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 AUTOIMMUNE DISEASES

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Background: BAFF and APRIL are TNF superfamily members that bind TACI and BCMA and function in vivo via their co-neutralization dramatically reduces B cell function, including antibody production, particularly for plasmablasts and plasma cells, and play critical roles in the pathogenesis of B cell-related autoimmune diseases. In nonclinical models, inhibition of either BAFF or APRIL alone mediates relatively modest effects, whereas combination of BAFF and APRIL as compared to WT TACI and BCMA and with the potential to improve clinical outcomes in B cell-mediated diseases. Methods: Our directed evolution platform was used to identify a potent vari- ant TNFR domain (vTD) of TACI that exhibits significantly enhanced affinity for BAFF and APRIL as compared to WT TACI; this TACI vTD domain was fused to a human IgG Fc to generate the therapeutic candidate ALPN-303. ALPN-303 was evaluated for functional activity in: 1) human lymphocyte assays, 2) the NOD mouse model, and 3) the spontaneous Sjogren’s syndrome (SjS) model. Results: ALPN-303 inhibited BAFF- and APRIL-mediated signaling in vitro in human lymphocyte assays, with significantly lower IC50 values than WT TACI-Fc and belimumab comparators. In all mouse models evaluated, administration of ALPN-303 rapidly and significantly reduced key lymphocyte subsets including CD45+CD11b- mainly T cell, and CD11b+Ly6G-Ly6C+ monocytes (Figure 1). Conclusion: ALPN-303 is a potent BAFF/APRIL antagonist derived from our directed evolution platform that consistently demonstrates enhanced immunomodulatory activity and efficacy in vitro and in vivo, superior in preclinical studies to anti-BFAB and APRIL and WT TACI-Fc. This novel Fc fusion molecule demonstrates favorable preliminary developability characteristics, including higher serum exposures and more potent immunosuppressive activities, which may enable lower clinical doses and/or longer dosing intervals than WT TACI-Fc therapies. ALPN-303 may thus be an attractive development candidate for the treatment of multiple autoimmune and inflammatory diseases, particularly B cell-related diseases such as SLE, SjS, and other connective tissue diseases. Preclinical development is underway to enable the initiation of clinical trials later this year.


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HIPOCCAMPAL IMMUNE CELL TRAFFICKING AND A MYSTERY PREDOMINANT IMMUNE RESPONSE WITH ENHANCED ANTIGEN PRESENTATION AND DECREASED LEVELS OF NEUROTRANSMITTERS UNDERLY THE NEUROPSYCHIATRIC PHENOTYPE OF THE NZW/NZB MURINE LUPUS MODEL

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Background: Neuropsychiatric events are common in patients with systemic lupus erythematosus (SLE), yet the underlying pathogenesis remains ill-defined, as the access to brain tissue is limited. We have previously shown that NZW/NZB F1 murine lupus model recapitulates the neuropsychiatric lupus phenotype including depressive-like behavior, increased rates of anxiety, cognitive dysfunc-

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Conclusion: ALPN-303 is a potent BAFF/APRIL antagonist derived from our directed evolution platform that consistently demonstrates enhanced immunomodulatory activity and efficacy in vitro and in vivo, superior in preclinical studies to anti-BAFF antibody and WT TACI-Fc. This novel Fc fusion molecule demonstrates favorable preliminary developability characteristics, including higher serum exposures and more potent immunosuppressive activities, which may enable lower clinical doses and/or longer dosing intervals than WT TACI-Fc therapies. ALPN-303 may thus be an attractive development candidate for the treatment of multiple autoimmune and inflammatory diseases, particularly B cell-related diseases such as SLE, SjS, and other connective tissue diseases. Preclinical development is underway to enable the initiation of clinical trials later this year.


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