Plenary III (1424–1429)

Monday, November 8, 2021 10:30 AM – 12:00 PM ET

Abstract Moderator(s)

Diane Kamen, MD, MS

Medical University of South Carolina, United States

Disclosure: Equillium (Individual(s) Involved: Self; Ongoing): Advisor or Review Panel member

Jennifer Anolik, MD;PhD

University of Rochester Medical Center, United States

Disclosure: I have no relevant financial relationship(s) with ineligible companies to disclose.

11:45 AM – 11:55 AM ET	ALPN-303, an Enhanced, Potent Dual BAFF/APRIL Antagonist Engineered by Directed Evolution for the Treatment of Systemic Lupus Erythematosus (SLE) and Other B Cell-Related Diseases Presenting Author: Stacey R. Dillon, PhD – Alpine Immune Sciences
11:55 AM – 12:00 PM ET	Q&A Q & A Moderator: Diane Kamen, MD, MS – Medical University of South Carolina Q & A Moderator: Jennifer Anolik, MD;PhD – University of Rochester Medical Center Q & A Presenter: Stacey R. Dillon, PhD – Alpine Immune Sciences

ACR Convergence 2021

Abstract # 1429

ALPN-303, an Enhanced, Potent Dual BAFF/APRIL Antagonist Engineered by Directed Evolution for the Treatment of Systemic Lupus Erythematosus (SLE) and Other B Cell-Related Diseases

Stacey R. Dillon,* Lawrence S. Evans, Katherine E. Lewis, Jing Yang, Mark W. Rixon, Joe Kuijper, Daniel Demonte, Janhavi Bhandari, Steven D. Levin, Kayla Kleist, Sherri Mudri, Susan Bort, Daniel Ardourel, Michelle A. Seaberg, NingXin Wang, Chelsea Gudgeon, Russell Sanderson, Martin F. Wolfson, Jan L. Hillson, Pamela Holland, and Stanford L. Peng

Alpine Immune Sciences, Inc., 188 E. Blaine St., Suite 200, Seattle, WA USA 98102

