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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

Kenneth 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 systemic, heterogenous inflammatory disease where pathogenesis is driven by Th1, Th2, Th17, Th22, and DCs in tissue and the periphery
- 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 preferentially on activated T cells, B cells, and DCs, key contributors to inflammatory diseases such as AD
- Preclinical studies demonstrated that BTLA-deficient mice show increased T cell proliferation and susceptibility to spontaneous development of autoimmune diseases, including dermatitis, further supporting data that BTLA negatively regulates T cell activation and proliferation[1,2]
- BTLA engagement on T cell inhibits T cell proliferation and secretion of inflammatory cytokines

ANB032

- ANB032 is an investigational non-depleting BTLA agonist antibody that does not compete with the binding of BTLA to herpesvirus entry mediator (HVEM), its ligand (**Figure 1**)
- 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]

Proposed Mechanism of Action for ANB032

BTLA is a key node of immune regulation

- BTLA is a potent checkpoint receptor
- Expressed only on immune cells and preferentially on activated immune cells
- Dysregulation of BTLA pathway accelerates onset and exacerbates disease

ANB032: IgG4 antibody (non-depleting)

- Binds BTLA proximal to immune cell
- Fc receptor binding contributes to differentiated potency
- Non-blocking of HVEM engagement

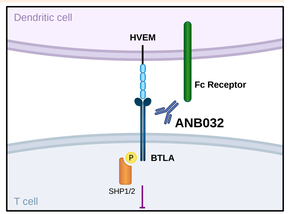

Figure 1. Schematic of proposed MOA.

OBJECTIVES

Primary Outcome Measures

- Safety and tolerability of single and multiple doses of ANB032 in healthy subjects

Key Secondary & Exploratory Outcome Measures

- Pharmacokinetics after single and multiple doses of ANB032
- BTLA receptor occupancy following ANB032 administration
- BTLA expression following ANB032 administration

METHODS

Study Design

- First-in-human, double-blind, randomized, placebo-controlled study of ANB032 in healthy subjects (**Figure 2**)
- 96 healthy subjects enrolled:
  - All cohorts consisted of 8 subjects each (6 ANB032, 2 placebo)
  - SAD (9 cohorts): Dosed IV or SC
  - MAD (3 cohorts): Dosed SC weekly for 4 weeks

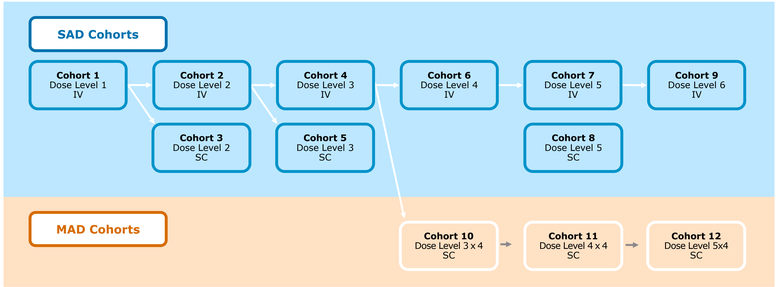

Figure 2. ANB032 Phase 1 study design. SAD = single ascending dose; MAD = multiple ascending dose; IV = intravenous; SC = subcutaneous.

RESULTS

Safety and Tolerability

- ANB032 was well-tolerated with no dose-limiting toxicities
- Most adverse events were mild-to-moderate, of short duration, dose 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

RESULTS

Pharmacodynamics

- Rapid and sustained target engagement on both T cells and B cells (**Figure 3**)
- Full BTLA receptor occupancy (RO) was observed within hours post-dose 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

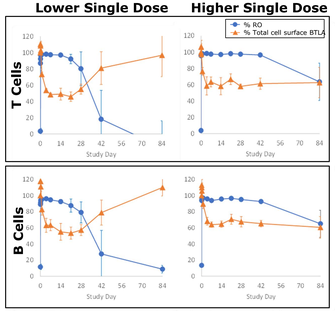

Figure 3. BTLA receptor occupancy and total cell surface expression following ANB032 dosing.

CONCLUSIONS

Phase 1 Evaluation of ANB032 demonstrated:

- ANB032 was well-tolerated after single and multiple doses
- Similar results were observed between SAD and MAD cohorts
- Favorable PK profile
- Robust target engagement in healthy subjects

Future Directions:

- AD pathophysiology includes dysregulation of multiple proinflammatory pathways driven by Th1, Th2, Th17, and Th22 T cells and dendritic cells
- Based on the role of BTLA in activated T cells, B cells, and DCs and these Phase 1 data, ANB032 has progressed into a phase 2 trial for patients with moderate-to-severe AD
- ARISE AD (NCT05935085) commenced Q2 2023 and topline data are expected by end of year 2024

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