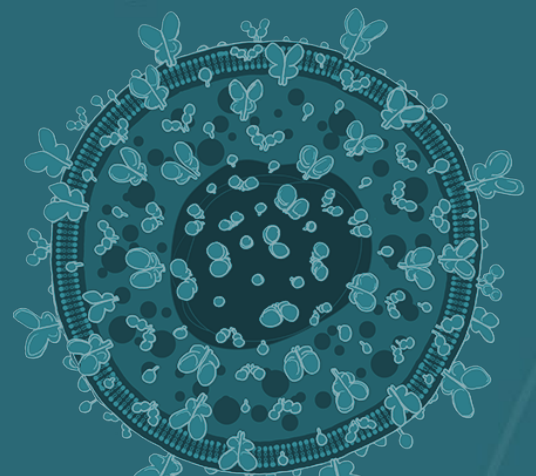
# Povetacicept (ALPN-303), a Potent Dual BAFF/APRIL Antagonist, for the Treatment of Autoimmune Cytopenias and Other Antibody-Related Diseases

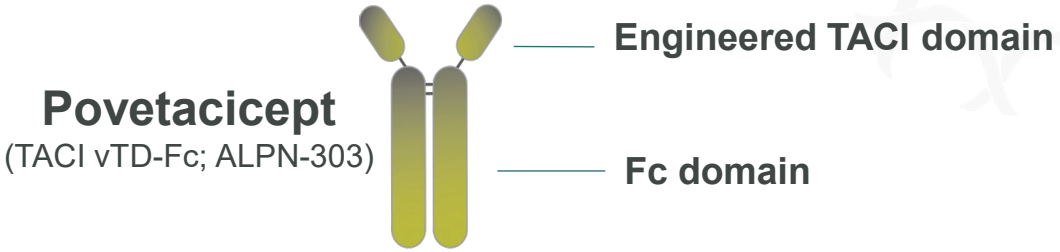
Stacey R. Dillon[1], Rupert Davies[1], Jason D. Lickliter[2], Kristi McLendon[3], Kristi L. Manjarrez[1], Alina Smith[1], Krystalyn E. Hudson[4], Lori Blanchfield[1], Russell J. Sanderson[1], Allison Chunyk[1], Tiffany Blair[1], Amanda Enstrom[1], Hany Zayed[1], Allison Naumovski[1], and Stanford L. Peng[1]

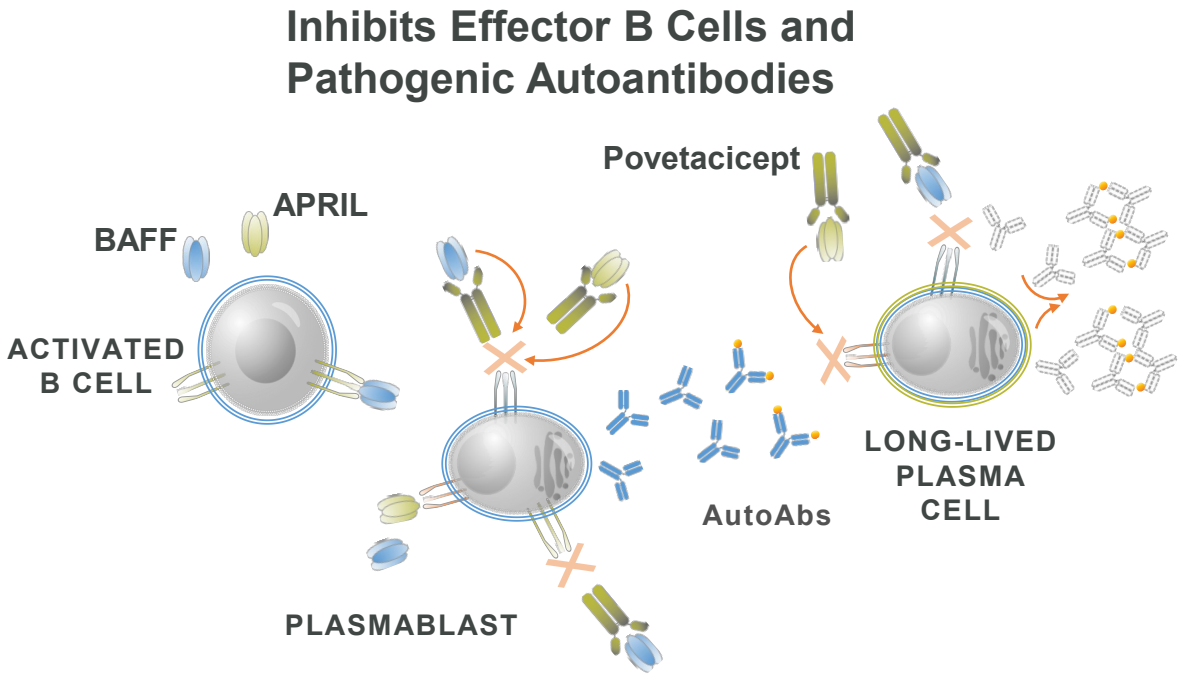
[1]Alpine Immune Sciences Inc., Seattle, United States of America
[2]Nucleus Network, Melbourne, Australia
[3]Nucleus Network, Brisbane, Australia
[4]Columbia University, New York, NY



