CUE-221 Phase 2 Chronic Spontaneous Urticaria

September 2026

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Positive Results from CUE-221 Phase 2 CSU Study Demonstrate Robust and Durable Clinical Benefit

- **Robust Dose-Responsive Results:** Primary endpoint of complete resolution of hives (HSS7=0) vs. placebo at week 12 was met, with treatment effect peaking at Week 22
- **Potent Disease Control:** Secondary endpoint of complete response (UAS7=0) was statistically significant in the high-dose group, further supporting clinically meaningful impact
- **Favorable Safety and Tolerability:** including no hypersensitivity reactions (i.e. anaphylaxis)
- **Durable Benefit:** both observations of complete hives resolution and complete response persisted for 12 weeks off-drug for the high-dose group, but not for omalizumab, **pointing to fundamental biological differences**
- **Potential as Disease Modifier:** We believe the stark contrast observed off-drug at week 28 against a sole IgE neutralizer provides clinical evidence supportive of CUE-221 engineered dual MOA with both neutralization and down-regulation of IgE synthesis
- **Next Steps:** Based on demonstrated potential for differentiated efficacy in CSU and clinical evidence of relevance for the dual MOA, we will plan both P2b/3 in CSU and P2 in food allergy

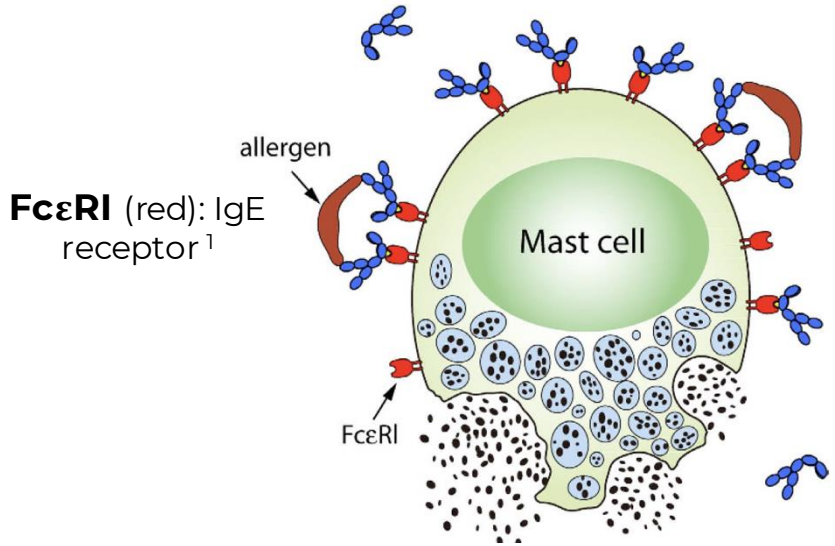
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IgE Drives Allergic Disease by Engaging Two Critical Receptors

FcεRI and CD23 (FcεRII) regulate the allergic response

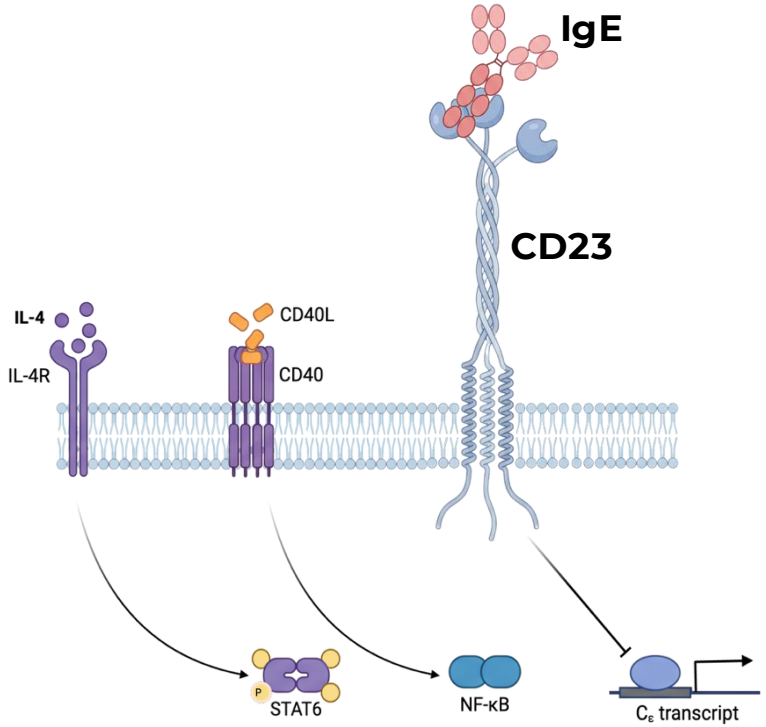
Cross-linking the FcεRI (high affinity) receptor leads to allergic reaction

IgE binds to FcεRI receptor on the surface of mast cells



B cell surface CD23 (low affinity receptor) decreases IgE production when engaged by IgE

CD23 receptor down-regulates IgE synthesis[2]



