A Phase 1 study of ANB019, an Anti-IL-36 Receptor Monoclonal Antibody, in Healthy Volunteers

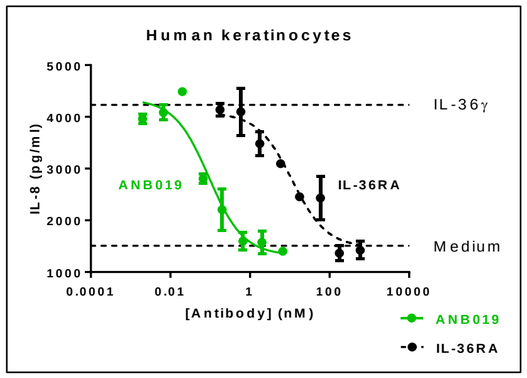
Irina Khanskaya, Jason Pinkstaff, Margaret H Marino, Traci Savall, Jie Li, Marco Londei. AnaptysBio, 10421 Pacific Center Court, San Diego, CA 92121

Introduction

The IL-36 pathway has been hypothesized to play a key role in inflammatory skin diseases. Dysregulation of IL-36 receptor (IL-36R) signaling, either due to genetic mutations or excess IL-36 cytokine expression levels, is believed to result in the incidence of Generalized Pustular Psoriasis (GPP) and Palmoplantar Pustulosis (PPP). Our anti-IL-36R antibody, also known as ANB019, is being developed to treat these two human inflammatory conditions.

ANB019 Characterization

ANB019 is a specific high affinity anti-human IL-36R antibody, generated using AnaptysBio's proprietary antibody discovery platform. In preclinical studies, ANB019 exhibited potent IL-36 inhibitory activity, as demonstrated by inhibition of IL-8 release by primary human keratinocytes stimulated with IL-36γ (similar results were obtained using IL-36 α and β). ANB019 inhibition of IL-36R was 100-fold more potent than IL-36RA, the physiological antagonist of IL-36 signaling.



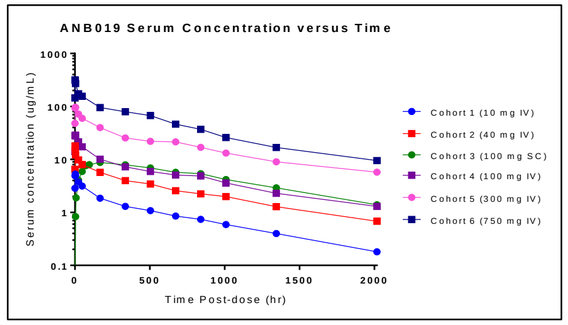
Study Outline

ANB019 was studied in a first-in-human Phase 1 trial to evaluate safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) properties in healthy volunteers who received either single (SAD) or multiple (MAD) ascending doses of ANB019. The study enrolled a total of 72 male and female subjects, 48 enrolled in the SAD and 24 in the MAD part of the study.

ANB019 was dosed over a range of 10 to 750 mg IV or SC in SAD cohorts, and 40 to 300 mg IV weekly for 4 weeks in the MAD cohorts. Subjects were randomized (3:1) to receive ANB019 or placebo, 54 subjects received ANB019 and 18 received Placebo. Safety and tolerability, PK, and *ex vivo* PD were assessed over a period of 85 days.

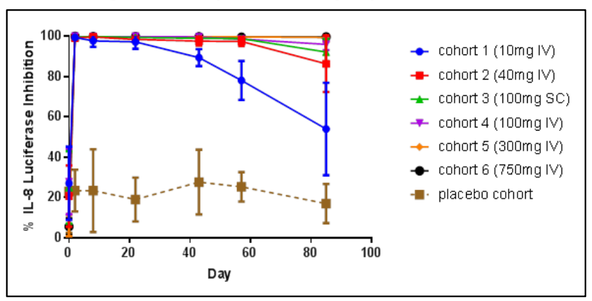
Pharmacokinetics

Mean serum concentration-time curves for all subjects receiving a single administration of ANB019 are shown below. Median terminal half life ranged between 597 and 689 hours (25 to 29 days). Bioavailability was approximately 90% and exposure as measured by Cmax and AUC increased in a dose dependent manner.



