

Olevaprubart (IMG-007), a non-depleting OX40 mAb: Optimizing peak loading concentration and exposure range to unlock the full potential of OX40-OX40L pathway targeting immune-mediated diseases

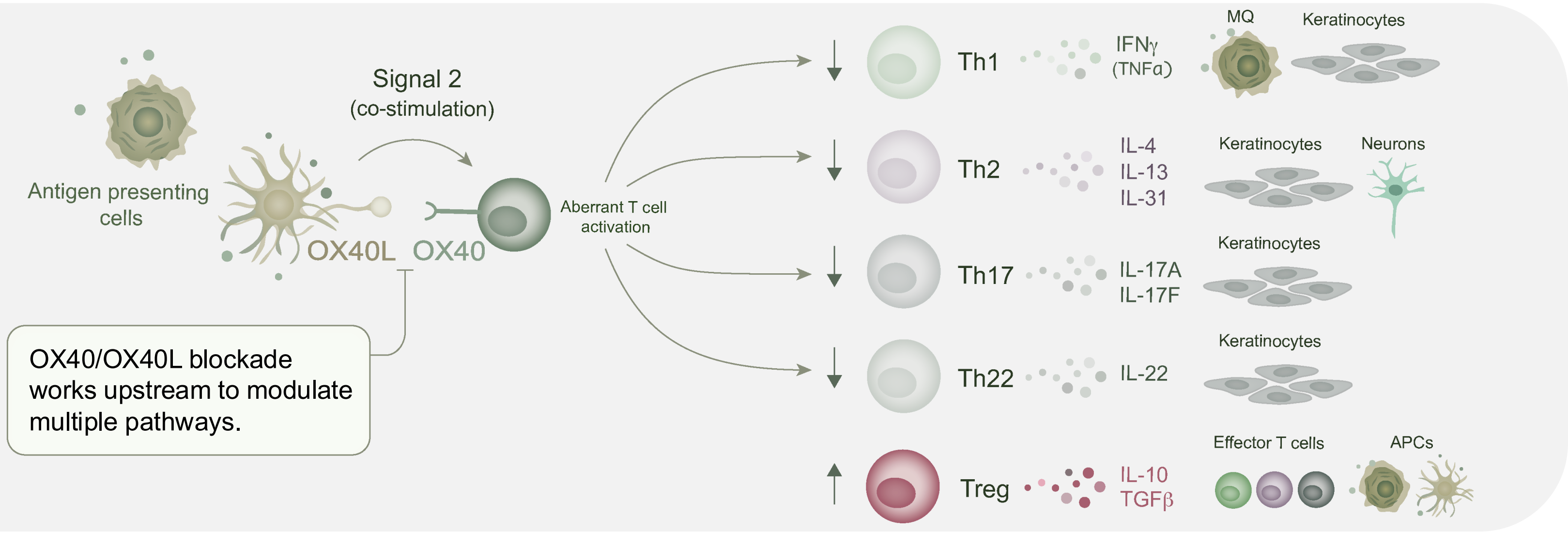
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BACKGROUND

OX40/OX40L signaling regulates activation and survival of pathogenic T cells central to atopic dermatitis (AD) development and progression. Accordingly, monoclonal antibodies suppressing the OX40/OX40L pathway have represented a promising upstream approach for the treatment of AD and other immune-mediated diseases. However, Phase 3 clinical outcomes to date from investigational agents in this class suggest that the therapeutic potential of OX40 blockade has not yet been fully realized, potentially due to molecule-specific mechanism of action, limitations in PK (loading, dosing, exposure), and selection of ligand versus receptor as target.