Source: [1] Wright et al 2015 Nature Scientific Reports

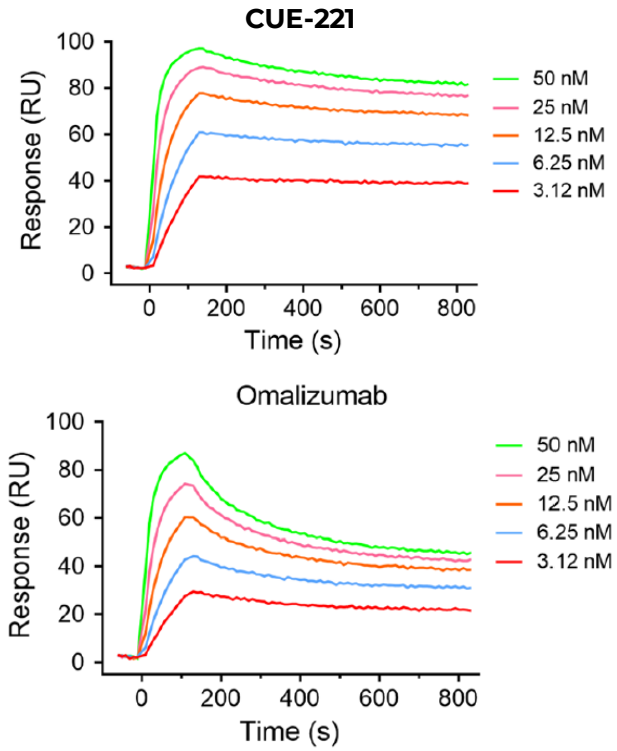
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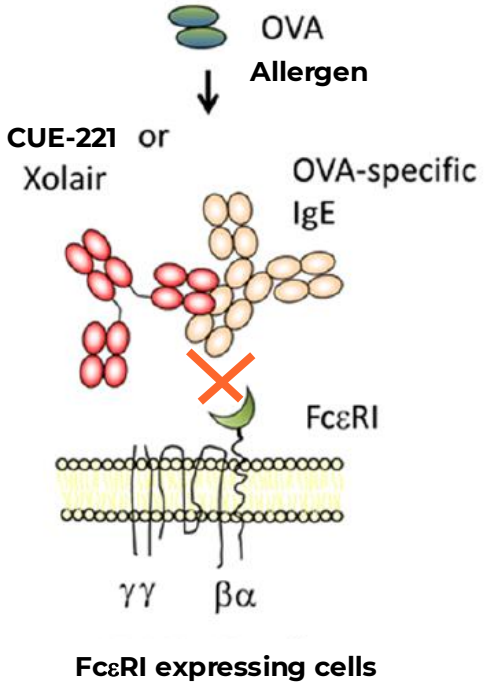
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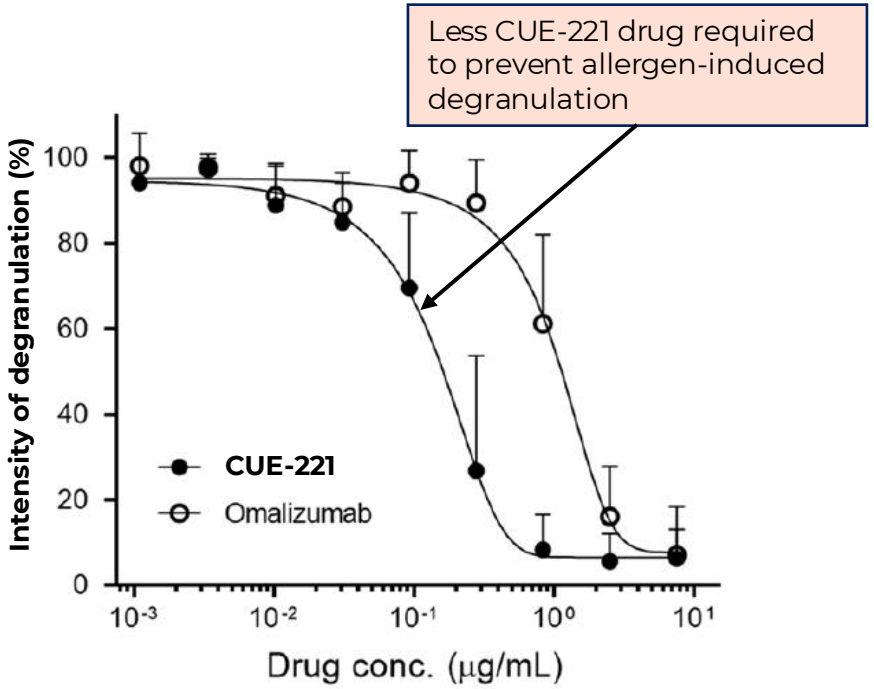
CUE-221 Blocks IgE Binding to FcεRI: Potent IgE Neutralization

4-8-fold higher binding affinity (picomolar range) and slower dissociation (off-rate) than omalizumab

Potent Inhibition of FcεRI binding results in 7-fold greater potency than omalizumab at blocking basophils degranulation





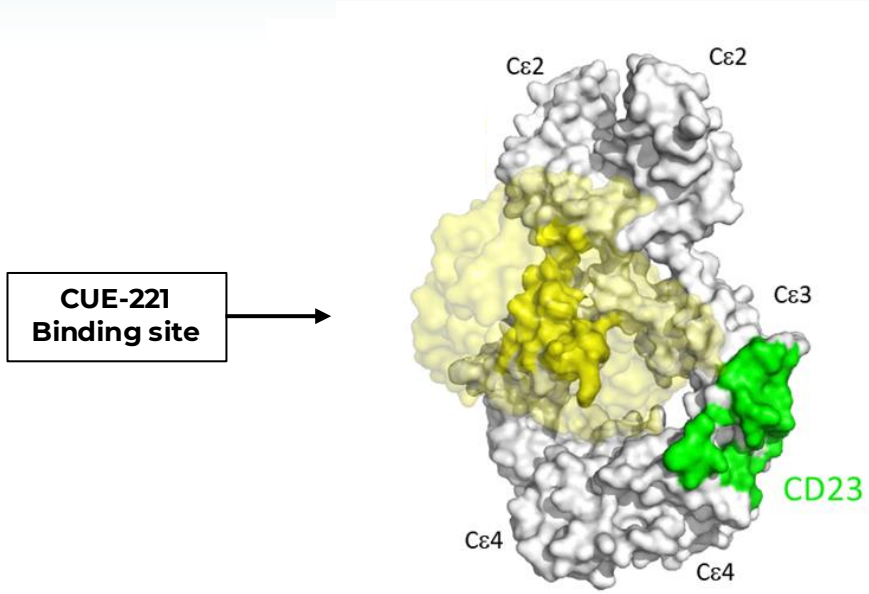


Source: Kuo et al. J Clin Invest. 2022 and data on file.