# Povetacicept: An Enhanced Dual APRIL/BAFF Antagonist for Autoimmune Cytopenias

- BAFF and APRIL are cytokines that play key roles in B cell maturation, proliferation, and survival.
- They are clinically validated targets in SLE, LN and other autoantibody-related diseases; additionally, they are elevated and correlate with disease activity in patients with autoimmune cytopenias.[1-7]
- BAFF and APRIL may mediate escape/resistance to rituximab and other B cell-depleting therapies.
- Povetacicept is a decoy receptor Fc fusion containing an engineered TACI domain with superior inhibitory activity against BAFF and APRIL.
- In preclinical studies, povetacicept demonstrates superior efficacy versus anti-CD20 mAb, WT TACI-Ig, or BAFF or APRIL inhibition alone.[8]




1.Sa H, et al. Int Rev Immunol. 2017;36(3):182-203.
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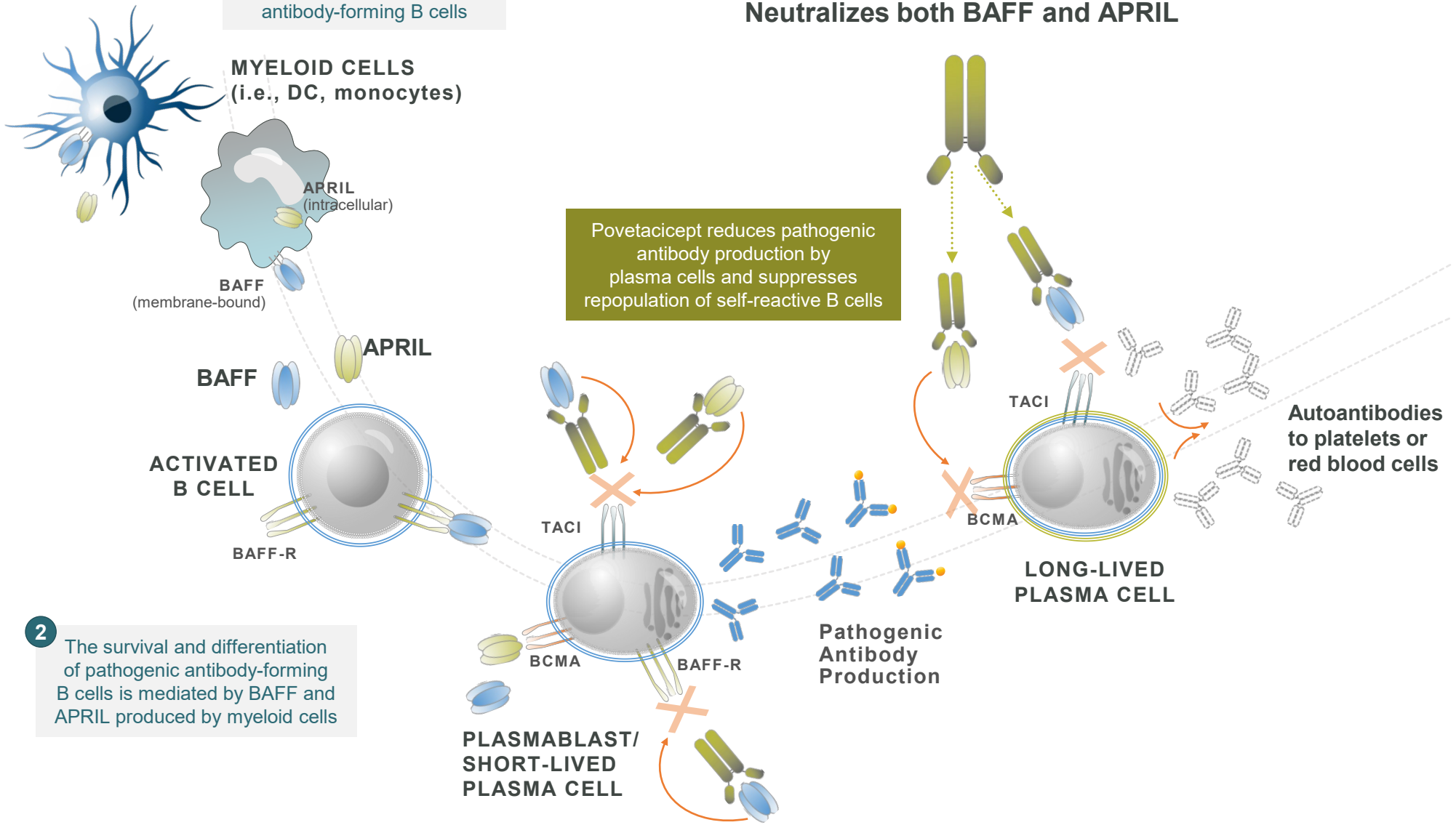
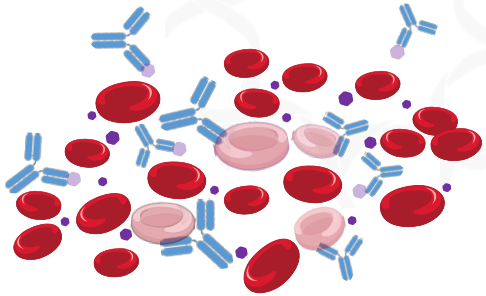
# Povetacicept

## Neutralizes both BAFF and APRIL

1 Multiple immunogenic factors can trigger pathogenic antibody-forming B cells




Povetacicept reduces pathogenic antibody production by plasma cells and suppresses repopulation of self-reactive B cells