Anti-OX40 and anti-OX40L mAbs are emerging biologics with novel mechanisms of action

Molecule	Rocatinlimab	Amlitelimab	Olevaprubart
Target molecule/subset	OX40 Receptor / T cell	OX40 Ligand / APC	OX40 Receptor / T cell
mAb isotype	IgG1	IgG4	IgG1
ADCC	Enhanced (Fc defucosylation)	Minimal (CH2 L235E)	Silenced (Fc N297A)
Mean half-life	7.4–12.0 days ¹ <i>Single SC dose, 3 mg/kg, healthy adults</i>	20.3 days ² <i>IV 4 mg/kg Day 1, then 2 mg/kg Days 4 and 8, healthy adults</i>	34.7 days ³ <i>Single SC dose, 600 mg, healthy adults</i>
Dosing frequency in late-stage trial	Q4W	Q4W or Q12W	Potential for less frequent dosing (Q4W and Q12W in Phase 2b)
Development status	Discontinued	Discontinued in AD <i>Ongoing Ph2 (CeD)</i>	Ph2b (AD) <i>Ph2* (AA)</i>

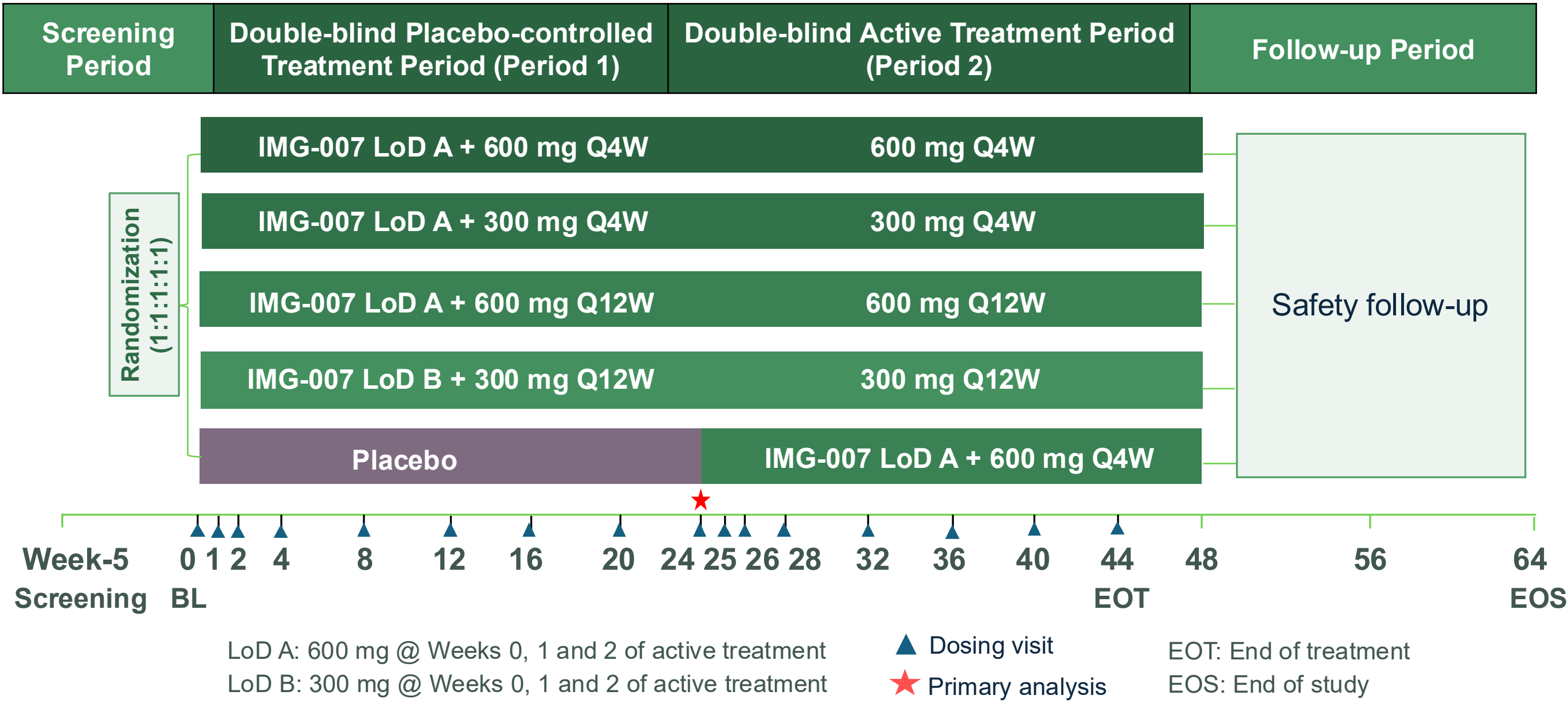
APC: antigen-presenting cell; CeD: Celiac Disease; AD: Atopic Dermatitis; AA: Alopecia Areata; * To be initiated

OX40/OX40L targeting is mechanistically compelling. Although first-generation agents demonstrated modest efficacy, their clinical performance may have been constrained by incomplete exposure-response characterization, including the possibility of insufficient exposure. This may have limited realization of the full therapeutic potential of OX40/OX40L blockade. It also remains unknown whether targeting the receptor versus the ligand has distinct pharmacologic implications.