*E-mail: Stacey.Dillon@alpineimmunesciences.com

November 8, 2021

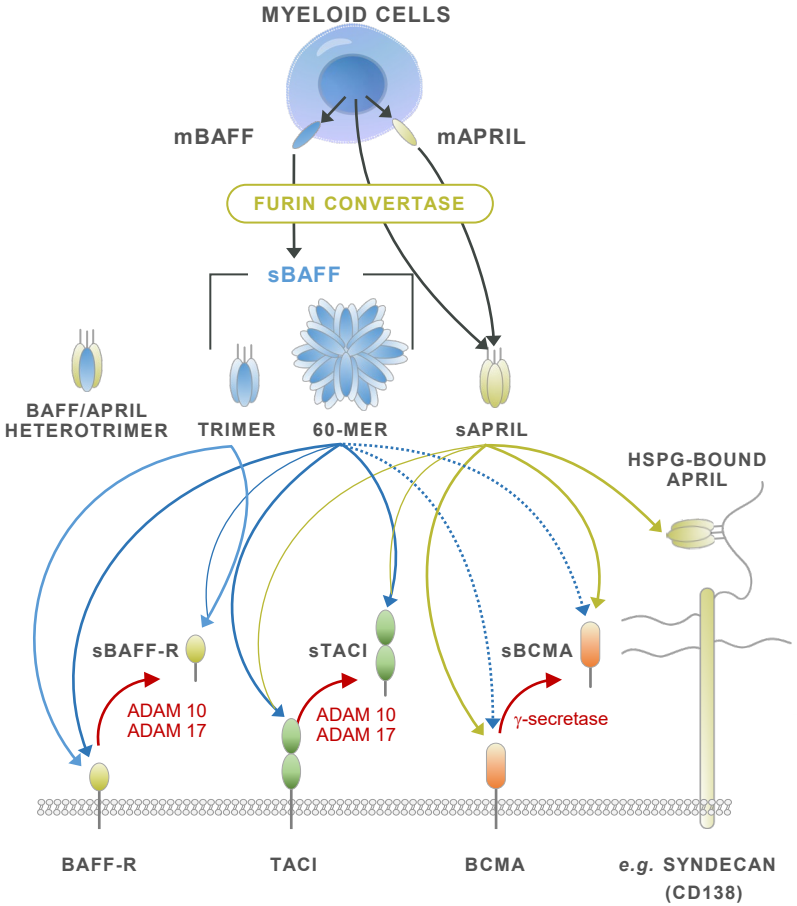
Disclosures

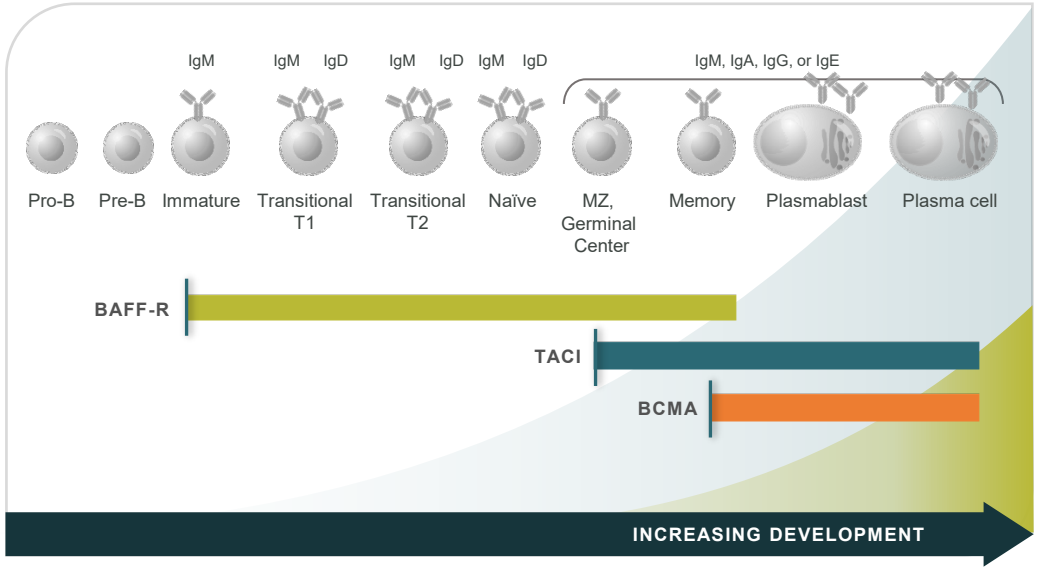
- Presenter is an employee and shareholder of Alpine Immune Sciences, Inc.

Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, Section 21E of the Securities Exchange Act of 1934 and the Private Securities Litigation Reform Act of 1995. These forward-looking statements are not based on historical fact and include statements regarding Alpine's platform technology, potential therapies, potential milestone and royalty payments, future development plans, clinical and regulatory objectives and the timing thereof, expectations regarding the sufficiency of cash to fund operations through 2023, expectations regarding the plans of its collaborators, expectations of future collaborations, and expectations regarding the potential efficacy and commercial potential of Alpine's and its collaborator's product candidates. Forward-looking statements generally include statements that are predictive in nature and depend upon or refer to future events or conditions, and include words such as "may", "will", "should", "would", "expect", "plan", "intend", and other similar expressions among others. These forward-looking statements are based on current assumptions involving risks, uncertainties, and other factors that may cause actual results, events, or developments to be materially different from those expressed or implied by such forward-looking statements. These risks and uncertainties, many of which are beyond our control, include, but are not limited to: Alpine's programs may not advance into the clinic or result in approved products on a timely or cost-effective basis or at all; Alpine may not achieve additional milestone payments pursuant to its collaborations; the impact of competition; adverse conditions in the general domestic and global economic markets; as well as the other risks identified in our filings with the Securities and Exchange Commission. These forward-looking statements speak only as of the date hereof, Alpine undertakes no obligation to update forward-looking statements, and readers are cautioned not to place undue reliance on such forward-looking statements.

BAFF and APRIL Play Key Roles in B Cell Development and Function





Adapted from Sakai J, et al. (2017) Clin Microbiol Rev. 30:991

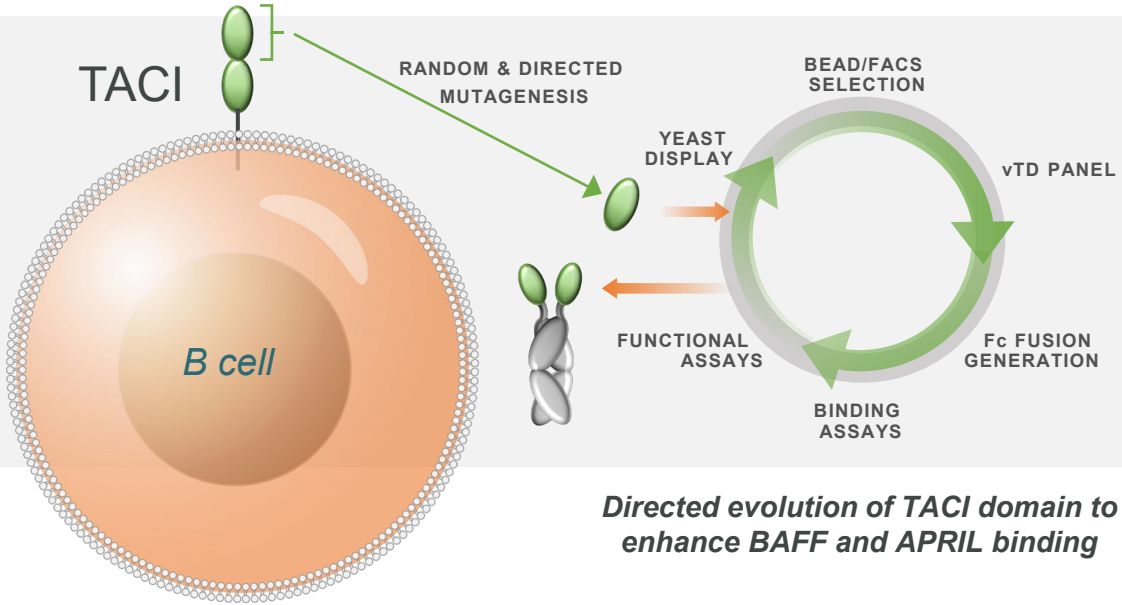
Dual BAFF/APRIL Inhibition Provides Deeper and More Sustained B Cell Suppression than Anti-BAFF or Anti-APRIL Therapy

