**Introduction**

APG777 is a high-affinity humanized anti-IL-13 IgG1 monoclonal antibody (mAb) that blocks formation of the IL-13/IL-13Rα1/IL-4Rα complex, preventing receptor heterodimerization and downstream signaling.1 APG777 contains a triple amino acid modification, M253Y/S255T/D257E (referred to as a “YTE” modification), in the fragment crystallizable (Fc) region that extends half-life (t1/2) in humans by increasing binding to neonatal Fc receptor (FcRn) under acidic pH conditions.1,2 APG777 also contains two additional amino acid modifications L235A/L236A (referred to as a “LALA” modification) in the Fc region, designed to ablate Fc and complement effector functions.1 APG777 is a high-affinity humanized anti-IL-13 IgG1 monoclonal antibody (mAb) that blocks formation of the IL-13/IL-13Rα1/IL-4Rα complex, preventing receptor heterodimerization and downstream signaling.1 APG777 also contains two additional amino acid modifications L235A/L236A (referred to as a “LALA” modification) in the Fc region, 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modification) in the Fc region, designed to ablate Fc and complement effector functions.1

Materials and methods

This phase 1, randomized, double-blind, placebo (PBO)-controlled trial evaluated safety, tolerability, PK, and PD of APG777 in healthy participants. The study was conducted in Australia and consisted of single ascending dose (SAD) and multiple dose (MD) cohorts. Participants received single subcutaneous (SC) doses of 300 mg, 600 mg, or 1200 mg of APG777 or matched PBO in the SAD cohorts, and repeat doses of 300 mg SC on Days 1 and 29, or Days 1 and 15 in the MD cohorts. Each cohort consisted of 8 participants randomized 2:2 to APG777 or PBO. Safety assessments were conducted throughout the study and blood draws for PK and PD were obtained at multiple timepoints. Exploratory biomarkers – phosphorylated Signal Transducer and Activator of Transcription 6 (pSTAT6) and Thymus and Activation Regulated Chemokine (TARC) – were assessed through 12 weeks, the longest available follow-up at the time of this analysis:

- Inhibition of pSTAT6 was assessed ex vivo in whole blood via flow cytometry.
- TARC levels were quantified in serum by an electrochemiluminescence immunoassay.

**Results**

40 participants were enrolled. Demographics were well-balanced across cohorts and baseline characteristics were in line with expectations for a phase 1 study in healthy participants (Table 1).

**Table 1: Demographics and baseline characteristics**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Placebo (n=6)</th>
<th>Cohort 1 (300 mg n=6)</th>
<th>Cohort 2 (600 mg n=6)</th>
<th>Cohort 3 (1200 mg n=6)</th>
<th>Placebo (n=6)</th>
<th>Cohort 1 (300 mg n=6)</th>
<th>Cohort 2 (600 mg n=6)</th>
<th>Cohort 3 (1200 mg n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>41.3 (16.2)</td>
<td>30.2 (12.2)</td>
<td>40.2 (18.4)</td>
<td>29.7 (4.6)</td>
<td>43.0 (12.1)</td>
<td>43.7 (13.9)</td>
<td>40.2 (13.9)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>6 (100.0)</td>
<td>4 (66.7)</td>
<td>5 (83.3)</td>
<td>2 (33.3)</td>
<td>4 (100.0)</td>
<td>3 (50.0)</td>
<td>3 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Cytocentrifugation, n (%)</td>
<td>6 (100.0)</td>
<td>2 (33.3)</td>
<td>5 (83.3)</td>
<td>6 (100.0)</td>
<td>6 (100.0)</td>
<td>2 (33.3)</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>72.5 (12.6)</td>
<td>74.3 (14.6)</td>
<td>78.8 (14.0)</td>
<td>77.2 (16.3)</td>
<td>63.2 (9.5)</td>
<td>80.5 (8.5)</td>
<td>66.7 (12.9)</td>
<td></td>
</tr>
</tbody>
</table>

APG777 demonstrated dose proportional increases in Cmax and AUC from 300 mg up to 1200 mg (Table 3), with mean t1/2 of approximately 75 days across SAD cohorts (Figure 1A). Preliminary data from the HD cohorts is consistent with the PK profile from the SAD cohorts (Figure 1B).

Conclusions

In this first-in-human study, APG777 was well-tolerated at doses up to 1200 mg. The t1/2 of APG777, due to its YTE modification, is at least three times longer than mAbs currently approved for the treatment of moderate-to-severe AD.

Exploratory biomarker assessments showed sustained inhibition of pSTAT6 and TARC, key biomarkers for IL-13 targeting and atopic dermatitis, for up to 12 weeks after single doses of APG777.

The initial safety, PK, and biomarker results are encouraging, but given the small sample size in this interim analysis, further exploration of APG777 is warranted.

The favorable safety profile and optimized PK of APG777 support the initiation of a phase 2 study in adults with moderate-to-severe atopic dermatitis where every 3- to 6-month maintenance dosing will be evaluated.

**References**


**Acknowledgements**

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