APG808, an anti-IL-4Rα monoclonal antibody, demonstrates safety, extended half-life, and sustained inhibition of type 2 inflammatory biomarkers

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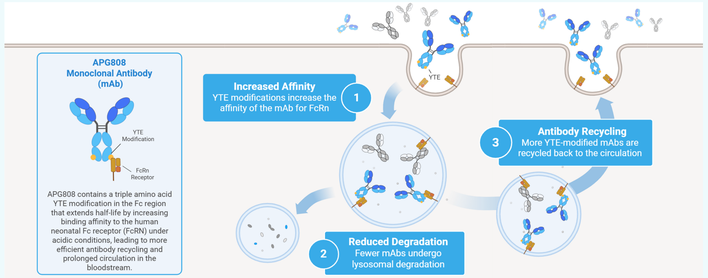
INTRODUCTION

- The interleukin-4 receptor alpha chain (IL-4Rα) is a transmembrane protein that mediates the signaling of IL-4 and IL-13,[1] which are key cytokines responsible for the dysregulated type 2 inflammation in diseases such as asthma, COPD, and atopic dermatitis.[2,3]
- APG808 is novel, half-life extended anti-IL-4Rα monoclonal antibody that inhibits IL-4 and IL-13 signaling by blocking formation of their active heterodimeric receptors.
- APG808 demonstrated high affinity for human IL-4Rα and similar potency in multiple functional assays compared with dupilumab.[4]

STUDY OBJECTIVE

- **This first-in-human, phase 1 study aims to evaluate the safety, PK, and PD of single-dose APG808 in healthy adult participants**

Figure 1: APG808 half-life extension through YTE modification



CONCLUSIONS

- In this first-in-human study, APG808 was well tolerated at doses up to 1200 mg in healthy adult participants.
- APG808 exhibited optimized PK with potential for dosing once every 6 to 8 weeks.
- The deep and sustained effect on type 2 inflammatory biomarkers may indicate the potential for improved outcomes, with a reduced dosing frequency compared to biweekly dosing for current anti-IL-4Rα therapy, in patients with type 2 inflammatory diseases.

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RESULTS

Baseline Characteristics

- This interim analysis reports results from all single-dose cohorts through 12 weeks of follow-up.
- A total of 32 healthy participants were evaluated across 4 single-ascending dose cohorts.
- Baseline characteristics were generally balanced across cohorts and consistent with expectations for phase 1 investigation in healthy subjects (**Table 1**).

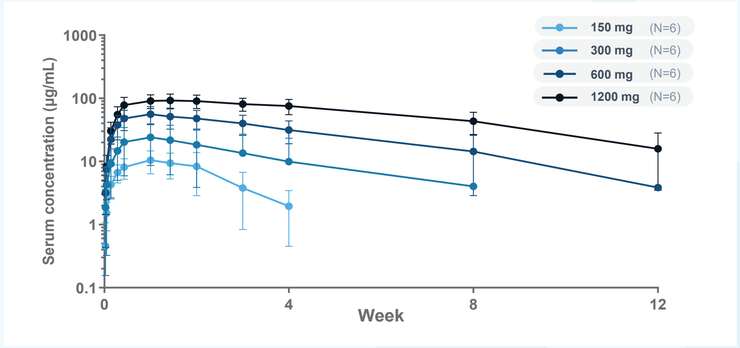
Table 1: Demographics and baseline characteristics

	Single-dose cohorts				
	Placebo N=8	Cohort 1 APG808 150 mg N=6	Cohort 2 APG808 300 mg N=6	Cohort 3 APG808 600 mg N=6	Cohort 4 APG808 1200 mg N=6
Age (years), mean (SD)	46.6 (15.4)	48.5 (12.9)	32.0 (10.6)	41.3 (14.8)	41.7 (14.1)
Female, %	62.5%	66.7%	83.3%	33.3%	66.7%
Caucasian, %	75.0%	83.3%	50.0%	66.7%	100%
Weight (kg), mean (SD)	74.5 (15.0)	73.3 (17.1)	75.8 (19.7)	82.1 (15.2)	81.0 (18.9)

Pharmacokinetics

- APG808 exhibited non-linear PK consistent with target-mediated drug disposition (TMDD) and the membrane-bound target of IL-4Rα (**Figure 2**).
- The model-estimated half-life of APG808 was approximately 55 days at projected, clinically relevant, steady-state exposure levels within the linear range.

Figure 2: APG808 single-dose concentration-time profile



Graph shows the mean ± SD.