- In nonclinical models, BAFF or APRIL inhibition alone mediates modest effects*
  - Co-neutralization dramatically reduces B cell function, including antibody production
- BAFF and APRIL antagonism with wild-type (WT) TACI-Fc (atacicept, telitacicept) shows encouraging clinical potential in systemic lupus erythematosus (SLE) and IgA nephropathy
  - Many patients still fail to respond and/or experience clinically significant flares†; thus, there remains a significant unmet medical need
- ALPN-303 (TACI vTD-Fc) was engineered to have optimal BAFF and APRIL inhibition to provide superior efficacy and clinical benefit compared to WT TACI-Fc and BAFF- or APRIL-specific mAbs

* *e.g.,* Ramanujam et al. (2010), *Arthritis Rheum.* 62:1457-68 and Benson et al. (2008), *J. Immunol* 180:3655-59.

† Wu et al., ACR 2019, *"Telitacicept (RC18) in Patients with SLE: Results of a Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study"*

ALPN-303 is a Modified TACI-Fc Fusion Protein Generated Via Directed Evolution that Mediates Enhanced BAFF and APRIL Inhibition vs. WT TACI-Fc



Directed evolution of TACI domain to enhance BAFF and APRIL binding

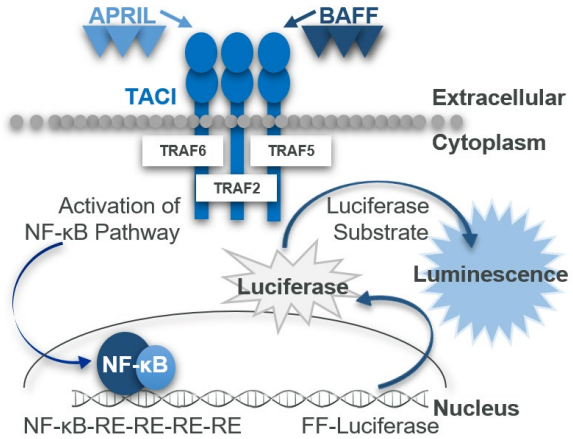
TACI Variant TNFR Domain (vTD)

Fc domain

ALPN-303
(TACI vTD-Fc)

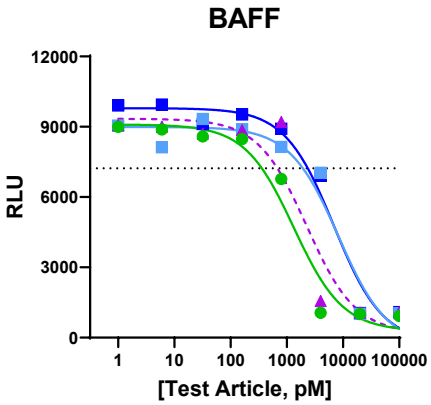
ALPN-303 Neutralizes APRIL and BAFF Activity More Potently than WT TACI-Fc or Combined αBAFF+APRIL mAbs in a Cell-Based Reporter Assay

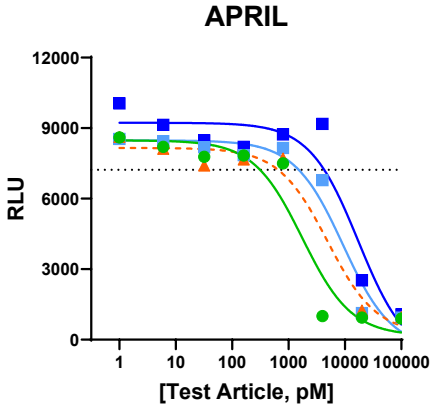
TACI-Jurkat Functional Assay:

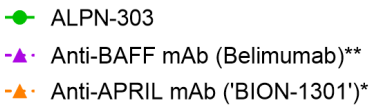


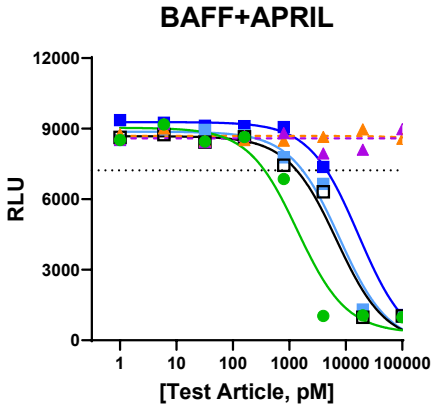
* *Generated at Alpine based on published sequences*:
BION-1301: US Patent 10,377,830 B2 SEQ ID NO: 50 and SEQ ID NO: 52
Atacicept : US Patent 8,815,238 B2 SEQ ID NO: 54

