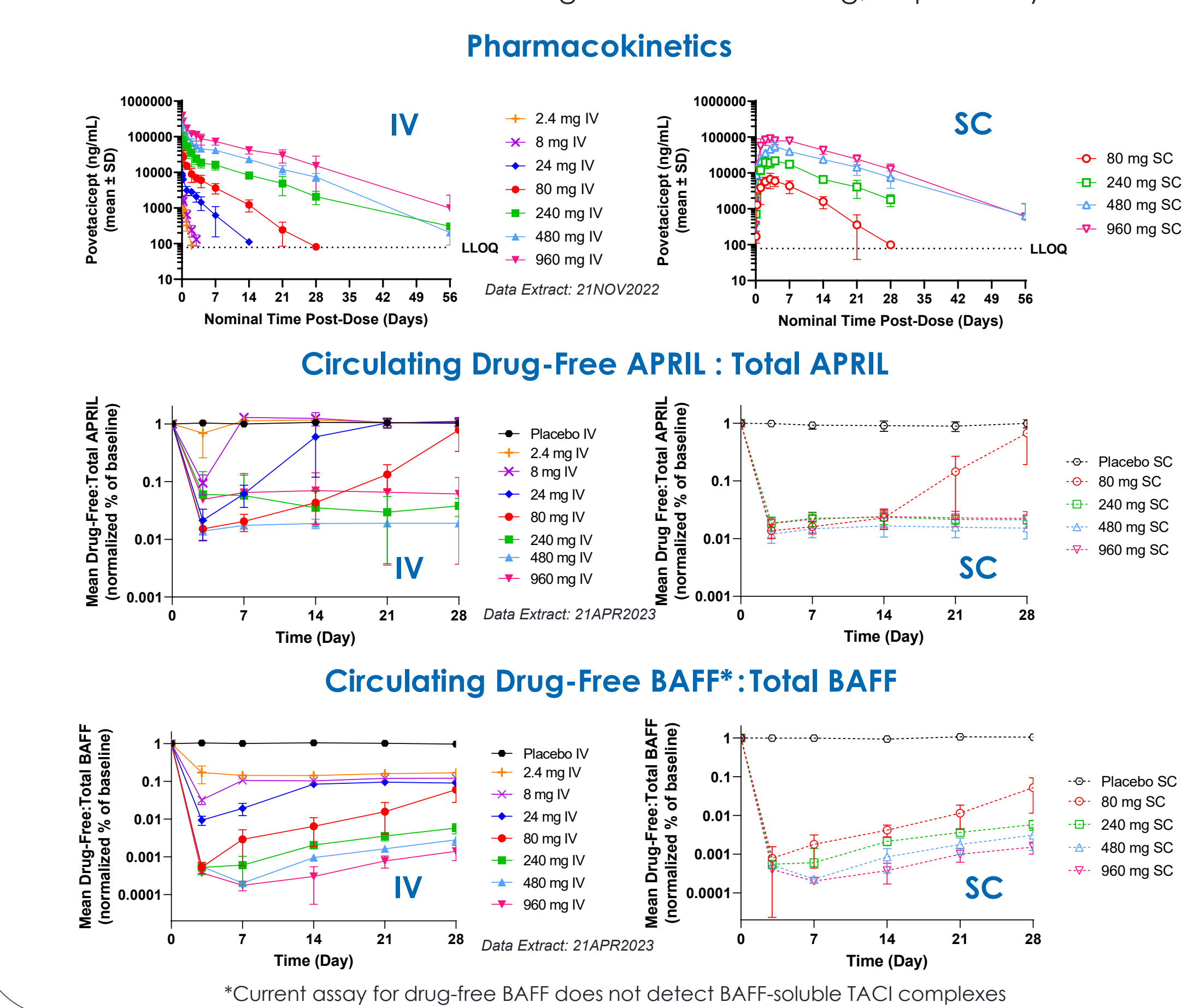


Figure 6: Povetacicept Dose-Dependently Reduces Circulating