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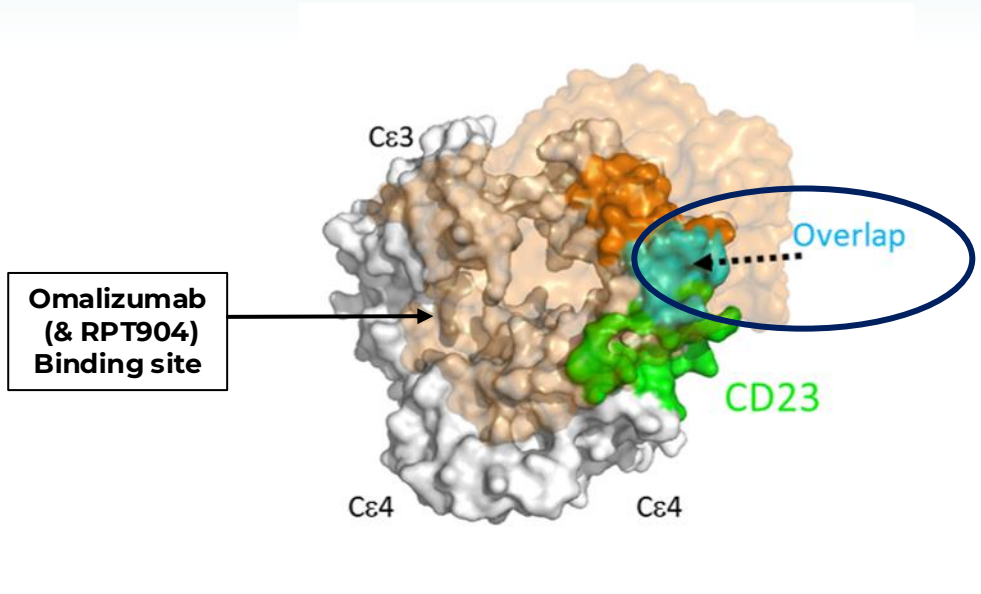
CUE-221 Preserves IgE Binding to FcεRII (CD23): Maintains Regulation of IgE synthesis

CUE-221



CUE-221 binds to IgE (yellow) at a location that is distant from where IgE (grey) and CD23 interact (green)

OMALIZUMAB



Omalizumab and RPT904 (brown) bind IgE at a location that substantially overlaps the sites where IgE and CD23 interact (cyan)

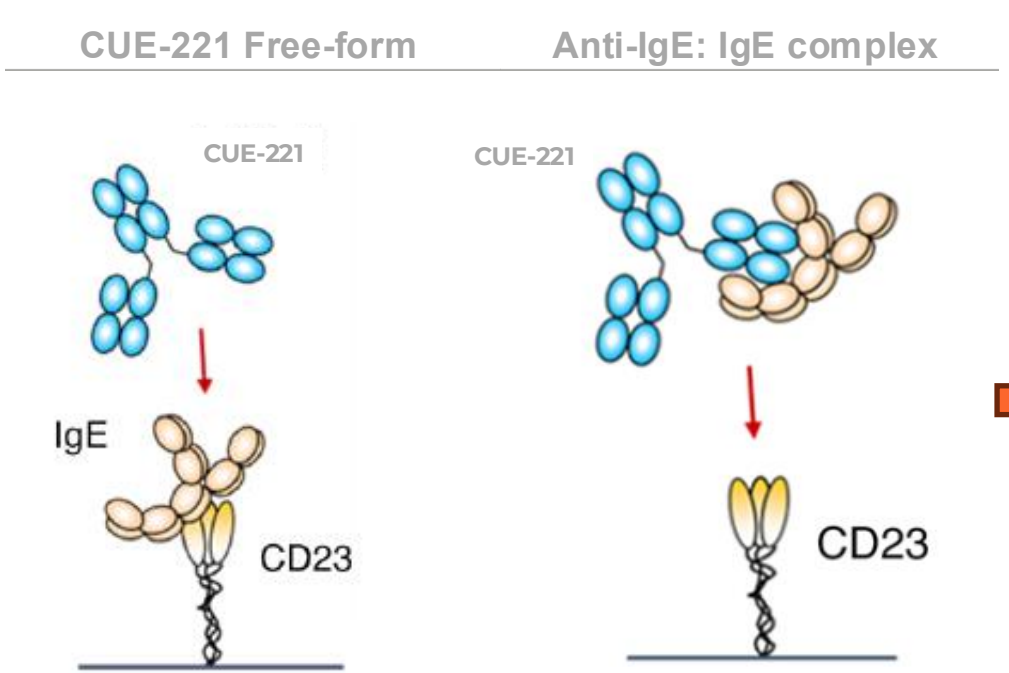
CUE-221 was engineered to provide greater control of IgE than that achieved by solely blocking the high affinity receptor