** *Purchased clinical drug product*:
Belimumab (Benlysta®)
Telitacicept (Tai'ai®)



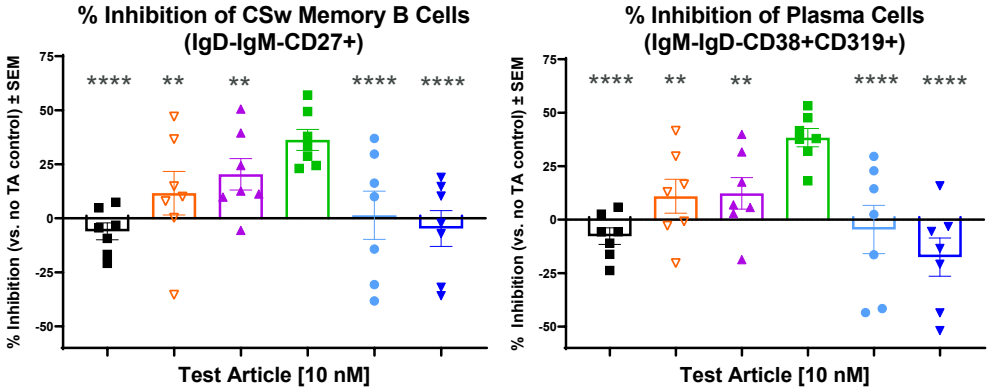




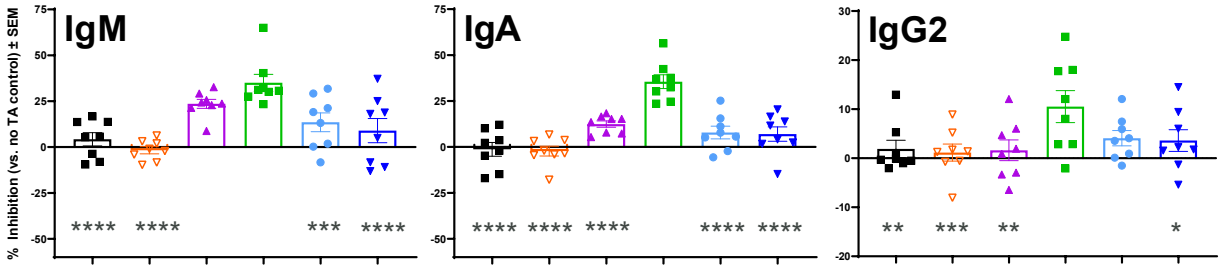


Test Articles	IC50 (pM)		
	BAFF	APRIL	BAFF + APRIL
ALPN-303	1337	1758	1390
Belimumab	2263	--	>100,000
'BION-1301'	--	4901	>100,000
Belimumab + 'BION-1301'	6848	2100	6805
'Atacicept'	8285	9258	7718
Telitacicept	6852	17244	16751

ALPN-303 Inhibits Class-Switched (CSw) Memory B Cell and Plasma Cell Survival and Ig Secretion More Potently than WT TACI-Fc in Primary Human B Cell Assays



- Fc control
- Anti-APRIL ('BION-1301')†
- Anti-BAFF (Belimumab)
- ALPN-303
- WT TACI-Fc ('Ataicept')†
- WT TACI-Fc ('Telitacicept')†



- CD19+ B cells purified from huPBMC (N=7 donors) were activated with 2nM rhCD40L for 3d, washed, and incubated for another 4d with 50ng/mL rhIL-21 + 10nM BAFF + 10nM APRIL
- Points represent the average value from triplicate wells for each donor
- Similar inhibition by ALPN-303 was observed for other IgG subtypes (IgG1, IgG3, IgG4)

Asterisks indicate *p* values vs. ALPN-303 group:

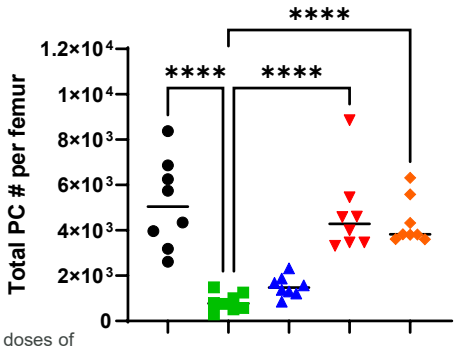
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$
**** $p < 0.0001$

†*Generated at Alpine based on published patent sequences*

ALPN-303 Significantly Decreases Plasma Cell Numbers in Mice and Non-Human Primates

Mouse

Bone Marrow



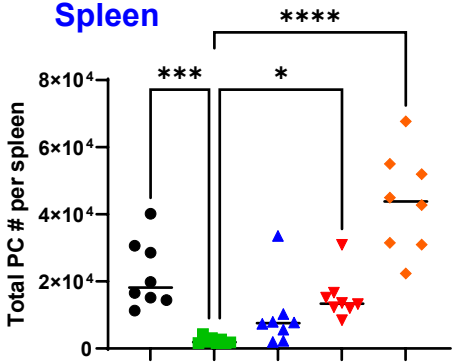
PC = CD138^{high} TACI^{high}

- Fc Control
- ALPN-303
- WT TACI-Fc†
- mBAFF-R-Fc†
- Anti-mAPRIL mAb†

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$
**** $p < 0.0001$

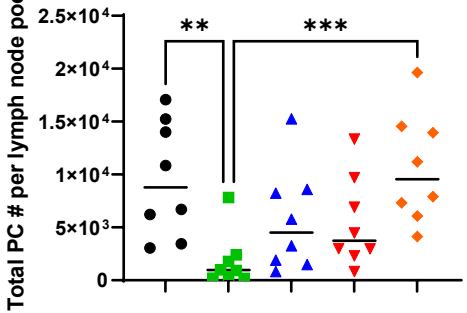
Mice received 6 doses of each test article twice weekly (10 mg/kg)