Immunoglobulins

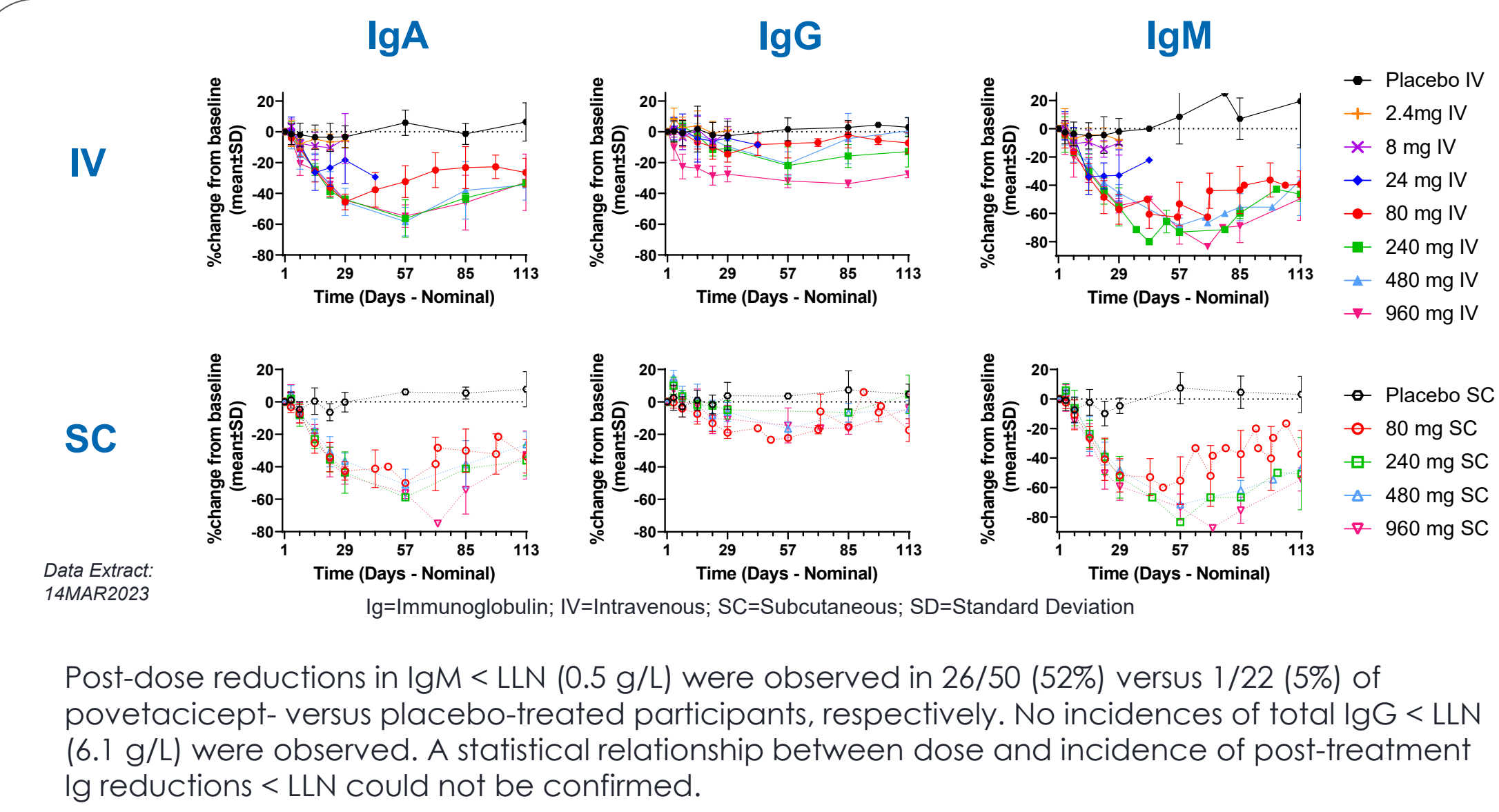
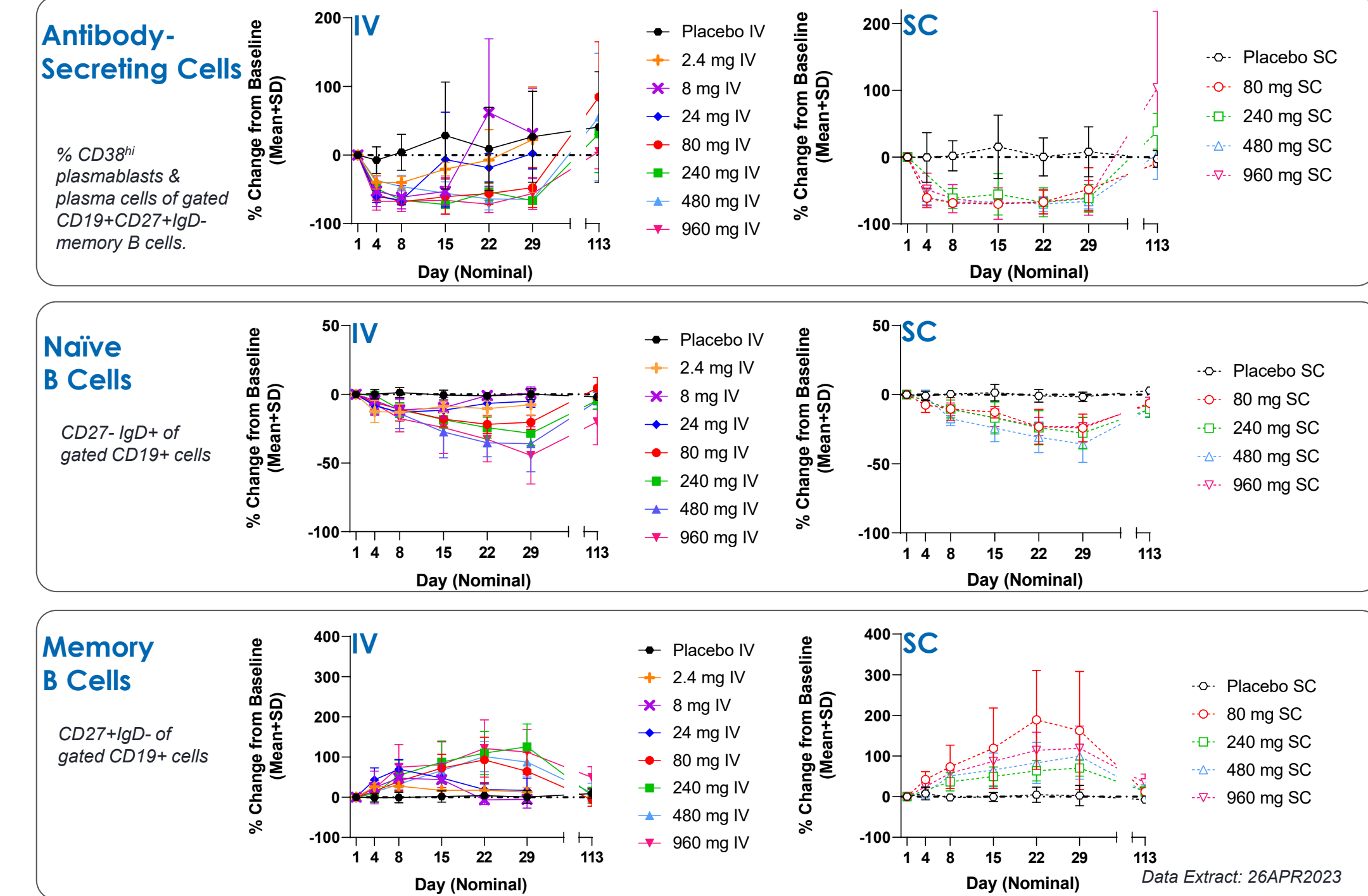


