Sustained suppression of type 2 inflammatory biomarkers in asthma with APG808, a half-life extended anti-IL-4Rα monoclonal antibody

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INTRODUCTION

- APG808 is a novel, half-life extended anti-IL-4Rα monoclonal antibody that inhibits IL-4- and IL-13-mediated signaling.
- 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.[1]
- APG808 demonstrated high affinity for human IL-4Rα and similar potency in multiple functional assays compared with dupilumab.[2]
- A first-in-human, single-ascending dose study in healthy volunteers demonstrated safety and tolerability of APG808 at doses up to 1200 mg and optimized pharmacokinetics of APG808 with potential for dosing once every 6 to 8 weeks (refer to ERS Poster #PA2474).[3]

STUDY OBJECTIVE

- **This phase 1b, proof of mechanism study aims to evaluate the safety of multiple doses of APG808 and the effect on type 2 inflammatory biomarkers in participants with mild-to-moderate asthma.**

Figure 1: Biomarkers reflecting inhibition of IL-4Rα signaling and type 2 inflammation in asthma

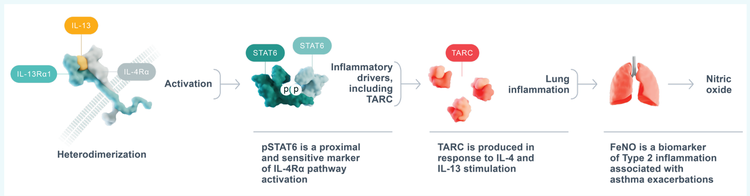

Image depicts IL-13 bound to the IL-13Rα1/IL-4Ra heterodimeric receptor; IL-4 also signals through the IL-4Rα/γc type I IL-4R.

CONCLUSIONS

- In this multiple-dose study in participants with mild-to-moderate asthma, APG808 demonstrated a favorable safety profile consistent with the anti-IL-4Rα class.
- Multiple doses of APG808 resulted in rapid and durable suppression of FeNO out to 12 weeks.
- The improved pharmacokinetics of APG808 enabling less frequent dosing, together with the rapid and sustained suppression of type 2 inflammatory biomarkers, support continued clinical development of APG808.

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RESULTS

Baseline Characteristics

- This interim analysis reports results from the multiple-dose cohort through 12 weeks of follow-up.
- A total of 22 participants (N=17 APG808; N=5 placebo) with mild-to-moderate asthma and elevated FeNO (≥25 ppb) at baseline were included.
- Baseline characteristics were generally balanced and consistent with expectations (**Table 1**).

Table 1: Demographics and baseline characteristics

	Multiple-dose cohort	
	Placebo D1, D29 N=5	APG808 600 mg D1, D29 N=17[1]
Age (yrs), mean (SD)	33.0 (12.6)	26.5 (6.7)
Female, %	40.0%	35.3%
Caucasian, %	100.0%	70.6%
Weight (kg), mean (SD)	73.7 (14.5)	75.8 (13.7)
Patients on daily ICS ± LABA, %	60.0%	41.2%
Tobacco use[2], %		
Never	40.0%	88.2%
Current	20.0%	0.0%
Former	40.0%	11.8%
FeNO (ppb), mean (SD)	47.6 (10.8)	52.6 (27.4)

[1]APG808 safety population includes 1 patient who was misdosed (received placebo at D1 and APG808 at D29). [2]Tobacco use is inclusive of cigarettes, cigars, and smokeless tobacco or nicotine products.

Safety

- Through 12 weeks of available follow-up, multiple doses of APG808 were well-tolerated in participants with asthma.
- There were no Grade 3 TEAEs or severe adverse events. No adverse events led to study discontinuation (**Table 2**).

