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

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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 induced antigen-specific T cell activation and cytokine production that was dose-dependent and correlated with receptor occupancy. ANB032 also reduced inflammatory cytokine (IL-6, IL-17, TNFα, IL-23) and chemokine (CCL2, CCL3, CCL5) production in vitro and in vivo in a dose-dependent manner. ANB032 treatment downregulated BTLA expression on T and B cells in-vitro and in-vivo. In Phase 1 trials, 7 healthy subjects received escalating doses of ANB032 intravenous and subcutaneous administrations. Pharmacokinetics, safety, and tolerability were dose proportional and were maintained for at least 30 days. 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 antibodies have improved AD, the treatment of moderate-to-severe AD for some patients, remains an unmet need for therapies that reflect the heterogenous pathophysiology of AD

B and T lymphocyte attenuator (BTLA) is a systemic, heterogenous inflammatory disease where pathogenesis is driven by Th1, Th2, Th17, Th22, and DCs in tissue and the periphery

• Preclinical studies demonstrated that BTLA-deficient mice showed 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.

BTLA engagement on T cells 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, Th22) and increased DCS in tissue and the periphery
• ANB032 has broad potential applicability to inflammatory diseases due to breadth of BTLA expression across immune cell types.

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

RESULTS

Potential to modulate the pathogenic inflammatory response with broad applicability to inflammatory diseases where the BTLA pathway is dysregulated. In preclinical studies, ANB032 induced antigen-specific T cell activation and cytokine production that was dose-dependent and correlated with receptor occupancy. ANB032 also reduced inflammatory cytokine (IL-6, IL-17, TNFα, IL-23) and chemokine (CCL2, CCL3, CCL5) production in vitro and in vivo in a dose-dependent manner. ANB032 treatment downregulated BTLA expression on T and B cells in-vitro and in-vivo. In Phase 1 trials, 7 healthy subjects received escalating doses of ANB032 intravenous and subcutaneous administrations. Pharmacokinetics, safety, and tolerability were dose proportional and were maintained for at least 30 days. 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.

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)
  - Dose escalation

Safety and Tolerance
• ANB032 was well-tolerated with no dose-limiting toxicities
• Most adverse events were mild, of short duration, dose independent and resolved without sequelae
• No serious adverse events were observed

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

CONCLUSIONS

Phase 1 Evaluation of ANB032 demonstrated:
• ANB032 was well-tolerated after single and multiple doses
• Similar results were observed between MAD 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

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REFERENCES