Figure 7: Povetacicept Impacts Naïve & Memory B Cells and Antibody-Secreting Cells



Summary and Conclusions

- In the EAMG mouse model, povetacicept treatment initiated after disease onset led to statistically significant reductions in clinical scores, as compared to Fc control treatment, whereas efgartigimod and anti-CD20 mAb treatments were not significantly more effective than Fc control. Furthermore, povetacicept significantly reduced anti-AChR IgG autoAbs and all serum Ig isotypes, including IgM and IgA.
- 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 serious or severe infections, IgG < 3 g/L, or cytokine release were observed.
- Povetacicept demonstrates dose-dependent PK/PD. Preliminarily, coverage of circulating APRIL and BAFF appeared to be maintained for 2–3 and ≥4 wks after dosing with 80 and 240 mg, respectively, corresponding to anticipated reductions in serum Ig, naïve B cells, and antibody-secreting cells, supporting dose regimens of 80–240 mg SC every 4 wks in future studies.
- Dose-related increases in circulating memory B cells were also observed, consistent with reported effects of prior BAFF inhibitors.⁶⁻⁸
- Future clinical study of povetacicept in MG and other autoantibody-related neurological diseases is strongly supported. Studies in autoimmune glomerulonephritis (RUBY-3; NCT05732402) & cytopenias (RUBY-4; NCT05757570) are currently enrolling.

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