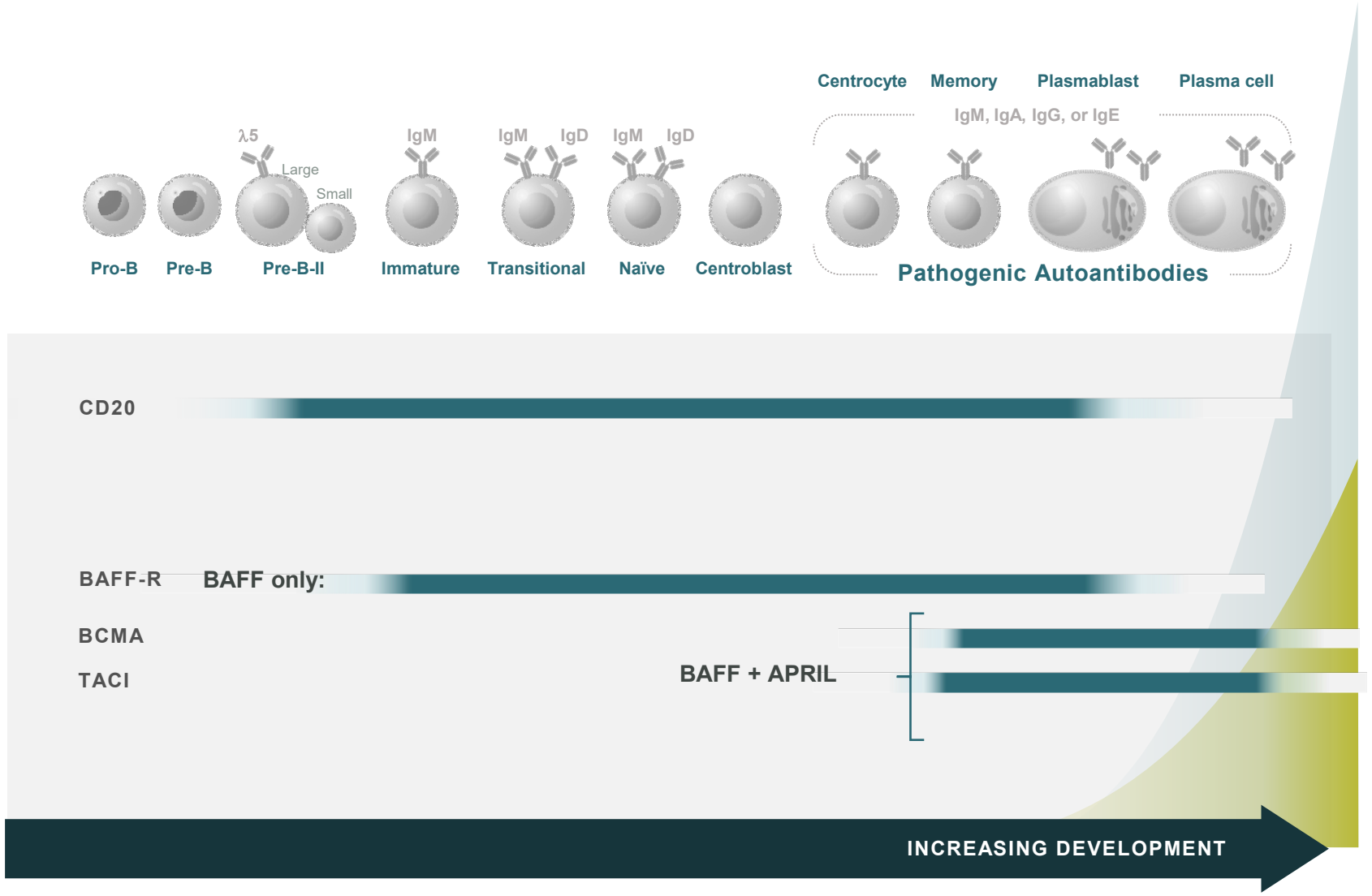
3 Autoantibodies lead to destruction of platelets in ITP and destruction of red blood cells in wAIHA and CAD

2 The survival and differentiation of pathogenic antibody-forming B cells is mediated by BAFF and APRIL produced by myeloid cells

