APG808, a high-affinity fully human IgG1 monoclonal antibody targeting IL-4Rα, demonstrates prolonged half-life in non-human primates

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#P675

Introduction

- Interleukin-4 receptor-alpha chain (IL-4Rα) is a transmembrane protein that mediates the signaling of interleukin-4 (IL-4) and interleukin-13 (IL-13), which are key cytokines promoting type 2 inflammation.[1]
- Dysregulation of type 2 inflammation plays a central role in several human diseases such as some forms of chronic obstructive pulmonary disease (COPD), asthma, and atopic dermatitis.[2,3]
- APG808 is an optimized, high-affinity, fully human IgG1 monoclonal antibody (mAb) that binds IL-4Rα and prevents formation of the IL 13Rα1/IL-4Rα active heterodimer and disrupts subsequent IL-13 and IL-4 mediated signaling (**Figure 1**).
- APG808 contains a triple amino acid modification, M253Y/S255T/T257E (referred to as a 'YTE' substitution) in the fragment crystallizable (Fc) region, designed to extend its half-life in non-human primates (NHPs) and humans by increasing binding to the neonatal Fc receptor (FcRn) under acidic pH conditions (**Figure 2**).[4,5]
- APG808 also contains two additional amino acid substitutions, L235A/L236A (referred to as 'LALA' substitution) in the Fc region, designed to ablate Fc and complement effector functions.
- In this report, we present the pharmacokinetics of APG808 and dupilumab following subcutaneous dosing in cynomolgus monkeys.

Figure 1: APG808 is designed to disrupt IL-13 and IL-4 mediated Th2 signaling by preventing formation of the IL-13Rα1/IL-4Rα heterodimer

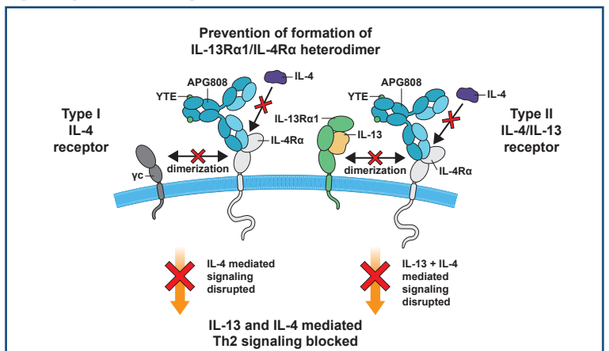
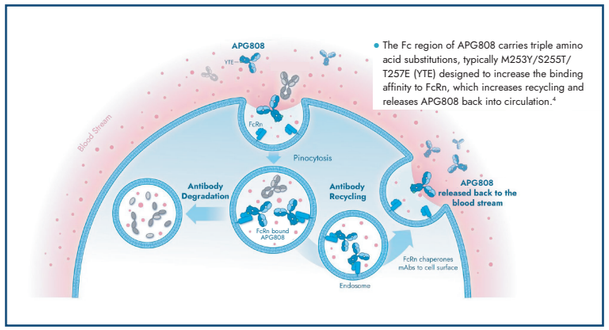


Figure 2: Mechanism of APG808 half-life extension



Materials and methods

- The binding affinity to FC receptors [FcγRI, FcγRIIa (H131), FcγRIIa (R131), FcγRIIb, FcγRIIIa (F158), FcγRIIIa (V158), FcγRIIIb, C1q] was determined by surface plasmon resonance (SPR).
- The pharmacokinetics of APG808 and a monoclonal antibody based on the published sequence of dupilumab (PAL001-0001-4; herein referred to as dupilumab) were studied in female cynomolgus monkeys following a single bolus dose of 25.9 mg/kg (APG808) or 24.3 mg/kg (dupilumab) given subcutaneously (SC).
- Serial blood samples were collected through 91 days post-administration.
- Pharmacokinetic parameters included:
  - Area under the serum concentration versus time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$)
  - Clearance (Cl)
  - Volume of distribution at steady-state (V_{ss})
  - Half-life ($t_{1/2}$)
  - Absolute subcutaneous bioavailability (F).

Results

- APG808 exhibited a higher affinity ($1.66x10^{-7}$ M) to human FcRn at pH 6.0 compared to a IgG1 positive control antibody ($1.37x10^{-6}$ M) (**Table 1**).
- APG808 had reduced affinity to human FcγRI, IIa, IIb, IIIa, IIIb, and C1q compared to an IgG1 positive control antibody (**Table 1**).

