POSTER #88

ANB032, a Novel BTLA Agonist Monoclonal Antibody, Inhibits T Cell Proliferation, Reduces Inflammatory Cytokines, and Down Modulates BTLA Expression on Circulating T and B Cells: Results from a First-in-Human Phase 1 Study

Ken Luu, Bruce Randazzo, Eric Hare, Matthew Hsu, Chris Haines, Martin Dahl, Cailin Sibley, Paul Lizzul
AnaptysBio, Inc., San Diego, CA, USA

ABSTRACT

ANB032, a BTLA agonist antibody, has potential to modulate the pathogenic inflammatory response with broad applicability to inflammatory diseases where the BTLA pathway is dysregulated. In preclinical studies, ANB032 inhibited activated T cell proliferation, reduced inflammatory cytokine secretion (Th1, Th2, Th17, Th22) and modulated dendritic cell function, including inducing T regs. We report a Phase 1 double-blind, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) study of ANB032 in 96 healthy subjects. SAD and MAD consisted of 8 subjects each (6 ANB032, 2 placebo via intravenous or subcutaneous injection). SAD included 9 cohorts while MAD included 3 cohorts with each cohort dosed with ANB032 or placebo weekly for 4 weeks. Results were similar for both cohorts. ANB032 was well-tolerated with no dose limiting toxicities, no discontinuations due to adverse events (AEs) (except for one subject with potential COVID infection), or SAEs. Most AEs were mild-to-moderate, of short duration, resolved without sequelae, occurred sporadically, and were dose-independent. PK profile was favorable, including a 2-week half-life. Full BTLA receptor occupancy (RO) occurred within hours and was maintained for >30 days after a single dose. Moderate reduction (~50%) of cell surface BTLA expression on T and B cells was observed. The duration of reduced BTLA expression dose-dependently correlated with RO and was maintained for >30 days after a single dose. This study demonstrated robust PK, favorable safety, and target engagement in humans. A global Phase 2b trial in AD began May 2023 with results expected EOY 2024.

