A Phase 1 Study of ANB020, an Anti-IL-33 Monoclonal Antibody, in Healthy Volunteers

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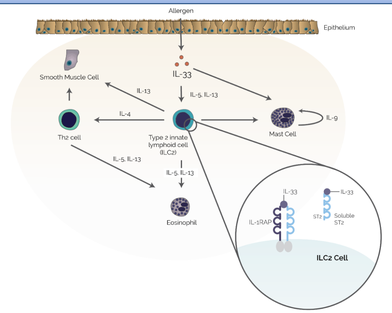
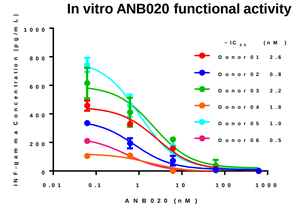
Introduction



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 response. During the initiation phase, IL-33 release leads to the rapid activation of Type 2 innate lymphoid cells (ILC2) which then secrete large quantities of effector Th2 cytokines, including IL-4, IL-5 and IL-13. Propagation of Th2 function can occur through the activity of IL-33 on allergen-specific T cells activated through antigen-presenting cells, which then also express effector Th2 cytokines further acting on B cells and ultimately leading to 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.

ANB020 Characterization

In vitro ANB020 functional activity



ANB020 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. ANB020 has high affinity (KD ~1pM) to human IL-33 and efficiently inhibits IL-33 activity (IC50 ~1.5 nM) on primary human cells (basophils, PBMC and whole blood) in *in-vitro* assays. The figure above illustrates ANB020-mediated inhibition of IL-33/IL-12 induced IFN-γ release in whole blood.

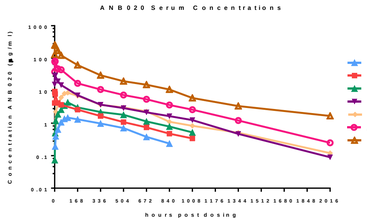
ANB020-001 Phase 1 Clinical Study Outline

ANB020 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 ANB020 and 24 with placebo. The study subdivided 64 subjects into single ascending dose (SAD) cohorts and and 32 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 ANB020 or placebo in each SAD and MAD cohort. ANB020 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.

SAD Pharmacokinetics and ADA Profiles



As illustrated in the figure above, a linear ANB020 serum exposure was observed for all doses and routes of administration tested. Samples were BLQ (below limit of quantitation) for the 10 mg cohort and therefore not included in the figure above.

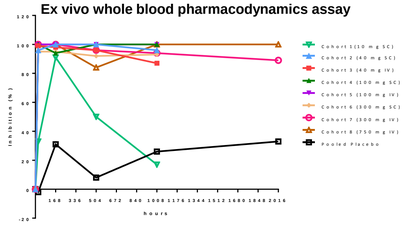
The terminal half-life of ANB020 was approximately 372 hours (15–16 days) with comparable values across all doses and regardless of route (IV or SC) of administration.

ADA were detected at only low titer 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 1008 hours (day 43) were below the lower limit of quantitation (LLOQ = 0.4 µg/mL).

SAD Pharmacodynamic Profiles

Ex vivo whole blood pharmacodynamics assay



Blood samples were collected at different time points and ANB020 inhibitory activity was tested in a whole blood *ex-vivo* assay upon stimulation with IL-33/IL-12, where ANB020 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 than10 mg SC ANB020, 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 2040 hours (day 85), and nearly complete IFN-γ inhibition was observed through this time point. Some samples in the 10 mg cohort (24hrs post-dose) were unavailable for testing due to sample handling.

