Prolonged half-life and sustained inhibition of key inflammatory biomarkers: a phase 1 study of APG777, a high-affinity humanized IgG1 monoclonal antibody targeting IL-13

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Introduction

- APG777 is a high-affinity humanized anti-IL-13 IgG1 monoclonal antibody (mAb) that blocks formation of the IL-13/IL-13Rα1/IL-4Rα complex, preventing receptor heterodimerization and downstream signaling.[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 ($t_{1/2}$) 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]
- Interim results of the ongoing phase 1 study of APG777 in healthy participants, including safety, pharmacokinetics (PK), and pharmacodynamics (PD) through February 29, 2024, are reported.

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 is being conducted in Australia and consists of single ascending dose (SAD) and multiple dose (MD) cohorts.
- Participants received single subcutaneous (SC) doses of 300 mg, 600 mg, or 1200 mg of APG777 or matched PBO in the SAD cohorts, and repeat doses of 300 mg SC on Days 1 and 29, or Days 1 and 15 in the MD cohorts.
- 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.
- Exploratory biomarkers – phosphorylated Signal Transducer and Activator of Transcription 6 (pSTAT6) and Thymus and Activation-Regulated Chemokine (TARC) – were assessed through 12 weeks, the longest available follow-up at the time of this analysis:
  - Inhibition of pSTAT6 was assayed ex vivo in whole blood via flow cytometry.
  - TARC levels were quantified in serum by an electrochemiluminescence immunoassay.

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**).

Figure 1: Concentration-time profile of APG777

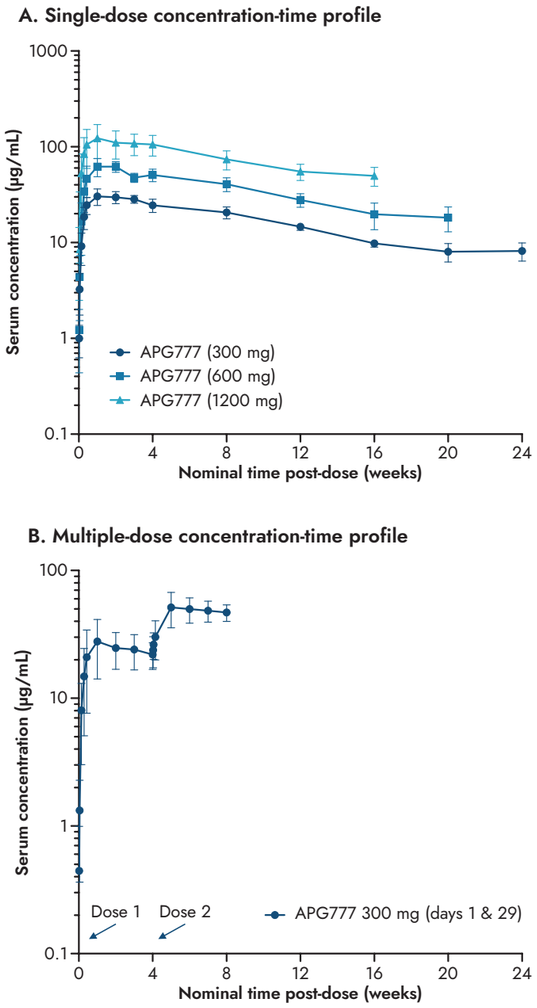


Table 1: Demographics and baseline characteristics

	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.

- To date, adverse events (AEs) were mild and generally unrelated to study drug (**Table 2**).
- There have been no serious AEs or dose-dependent trends (**Table 2**).

Table 2: Overall adverse events

	SAD cohorts				MD cohorts			Overall trial	
	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 D 1 300 mg at D 29 (n=6)	Cohort 1 300 mg at D 1 300 mg at D 15 (n=6)	Placebo (n=10)	APG777 (N=30)
Participants with ≥1 TEAE, n (%)	5 (83.3)	4 (66.7)	5 (83.3)	2 (33.3)	2 (50.0)	5 (83.3)	1 (16.7)	7 (70.0)	17 (56.7)
Participants with ≥1 TE-SAE, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Participants with ≥1 drug-related AE, n (%)	3 (50.0)	0 (0)	1 (16.7)	1 (16.7)	0 (0)	1 (16.7)	0 (0)	3 (30.0)	3 (30.0)
Participants with ≥1 Grade 3 TEAE, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Participants that discontinued study due to TEAE, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Participants that decreased dose due to TEAE, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

AE, adverse event; D, day; MD, multiple dose; SAD, single ascending dose; SD, standard deviation; TEAE, treatment-emergent adverse event; TE-SAE, treatment-emergent serious adverse event.

