APG777, anti-IL-13 monoclonal antibody, demonstrates extended half-life and sustained inhibition of Type 2 inflammatory biomarkers

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Introduction

- APG777 is a humanized IgG1 monoclonal antibody that binds with high-affinity to IL-13 and disrupts Th2-driven inflammation by preventing formation of the IL-13Rα1/IL-4Rα heterodimer and subsequent IL-13-mediated signaling (**Figure 1**).[1]
- APG777 contains a triple amino acid modification, M253Y/S255T/T257E (referred to as a 'YTE' modification), in the fragment crystallizable (Fc) region that extends half-life in humans by increasing binding to neonatal Fc receptor (FcRn) under acidic pH conditions.[1,2]
- APG777 also contains two additional amino acid modifications L235A/L236A (referred to as a 'LALA' modification) in the Fc region, designed to ablate Fc and complement effector functions.[1]

Figure 1: Mechanism of action of APG777

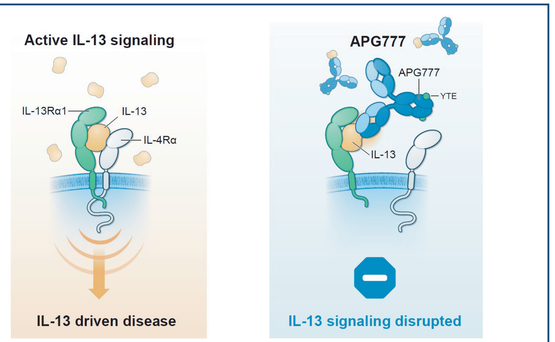
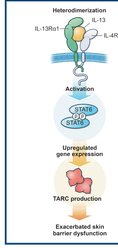


Figure 2: pSTAT6 and TARC are biomarkers of IL-13 receptor activation and atopic dermatitis severity



- pSTAT6 is an early biomarker of IL-13 receptor activation.[3]
- TARC is an objective biomarker that is strongly correlated with the severity of atopic dermatitis.[4]
- Circulating IL-13 binds to IL-13Rα1, which subsequently forms a heterodimer with IL-4Rα. This receptor-ligand complex on the membrane initiates the phosphorylation (p) of Signal Transducer and Activator of Transcription 6 (STAT6).[3,5]
- pSTAT6 translocates into the nucleus, where it promotes the transcription of inflammatory mediators, including Thymus and Activation Regulated Chemokine (TARC, also referred to as CCL17).[3–5]

Objective

- Here we present interim results from an ongoing phase 1 study of APG777 in healthy human participants, including safety, pharmacokinetics (PK), pharmacodynamics (PD), and biomarker results up to 6 to 9 months.

Materials and methods

- This phase 1, randomized, double-blind, placebo (PBO)-controlled trial evaluated safety, tolerability, PK, and PD of APG777 in healthy participants.
- The study was conducted in Australia and consisted of single ascending dose (SAD) and multiple dose (MD) cohorts.
- In the SAD cohorts, participants received single subcutaneous (SC) doses of 300 mg, 600 mg, or 1200 mg of APG777 or matched PBO. In the MD cohorts, participants received repeat doses of 300 mg SC on Days 1 and 29 (MD cohort 1), or Days 1 and 15 (MD cohort 2).
- Each cohort consisted of 8 participants randomized 6:2 to APG777 or PBO.
- Safety assessments were conducted throughout the study and blood draws for PK and PD were obtained at multiple timepoints.
- Biomarkers pSTAT6 and TARC were tracked throughout the study:
  - Inhibition of pSTAT6 was determined using IL-13 stimulation with recombinant human IL-13 (10 ng/mL) in a flow-cytometry based assay with live cells.
  - TARC levels were quantified in serum by an electrochemiluminescence immunoassay.
- The data presented here represents the longest available follow up for cohorts.

Results

- 40 participants were enrolled.
- Demographics were well-balanced across cohorts and baseline characteristics were in line with expectations for a phase 1 study in healthy participants (**Table 1**).
- Treatment-emergent adverse events (TEAEs) were generally mild-to-moderate and generally unrelated to study drug (**Table 2**).
- There were no serious TEAEs or dose-dependent trends (**Table 2**).

Table 1: Demographics and baseline characteristics

	SAD cohorts				MD cohorts		
	Placebo (n=6)	Cohort 1 300 mg (n=6)	Cohort 2 600 mg (n=6)	Cohort 3 1200 mg (n=6)	Placebo (n=4)	Cohort 1 300 mg at Day 1 300 mg at Day 29 (n=6)	Cohort 2 300 mg at Day 1 300 mg at Day 15 (n=6)
Mean age, years (SD)	41.3 (16.2)	30.2 (12.2)	40.2 (18.4)	29.7 (4.6)	42.0 (12.1)	42.7 (13.9)	40.2 (13.8)
Female, n (%)	6 (100.0)	4 (66.7)	5 (83.3)	2 (33.3)	4 (100.0)	3 (50.0)	3 (50.0)
Caucasian, n (%)	6 (100.0)	2 (33.3)	5 (83.3)	6 (100)	3 (75.0)	6 (100.0)	2 (33.3)
Mean weight, kg (SD)	72.5 (12.6)	74.3 (14.6)	78.8 (14.0)	77.2 (16.2)	62.3 (9.5)	80.5 (8.9)	66.7 (12.9)

MD, multiple dose; SAD, single ascending dose; SD, standard deviation.

