Plenary III (1424–1429)

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

Abstract Moderator(s)

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

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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
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

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November 8, 2021
Disclosures

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

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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

† 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

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:

**Test Articles**

<table>
<thead>
<tr>
<th></th>
<th>BAFF IC50 (pM)</th>
<th>APRIL IC50 (pM)</th>
<th>BAFF + APRIL IC50 (pM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPN-303</td>
<td>1337</td>
<td>1758</td>
<td>1390</td>
</tr>
<tr>
<td>Belimumab</td>
<td>2263</td>
<td>--</td>
<td>&gt;100,000</td>
</tr>
<tr>
<td>‘BION-1301’</td>
<td>--</td>
<td>4901</td>
<td>&gt;100,000</td>
</tr>
<tr>
<td>Belimumab + ‘BION-1301’</td>
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<td>2100</td>
<td>6805</td>
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<tr>
<td>‘Atacicept’</td>
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<td>7718</td>
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<tr>
<td>Telitacicept</td>
<td>6852</td>
<td>17244</td>
<td>16751</td>
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</tbody>
</table>

* Generated at Alpine based on published sequences:
  Atacicept: US Patent 8,815,238 B2 SEQ ID NO: 54

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

Generated at Alpine based on published patent sequences

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

Mouse

**Bone Marrow**

![Graph showing plasma cell counts in bone marrow from mice treated with ALPN-303.]

**Spleen**

![Graph showing plasma cell counts in spleen from mice treated with ALPN-303.]

**Lymph Node**

![Graph showing plasma cell counts in lymph nodes from mice treated with ALPN-303.]

NHP

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

![Graph showing plasma cell counts in bone marrow from NHP treated with ALPN-303.]

NHP were treated once weekly for 5 doses

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*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)F₁ Spontaneous Lupus Model

**Proteinuria**

Mean Proteinuria Score (±SEM)

**Anti-dsDNA**

[Anti-dsDNA] ± SEM (units/mL)

**Survival**

Percent Survival

**Blood Urea Nitrogen**

(Blood Urea Nitrogen (week 43))

BUN ± SEM (mg/dL)

**Nephritis**

Kidney Histology Score ± SEM (max score=21)

**Renal Immune Complexes**

IgG Deposit Score (0-4)

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

![Dose normalized conc. (µg/mL per mg/kg)]

<table>
<thead>
<tr>
<th>C\text{\text{_max/}\text{Dose}} (µg/mL per mg/kg)</th>
<th>AUC/Dose (µg*hr/mL per mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPN-303</td>
<td>27</td>
</tr>
<tr>
<td>WT TACI-Fc*</td>
<td>25</td>
</tr>
<tr>
<td>Atacicept</td>
<td>23</td>
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</table>

### Serum Immunoglobulins

- IgM
- IgA
- IgG

**IgM**
- Vehicle Control
- ALPN-303
- WT TACI-Fc (Telitacicept*)

**IgA**
- Vehicle Control
- ALPN-303
- WT TACI-Fc (Telitacicept*)

**IgG**
- Vehicle Control
- ALPN-303
- WT TACI-Fc (Telitacicept*)

*Single 9 mg/kg IV infusion on Day 0

*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

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

1-Month GLP Toxicology Studies:

<table>
<thead>
<tr>
<th>Species</th>
<th>NOAEL¹</th>
<th>AEs</th>
<th>Non-Adverse Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cynomolgus monkey</td>
<td>150</td>
<td>None</td>
<td>• None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No cytokine release²</td>
</tr>
<tr>
<td>Rat</td>
<td>200</td>
<td>None</td>
<td>• ↓ Spleen weight and lymphocyte cellularity, ↓ serum IgA, IgM, IgG</td>
</tr>
</tbody>
</table>

¹ mg/kg, IV, Q1W x 5

Dose-Dependent PK (Cyno)

PD: Circulating B Cells, D29 (Cyno)

PD: Serum Ig (Cyno)

N=6

%F = 87.4% @ 150 mg/kg
T₁/₂ ~ 2.9 days

1-2 IFNγ, IL-2/-4/-6/-8/-10, TNFα
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**
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- Lori Blanchfield
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- Michelle Seaberg
- Alina Smith
- NingXin Wang
- Martin Wolfson
- Jennifer Wiley
- Jing Yang

**Additional Pharmacology/PK/Tox Studies**
- Hooke Laboratories (Lawrence, MA)
- Altasciences (Everett, WA)