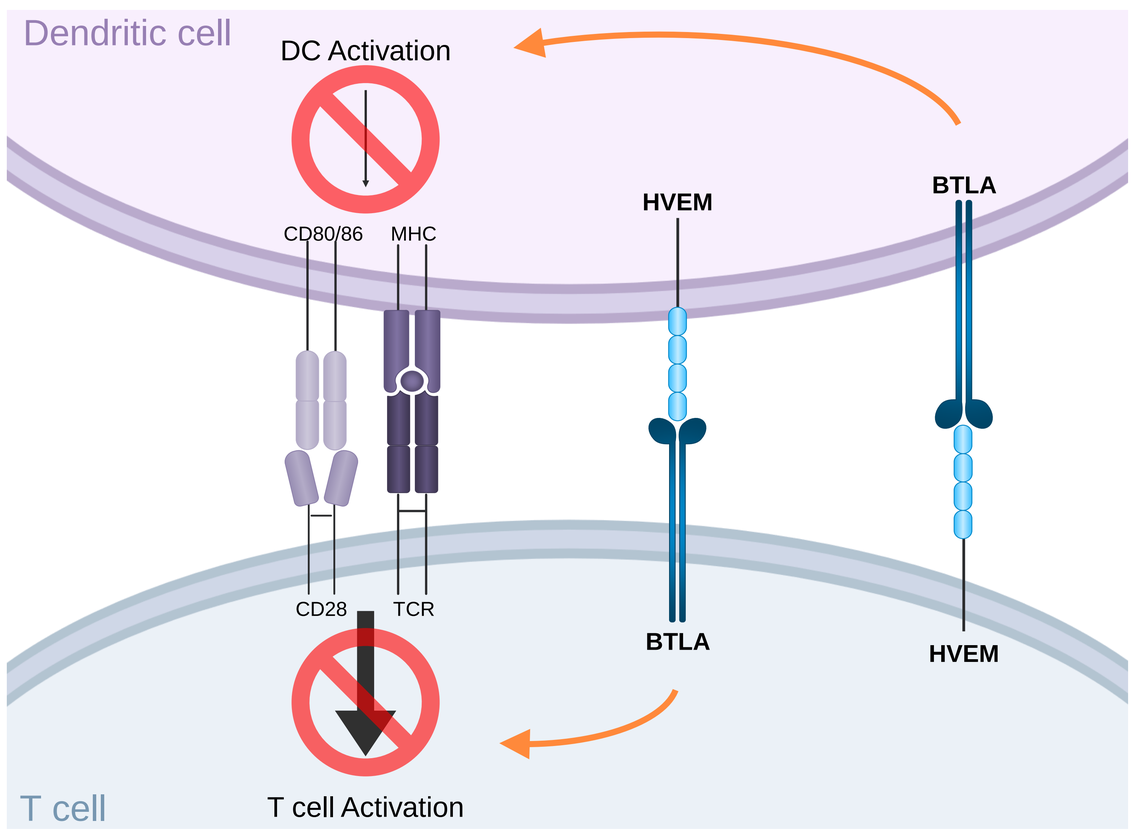
INTRODUCTION

- Atopic dermatitis (AD) is a common chronic inflammatory disorder with immunologic drivers, including broad T cell (Th1, Th2, Th17, Th22) and dendritic cell activation
- Although cytokine-specific monoclonal antibody therapies have improved the treatment of moderate to severe AD for some patients, there remains an unmet need for therapies that reflect the heterogenous pathophysiology of AD

B and T cell lymphocyte attenuator (BTLA)

- BTLA is a co-inhibitory checkpoint receptor expressed on T cells (Th1, Th2, Th17 and Th22), B cells and dendritic cells (DC), key contributors to inflammatory diseases such as atopic dermatitis (AD)
- BTLA-deficient mice showed increased T cell proliferation and susceptibility to spontaneous development of autoimmune diseases, including dermatitis, demonstrating that BTLA negatively regulates T cell activation and proliferation[1,2]
- T cell activation requires both antigen presentation via major histocompatibility complex (MHC) and T cell receptor (TCR) and co-stimulation via CD80/86 and CD28 (**Figure 1**)
- BTLA on T cell inhibits priming, activation, and expansion of inflammatory T cells
- BTLA on dendritic cells modulates maturation and function, reducing both antigen presentation by MHC and expression of co-stimulatory molecules

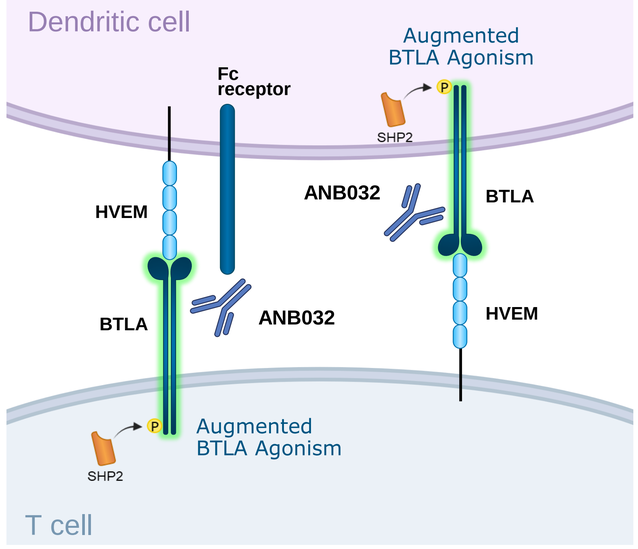
Figure 1. BTLA Checkpoint Receptor



ANB032

- ANB032 is a humanized IgG4/κ monoclonal antibody to BTLA that modulates BTLA activity in a non-competitive fashion with its ligand, herpesvirus entry mediator (HVEM) (**Figure 2**)
- In preclinical studies, ANB032 reduced cytokine secretion (Th1, Th2, Th17 and Th22) in AD patient-derived PBMCs[3] and reduced dendritic cell maturation[4]
- ANB032 has potential broad applicability to inflammatory diseases due to breadth of BTLA expression across immune cell types[5]