Table 2: Overall treatment-emergent adverse events

	SAD cohorts				MD cohorts			Overall trial	
n (%)	Placebo (n=6)	Cohort 1 300 mg (n=6)	Cohort 2 600 mg (n=6)	Cohort 3 1200 mg (n=6)	Placebo (n=4)	Cohort 1 300 mg at Day 1 300 mg at Day 29 (n=6)	Cohort 2 300 mg at Day 1 300 mg at Day 15 (n=6)	Placebo (n=10)	APG777 (N=30)
≥1 TEAE	5 (83.3%)	5 (83.3%)	6 (100%)	3 (50%)	3 (75%)	5 (83.3%)	6 (100%)	8 (80%)	25 (83.3%)
≥1 serious TEAE	0	0	0	0	0	0	0	0	0
≥1 drug-related TEAE	3 (50%)	0	1 (16.7%)	1 (16.7%)	1 (25%)	1 (16.7%)	2 (33.3%)	4 (40%)	5 (16.7%)
≥1 Grade 3 TEAE	0	0	1 (16.7%)*	0	0	0	0	0	1 (3.3%)*
Discontinued study due to TEAE	0	0	0	0	0	0	0	0	0
Decreased dose due to TEAE	0	0	0	0	0	0	0	0	0

*Transient Grade 3 AST elevation (7.6 – 8.3x ULN) due to rhabdomyolysis from exercise from Day 253-256 of the study. TEAE was deemed not related to study drug. D, day; MD, multiple dose; SAD, single ascending dose; SD, standard deviation; TEAE, treatment-emergent adverse event.

Table 3: APG777 demonstrates dose-proportional increases in C_{max} and AUC

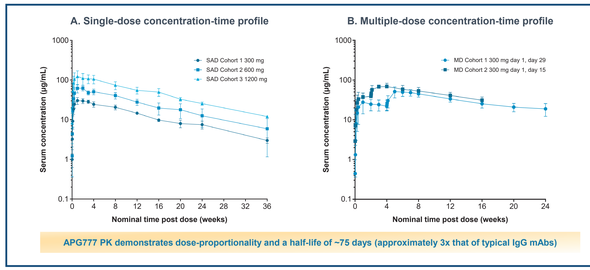
		PK parameters in SAD Cohorts mean (%CV)		
Cohort	Dose (mg)	T_{max}* (hours)	C_{max} (µg/mL)	AUC_{inf} (hour*µg/mL)
1	300	168.00 (168–504)	31.48 (14.9)	83137.8 (7.3)
2	600	252.00 (168–504)	64.94 (17.2)	166098.2 (28.7)
3	1200	420.00 (168–672)	129.98 (29.9)	328031.4 (16.6)

*T_{max} = Median (Min–Max).

AUC_{inf} area under the serum concentration curve extrapolated to infinity; C_{max}, maximum observed serum concentration; CV, coefficient of variation; PK, pharmacokinetic; SAD, single ascending dose; T_{max}, time to maximum observed serum concentration.

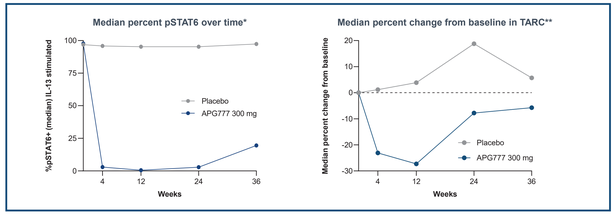
- APG777 demonstrated dose-proportional increases in C_{max} and AUC from 300 mg up to 1200 mg (**Table 3**), with mean $t_{1/2}$ of approximately 75 days across SAD cohorts (**Figure 3A**).
- Data from the MD cohorts is consistent with the PK profile from the SAD cohorts (**Figure 3B**).
- Single and multiple doses of APG777 resulted in rapid and sustained inhibition of pSTAT6 and TARC for up to 6 to 9 months (**Figures 4 and 5**).

Figure 3: PK Profile of APG777



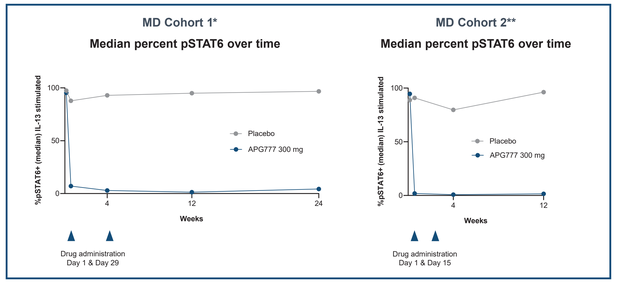
APG777 PK demonstrates dose-proportionality and a half-life of ~75 days (approximately 3x that of typical IgG mAbs)

Figure 4: Single doses of APG777 result in rapid and sustained inhibition of pSTAT6 and TARC



*n=1 in APG777 300 mg group because the pSTAT6 assay was not available when the first participants reached the pre-specified study visits; n=4 in the placebo group.
**n=6 in APG777 300 mg group; n=6 in placebo group.
Placebo data are pooled across SAD dose cohorts.

Figure 5: Multiple doses of APG777 resulted in rapid and sustained inhibition of pSTAT6 through longest available follow up



*n=6 in APG777 300 mg group; n=2 in placebo group.
**n=5 in APG777 300 mg group; n=2 in placebo group.

Conclusions

- In this interim analysis of a first-in-human study, APG777 was well-tolerated at doses up to 1200 mg.
- The $t_{1/2}$ of APG777 is ~75 days.
- Administration of APG777 resulted in sustained inhibition of pSTAT6 and TARC, key biomarkers for IL-13 targeting and atopic dermatitis, for up to 6 to 9 months after single and multiple doses of APG777.
- The favorable safety profile and optimized PK of APG777 support the initiation of a phase 2 study in adults with moderate-to-severe atopic dermatitis where every 3- to 6-month maintenance dosing will be evaluated.

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