Spleen



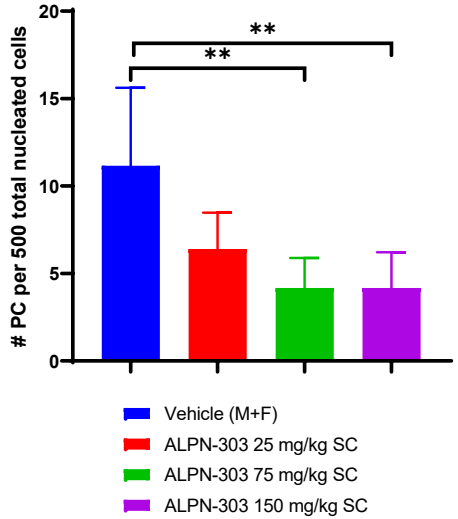
Lymph Node

(pooled popliteal, axillary, and brachial LN)



NHP

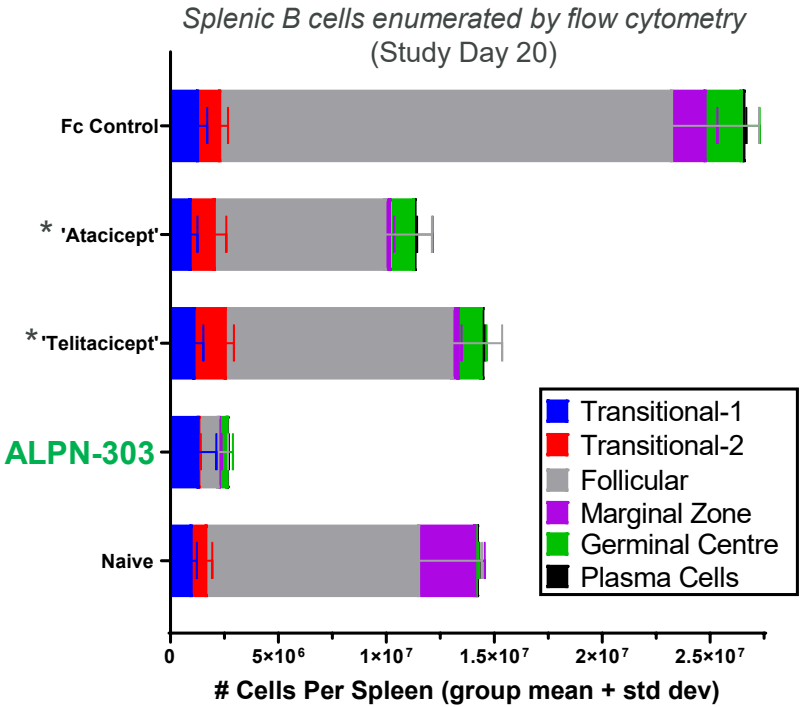
Plasma cell counts in BM smears from cynomolgus monkeys treated with ALPN-303