IMG-007 (INN: Olevaprubart) is an Fc-silenced (N297A) IgG1 antibody targeting OX40, designed to block OX40-OX40L costimulation while avoiding FcγR-mediated depletion. This enables upstream inhibition of T cell activation across multiple pathogenic pathways, limiting clonal expansion of effector and memory T cells. Olevaprubart is designed to preserve T cell diversity by avoiding FcγR-mediated depletion, a feature that differentiates it from depleting anti-OX40 antibodies, with which treatment-related pyrexia and chills have been reported but have not been observed with olevaprubart to date. Olevaprubart is being evaluated in a Phase 2b dose-ranging study employing different loading-dose regimens to rapidly achieve therapeutically relevant concentrations.

RESULTS

IMG-007-203: AD Ph2b study design schema



Parameter Dose/ Regimen	C _{max} ^a (μg/mL)	T _{max} ^b (hr)	Conc _{C24 wk} (μg/mL)	C _{max,ss} ^c (after last dose) (μg/mL)	AUC _{ss} ^d (after last dose) (μg·day/mL)	Conc _{C48 wk} (μg/mL)	Cum dose by wk 24 post-dose	Safety margins to NOAEL exposure ^e for C _{max}	for AUC _{ss}
LoD A + 600 mg Q4W	163	113 (785)	57.5	104	2327	56.6	4800	~70x	~120x
LoD A + 300 mg Q4W	154	122 (458)	29.1	52	1151	27.8	3300	~75x	~240x
LoD A + 600 mg Q12W	154	122 (458)	6.6	63	2278	5.4	2400	~75x	~365x
LoD B + 300 mg Q12W	77	124 (460)	2.8	31	1100	2.2	1200	~150x	~755x
Placebo cross-over: LoD A + 600 mg Q4W starting from Week 24	163	113 (785)	---	106	2367	57.5	4800	~70x	~117x