Pharmacodynamics

The inhibitory function of ANB019 present in serum samples from subjects receiving a single dose of ANB019 was quantified using a HEK293 hIL36-R/IL-8 luciferase cell based assay. Each point in the graph below represents mean values and SD from 6 subjects in each cohort. Sera from placebo treated subjects (n=2/Cohort) were pooled for each timepoint. *Ex vivo* PD activity was measured in all cohorts after a single administration. Approximately 100% inhibitory activity was observed in all dose levels above 10mg IV for up to 85 days post-administration



Clinical Safety: SAD

Forty of 48 subjects (83%) experienced at least one TEAE. The frequency of TEAEs was similar across treatment groups: 29 of 36 subjects (81%) in ANB019 and 11 of 12 subjects (92%) in Placebo. The majority of TEAEs were categorized as mild (73%) or moderate (26%), with exception of one severe event of elevated creatine kinase deemed unrelated to study treatment. No serious adverse events (SAEs) were reported. The most common TEAEs were upper respiratory tract infection (28% ANB019, 50% Placebo) and headache (28% ANB019, 25% Placebo).

Number of Subjects	Number (%) of Subjects with at least one TEAE [Number of TEAEs]											
	IV							SC		Total		
	10 mg (N=6)	40 mg (N=6)	100 mg (N=6)	300 mg (N=6)	750 mg (N=6)	Active (N=30)	Placebo (N=10)	100 mg (N=6)	Placebo (N=2)	Active (N=36)	Placebo (N=12)	All Subjects (N=48)
TEAEs	5 (83%) [11]	4 (67%) [4]	5 (83%) [10]	6 (100%) [18]	4 (67%) [19]	24 (80%) [62]	9 (90%) [17]	5 (83%) [11]	2 (100%) [2]	29 (81%) [73]	11 (92%) [19]	40 (83%) [92]
Related TEAEs*	3 (50%) [3]	1 (17%) [1]	3 (50%) [4]	5 (83%) [8]	4 (67%) [13]	16 (53%) [29]	5 (50%) [8]	2 (33%) [3]	2 (100%) [2]	18 (50%) [32]	7 (58%) [10]	25 (52%) [42]
Moderate or severe TEAEs	2 (33%) [3]	-	2 (33%) [2]	4 (67%) [4]	3 (50%) [6]	11 (37%) [15]	4 (40%) [4]	4 (67%) [6]	-	15 (42%) [21]	4 (33%) [4]	19 (40%) [25]
Related moderate or severe TEAEs	1 (17%) [1]	-	1 (17%) [1]	-	2 (33%) [2]	4 (13%) [4]	2 (20%) [2]	-	2 (33%) [2]	6 (17%) [6]	2 (17%) [2]	8 (17%) [8]
SAEs	-	-	-	-	-	-	-	-	-	-	-	0 (0%) [0]

*Related TEAEs = possibly related and related

Clinical Safety: MAD

TEAEs were reported for 19 of 24 subjects (79%). This included 16 of 18 subjects (89%) following administration of ANB019 and 3 of 6 subjects (50%) who received Placebo. The majority of TEAEs were mild (83%) or moderate (17%) in severity with no severe events reported.

Number of Subjects	Number (%) of Subjects with at least one TEAE [Number of TEAEs]					
	IV					
	40 mg (N=6)	100 mg (N=6)	300 mg (N=6)	Active Total (N=18)	Placebo Total (N=6)	All Subjects (N=24)
TEAEs	5 (83%) [8]	6 (100%) [18]	5 (83%) [6]	16 (89%) [32]	3 (50%) [4]	19 (79%) [36]
Related TEAEs*	3 (50%) [3]	4 (67%) [11]	3 (50%) [4]	10 (56%) [18]	1 (17%) [1]	11 (46%) [19]
Moderate or severe TEAEs	2 (33%) [2]	2 (33%) [2]	1 (17%) [1]	5 (28%) [5]	1 (17%) [1]	6 (25%) [6]
Related moderate or severe TEAEs	2 (33%) [2]	1 (17%) [1]	1 (17%) [1]	4 (22%) [4]	-	4 (17%) [4]
SAEs	-	-	-	-	-	0 (0%) [0]

*Related TEAEs = possibly related and related

No SAEs were observed. The most common TEAEs were headache (39% ANB019, 17% Placebo) and upper respiratory tract infection (17% ANB019, 17% Placebo).

Conclusions

ANB019 demonstrated favorable safety, PK and PD properties in this Phase 1 first-in-human healthy volunteers trial.

Single and multiple doses of ANB019 did not exhibit safety signals in this trial. PK was linear at all doses tested for both IV and SC routes of administration. *Ex vivo* PD activity was observed after a single dose for over 85 days at certain dose levels. The PK and PD of ANB019 are shown to be compatible with infrequent dosing.

The results of this Phase 1 study support the advancement of ANB019 into clinical studies in patients with GPP and PPP.