Poster #617

ANB032, a novel BTLA agonist monoclonal antibody, inhibited T cell proliferation, reduced inflammatory cytokines, and down modulated BTLA expression on circulating T and B cells in Phase 1, progresses into a Phase 2 study in atopic dermatitis

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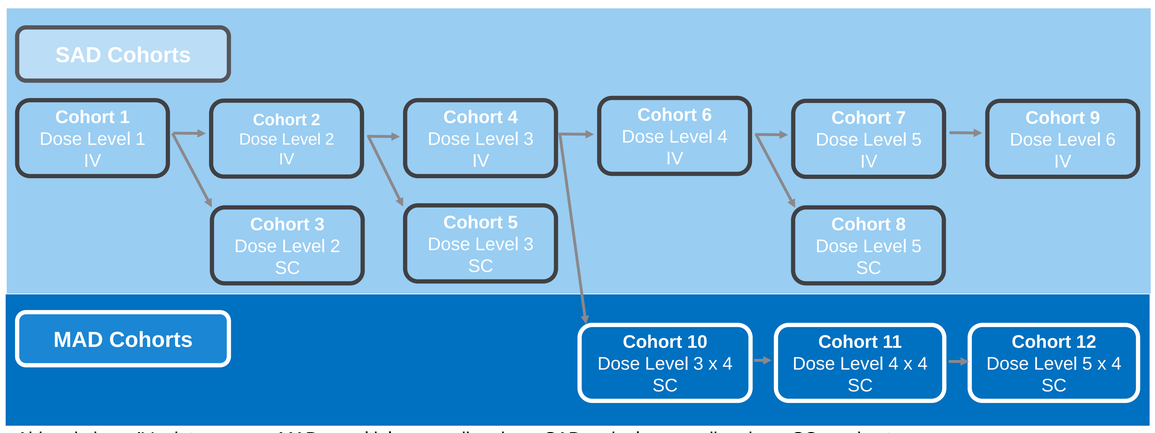
ABSTRACT

BTLA is a member of the CD28 superfamily that negatively regulates T cell, B cell, and DC cell-mediated inflammation. ANB032, a novel BTLA agonist monoclonal antibody, is being developed for the treatment of autoimmune and inflammatory diseases such as atopic dermatitis (AD). Because AD is not just a Th2 disease, but also has Th1 and Th17 involvement, immune modulators that downmodulated cells that contribute to the pathology of AD, such as ANB032, have the potential to better treat the disease than with single cytokine targeted biologics. Preclinical data from AD patient-derived peripheral blood mononuclear cells (PBMCs) demonstrate ANB032 reduced T cell proliferation and secretion of inflammatory cytokines, including IFNγ, IL-5, IL-13 and IL-17A, which are mediators in chronic AD. ANB032 also downregulates BTLA expression during T cell stimulation. Phase 1 healthy subjects data demonstrated that ANB032 was well-tolerated with no dose limiting toxicities or serious adverse events (AEs). Most AEs were mild-to-moderate, resolved without sequelae, occurred sporadically and were dose-independent. PK profile was favorable, including a 2-week half-life. ANB032 exhibited rapid and sustained target engagement on T and B cells. Full BTLA receptor occupancy (RO) occurred within hours and was maintained for more than 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 also maintained for more than 30 days after a single dose. The phase 1 data demonstrated robust PK and target engagement in humans. These clinical data, in conjunction with preclinical translational data from AD patients, support progression of ANB032 into a phase 2 trial in AD.

