APG808, a novel anti-IL-4Rα antibody with half-life extension technology: safety, pharmacokinetics, and pharmacodynamics

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INTRODUCTION

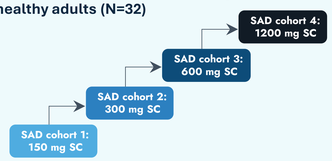
- The interleukin-4 receptor alpha chain (IL-4Rα) is a transmembrane protein that mediates the signaling of IL-4 and IL-13,[1] which are key cytokines responsible for the dysregulated type 2 inflammation in diseases such as asthma, COPD, and atopic dermatitis.[2,3]
- APG808 is a novel, half-life extended anti-IL-4Rα monoclonal antibody that inhibits IL-4- and IL-13-mediated signaling by blocking formation of their active heterodimeric receptors.
- APG808 contains a triple amino acid YTE modification in the Fc region that extends half life through increased recycling, reduced degradation, and prolonged circulation of the antibody in the bloodstream.[4]
- APG808 demonstrated high affinity for human IL-4Rα and similar potency in multiple functional assays compared with dupilumab.[5]

STUDY OBJECTIVE & DESIGN

This phase 1 study evaluated the safety, PK, and PD effect of APG808 on type 2 inflammatory biomarkers in healthy participants and patients with mild-to-moderate asthma.

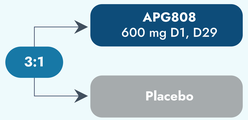
Figure 1: APG808 phase 1 study design

A. First-in-human, single-ascending dose portion in healthy adults (N=32)



Study registered as ACTRN12624000238572.
Dose escalation was based on day 15 safety data from the previous dose.

B. Multiple-dose portion in adults with mild-to-moderate asthma (N=22)



Participants with mild-to-moderate asthma and elevated FeNO (≥25 ppb) at baseline were included. Exclusion criteria included a history of asthma exacerbation requiring systemic corticosteroids within 12 weeks of screening or hospitalization within 6 months of screening, or a history of biologic use for asthma.

CONCLUSIONS

- APG808 was well tolerated at doses up to 1200 mg, demonstrating a safety profile consistent with the anti-IL-4Rα class.
- APG808 exhibited a PK profile with potential for dosing once every 6 to 8 weeks, compared with biweekly dosing for current anti-IL-4Rα therapy.
- Multiple doses of APG808 resulted in rapid and durable suppression of FeNO out to 12 weeks.
- The improved PK of APG808 enabling less frequent dosing, together with the rapid and sustained suppression of FeNO and type 2 inflammatory biomarkers, support continued clinical development of APG808.

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RESULTS

Baseline Characteristics

- This interim analysis reports results from all cohorts through 12 weeks of follow-up.
- 32 healthy volunteers (N=24 APG808; N=8 placebo) were evaluated across 4 single-ascending dose cohorts.
- 22 participants (N=17 APG808; N=5 placebo) with mild-to-moderate asthma and elevated FeNO (≥25 ppb) were included in the multiple-dose cohort.
- Baseline characteristics were generally balanced and consistent with expectations (**Table 1**).

Table 1: Demographics and baseline characteristics

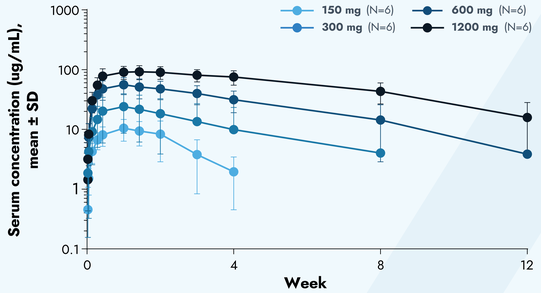
	Single-dose cohorts					Multiple-dose cohort	
	Placebo N=8	Cohort 1 APG808 150 mg N=6	Cohort 2 APG808 300 mg N=6	Cohort 3 APG808 600 mg N=6	Cohort 4 APG808 1200 mg N=6	Placebo D1, D29 N=5	APG808 600 mg D1, D29 N=17[a]
Age (years), mean (SD)	46.6 (15.4)	48.5 (12.9)	32.0 (10.6)	41.3 (14.8)	41.7 (14.1)	33.0 (12.6)	26.5 (6.7)
Female, %	62.5%	66.7%	83.3%	33.3%	66.7%	40.0%	35.3%
Caucasian, %	75.0%	83.3%	50.0%	66.7%	100%	100.0%	70.6%
Weight (kg), mean (SD)	74.5 (15.0)	73.3 (17.1)	75.8 (19.7)	82.1 (15.2)	81.0 (18.9)	73.7 (14.5)	75.8 (13.7)
Patients on daily ICS ± LABA, %	–	–	–	–	–	60.0%	41.2%
FeNO (ppb), mean (SD)	–	–	–	–	–	47.6 (10.8)	52.6 (27.4)

[a]APG808 safety population includes 1 patient who was misdosed (received placebo at D1 and APG808 at D29).

