APG777, a high-affinity humanized IgG1 mAb targeting IL-13, demonstrates prolonged half-life in non-human primates

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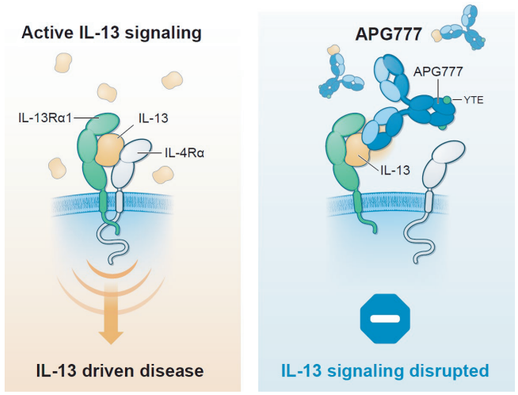
Introduction

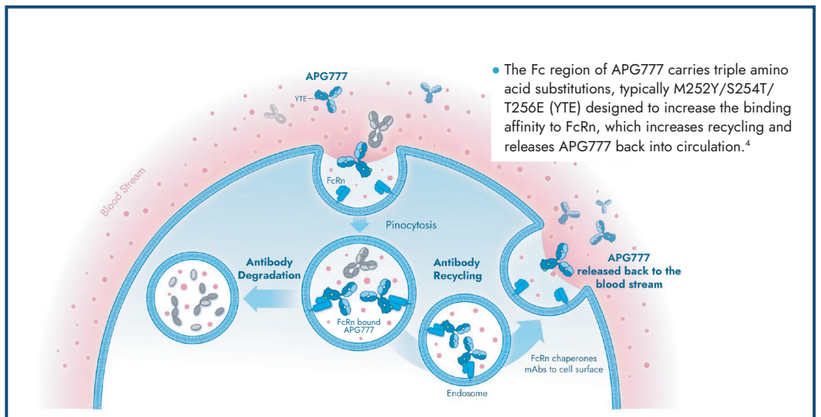
- Interleukin-13 (IL-13) is a T helper type 2 (Th2) cytokine that plays a key role in the pathogenesis of atopic dermatitis, asthma, and other inflammatory and immunologic conditions.[1–3]
- APG777 is a humanized IgG1 monoclonal antibody (mAb) that is engineered to have high affinity for IL-13 and which blocks the heterodimerization of the signaling complex of IL-13/IL-13Rα1/IL-4Rα and interrupts downstream inflammatory signaling (**Figure 1**).
- APG777 contains a triple amino acid modification, typically M252Y/S254T/T256E (referred to as a 'YTE' modification) in the fragment crystallizable (Fc) region designed to extend its half-life in nonhuman primates (NHPs) and humans by increasing binding to the neonatal Fc receptor (FcRn) under acidic pH conditions (**Figure 2**).[4,5]
- APG777 also contains two additional amino acid modifications, L235A/L236A (referred to as 'LALA' modification) in the Fc region, designed to ablate Fc and complement effector functions.
- Here we present the pharmacokinetics of APG777 and lebrikizumab following intravenous and subcutaneous dosing in cynomolgus monkeys.

Figure 1: APG777 is designed to bind IL-13, thereby disrupting Th2 signaling by preventing formation of the IL-13Rα1/IL-4Rα heterodimer



- IL-13 signaling begins with binding of IL-13 to IL-13Rα1.
- This forms an inactive complex that then binds to IL-4Rα to create a complete, active heterodimer.
- Active IL-13Rα1/IL-4Rα heterodimer sets off a signaling cascade that leads to:
  - Skin barrier defects.
  - Immune cell recruitment.
  - Tissue inflammation.
  - Lichenification.
  - Pruritus.

Figure 2: Mechanism of APG777 half-life extension



- The Fc region of APG777 carries triple amino acid substitutions, typically M252Y/S254T/T256E (YTE) designed to increase the binding affinity to FcRn, which increases recycling and releases APG777 back into circulation.[4]

