Rationale and Design of a Phase 1b Trial Evaluating APG279, the Combination of Half-life-extended Anti-IL-13 and Anti-OX40L Monoclonal Antibodies, Compared with Dupilumab in Moderate-to-Severe Atopic Dermatitis

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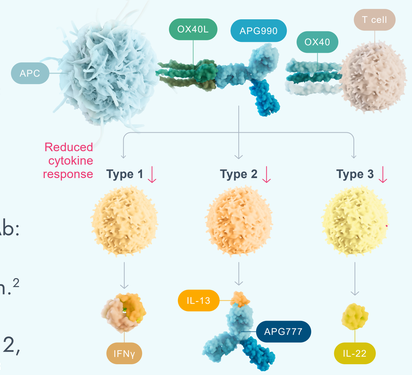
RATIONALE

- AD is a chronic skin disease primarily driven by type 2 inflammation.
- Other pathways, including type 1 and type 3 inflammation, are known to contribute to disease heterogeneity.[1]
- APG279 is a combination of APG777, a half-life-extended anti-IL-13 mAb, and APG990, a half-life-extended anti-OX40L mAb:
  - APG777 targets IL-13 for deep inhibition of type 2 inflammation.[2]
  - APG990 targets OX40L for broad inhibition across types 1, 2, and 3 inflammation (**Figure 1**).[3]

Figure 1: APG279 targets types 1, 2, and 3 inflammation in AD



STUDY OBJECTIVES

- **This phase 1b study (NCT07027527) evaluates the safety, tolerability, PK, and PD of APG279 (the combination of APG777 + APG990) in adults with moderate-to-severe AD.**

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For questions, please contact MedAffairs@apogeetherapeutics.com

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BACKGROUND

Preclinical Experience

- In an allogeneic lymphocyte reaction (ALR) co-culture of alarmin TSLP-primed myeloid dendritic cells with CD4+ T cells, the combination of APG777 and APG990 elicited a broader and deeper cytokine/chemokine suppression compared with benchmark mAbs.[4]
- APG279 preserved viral antigen memory response in preclinical assays and was well tolerated in nonhuman primate studies.[4,5]

Figure 2: APG279 suppressed types 1, 2, and 3 inflammation in preclinical assay

Ex vivo human ALR assay

	Type 1 IFNγ	Type 2 TARC	Type 3 IL-22
Lebrikizumab (IL-13)	121	25	154
Dupilumab (IL-4Rα)	123	16	389
Amlitelimab (OX40L)	46	69	53
APG279 (IL-13 + OX40L)	45	17	76
Upadacitinib (JAK)	8	10	30

Cytokine level (% of untreated): 125+, 100, 75, 50, 25, 0

Untreated = 100%

The ALR assay was performed using TSLP-primed mDCs paired with allogeneic CD4 cells for 5 days. Cytokine levels for lebrikizumab, dupilumab, amlitelimab, and APG279 are reported as the mean percent of isotype control across four donor pairs; upadacitinib is reported as mean percent of DMSO control across four donor pairs.

Clinical Experience With APG777 and APG990 Monotherapy

- In phase 1 studies, both mAbs demonstrated favorable safety and PK, with APG777 exhibiting a half-life of 75.3–77.5 days and APG990 demonstrating a half-life of ~60 days (interim results), supporting exploration of extended dosing intervals compared with available biologics.[3,6]

Phase 1 half-life

APG777 75.3–77.5 days

APG990 ~60 days

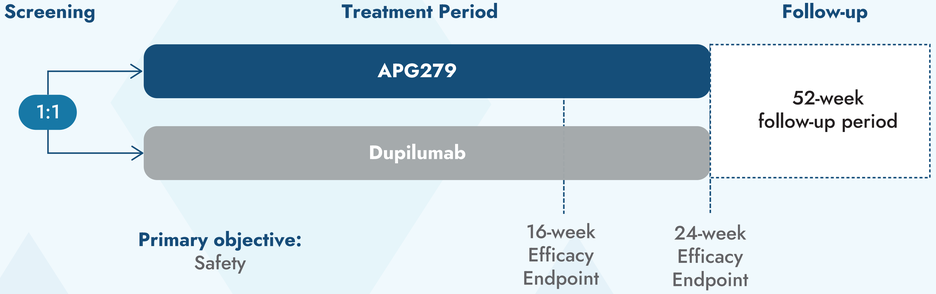
- Part A of a two-part phase 2 study of APG777 monotherapy in adults with AD met the primary endpoint and achieved a statistically greater percentage reduction in EASI at Week 16 compared with placebo.[7]
- 12- and 24-week dose intervals are being evaluated in the maintenance period of Part A; dose exploration is ongoing in Part B.[7]

METHODS

Study Overview

- This is a phase 1b, open-label, assessor-blinded, randomized, multicenter, active-comparator study.
- The study consists of a screening period (up to 6 weeks), treatment period (24 weeks), and follow-up period (52 weeks).
- Participants will be randomized to APG279 or dupilumab in a 1:1 ratio. Randomization will be stratified on Day 1 according to baseline disease severity and geographic region. APG279 will be co-administered in the proof-of-concept Ph1b trial.
- The primary endpoint is safety through week 24. Secondary endpoints include PK of APG777 and APG990. Exploratory endpoints include efficacy (including EASI-75, IGA 0/1), ADAs, and biomarkers.

Figure 3: Design of the phase 1b APG279 study (N~50)



Inclusion Criteria

- Adults ≥18 years of age.
- Diagnosis of AD that has been present for ≥1 year prior to the screening visit.
- Moderate-to-severe AD at Screening and Baseline (Day 1) visits:
  - EASI ≥16, IGA ≥3, and BSA ≥10%.
- History of inadequate response to treatment with topical medications.

Exclusion Criteria

- Participation in a prior study with APG777 or APG990.
- Prior treatment with protocol-specified monoclonal antibodies.
- Use of any AD-related topical medications within 7 days prior to baseline visit.
- Use of systemic treatments (other than biologics) and/or phototherapies and/or laser therapy that could affect AD within 4 weeks prior to baseline visit.

STUDY STATUS

- This study (NCT07027527) is currently enrolling in Australia, Canada, and New Zealand.

For further information, please contact ClinicalTrials@apogeetherapeutics.com

ABBREVIATIONS

AD, atopic dermatitis; ADA, anti-drug antibody; ALR, allogeneic lymphocyte reaction; APC, antigen-presenting cell; BSA, body surface area; DMSO, dimethyl supfoxide; EASI, Eczema Area and Severity Index; IFN, interferon gamma; IGA, investigator global assessment; IL, interleukin; mAb, monoclonal antibody; mDCs, myeloid dendritic cells; OX40/L, tumor necrosis factor superfamily member 4/ligand; PD, pharmacodynamics; PK, pharmacokinetics; TARC, thymus and activation-regulated chemokine; TEAE, treatment-emergent adverse event; TSLP, thymic stromal lymphopoietin.

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