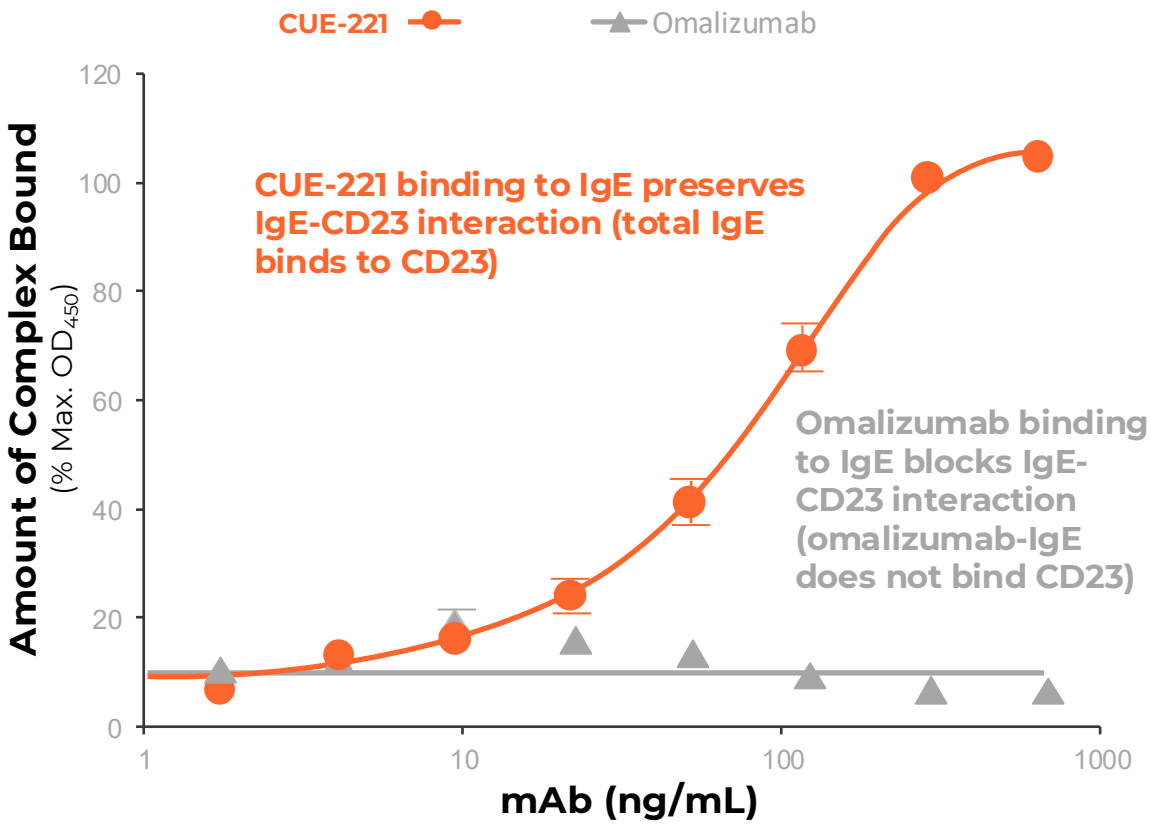
Source: Kuo et al. J Clin Invest. 2022

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CUE-221 Differentiated IgE Binding Enables Distinct Functional Properties

IgE binding to CD23 is Preserved Despite Binding of CUE-221 to IgE





Binding of mAb-IgE complexes to immobilized CD23

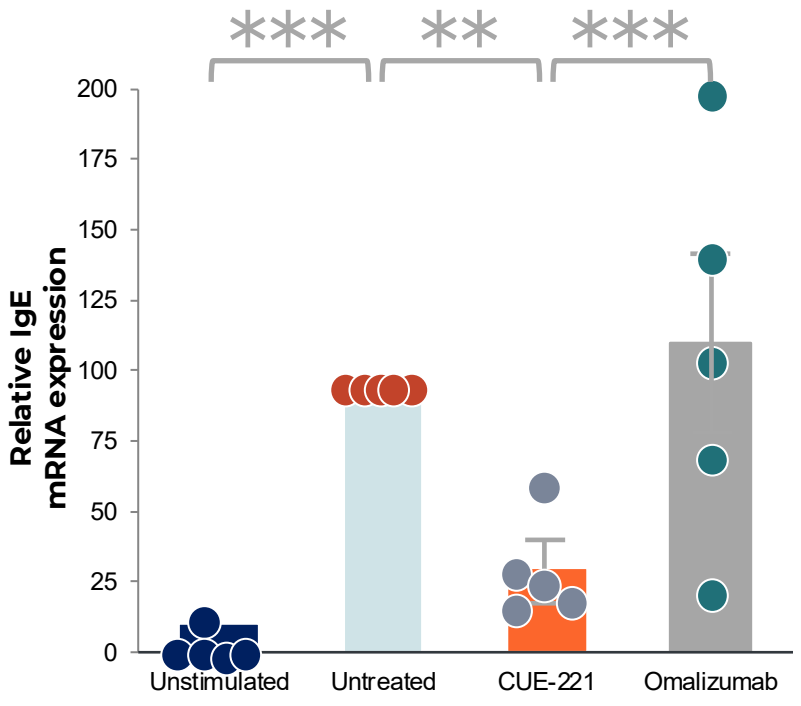
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Source: Kuo et al. J Clin Invest. 2022

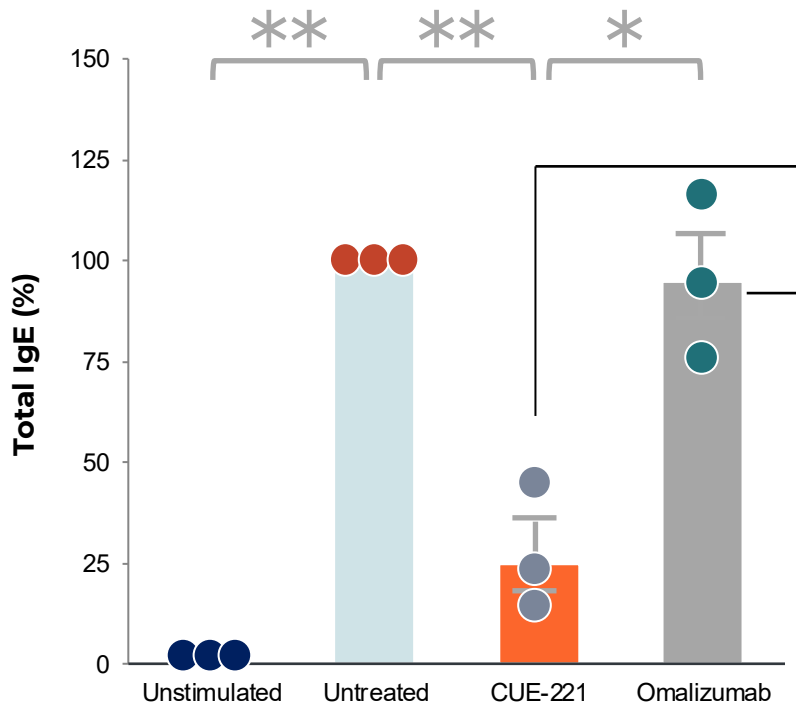
CD23 Acts as a Natural Brake on IgE Production When IgE is Abundant

CUE-221 leverages the CD23-mediated IgE downregulation pathway, decreasing new IgE mRNA and protein synthesis[1]

IgE mRNA[2]



IgE protein synthesis[3]



CUE-221-IgE binds CD23 and downregulates new IgE synthesis

Omalizumab-IgE cannot bind CD23 and does not impact new IgE synthesis

Source: Adapted from Kuo et al. J Clin Invest. 2022

Note: [1] Human PBMCs were stimulated with IL-4 and anti-CD40 to induce IgE production, treated with mAbs for 11 days; Total IgE (by ELISA) and IgE mRNA levels (by real-time PCR; data not shown) measured relative to untreated controls; The unstimulated group corresponds PBMCs in which NO IL-4 and NO anti-CD40 was added, and thus is the background IgE (low/undetectable); The untreated group corresponds to a group that was stimulated with IL-4 + anti-CD40 but NO anti-IgE antibody added. This group produces a full IgE response and is used as the reference/baseline (100%). [2] 1 µg/mL; [3] 10 µg/mL