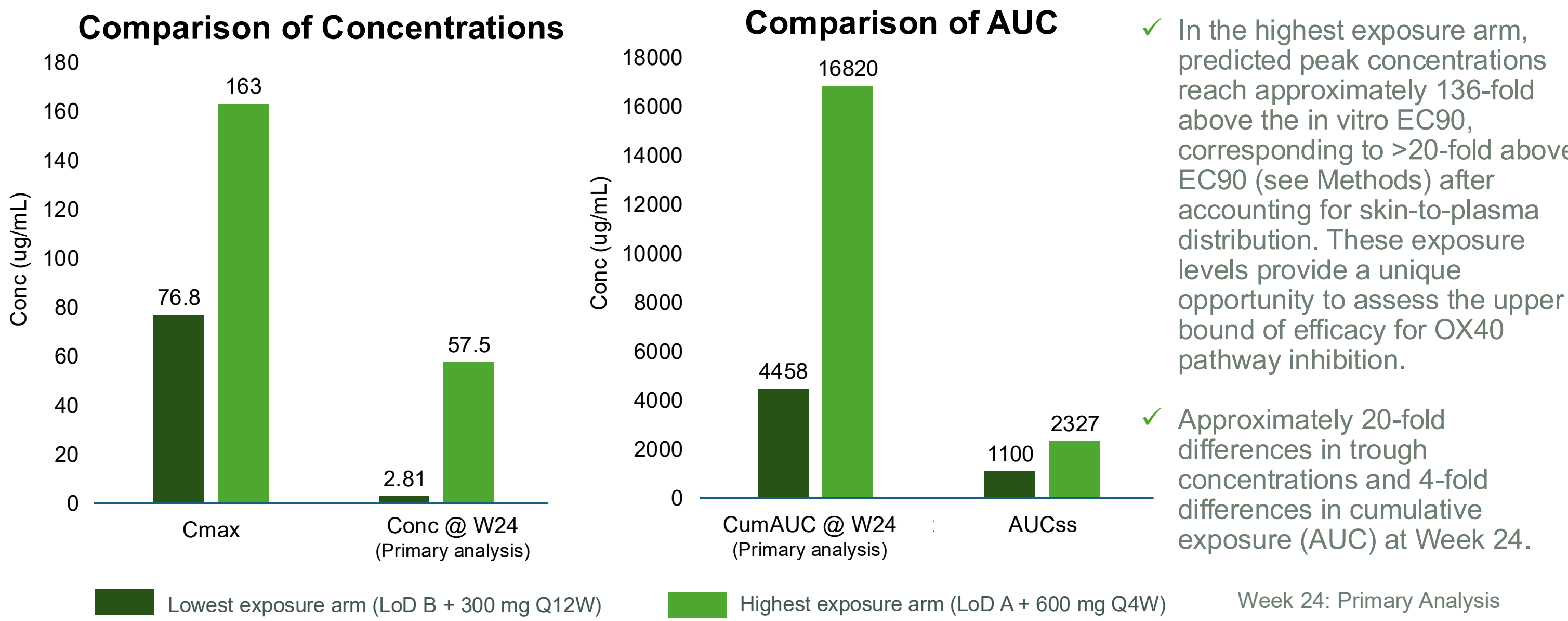
^a Exposures calculated based on simulations performed with the population pharmacokinetic parameters obtained from the final PopPK model
^b C_{max} is calculated as the maximum concentration observed up to week 20, and for Placebo cross-over it is the maximum concentration observed after week 20
^c T_{max} is expressed as the time to C_{max} after the preceding dose
^d C_{max,ss} is calculated as the maximum concentration after the last dose administration (after wk 44 for Dose groups 1, 2 & Placebo cross-over and after wk 36 for Dose groups 3 & 4)
^e AUC_{ss} is calculated as the AUC after last dose administration according to dosing interval (AUC_{0-48 wk} for Dose groups 1, 2 & Placebo cross-over and AUC_{0-48 wk} for Dose groups 3 & 4)
^f Safety margins are calculated from comparison between estimated steady state clinical exposures and dosing-interval adjusted steady state exposures at the NOAEL dose from the 26-wk GLP toxicity study in cynomolgus monkeys

QUANTITATIVE BASIS FOR THE SELECTED REGIMENS

- Two loading regimens in Treatment Period 1: three 600 mg or 300 mg doses at Weeks 0, 1 and 2, followed by a 600 mg or 300 mg flat dose (Q4W or Q12W) (see Table); the 2x loading range tests the hypothesis that a higher C_{max} is needed to achieve adequate skin penetration and to initiate sufficient upstream OX40 blockade for effects to propagate through the downstream signaling cascade.
- Dose groups (300/600 mg at Q4W/Q12W) give well-separated cumulative doses to Week 24: 1200, 2400, 3300 and 4800 mg
- At the Week 24 primary endpoint these cumulative doses give all participants on active treatment a reasonable chance of clinical benefit, while allowing exploration of a potential dose-response (PK-PD) relationship

SAFETY MARGINS

- NOAEL of 300 mg/kg/dose weekly in a GLP-compliant 26-week repeat IV and SC dose toxicity study in cynomolgus monkeys (27 once-weekly doses: 120 mg/kg IV, 120 mg/kg SC, 300 mg/kg SC) with no evidence of toxicity at any dose tested; providing a 120x–755x margin to the selected doses with respect to AUC
- At the NOAEL dose on Day 176: AUC_{T,ss} 69,200 μg·day/mL and C_{max,ss} 11,500 μg/mL
- Conservative margins at the highest proposed dose (70% SC bioavailability assumed): ~70x for C_{max} and ~120x for AUC_{T,ss}



TROUGH CONCENTRATIONS

- Projected Week 24 troughs (Conc_{C24wk}) across the four active arms span ~7x to 0.4x the estimated minimal effective serum concentration of 8 μg/mL, a wide exposure range
- The Q4W exposure arms (600 mg Q4W and 300 mg Q4W) test a potential efficacy ceiling, well within the safety margins afforded by the NOAEL
- The Q12W exposure arms (600 mg Q12W and 300 mg Q12W) offer the lower bound of exposure, while testing convenient, quarterly dosing regimens