Pharmacokinetics

- APG808 exhibited nonlinear PK consistent with target-mediated drug disposition 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

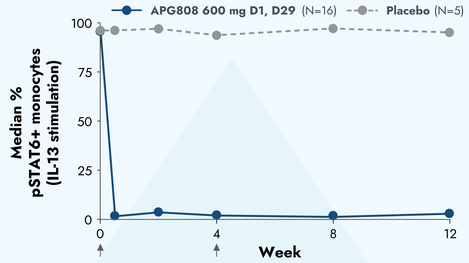


Biomarkers

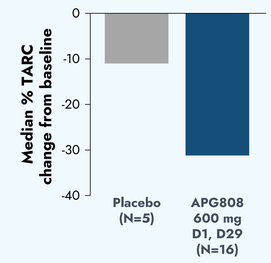
- A single dose of APG808 led to rapid, near-complete inhibition of pSTAT6, which was sustained for up to 12 weeks after a single dose of 1200 mg. Dose-dependent recovery trends were observed, with higher doses showing more prolonged suppression.
- Multiple doses of APG808 600 mg led to rapid and near-complete inhibition of pSTAT6 through 12 weeks (**Figure 3A**).
- Serum levels of TARC were reduced across all single-dose groups as early as day 4 after treatment, with a maximum median change from baseline of -32.6% in the APG808 600 mg dose group. Multiple doses of APG808 600 mg led to a 31% reduction from baseline in TARC at week 12 (**Figure 3B**).

Figure 3: Multiple doses of APG808 led to rapid and sustained suppression of pSTAT6 and TARC through week 12

A. pSTAT6+ monocytes through week 12



B. TARC % change from baseline at week 12



Arrows indicate dosing on D1 and D29. One participant was excluded from the PD analysis population due to misdosing (received placebo at D1 and APG808 at D29). pSTAT6 was measured using flow cytometry of whole blood samples stimulated with 10 ng/mL IL-13.

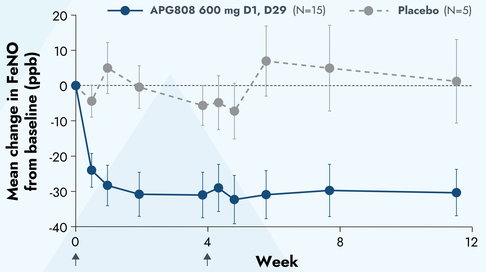
Biomarkers, cont.

- In patients with asthma, treatment with APG808 600 mg on days 1 and 29 resulted in rapid suppression of FeNO, with maximal reduction from baseline of 53% and maintained >30 ppb reduction from baseline through week 12 (**Figure 4**).

Safety

- Single and multiple doses of APG808 were well tolerated through 12 weeks of available follow-up (**Table 2**).
- One serious TEAE, which was transient and deemed not related to study drug, occurred in the APG808 600 mg single-dose cohort.

Figure 4: Multiple doses of APG808 led to rapid and durable suppression of FeNO



Graph shows the mean ± SE FeNO values in ppb. Arrows indicate dosing on D1 and D29. Two participants were excluded from the FeNO analysis population. One participant was misdosed (received placebo at D1 and APG808 at D29), and 1 participant had FeNO below 25 ppb at the baseline D1 measurement.

Table 2: Overall treatment-emergent adverse events

	Single-dose cohorts					Multiple-dose cohort	
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	Placebo D1, D29 N=5	APG808 600 mg D1, D29 N=17[a]
≥1 TEAE	5 (62.5%)	4 (66.7%)	5 (83.3%)	4 (66.7%)	4 (66.7%)	5 (100.0)	16 (94.1)
≥1 serious TEAE	0	0	0	1 (16.7%)[b]	0	0	0
≥1 grade 3 TEAE	0	0	0	1 (16.7%)[b]	0	0	0
≥1 drug-related TEAE	1 (12.5%)	1 (16.7%)	0	2 (33.3%)	2 (33.3%)	2 (40.0)	5 (29.4)
≥1 drug-related serious TEAE	0	0	0	0	0	0	0
≥1 drug-related grade 3 TEAE	0	0	0	0	0	0	0

[a]APG808 safety population includes 1 participant who was misdosed (received placebo at D1 and APG808 at D29). [b]SAE for grade 3 noncardiac chest pain onset day 55 that resolved in 1 day without acute intervention. Noncardiac chest pain was deemed as not related to study drug and likely related to dyspepsia or musculoskeletal causes.
Interim data include AEs reported as of 5 November 2024 (single-dose cohorts) and 31 March 2025 (multiple-dose cohort).

ABBREVIATIONS

AE, adverse event; COPD, chronic obstructive pulmonary disease; D, day; Fc, fragment crystallizable; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; IL-4Rα, interleukin-4 receptor alpha chain; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; MD, multiple-dose; PD, pharmacodynamic; PK, pharmacokinetic; ppb, parts per billion; ppFEV, percent predicted forced expiratory volume; pSTAT6, phosphorylated signal transducer and activator of transcription 6; SAD, single-ascending dose; SC, subcutaneous; SCS, systemic corticosteroids; TARC, thymus and activation-regulated chemokine; TEAE, treatment-emergent adverse event.

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