**LEGEND** APRIL · BAFF · Povetacicept · Autoantibodies · Autoantigens · Red blood cells · Platelets

# Dual BAFF/APRIL Inhibition for Potentially Superior Clinical Outcomes

## Improved Targeting of Pathogenic B Cells (Memory, Plasmablasts, Plasma Cells) and Autoantibodies

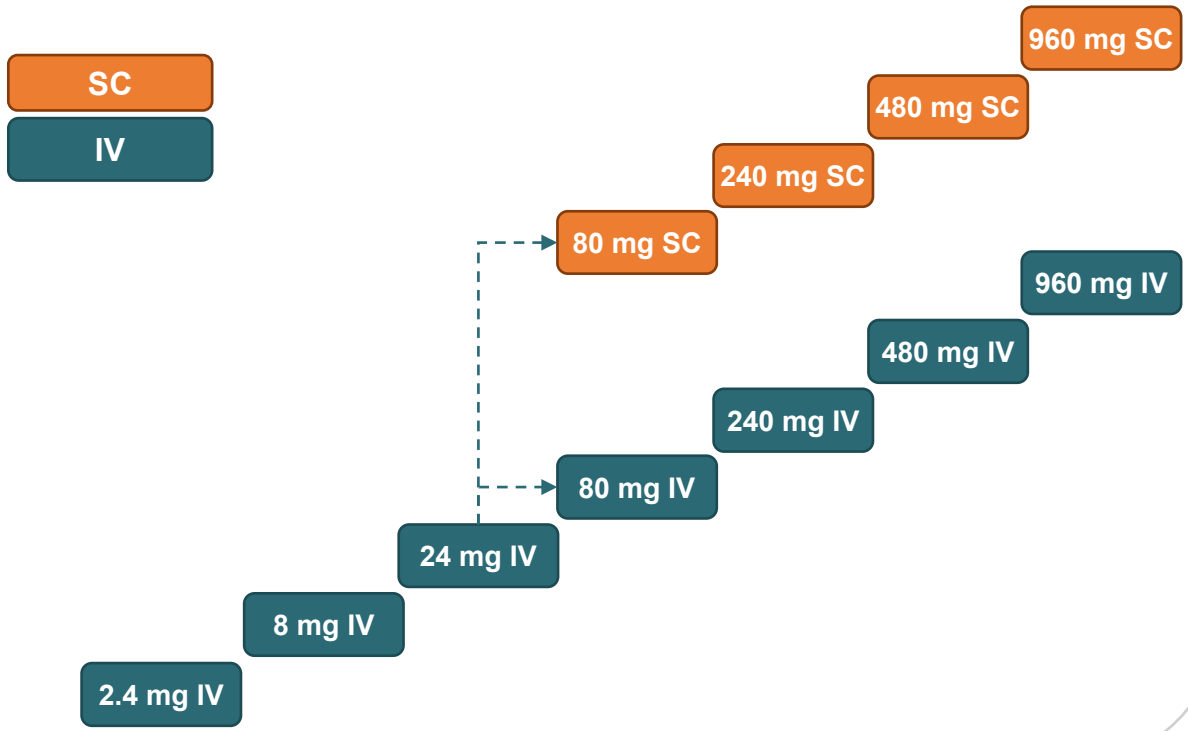



Adapted from Krumbholz M, et al. Nat Rev Neurol. 2012;8(11):613-23.

# 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:** AEs, 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;45:2740.
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] |
| Grade 4 or 5 | 0 | 0 |
| **Serious Adverse Event (AE)** | 0 | 0 |
| **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 | 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

# Most Common TEAEs [1]

| Treatment-Emergent Adverse Event (TEAE) | 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%) |

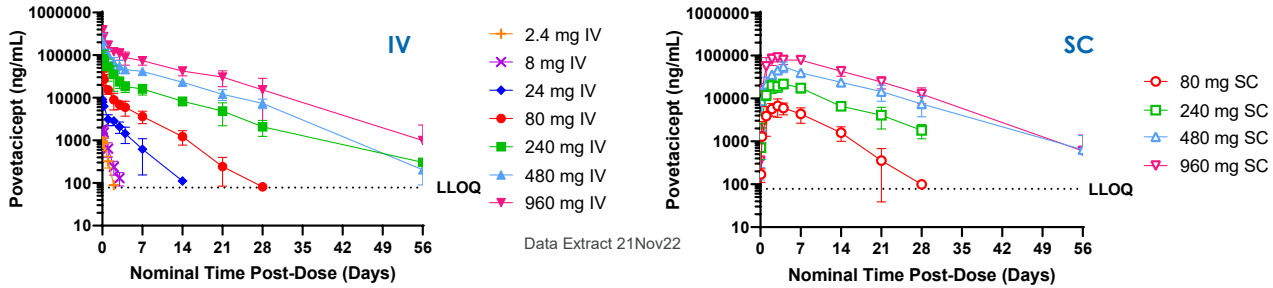
[1] Non-Ig TEAEs observed in > 10% of povetacicept-treated participants.
[2] COVID-19 (n=2) or URTI (n=2).
[3] Furuncle (n=1), or COVID-19 (n=3).
[4] URTI or COVID-19 (n=1) each.
[5] COVID-19, Staphylococcal infection, urinary tract infection, Varicella zoster virus infection (n=1) each, URTI (n=4).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