SAD Safety Profile

Adverse Events	Subcutaneous (mg)					Intravenous (mg)					Totals		
	0	10	40	100	300	0	40	100	300	750	Placebo	Active	All Subjects
Number of Subjects	N=8	N=6	N=6	N=6	N=6	N=8	N=6	N=6	N=6	N=6	N=16	N=48	N=64
Total TEAEs	7 (88%)	3 (50%)	6 (100%)	6 (100%)	5 (83%)	6 (75%)	5 (83%)	5 (83%)	2 (33%)	6 (100%)	13 (81%)	38 (79%)	51 (80%)
Study Drug Related* TEAEs	4 (50%)	1 (17%)	3 (50%)	4 (67%)	4 (67%)	3 (38%)	2 (33%)	3 (50%)	-	4 (67%)	7 (44%)	21 (44%)	28 (44%)
Moderate - Severe TEAEs	4 (50%)	1 (17%)	1 (17%)	5 (83%)	2 (33%)	5 (63%)	2 (33%)	3 (50%)	2 (33%	5 (83%)	9 (56%)	21 (44%)	30 (47%)
Moderate - Severe Study Drug Related* TEAEs	3 (38%)	-	-	2 (33%)	1 (17%)	2 (25%)	-	2 (33%)	-	4 (67%)	5 (31%)	9 (19%)	14 (22%)
SAEs	-	-	-	-	-	-	-	-	-	1 (17%)	-	1 (2%)	1 (2%)

*Related TEAEs = Possibly Related + Related; TEAE= Treatment-Emergent Adverse Event; SAE = Serious Adverse Event

Fifty-one subjects (80%) experienced at least one treatment-emergent adverse event (AE). However there was little difference in the number of subjects with AEs between ANB020 (38 of 48, 79%) and placebo (13 of 16, 81%).

The most common AEs for subjects receiving a single dose were upper respiratory tract infection (ANB020 48%, placebo 50%) and headache (ANB020 27%, placebo 31%). One serious adverse event (SAE) was reported as a result of severe neutropenia on Day 22 post-dose in a single individual in cohort 8, however neutrophil levels in this subject returned to within normal range by Day 29 post-dose. The subject reported prodromal viral symptoms prior to the observance 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.

MAD Safety Profile

Adverse Events	Subcutaneous (mg)		Intravenous (mg)				Totals		
	0	100	0	40	100	300	Placebo	Active	All Subjects
Number of	N=2	N=6	N=6	N=6	N=6	N=6	N=8	N=24	N=32
Total TEAEs	1 (50%)	5 (83%)	5 (83%)	6 (100%)	5 (83%)	2 (33%)	6 (75%)	18 (75%)	24 (75%)
Study Drug Related* TEAEs	1 (50%)	2 (33%)	3 (50%)	4 (67%)	5 (83%)	2 (33%)	4 (50%)	13 (54%)	17 (53%)
Moderate - Severe TEAEs	-	2 (33%)	4 (67%)	3 (50%)	4 (67%)	2 (33%)	4 (50%)	11 (46%)	15 (47%)
Moderate - Severe Study Drug Related* TEAEs	-	-	2 (33%)	2 (33%)	4 (67%)	2 (33%)	2 (25%)	8 (33%)	10 (31%)
SAEs**	-	-	-	-	-	-	-	-	0 (0%)

*Related TEAEs = Possibly Related + Related; TEAE= Treatment-Emergent Adverse Event; SAE = Serious Adverse Event

Twenty-four subjects (75%) 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 ANB020 (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 (ANB020 21%, placebo 38%) and headache (ANB020 33%, 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 titer anti-drug antibodies were detected in 2 out of 24 ANB020 dosed subjects with no detectable effect on PK parameters in either of these subjects.

Conclusions

IL-33 inhibition represents a potential new therapy for the treatment atopic diseases. ANB020 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 ANB020, when administered as single dose or multiple dose by IV or SC injection, is generally well tolerated. AEs were observed in up to 80% of the subjects participating to the study, but were evenly distributed between ANB020 and placebo dosed subjects.

The pharmacokinetic (PK) parameters of ANB020 are compatible with IgG1 monoclonal antibodies and a linear exposure was observed in both IV or SC dosed subjects.

The pharmacodynamic (PD) effect of ANB020 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 ANB020. 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 MHRA) and ANB020 is currently enrolling atopic disease patients in Phase 2a clinical studies.