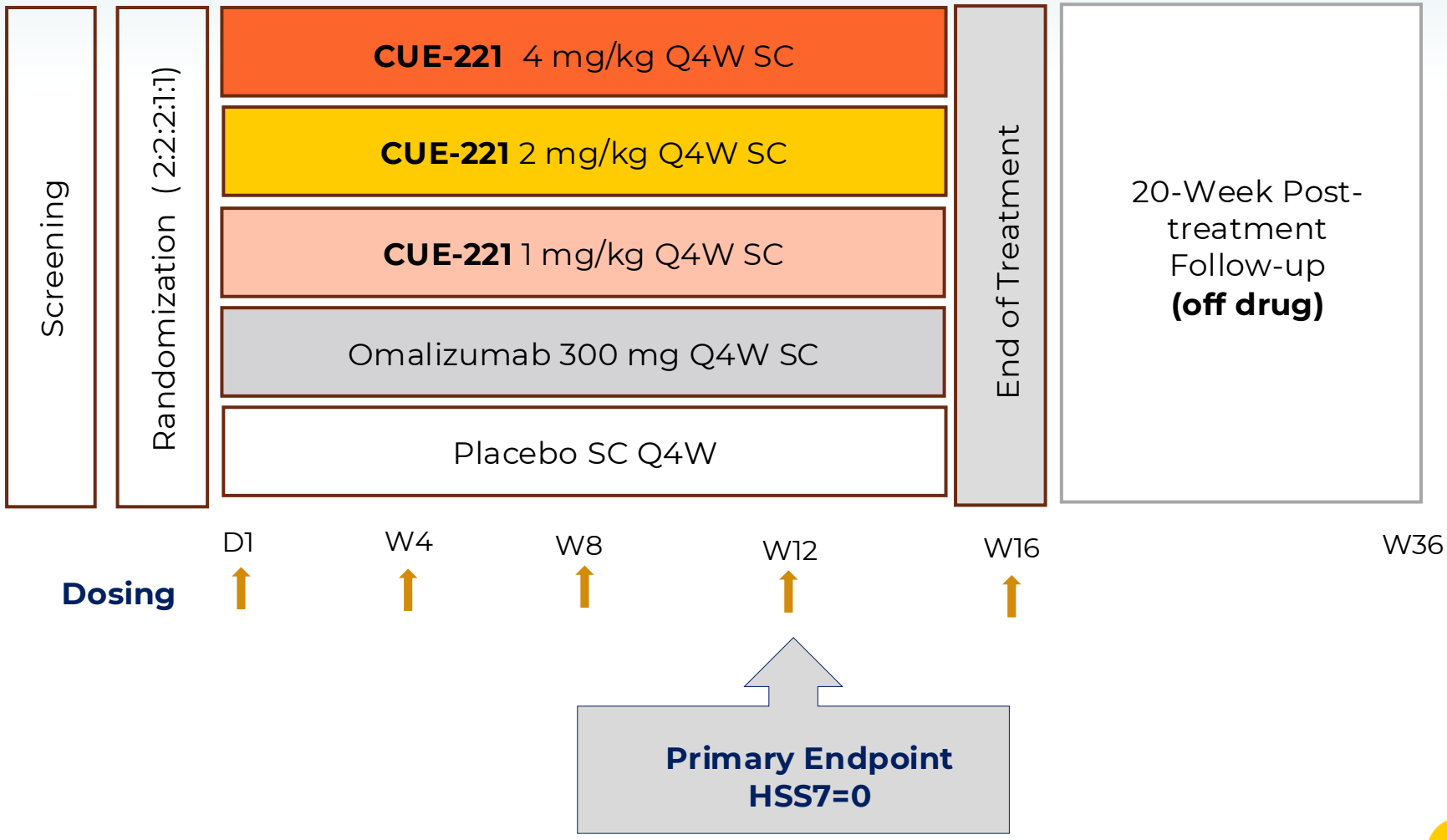
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CSU P2 Study Design

Randomized Double-Blind Placebo Controlled Study with Active Comparator

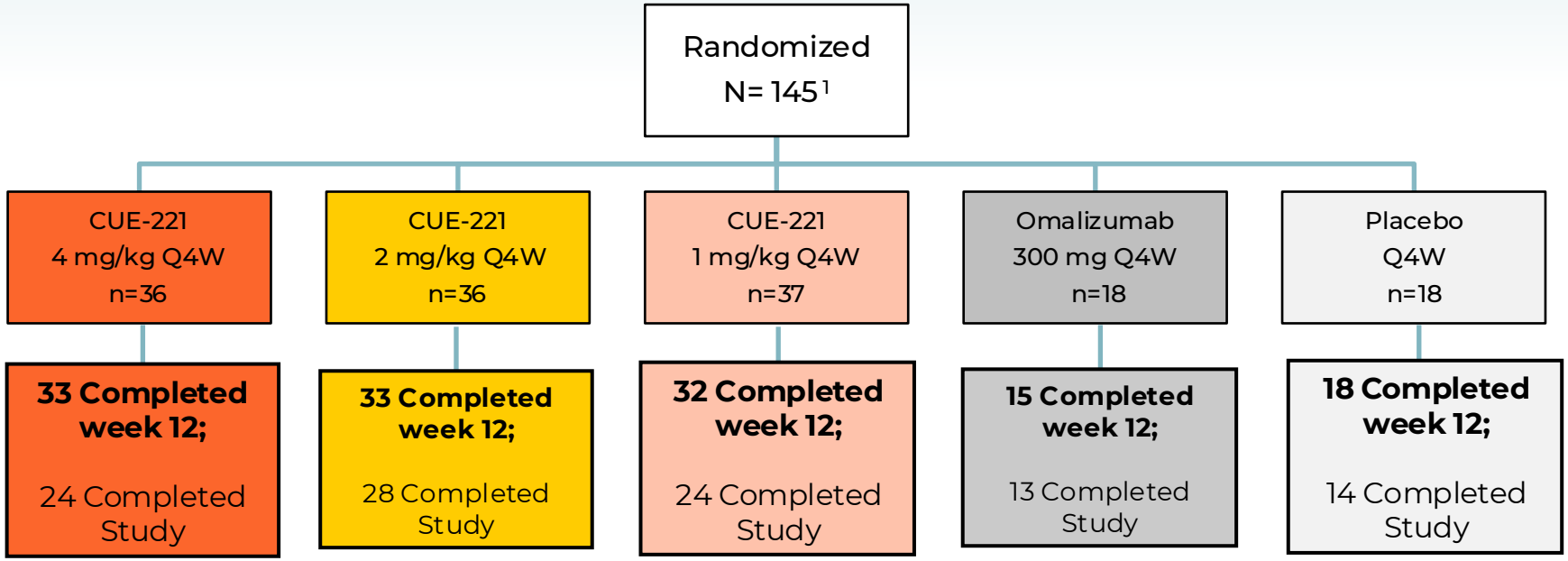
Adults with CSU inadequately controlled with H1 antihistamines

Moderate-to-Severe CSU: UAS7 score ≥ 16 and HSS7 ≥ 8 during 7 days prior to Day 1



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Subject Disposition



[1] The study through week 36 was analyzed using a modified ITT approach. Twosubjects were randomized but not dosed: one in the 4 mg/kg group and one in the omalizumab group. These two subjects were not part of the analysis, but all other subjects were included in the mITT analysis. Subjects with missing data were treated as non-responders.