Figure 2. Proposed Mechanism of Action for ANB032



ANB032 binds to BTLA epitope on Th1, Th2, Th17 and Th22 T cells and dendritic cells

- Direct agonism of BTLA
- Does not block engagement of native ligand HVEM allowing endogenous inhibitory pathway to remain active
- Fc receptor binding profile contributes to differentiated potency

BTLA agonism augmented and potentiated by ANB032

OBJECTIVES

Primary:

- Assess safety and tolerability of single and multiple doses of ANB032 in healthy participants

Key Secondary & Exploratory:

- Characterize pharmacokinetics after single and multiple doses of ANB032
- Assess percent BLTA receptor occupancy following ANB032 administration
- Assess BTLA expression following ANB032 administration

METHODS

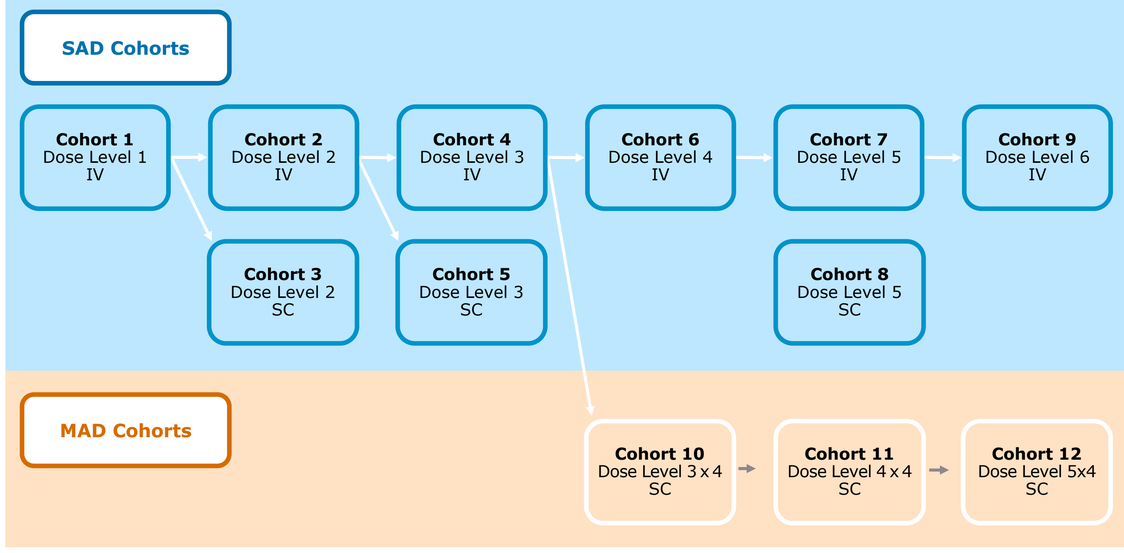
Study Design:

- First-in-human, double-blind, randomized, placebo-controlled single ascending dose (SAD) and multiple ascending dose (MAD) study of ANB032 in healthy subjects (**Figure 3**)

Participants and Dosing:

- 96 healthy volunteers enrolled
- 8 participants in each cohort: 6 dosed with ANB032 and 2 with placebo IV or SC
- SAD phase included 9 cohorts
- MAD phase included 3 cohorts; each dosed with ANB032 or placebo SC weekly for 4 weeks

Figure 3. ANB032 Phase 1 Study Design



MAD, multiple ascending dose; SAD, single ascending dose; SC, subcutaneous

RESULTS

Safety and Tolerability

- ANB032 was well-tolerated with no dose-limiting toxicities
- Most adverse events were mild-to-moderate, of short duration, dose and timing from dose independent and resolved without sequelae
  - No serious adverse events were observed

