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

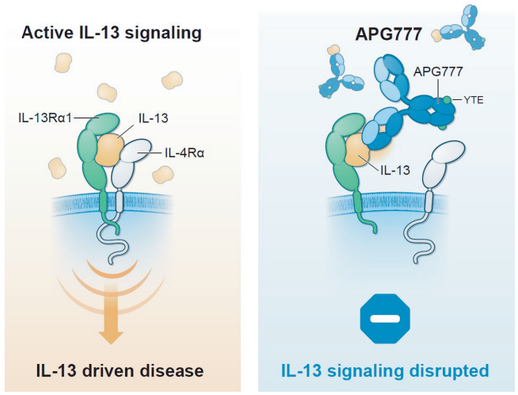
Eric Zhu[1], Jason Oh[1], Carl Dambkowski[2], and Hussam Shaheen[1]

[1]Paragon Therapeutics, Inc. Waltham, MA, USA; [2]Apogee Therapeutics, Inc. Waltham, MA, USA

Introduction

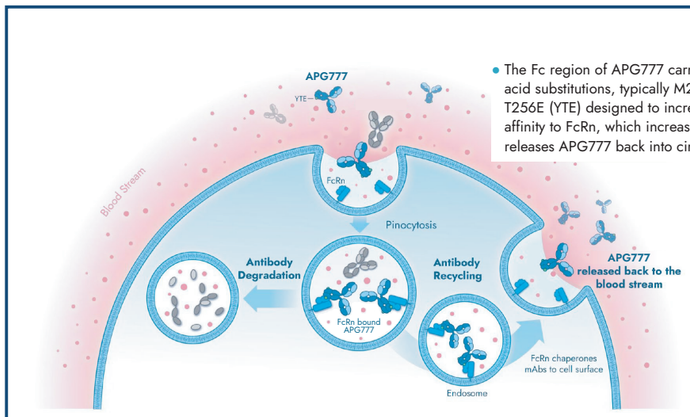
- Interleukin-13 (IL-13) is a T helper type 2 (Th2) cytokine that plays a key role in the pathogenesis of atopic dermatitis, asthma, and other inflammatory and immunologic conditions.[1–3]
- APG777 is a humanized IgG1 monoclonal antibody (mAb) that is engineered to have high affinity for IL-13 and which 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]

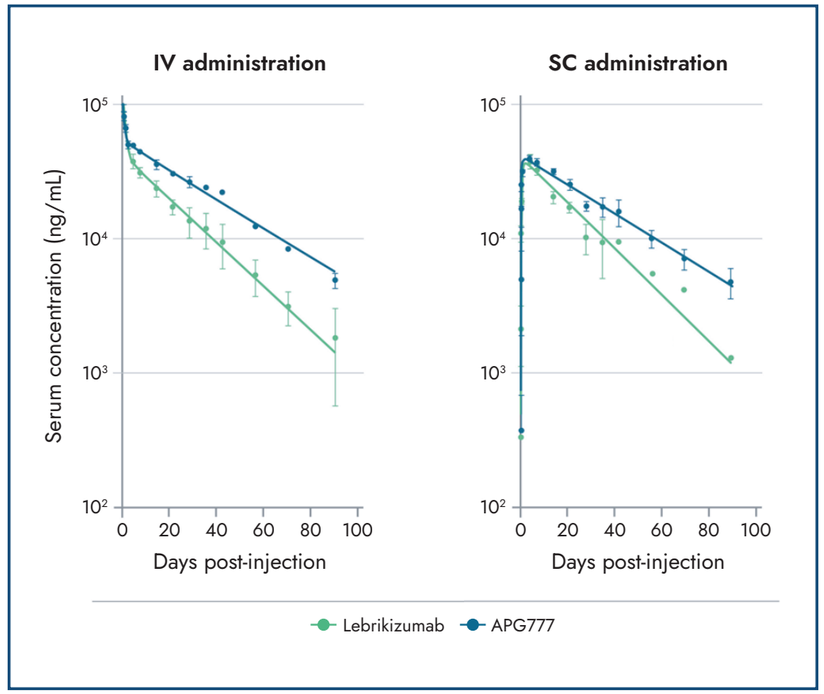
Materials and methods

- 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).

Acknowledgements

Editorial and layout assistance for this poster was provided by Miller Medical Communications Ltd.
This work was funded by the study sponsor (Apogee Therapeutics, Inc.).

For further information please contact Carl Dambkowski (carl.dambkowski@apogeetherapeutics.com)