Data Extract: 14 Mar 2023

# Povetacicept Exhibits Dose-Dependent Pharmacokinetics

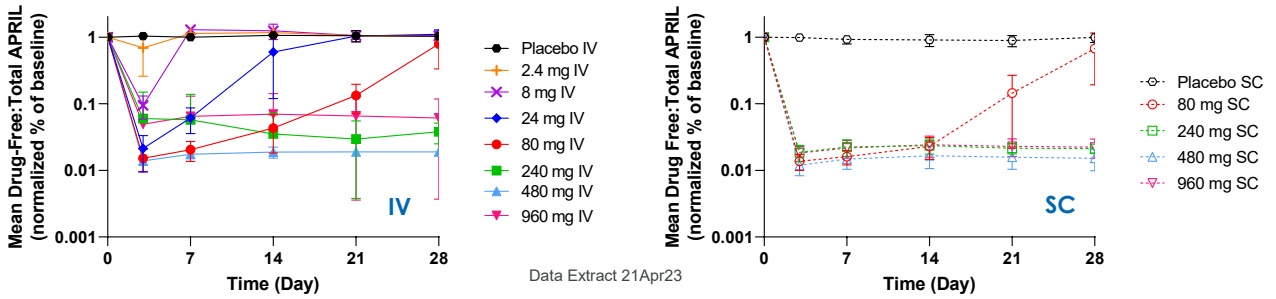
## Achieves Durable Pharmacodynamic Coverage (Preliminary)