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Key Baseline Characteristics[1]

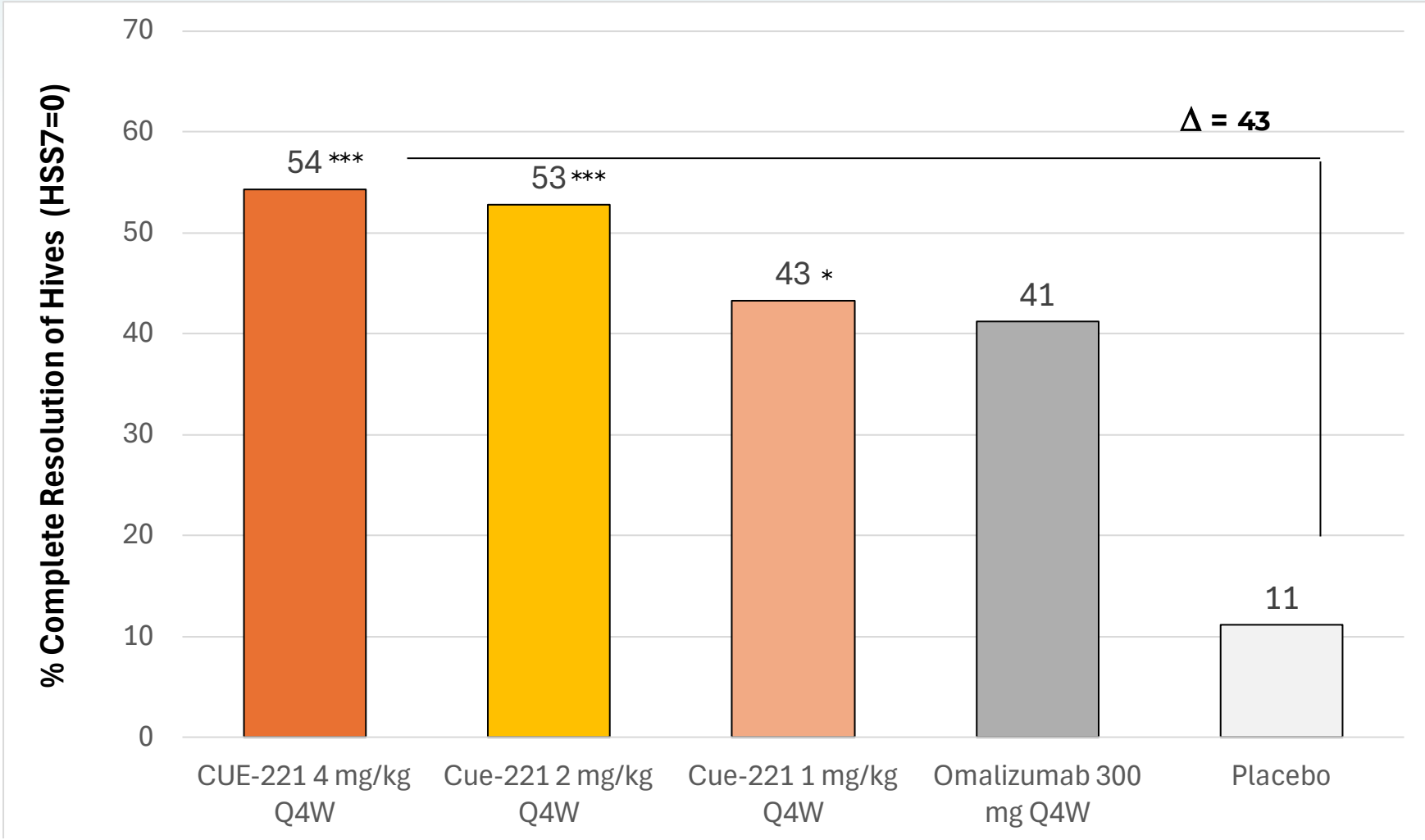
Characteristic	CUE-221 Q4W 4 mg/kg N=35	CUE-221 Q4W 2 mg/kg N=36	CUE-221 Q4W 1 mg/kg N=37	Omalizumab 300 mg N=17	Placebo N=18
Age (years)	41.7 (11.9)	39.1 (13.6)	42.8 (13.1)	42.3 (13.4)	37.8 (15.6)
Female, n (%)	19 (54.3%)	18 (50.0%)	23 (62.2%)	6 (35.3%)	11 (61.1%)
Weight (kg)	66.6 (11.5)	68.6 (14.8)	69.5 (13.9)	77.2 (16.0)	65.3 (15.3)
CSU duration (years)	4.1 (3.3)	6.1 (6.6)	4.0 (6.3)	3.3 (3.9)	4.5 (5.1)
UAS7	28.5 (7.1)	31.0 (6.8)	29.5 (6.9)	30.6 (7.3)	31.7 (8.5)
HSS7	13.8 (4.1)	15.3 (4.0)	14.4 (3.6)	15.0 (3.8)	15.2 (4.6)
ISS7	14.7 (3.5)	15.7 (4.3)	15.1 (3.8)	15.6 (3.6)	16.6 (4.1)
Previous experience with omalizumab (Yes; n [%])	2 (5.7%)	2 (5.6%)	0 (0%)	0 (0%)	2 (11.1%)

[1] Data shown are mean (SD), unless otherwise specified; UAS7≥28 defines severe disease activity