PHASE 1 STUDY DESIGN

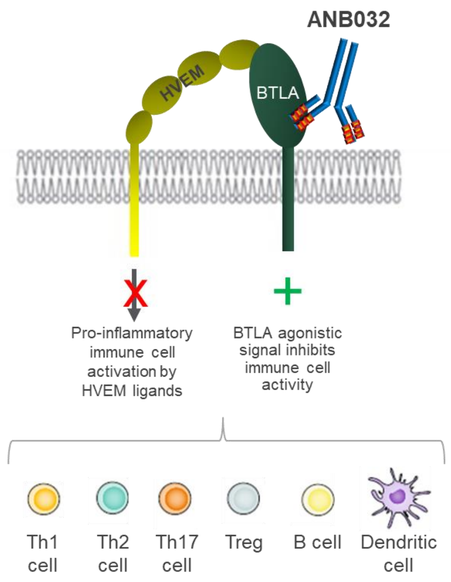


Abbreviations: IV = intravenous; MAD = multiple ascending dose; SAD = single ascending dose; SC = subcutaneous.

BACKGROUND & INTRODUCTION

- B and T cell lymphocyte attenuator (BTLA) is a coinhibitory checkpoint receptor responsible for regulating activation of lymphoid (T and B) cells and dendritic cells.
- ANB032 is a humanized IgG4/κ monoclonal antibody to human BTLA that modulates BTLA activity in a non-competitive fashion with its ligand, herpesvirus entry mediator (HVEM; **Figure 1**).
- ANB032 inhibits T cell proliferation, reduces inflammatory cytokine secretion and inhibits dendritic cell maturation.
- Thus, ANB032 has potential broad applicability to inflammatory diseases due to breadth of BTLA expression across immune cell types.[1]

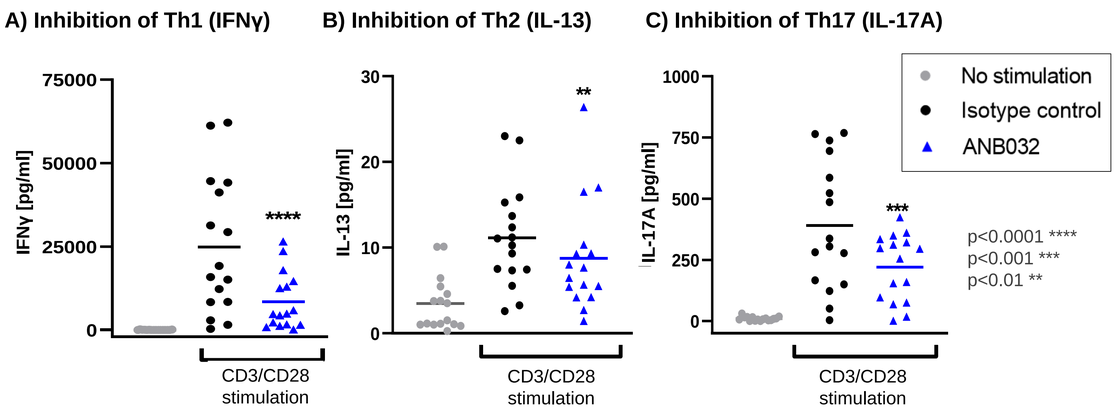
Figure 1. ANB032 Mechanism of Action



Abbreviations: BTLA = B and T cell lymphocyte attenuator; HVEM = herpesvirus entry mediator.

- Atopic dermatitis (AD), a common chronic inflammatory skin disorder, with complex immunologic drivers including broad T cell (Th1, Th2, Th17) and dendritic cell activation.
- BTLA-deficient T cells in mice show increased proliferation and susceptibility to spontaneous development of autoimmune diseases, including dermatitis, demonstrating that BTLA negatively regulates T cell activation and proliferation.[2,3]
- ANB032 inhibits Th1/Th2/Th17 cytokine secretion and cell proliferation in healthy and AD patient-derived peripheral blood mononuclear cells (PBMCs; **Figure 2**).

Figure 2. Cytokine Secretion in Atopic Dermatitis Patient-derived Peripheral Blood Mononuclear Cells



OBJECTIVES

Primary:

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

Key Secondary & Exploratory:

- Characterize pharmacokinetics (PK) after single and multiple doses of ANB032.
- Assess percent BLTA receptor occupancy (RO) following ANB032 administration.
- Assess BTLA expression following ANB032 administration.