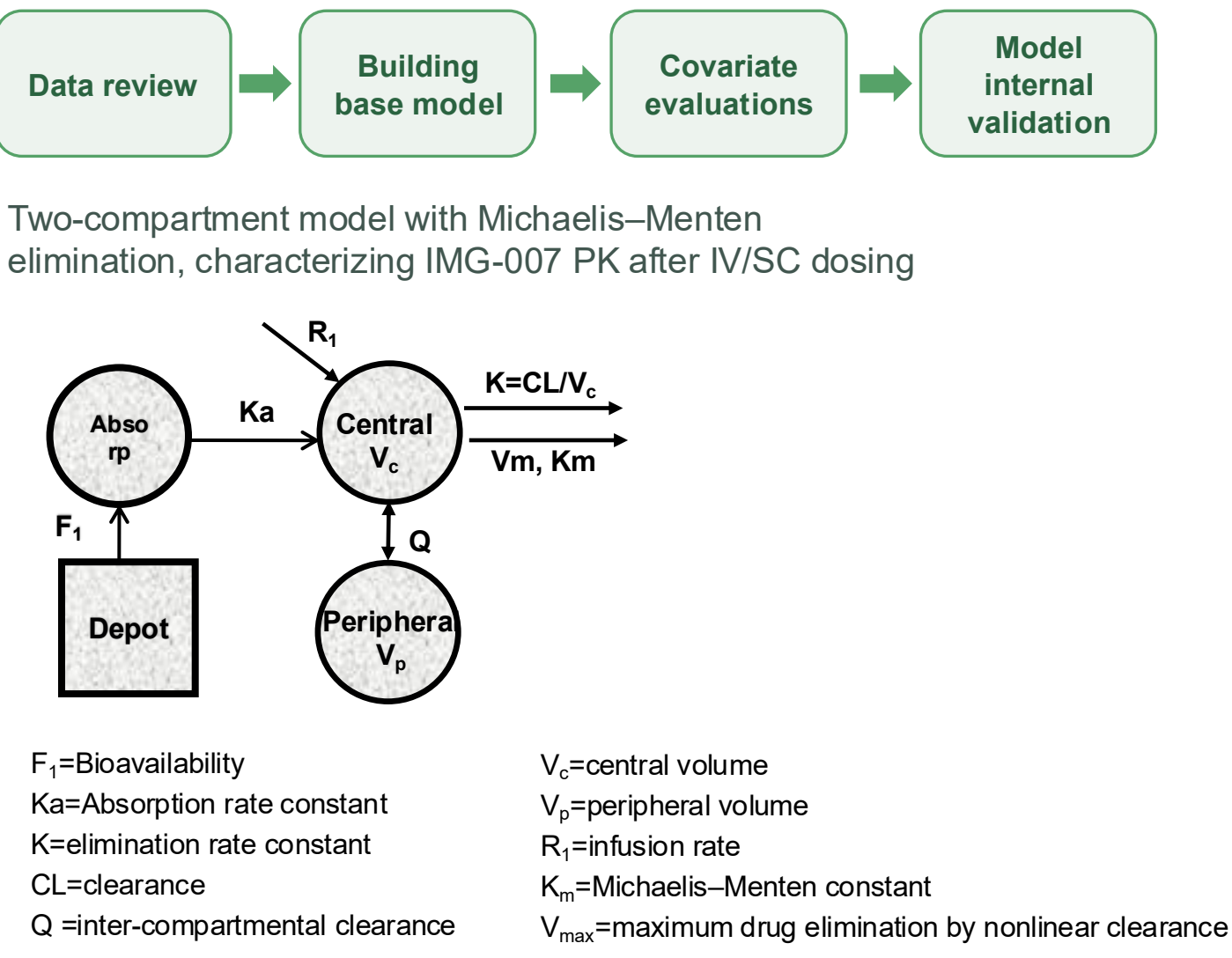
METHODS

TARGET EXPOSURE ESTIMATION

- Minimal target therapeutic level derived from the *in vitro* EC90, scaled for the higher exposure needed for target engagement in skin
- In vitro assays of IMG-007 inhibition of OX40L-induced NFκB activation and IFNγ release yielded an EC90 of ~1.2 μg/mL for peripheral PD dose responsiveness.
- PBPK modelling based on a skin:plasma biodistribution coefficient of 15.7%⁷
- Minimal target therapeutic level: Estimates ~8 μg/mL (6.4 × EC90) at the primary efficacy endpoint readout