- 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 1A**).
- Preliminary data from the MD cohorts is consistent with the PK profile from the SAD cohorts (**Figure 1B**).

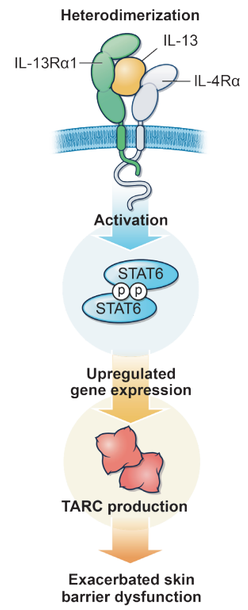
Table 3: PK parameters following single SC doses

		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)	83741.2 (11.2)
2	600	252.00 (168–504)	64.94 (17.2)	161098.7 (24.4)
3	1200	420.00 (168–672)	129.98 (29.9)	386088.4 (18.6)

*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.

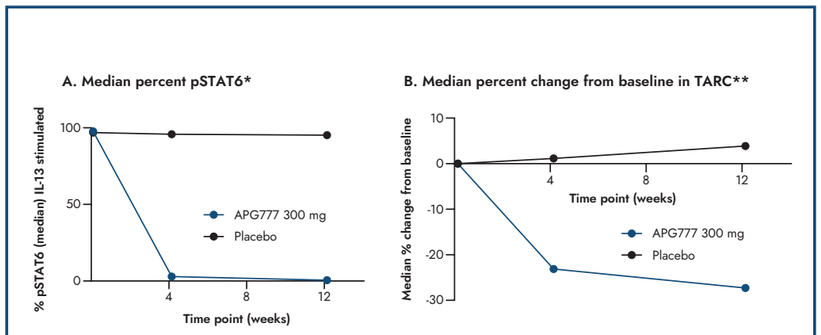
- pSTAT6 is one of the earliest upstream biomarkers of IL-13 receptor activation (**Figure 2**).[3]
- TARC is an objective biomarker which is strongly correlated with the severity of atopic dermatitis (**Figure 2**).[4]
- Single doses of APG777 resulted in rapid and sustained inhibition of pSTAT6 (**Figure 3A**) and TARC (**Figure 3B**) for 12 weeks, the longest available follow-up at the time of this analysis.

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



IL-13 signals through the IL-13Rα1 and IL-4Rα heterodimer.[3] The bound receptor/ligand complex leads to phosphorylation (p) of Signal Transducer and Activator of Transcription 6 (STAT6), which can then enter the nucleus to drive transcription of inflammatory mediators, including Thymus and Activation Regulated Chemokine (TARC, also known as CCL17).[5] TARC is an objective biomarker which is strongly correlated with the severity of atopic dermatitis.[4]

Figure 3: 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 placebo group
**n=5 in APG777 300 mg group, n=6 in placebo group
pSTAT6, phosphorylated Signal Transducer and Activator of Transcription 6; TARC, Thymus and Activation Regulated Chemokine

Conclusions

- In this first-in-human study, APG777 was well-tolerated at doses up to 1200 mg.
- The $t_{1/2}$ of APG777, due to its YTE modification, is at least three times longer than mAbs currently approved for the treatment of moderate-to-severe AD.
- Exploratory biomarker assessments showed sustained inhibition of pSTAT6 and TARC, key biomarkers for IL-13 targeting and atopic dermatitis, for up to 12 weeks after single doses of APG777.
- The initial safety, PK, and biomarker results are encouraging, but given the small sample size in this interim analysis, further exploration of APG777 is warranted.
- 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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