Table 1: APG808 has increased affinity to human FcRn and decreased affinity to human FcγR and C1q

Ligand	APG808 KD (M)	IgG1 positive control KD (M)
FcRn	1.66×10^{-7}	1.37×10^{-6}
FcγRI	1.47×10^{-5}	2.21×10^{-9}
FcγRIIa (H131)	no binding	1.60×10^{-6}
FcγRIIa (R131)	no binding	4.46×10^{-6}
FcγRIIb	no binding	1.28×10^{-5}
FcγRIIIa (F158)	2.74×10^{-5}	1.02×10^{-6}
FcγRIIIa (V158)	6.60×10^{-6}	2.08×10^{-7}
FcγRIIIb	no binding	5.06×10^{-6}
C1q	no binding	6.99×10^{-8}

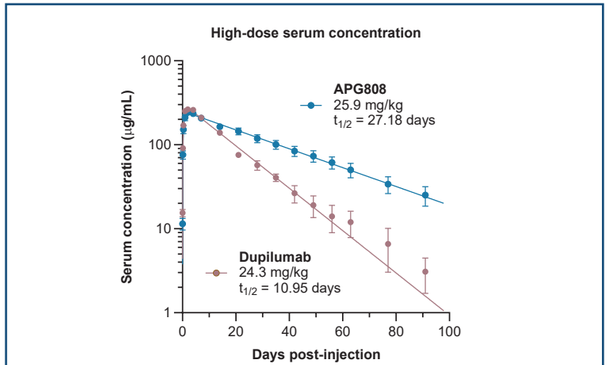
Table 2: PK parameters of APG808 and dupilumab following a single bolus SC dose in cynomolgus monkeys

Mean (SE)	APG808	Dupilumab*
$AUC_{0\text{-}inf}$ (ng h/mL)	9.77×10^6 (1.09×10^6)	4.90×10^6 (3.02×10^5)
Cl (mL/day/kg)†	2.79 (0.45)	5.03 (0.30)
V_{ss} (mL/kg)†	101.80 (5.82)	79.18 (4.11)
F (%)‡	97.51	100
Half-life (days)	27.18 (3.61)	10.95 (0.79)

*Monoclonal antibody based on the published sequence of dupilumab; †Both Cl and V_{ss} of subcutaneous administration were dose normalized using the subcutaneous bioavailability (F) indicated in the table; ‡F (%) was calculated by dividing the mean dose-normalized $AUC_{0\text{-}inf}$ following subcutaneous administration by the mean dose-normalized $AUC_{0\text{-}inf}$ following IV administration.
$AUC_{0\text{-}inf}$, area under the serum concentration versus time curve from time 0 extrapolated to infinity; Cl, clearance; F, bioavailability; IV, intravenous; PK, pharmacokinetic; SC, subcutaneous; SE, standard error; V_{ss}, volume of distribution at steady-state.

- APG808 exhibited a $t_{1/2}$ of 27.18 days (**Figure 3**) and Cl rate of 2.79 mL/day/kg (**Table 2**) in NHPs.
  - The V_{ss} was observed to be 101.80 mL/kg.
  - APG808 was well-absorbed, with subcutaneous F determined to be 97.51% (**Table 2**).
- Dupilumab exhibited a $t_{1/2}$ of 10.95 days (**Figure 3**) and Cl rate of 5.03 mL/day/kg (**Table 2**) in NHPs.
  - The V_{ss} was observed to be 79.18 mL/kg.
  - Dupilumab was well-absorbed, with subcutaneous F determined to be 100% (**Table 2**).

Figure 3: APG808 has a longer half-life compared to dupilumab in cynomolgus monkeys



Conclusions

- APG808 demonstrated an increase in $t_{1/2}$ and exposure, and reduced clearance compared with a monoclonal antibody based on the published sequence of dupilumab in NHPs.
- APG808 has a higher affinity to human FcRn and lower affinity to all other FcγR and C1q compared with the IgG1 benchmark antibody.
- The prolonged $t_{1/2}$ of APG808 may enable less frequent dosing compared with currently available treatments for COPD, which could reduce injection burden for patients and increase compliance.
- These data support the ongoing phase 1 study of APG808, which is currently enrolling in Australia.

References

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