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Primary Endpoint Met

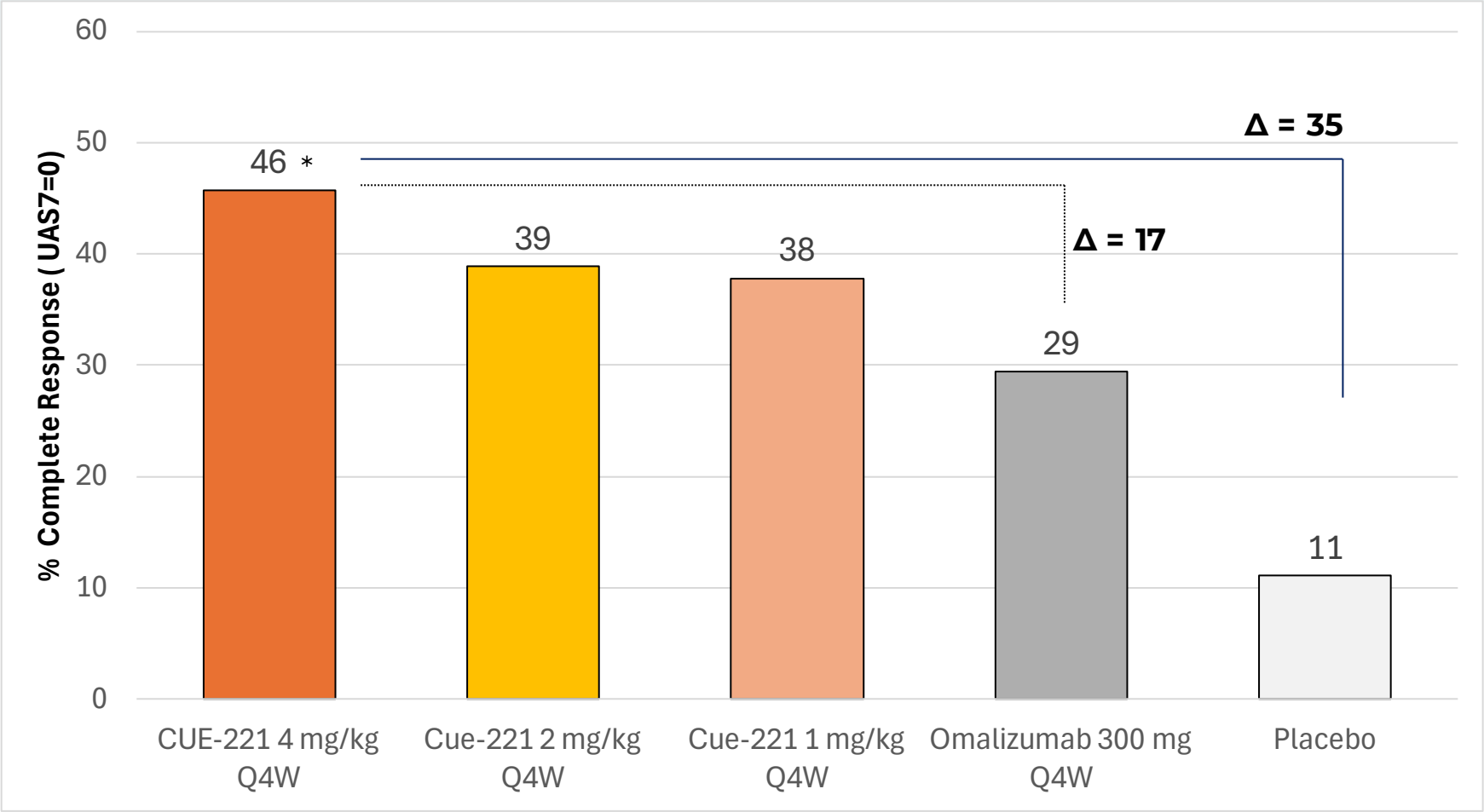
Complete Resolution of Hives (HSS7=0) at Week 12 Was Significantly Higher Versus Placebo and Dose Responsive Across CUE-221 Dose Groups



Statistical significance vs placebo: ***p <0.005; * p<0.05; The study was designed to test superiority over placebo. Omalizumab was included to enable comparative efficacy without planned statistical testing.

Key Secondary Endpoint Met

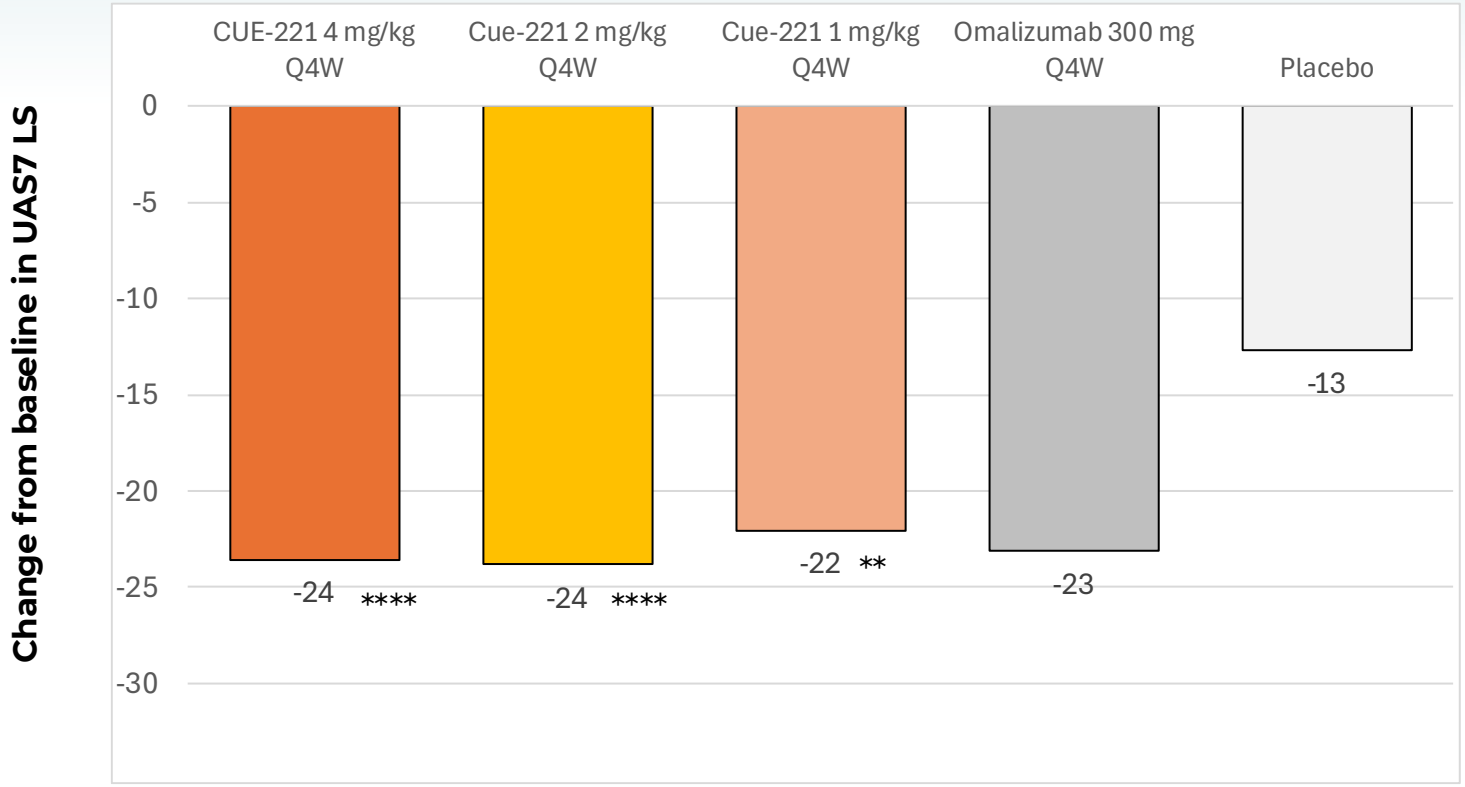
Complete Response (UAS7=0) at Week 12 was Significantly Higher Versus Placebo in the 4 mg/kg CUE-221 Dose Group