### Pharmacokinetics



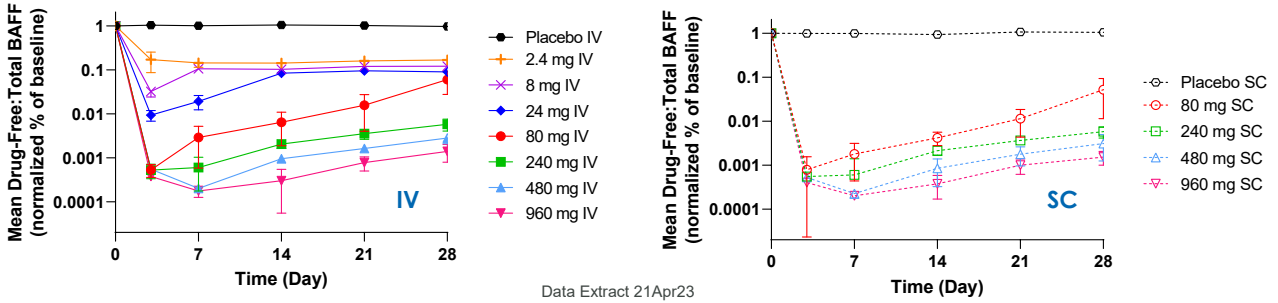

Data Extract 21Nov22

### Circulating Drug-Free APRIL : Total APRIL




Data Extract 21Apr23

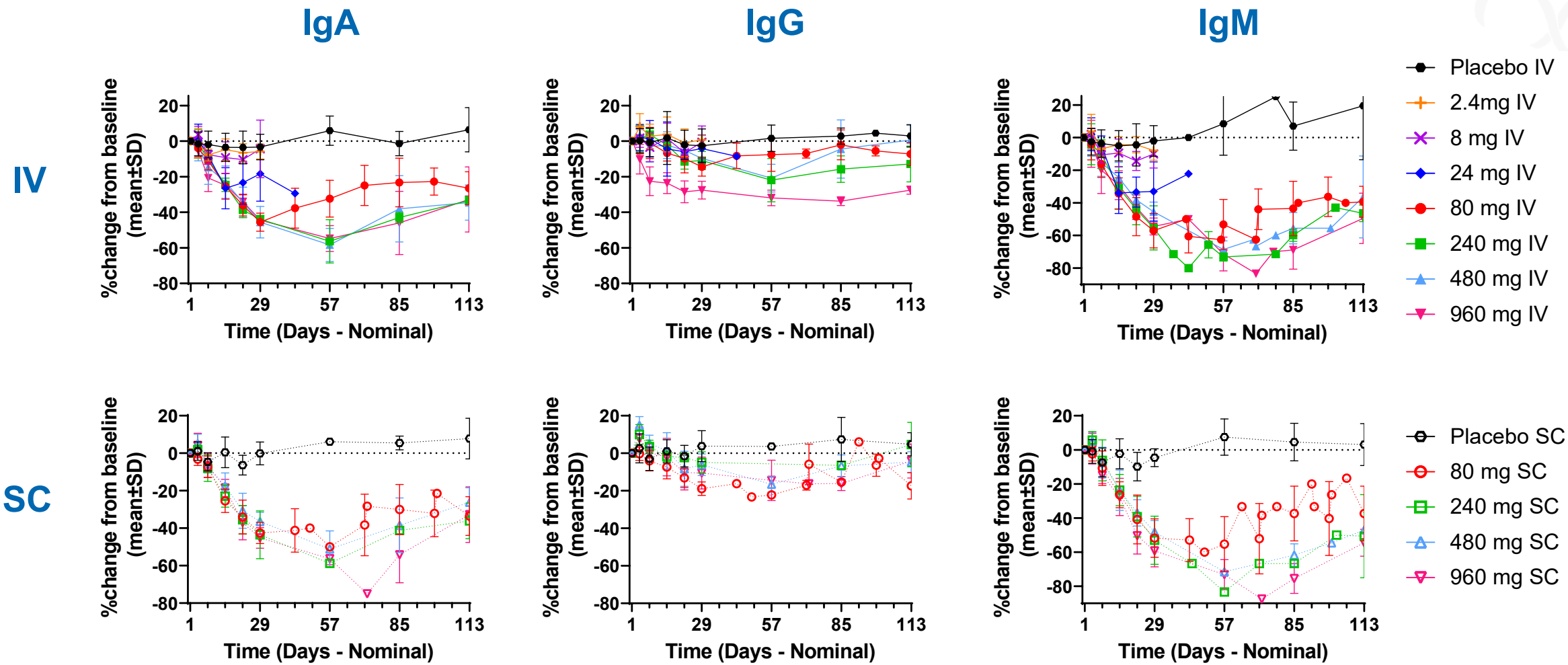
### Circulating Drug-Free BAFF*:Total BAFF




