**A Phase 1 Study of ANB200, an Anti-IL-33 Monoclonal Antibody, in Healthy Volunteers**

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IL-33 is a preformed alarmin cytokine released by a number of cell types upon allergen challenge. IL-33 acts as a gatekeeper of Th2 function with known roles in the initiation, propagation and amplification of allergic responses. During the initial phase, IL-33 release leads to the rapid activation of Type 2 innate lymphoid cells (ILC2s) which secrete large quantities of efferocytosis cytokines, including IL-4, IL-5 and IL-13. Propagation of Th2 function can occur through the activity of ILC3s on alarmin-specific T cells activated through antigen-presenting cells, which then also express efferocytosis cytokines further acting on B cells and ultimately driving allergen-specific IgE production. Amplification of Th2 response is mediated by IL-33-mediated activation of mast cells and basophils, which are key effector cells involved in allergic reactions. We believe that inhibition of IL-33 may provide a significant therapeutic benefit to patients suffering from allergic diseases.

**ANB200 Characterisation**

**In vitro ANB200 functional activity**

As illustrated in the figure above, a linear ANB200 serum exposure was observed across doses and time points post-dosing. Twenty-four subjects were dosed with ANB200. The terminal half-life of ANB200 was approximately 372 hours (15–16 days) with comparable values across all doses and regardless of route (IV or SC) of administration.

ADA were detected at only low tier levels, and were observed in 5 of 48 dosed subjects. No effect was observed on PK parameters in subjects with ADA titers.

For the 40 mg SC, 40 mg IV and 100 mg IV cohorts, data for time points from 0–168 hours were below the lower limit of quantitation (LOQ) ≥ 0.4 μg/mL.

**Ex vivo whole blood pharmacodynamics assay**

Blood samples were collected at different time points and ANB200 inhibitory activity was tested in a whole blood ex vivo assay using stimulation with 5.5 mM IL-12, where ANB200 inhibition of IFN-γ release was measured. Persistent and nearly complete inhibition was observed at 1032 hours (day 43) for all cohorts dosed with greater than 10 mg SC ANB200, regardless of route (SC or IV) of administration. In the last 2 cohorts (300 mg and 750 mg IV), the PD test was also performed at 2048 hours (day 88), and nearly complete IFN-γ inhibition was observed through this time point. Some samples in the 10 mg cohort (24hrs post-dose) were unassessable for testing due to sample handling.

**ANB200 has been tested in a first in human phase 1 clinical trial to study its safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profiles. A total of 96 male and female healthy subjects were enrolled in the study, 72 dosed with ANB200 and 24 with placebo. The study subdivided 64 subjects into single ascending dose (SAD) cohorts and add subjects into multiple ascending dose (MAD) cohorts. Subjects in the MAD cohorts received 4 doses over 4 weeks. Subjects were randomized (3:1) to receive ANB200 or placebo in each SAD and MAD cohort. ANB200 was dosed over a range of 10 to 750 mg IV or SC in the SAD part of the study and 40 to 300 mg (IV or SC) in the MAD part of the study. For each arm of the study, participants were monitored over a period of 85 days post single dose (SAD) or first dose (MAD). Pharmacodynamic (PD) profiles were measured, using a whole blood ex vivo assay, for at least 43 days post-dosing in all SAD cohorts, while the highest dose SAD cohorts (cohorts 7 and 8) were measured for 85 days post-dosing. Anti-drug antibodies (ADA) were monitored in both SAD and MAD sections of the study. As shown in the above figure, a linear ANB200 serum exposure was observed across doses and time points post-dosing. Twenty-four subjects were dosed with ANB200. The terminal half-life of ANB200 was approximately 372 hours (15–16 days) with comparable values across all doses and regardless of route (IV or SC) of administration. ADA were detected at only low tier levels, and were observed in 5 of 48 dosed subjects. No effect was observed on PK parameters in subjects with ADA titers. For the 40 mg SC, 40 mg IV and 100 mg IV cohorts, data for time points from 0–168 hours were below the lower limit of quantitation (LOQ) ≥ 0.4 μg/mL.**

**ANB200 is a humanized anti-IL-33 IgG1 antibody, generated using AnaptysBio's proprietary antibody discovery platform, specific for human IL-33 with cross-reactivity to cynomolgus monkey IL-33. ANB200 has high affinity (KD ~1 m) to human IL-33 and efficiently neutralizes cytokine (LOD ~ 5 fM) and inflammatory human cells (basophils, PMBC and whole blood) in ex-vivo assays. The figure above illustrates ANB200-mediated inhibition of IL-33/IL-12 induced IFN-γ release in whole blood.**

**SAD Pharmacodynamics Profiles**

IL-33 inhibition represents a potential new therapy for the treatment of atopic diseases. ANB200 is a humanized IgG1 monoclonal with high affinity and neutralizing activity for human IL-33. Male and female healthy volunteers aged 18–45 years were enrolled in this first-in-human Phase 1 study. The study indicated that ANB200, when administered as a single dose or multiple dose by IV or SC injection, is generally well-tolerated. ADAs were observed in up to 80% of the subjects participating to the study, but were evenly distributed between ANB200 and placebo dose subjects.

The pharmacokinetic (PK) parameters of ANB200 are compatible with IgG1 monoclonal antibodies and a linear exposure was observed in both IV or SC dosed subjects. The pharmacodynamic (PD) effect of ANB200 was measured using a whole blood ex vivo assay and demonstrated a persistent inhibitory activity, up to 43 days post dosing, in all SAD cohorts (IV or SC) dosed with greater than 10 mg SC ANB200. In the last two SAD cohorts (300 mg and 750 mg IV), sustained PD effect was observed through day 85 post dosing. Results from this clinical study have been reviewed by health authorities (FDA and MRA) and ANB200 is currently enrolling atopic disease patients in Phase 2a clinical studies.

**MAD Safety Profile**

**Conclusion**

The most common AE’s for subjects receiving a single dose were upper respiratory tract infection (ANB200 48%, placebo 50%) and headache (ANB200 27%, placebo 31%). One serious adverse event (SAE) was reported as a result of severe neutropenia on Day 34 post-dose in a single individual in cohort 6; however neutrophil levels in this subject returned to within normal range by Day 29 post-dose. The subject reported pruritus and skin rashes prior to the observation of neutropenia with other symptoms, including c-reactive protein (CRP) increase, consistent with an ongoing viral infection. No significant neutrophil level changes were observed among any other subjects in the study. The study was well tolerated, with 100% of subjects maintaining low safety, key laboratory, and body system parameters across the MAD cohorts.

**Twenty-four subjects (7%) experienced at least one treatment-emergent AE. As in the SAD section of the study, there was no significant difference in the percentage of subjects with AEs between ANB200 (18 of 24, 75%) and placebo (6 of 8, 75%) among the MAD cohorts. As with the SAD portion of the study, the most common AEs were upper respiratory tract infections (ANB200 21%, placebo 38%) and headache (ANB200 35%, placebo 38%). No SAEs were observed in the MAD section of the study. No effect on neutrophils was observed in the subjects enrolled in the MAD section of the study. Low level anti-drug antibodies were detected in 2 out of 24 ANB200 dosed subjects with no detectable effect on PK parameters in either of these subjects.**