Study / Phase	Design	Population	Dosing (N), route	Status
IMG-007-101 Phase 1	Randomized, double-blind, placebo-controlled; safety, tolerability, PK	44 healthy adults	Single dose 1–600 mg (30) or placebo (14), IV	Completed
IMG-007-201 Phase 1b/2a	Safety, PK and efficacy in moderate-to-severe atopic dermatitis	13 adults with moderate-to-severe AD	3 × 300 mg over 4 weeks (13), IV	Completed
IMG-007-202 Phase 1b/2a	Safety, PK and efficacy in alopecia areata	29 adults with AA, ≥50% scalp hair loss	3 × 300 mg (6) or 600 mg (23) over 4 weeks, IV	Completed
IMG-007-102 Phase 1	Safety and PK of a single subcutaneous dose	16 healthy adults	Single dose 150 mg (6) or 600 mg (6) vs placebo (4), SC	Completed

MODEL STRUCTURE



POPULATION PK MODEL ANALYSIS & SUMMARY

- Pooled data from IMG-007-101, -102, -201 and -202: 943 concentration measurements from 84 subjects (body weight 47.9–142 kg, median 79.4 kg)
- PK best described by a two-compartment model with both linear and Michaelis–Menten elimination from the central compartment
- Intrinsic and extrinsic covariate effects tested on CL, Q, Vc and Vp
- Typical subject: CL 0.00449 L/hr, Vc 3.4 L, Q 0.0138 L/hr, Vp 1.92 L, Vmax 0.00689 mg/hr, Km 0.00737 μg/mL, Ka 0.0082 hr⁻¹, F 0.71
- Interindividual variability: CL 26.2%, Vc 23.1%, Q 49.2%, Vp 13.4%, Ka 64.4%
- Significant covariates: patient status (AD/AA), body weight
- No other evaluated covariates were significant

CONCLUSIONS

- IMG-007-203 is a Phase 2b dose-ranging trial designed to identify the optimal Phase 3 dose. It evaluates a broad range of dosing arms, spanning wide exposure while maintaining substantial safety margins.
- The trial characterizes exposure-response relationships, including loading dose, onset, efficacy with continuous dosing through Week 48, and dosing interval. Rapid therapeutic exposure and extended dosing intervals may support faster onset, greater efficacy, and patient convenience.
- Prior OX40/OX40L outcomes may reflect suboptimal exposure rather than limitations of OX40 as a target. Optimizing loading concentrations and the exposure range, enabled by improved PK and safety, may unlock the full potential of OX40-targeted therapy in immune-mediated disease.

References: (1) Furihata K et al. Clin Pharm Drug Dev 2021;10[8]:870-883; (2) Saghari M et al 2022; Clin Pharmacol & Therapeutics 111[5]:1121-1132; (3) IMG-007-102; (4) Croft et al., Am J Clin Dermatol. (2024) OX40 in the pathogenesis of atopic dermatitis – a new therapeutic target; (5) Guttman-Yassky et al., Br J Dermatol. (2024) The role of OX40 ligand/OX40 axis signaling in atopic dermatitis; (6) Wang et al., Protein Cell (2018) IgG Fc engineering to modulate antibody effector functions.; (7) Betts et al., mAbs (2013) Antibody biodistribution coefficients. **Disclosures:** Chandrasena Pamulapati, Jonatan Tuncel, Kurinji Pandiyan, and Kristin Yarema are employees of ImageneBio and may hold equity interests. No other relevant financial relationships to disclose.

Presented at European Academy of Dermatology & Venereology (EADV) Annual Meeting: Sept 30 – Oct 3, 2026; Vienna, Austria.