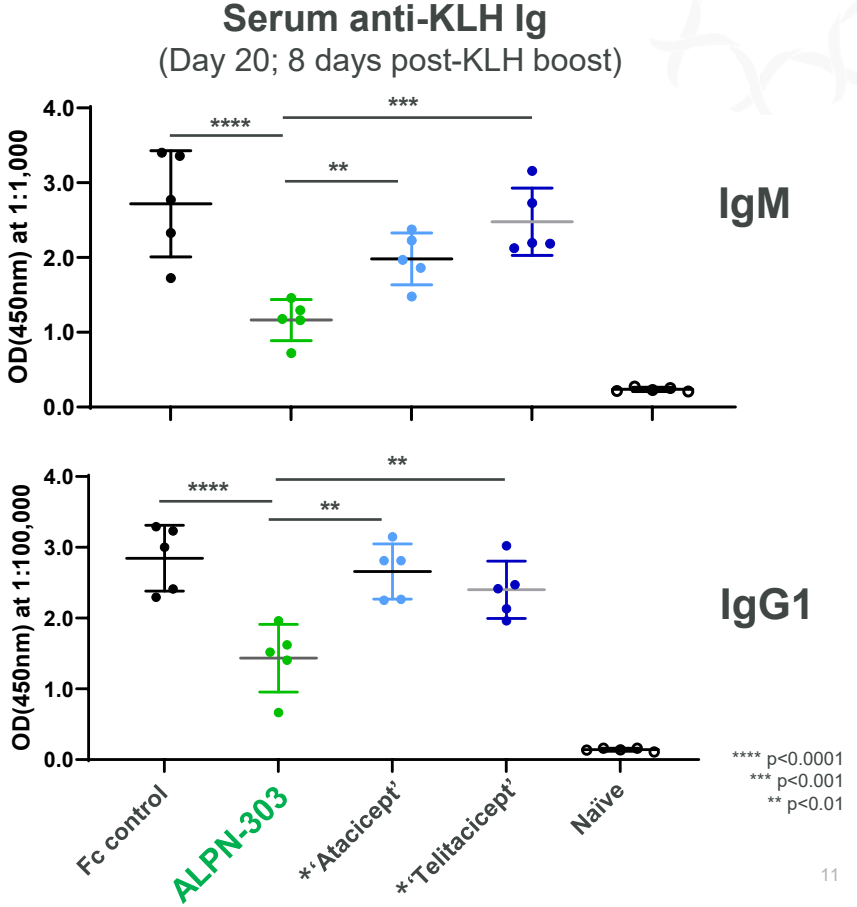


NHP were treated once weekly for 5 doses

† *Generated at Alpine from published sequences. WT TACI-Fc: US Patent 8,193,316 SEQ ID NO: 3; mBAFF-R-Fc: UniProt Q9D8D0; mAPRIL mAb: WO 2017/091683 A1 SEQ ID NO: 161 and 162*

ALPN-303 Inhibits T Cell-Dependent Antibody Formation More Potently than WT TACI-Fc in KLH-Immunized Mice

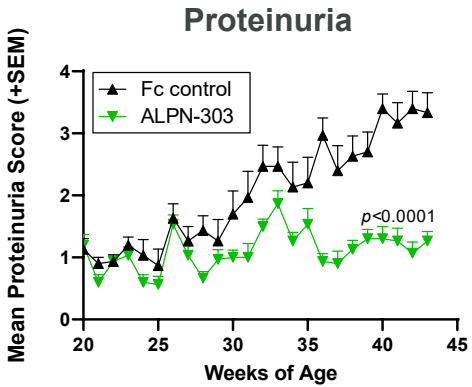


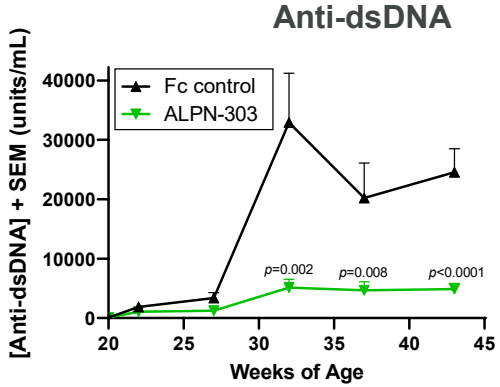


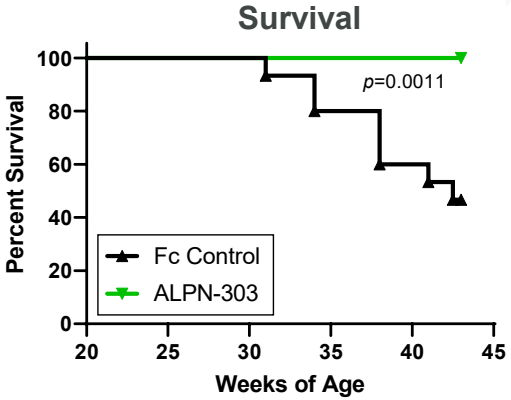
- Female C57BL/6 mice injected IP with 250 µg KLH in PBS w/o adjuvant on Days 0 & 12
- Test articles were molar matched to 15 mg/kg ALPN-303 and administered IP on Days 4 & 11 (n=5)

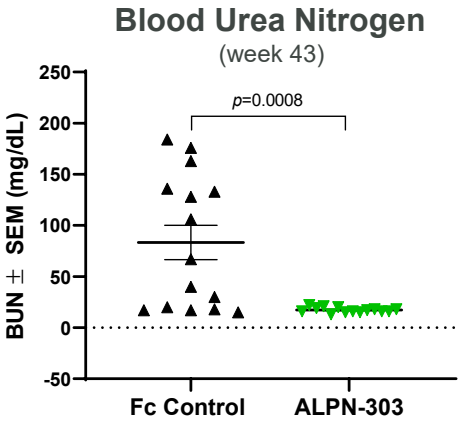
**Generated at Alpine based on published patent sequences*

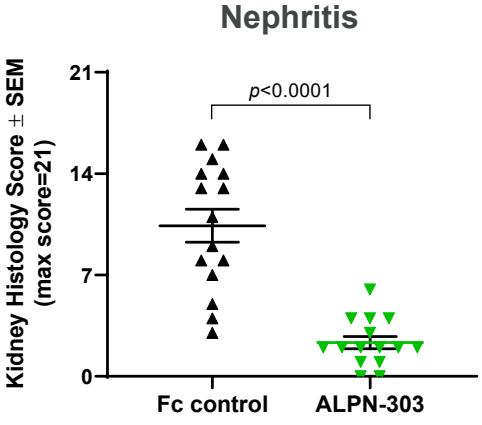
ALPN-303 Suppresses Disease in the (NZBxNZW)F_1 Spontaneous Lupus Model