Biomarkers

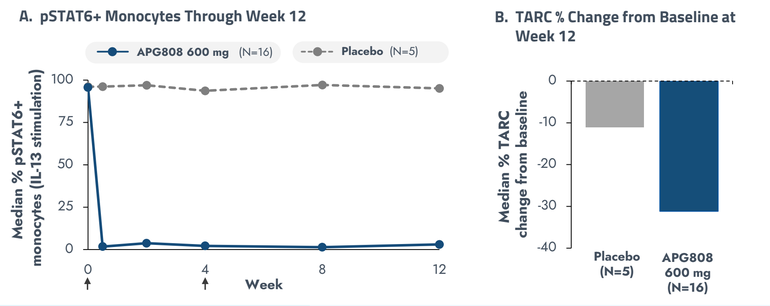
- Multiple doses of APG808 led to rapid and near-complete inhibition of pSTAT6 through 12 weeks (**Figure 2A**) and a 31% reduction from baseline in TARC at week 12 (**Figure 2B**).
- Treatment with APG808 resulted in rapid suppression of FeNO with maintained >30 ppb reduction from baseline through week 12 (**Figure 3**).
- Maximal reduction in FeNO from baseline with APG808 treatment was 53% at week 5, with a sustained FeNO decrease from baseline of 50% at week 12.

Table 2: Overall treatment-emergent adverse events

	Multiple-dose cohort	
n (%)	Placebo D1, D29 N=5	APG808 600 mg D1, D29 N=17[1]
≥1 TEAE	5 (100.0%)	16 (94.1%)
≥1 serious TEAE	0	0
≥1 Grade 3 TEAE	0	0
≥1 drug-related TEAE	2 (40.0%)	5 (29.4%)
≥1 drug-related serious TEAE	0	0
≥1 drug-related Grade 3 TEAE	0	0
Discontinued study due to TEAE	0	0

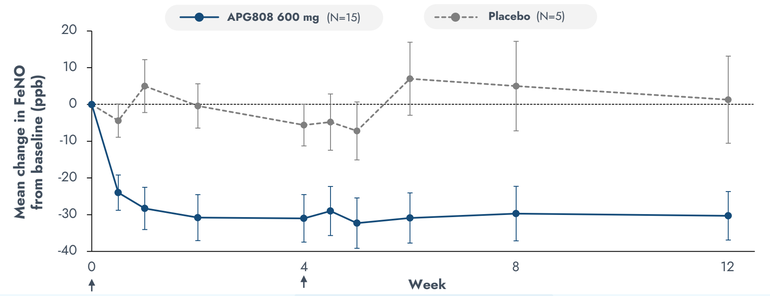
Interim data includes AEs reported as of 31 March 2025. The trial is ongoing. [1]APG808 safety population includes 1 patient who was misdosed (received placebo at D1 and APG808 at D29).

Figure 2: Multiple doses of APG808 led to sustained suppression of pSTAT6 and TARC through 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.

Figure 3: APG808 led to rapid and durable suppression of FeNO through week 12



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 one participant had FeNO below 25 ppb at the baseline D1 measurement.

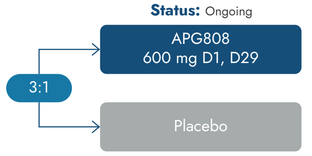
METHODS

- This phase 1, multiple-dose, randomized, double-blind, placebo-controlled trial evaluated multiple doses of APG808 in adult participants with mild-to-moderate asthma and elevated FeNO at baseline (ACTRN12624000238572).
- Participants were randomized 3:1 to receive subcutaneous APG808 600 mg or placebo on D1 and D29.
- Safety, FeNO, and other pharmacodynamic biomarkers were assessed at multiple timepoints.

Figure 4. Design of the APG808 phase 1b study in asthma (N=22)

Key inclusion criteria:
- Adults 18-65 years of age
- Diagnosis of mild-to-moderate asthma for ≥1 year prior to screening
- FeNO ≥25 ppb
- Pre-bronchodilator ppFEV$_1$ ≥60%
- Maintained control on as-needed rescue medication with or without stable dose of ICS, ICS/LABA, or LTRA

Key exclusion criteria:
- History of asthma exacerbation requiring SCS within 12 weeks of screening or hospitalization within 6 months of screening
- History of biologic use for asthma



ABBREVIATIONS

D, day; Fc, fragment crystallizable; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; IL, interleukin; LABA, long-acting Beta2-agonist; LTRA, leukotriene receptor antagonist; PD, pharmacodynamic; pSTAT6, phosphorylated signal transducer and activator of transcription 6; SCS, systemic corticosteroids; SD, standard deviation; SEM, standard error of the mean; TARC, thymus and activation-regulated chemokine; TEAE, treatment-emergent adverse event

REFERENCES

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3. Kamboj A et al. Presented at ERS 2025; PA2474

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