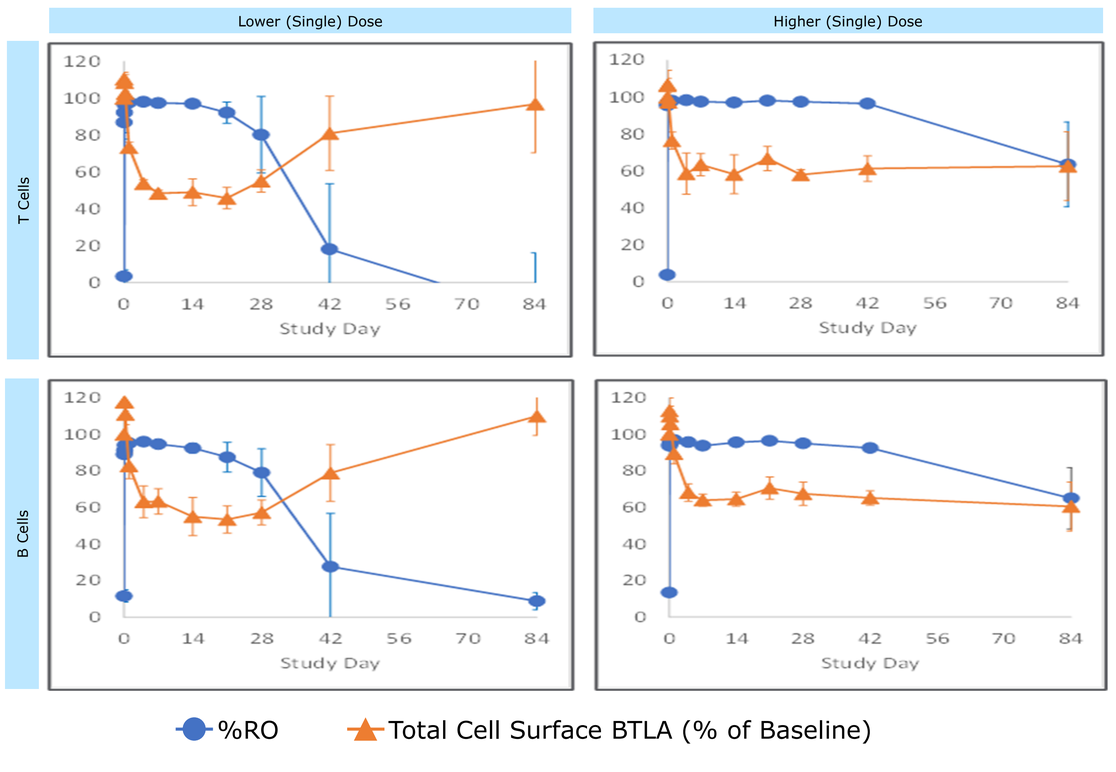
Pharmacokinetics

- PK profile was favorable demonstrating approximately 2-week half-life with IV and SC dosing and dose proportionality in C_{max} and AUC

Pharmacodynamics

- Rapid and sustained target engagement on both T cells and B cells (**Figure 4**)
- Full BTLA receptor occupancy (RO) was observed within hours and maintained for >30 days following IV or SC dosing
- Moderate reduction (50%) of cell surface BTLA expression
- Duration of reduced BTLA expression persisted in a dose-dependent manner

Figure 4. BTLA receptor Occupancy and Total Cell Surface Expression



CONCLUSIONS

ANB032 Phase 1:

- Well-tolerated after single and multiple doses
- Favorable PK profile
- Demonstrated robust target engagement in healthy participants

Beyond:

- Atopic dermatitis pathophysiology includes dysregulation of multiple proinflammatory pathways driven by Th1, Th2, Th17 and Th22 T cells and dendritic cells
- Based on a strong rationale and these Phase 1 data, ANB032 has progressed into a phase 2b trial for patients with moderate to severe atopic dermatitis
- ARISE-AD (NCT05935085) commenced Q2 2023 and topline data are expected end of year 2024 (see poster #89)

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2. All authors are employees of AnaptysBio, Inc.