METHODS

- First-in-human, double-blind, randomized, placebo-controlled single ascending dose (SAD) and multiple ascending dose (MAD) study of ANB032 in healthy subjects.
- All cohorts consisted of 8 subjects each (6 ANB032, 2 placebo via intravenous [IV] or subcutaneous [SC] injection).
- SAD phase included 9 cohorts.
- MAD phase included 3 cohorts; each cohort dosed with ANB032 or placebo weekly, for 4 weeks.

RESULTS

- 96 healthy subjects were randomized into the SAD and MAD cohorts.
- Results between SAD and MAD cohorts were similar.

Pharmacokinetics:

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

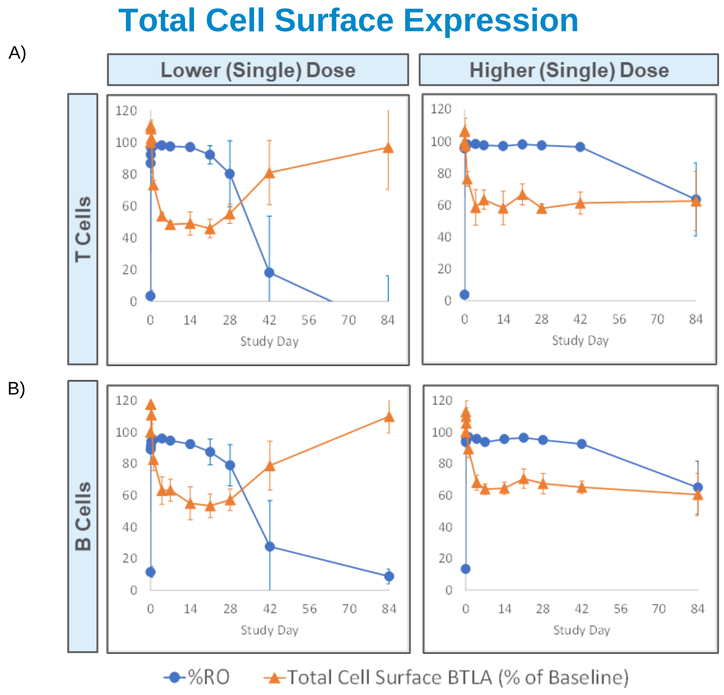
Pharmacodynamics (Figure 3):

- Full BTLA RO was observed within hours and maintained for > 30 days following IV or SC dosing.
- Rapid and sustained target engagement on both T cells and B cells.
- Reduction of cell surface BTLA expression.
- Duration of reduced BTLA expression persisted in a dose-dependent manner.

Safety:

- 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.

Figure 3. B and T Cell Lymphocyte Attenuator Receptor Occupancy and Total Cell Surface Expression



Abbreviations: BTLA = B and T cell lymphocyte attenuator; RO = receptor occupancy.

FUTURE DIRECTIONS

- Global Phase 2b study initiated Q2 2023 in moderate to severe AD.
- All comer population; including subjects with/without dupilumab/IL-13 experience.

Phase 2 Study Design

Dosing is every 2 weeks or monthly

Abbreviation: SC = subcutaneous.

CONCLUSIONS

ANB032:

- Well-tolerated after single and multiple doses
- Favorable PK profile
- Demonstrated robust target engagement in healthy subjects
- These human data are consistent with observations from pre-clinical animal models of inflammation and support the potential broad application of BTLA agonists for inflammatory diseases driven by T cells, B cells and dendritic cells

These clinical data support progression of ANB032 into a phase 2 trial for AD

REFERENCES

1. Murphy et al. 2010; 2. Nakagomi et al. 2013;
3. Bekiaris et al. 2013

ACKNOWLEDGEMENTS

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All authors are current or previous employees of AnaptysBio, Inc.

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