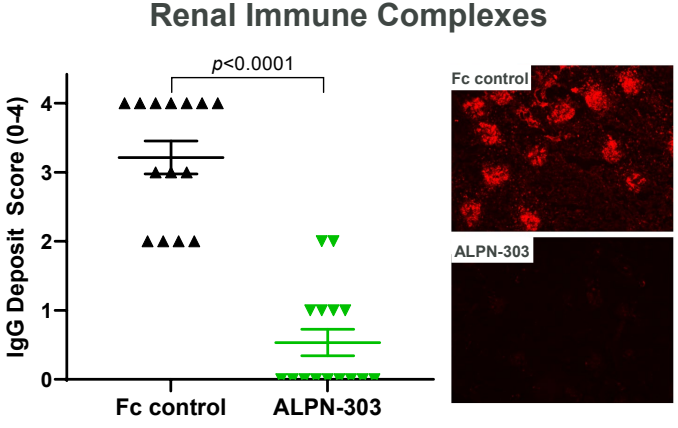










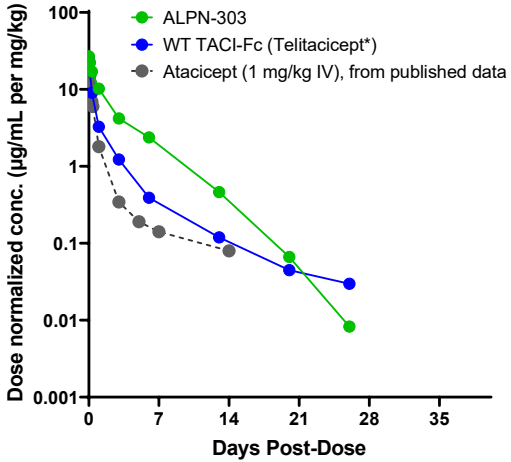


ALPN-303 dosed at 17 mg/kg IP 2x/week from 22-42 wks of age (vs. molar matched dose of Fc control)

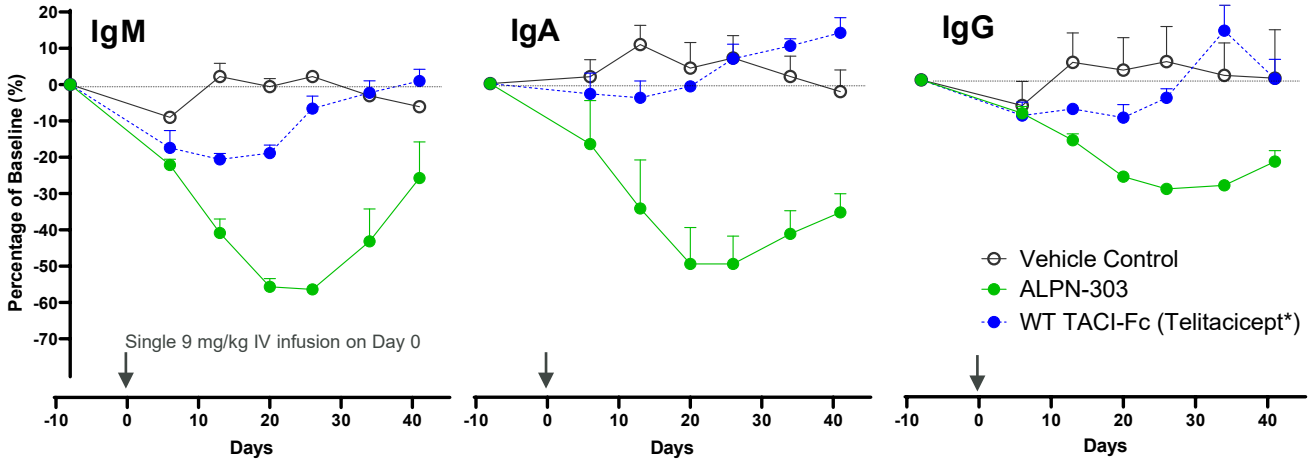
Following a Single Dose, ALPN-303 Exhibits Increased Exposure and Enhanced Ig Suppression vs. WT TACI-Fc in Non-Human Primates

- N=2 female cynomolgus monkeys/group
- Single dose, 9 mg/kg, 30 min IV infusion
- Serum Ig baseline collected on Day -8

Serum Concentration



Serum Immunoglobulins



	C_{max}/Dose (µg/mL per mg/kg)	AUC/Dose (µg*hr/mL per mg/kg)
ALPN-303	27	1167
WT TACI-Fc*	25	397
Atacicept	23	215

**Generated at Alpine based on the sequence included with the WHO INN submission, WHO Drug Information, Vol. 32, No. 4, 2018.; sequence subsequently confirmed by mass spectrometry analysis of telitacicept clinical drug product*

Atacicept PK data: Carbonatto et al. (2008) *Toxicol Sci* 105: 200–210

ALPN-303 is Well-Tolerated Following Multiple Doses in Rat and Cynomolgus Monkey

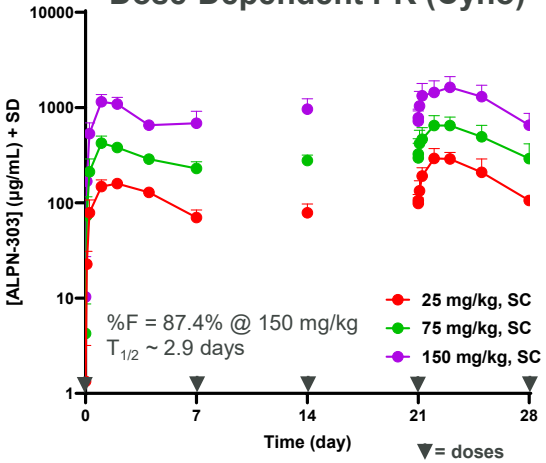
1-Month GLP Toxicology Studies:

Species	NOAEL[1]	AEs	Non-Adverse Findings
Cynomolgus monkey	150	None	• None • No cytokine release[2]
Rat	200	None	• ↓ Spleen weight and lymphocyte cellularity, ↓ serum IgA, IgM, IgG

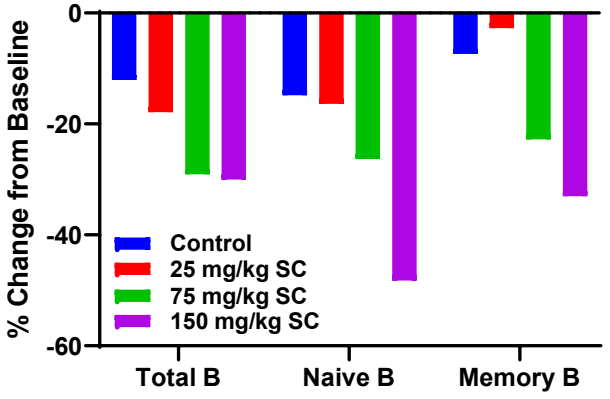
[1] mg/kg, IV, Q1W x 5

[2] IFNγ, IL-2/-4/-6/-8/-10, TNFα

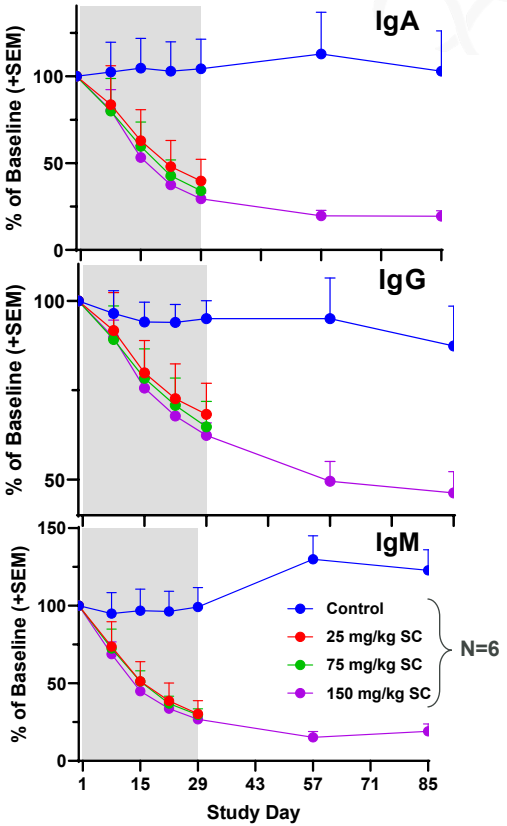
Dose-Dependent PK (Cyno)



PD: Circulating B Cells, D29 (Cyno)



PD: Serum Ig (Cyno)



Summary

- ALPN-303 is a potentially best-in-class BAFF/APRIL antagonist derived from our directed evolution platform
- ALPN-303 is well-tolerated in rodents and NHP and demonstrates encouraging immunomodulatory activity and efficacy, including significant reductions in plasma cells and Ig secretion *in vitro* and *in vivo*, typically superior in preclinical studies to anti-BAFF and/or anti-APRIL mAbs and WT TACI-Fc
- ALPN-303 exhibits favorable preliminary developability characteristics
  - Higher serum exposures and more potent immunomodulatory activities may translate in the clinic to lower doses, longer dosing intervals, and/or improved efficacy
- ALPN-303 is an attractive development candidate for the treatment of multiple autoimmune and inflammatory diseases, particularly SLE
  - Additional indications are under consideration, including Sjögren's syndrome and other connective tissue diseases, and antibody-related renal and skin diseases
- A Phase 1 study of ALPN-303 in adult healthy volunteers (NCT05034484) has been initiated

Acknowledgements

ALPN-303 Project Team

- Daniel Ardourel
- Janhavi Bhandari
- Lori Blanchfield
- Susan Bort
- Josiah Brown
- Daniel Demonte
- Lawrence Evans
- Luana Griffin
- Chelsea Gudgeon
- LuAnne Hebb
- Jan Hillson
- Pam Holland
- Kayla Kleist
- Joe Kuijper
- Heidi LeBlanc
- Steven Levin
- Katherine Lewis
- Kristi Manjarrez
- Gary Means
- Lisa Meyr
- Sherri Mudri
- Mark Rixon
- Andrea Peng
- Stanford Peng
- Russell Sanderson
- Michelle Seaberg
- Alina Smith
- NingXin Wang
- Martin Wolfson
- Jennifer Wiley
- Jing Yang

Additional Pharmacology/PK/Tox Studies

- Hooke Laboratories (Lawrence, MA)
- Altasciences (Everett, WA)