Data Extract 21Apr23

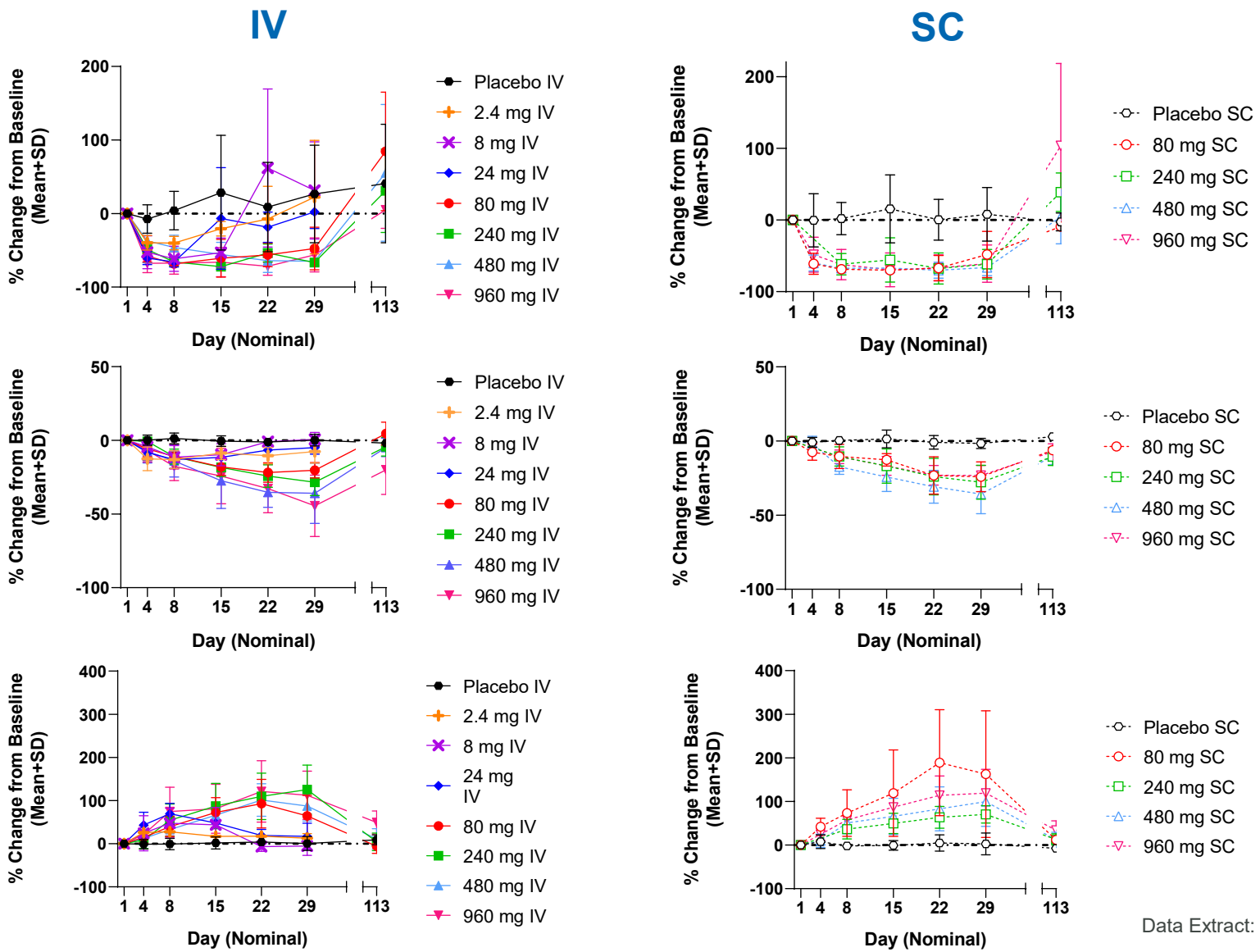
*Current assay for drug-free BAFF does not detect BAFF-soluble TACI complexes

# Povetacicept Dose-Dependently Reduces Circulating Immunoglobulins in Adult Healthy Volunteers




Data Extract: 14 Mar 2023

# Povetacicept Impacts Naïve & Memory B Cells, and Antibody-Secreting Cells (ASCs)




Data Extract: 26 Apr 2023

# Summary and Conclusions

- In this first-in-human study, povetacicept has been well-tolerated as single IV or SC doses of up to 960 mg in adult healthy volunteers.
  - The most frequent adverse event has been mild headache or migraine.
  - No severe infections or severe hypogammaglobulinemia, or cytokine release of any grade, have been observed.
- Povetacicept demonstrates dose-dependent PK/PD.
  - Preliminarily, target coverage for APRIL and BAFF appear to be achieved for 2–3 and ≥4 wks after dosing with 80 and 240 mg, respectively.
  - Target engagement corresponded to anticipated reductions in serum Ig, naïve and memory B cells, and antibody-secreting cells.
- These data support dose regimens of 80-240 mg SC every 4 weeks or longer in future studies.
- A clinical trial examining povetacicept in patients with autoimmune cytopenias (RUBY-4; NCT05757570) is open for enrollment, as well as a study in autoimmune glomerulonephritis (RUBY-3; NCT05732402). Studies in other diseases, such as SLE, are in preparation.