Safety

- Through 12 weeks of available follow-up, TEAEs that were related to APG808 were generally mild and consistent with the known safety profile of anti-IL-4Rα therapy (**Table 2**).
- There was one serious TEAE that was transient and considered not related to study drug.

Biomarkers

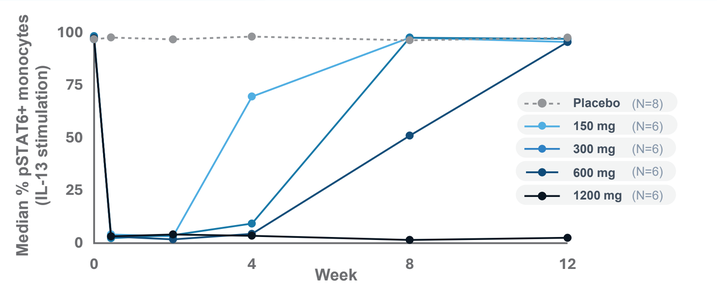
- APG808 led to rapid, near-complete inhibition of pSTAT6, a proximal and sensitive marker of IL-4 and IL-13 signaling, which was sustained for up to 12 weeks after a single dose of 1200 mg (**Figure 3**).
- Dose-dependent recovery trends for pSTAT6 were observed, with higher doses showing more prolonged suppression.
- Serum levels of TARC were reduced across all dose groups as early as Day 4 after treatment, with a maximum median change from baseline of −32.6% in the 600 mg APG808 dose group.

Table 2: Overall treatment-emergent adverse events

	Single-dose cohorts					
n (%)	Placebo N=8	Cohort 1 APG808 150 mg N=6	Cohort 2 APG808 300 mg N=6	Cohort 3 APG808 600 mg N=6	Cohort 4 APG808 1200 mg N=6	Overall APG808 N=24
≥1 TEAE	5 (62.5%)	4 (66.7%)	5 (83.3%)	4 (66.7%)	4 (66.7%)	17 (70.8%)
≥1 serious TEAE	0	0	0	1 (16.7%)*	0	1 (4.2%)*
≥1 Grade 3 TEAE	0	0	0	1 (16.7%)*	0	1 (4.2%)*
≥1 drug-related TEAE	1 (12.5%)	1 (16.7%)	0	2 (33.3%)	2 (33.3%)	5 (20.8%)
≥1 drug-related serious TEAE	0	0	0	0	0	0
≥1 drug-related Grade 3 TEAE	0	0	0	0	0	0

Interim analysis includes AEs reported as of 5 November 2024. The trial is ongoing. *SAE for Grade 3 non-cardiac chest pain onset Day 55 that resolved in 1 day without acute intervention. Non-cardiac chest pain was deemed as not related to study drug and likely related to dyspepsia or musculoskeletal causes.

Figure 3: Single-dose APG808 led to rapid and sustained inhibition of pSTAT6

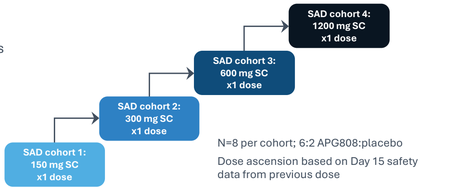


pSTAT6 was measured using flow cytometry of whole blood samples stimulated with 10 ng/mL IL-13.

METHODS

- This first-in-human, phase 1, randomized, double-blind, placebo-controlled trial evaluated single ascending doses of APG808 in healthy adult participants (ACTRN12624000238572).
- The study consisted of 4 single-ascending dose cohorts of 8 participants each, randomized 6:2 to APG808, at single subcutaneous doses of 150 mg, 300 mg, 600 mg, and 1200 mg, or matched placebo (**Figure 4**).
- Safety assessments were conducted throughout the study, and blood draws for PK and PD were obtained at multiple timepoints.

Figure 4: Design of the APG808 first-in-human phase 1 study in healthy volunteers (N=32)



ABBREVIATIONS

AEs, adverse events; COPD, chronic obstructive pulmonary disease; Fc, fragment crystallizable; FcRn, human neonatal Fc receptor; IL, interleukin; mAb, monoclonal antibody; PD, pharmacodynamic; PK, pharmacokinetic; pSTAT6, phosphorylated signal transducer and activator of transcription 6; SAD, single ascending dose; SAE, serious adverse event; SC, subcutaneous; SD, standard deviation; TARC, thymus and activation-regulated chemokine; TEAE, treatment-emergent adverse event; TMDD, target-mediated drug disposition; YTE, triple amino acid modification

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