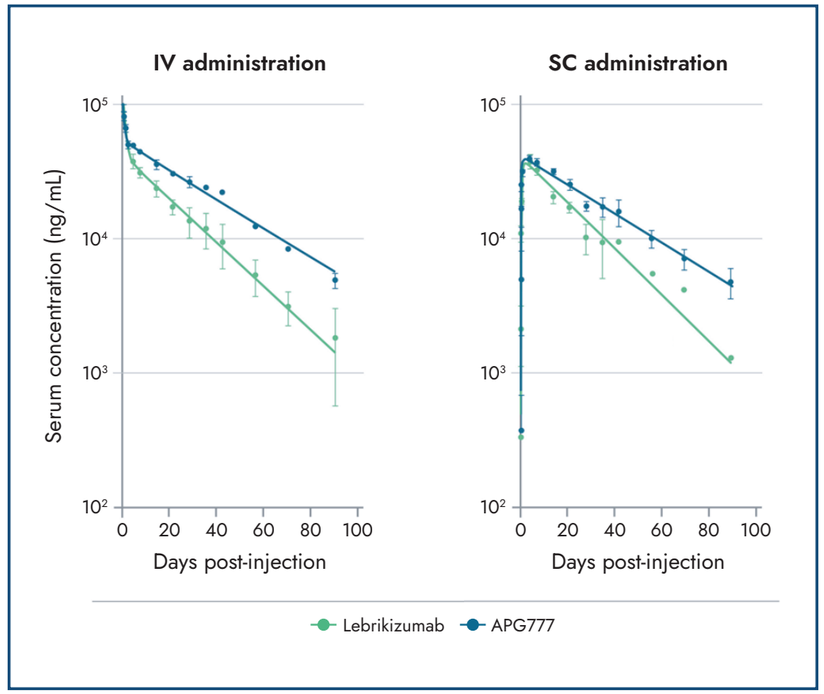
Materials and methods

- The pharmacokinetics of APG777 and a monoclonal antibody expressed based on the published sequence of lebrikizumab were studied in female cynomolgus monkeys following a single bolus dose of 3 mg/kg, given either intravenously (IV) or subcutaneously (SC).
- Blood samples were collected serially starting with a sample pre-dose and subsequently at 0.167, 1, 4, 8, 24, 48, 96, 168, 336, 504, 674, 840,1334,1680, and 2160 hours post-dose.
- Pharmacokinetic parameters included:
  - Maximum observed serum concentration (C_{max}).
  - Time to maximum observed serum concentration (T_{max}).
  - 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

- APG777 exhibited an average $t_{1/2}$ of 27.6 days and Cl rate of 1.45 (mL/day/kg) in NHPs (**Figure 3**).
- Lebrikizumab exhibited an average $t_{1/2}$ of 18.0 days and Cl rate of 2.93 (mL/day/kg) in NHPs (**Figure 3**).
- The V_{ss} was observed to be 55.65 (mL/kg). APG777 was well-absorbed, with subcutaneous F determined to be 81.22% (**Table 1**).
- The V_{ss} was observed to be 52.10 (mL/kg). Lebrikizumab was well-absorbed, with subcutaneous F determined to be 75.70% (**Table 1**).

Figure 3: Serum concentration-time curves for APG777 and lebrikizumab in NHPs



Values represent mean ± SEM serum concentration vs. time. IV, intravenous; SC, subcutaneous.

Table 1: Pharmacokinetics of APG777 and lebrikizumab following a single bolus IV or SC dose in cynomolgus monkeys

Mean (SE)	APG777		Lebrikizumab*	
	IV	SC	IV	SC
T_{max} (days)	0	3.33 (0.67)	0	2.33 (0.89)
C_{max} (ng/mL)	1.03×10^5 (4.50×10^3)	4.13×10^4 (1.65×10^3)	9.68×10^4 (4.65×10^3)	4.25×10^4 (1.16×10^3)
$AUC_{0\text{-}inf}$ (ng h/mL)	5.05×10^7 (1.99×10^6)	4.10×10^7 (5.39×10^6)	2.66×10^7 (4.76×10^6)	2.01×10^7 (4.18×10^6)
Cl (mL/day/kg)†	1.43 (0.05)	1.48 (0.20)	2.93 (0.61)	2.93 (0.53)
V_{ss} (mL/kg)†	54.06 (1.18)	57.24 (1.92)	59.26 (5.79)	44.95 (4.01)
F (%)‡	N/A	81.22 (13.70)	N/A	75.70 (27.40)
$t_{1/2}$ (days)	28.2 (1.16)	27.0 (2.45)	18.1 (3.87)	13.5 (2.66)

*Monoclonal antibody expressed based on the published sequence of lebrikizumab; †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; C_{max}, maximum observed serum concentration; F, bioavailability; IV, intravenous; PK, pharmacokinetic; SC, subcutaneous; SE, standard error; $t_{1/2}$, half-life; T_{max}, time to maximum observed serum concentration; V_{ss}, volume of distribution at steady-state.

Conclusions

- APG777 demonstrated an increase in $t_{1/2}$ and exposure and reduced clearance compared with a monoclonal antibody based on the published sequence of lebrikizumab in NHPs.
- APG777's prolonged $t_{1/2}$ may enable less frequent dosing compared with currently available treatments, which could reduce injection burden and increase compliance for patients living with atopic dermatitis and other IL-13-driven diseases.
- These data support the initiation of a Phase 1 study of APG777 in healthy volunteers, which has been initiated in Australia.

References

1. Bieber T. Allergy 2020;75:54–62.
2. Hershey GK. J Allergy Clin Immunol 2003;111:677–90.
3. Gandhi NA, et al. Expert Rev Clin Immunol 2017;13:425–37.
4. Dall'Acqua, et al. J Biol Chem 2006;281:23514–24.
5. Zhu E, et al. EADV 2023 (poster #P0437).

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