Statistical significance vs placebo: * p<0.05.

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Profound, Significant, and Clinically Meaningful Change From Baseline At Week 12 In Disease Activity Score (UAS7)

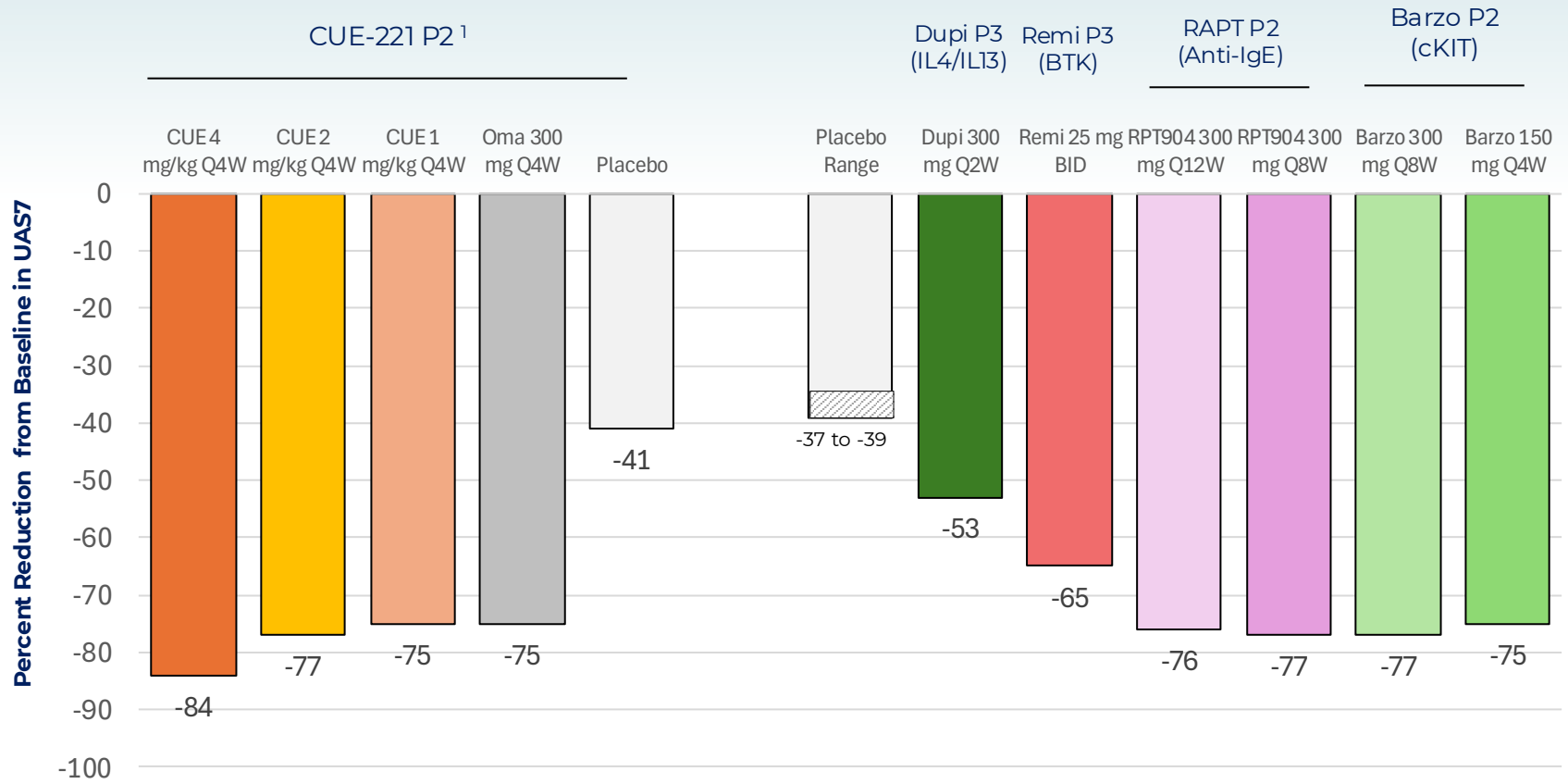


UAS7 change from baseline at week 12 was prespecified and analyzed as observed, as shown here. Post-hoc analyses using multiple imputation of the mITT population produced the same statistical conclusions.
Statistical significance vs placebo: **** p <0.001; , ** p<0.01

Level of UAS7 reduction well in excess of Minimal Clinically Important Difference of 9.5-10.5 points (Mathias et al., Ann. Allergy Asthma Immunol., 2012)

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Percent Mean Reduction From Baseline in UAS7 at Week 12 Across Mechanisms



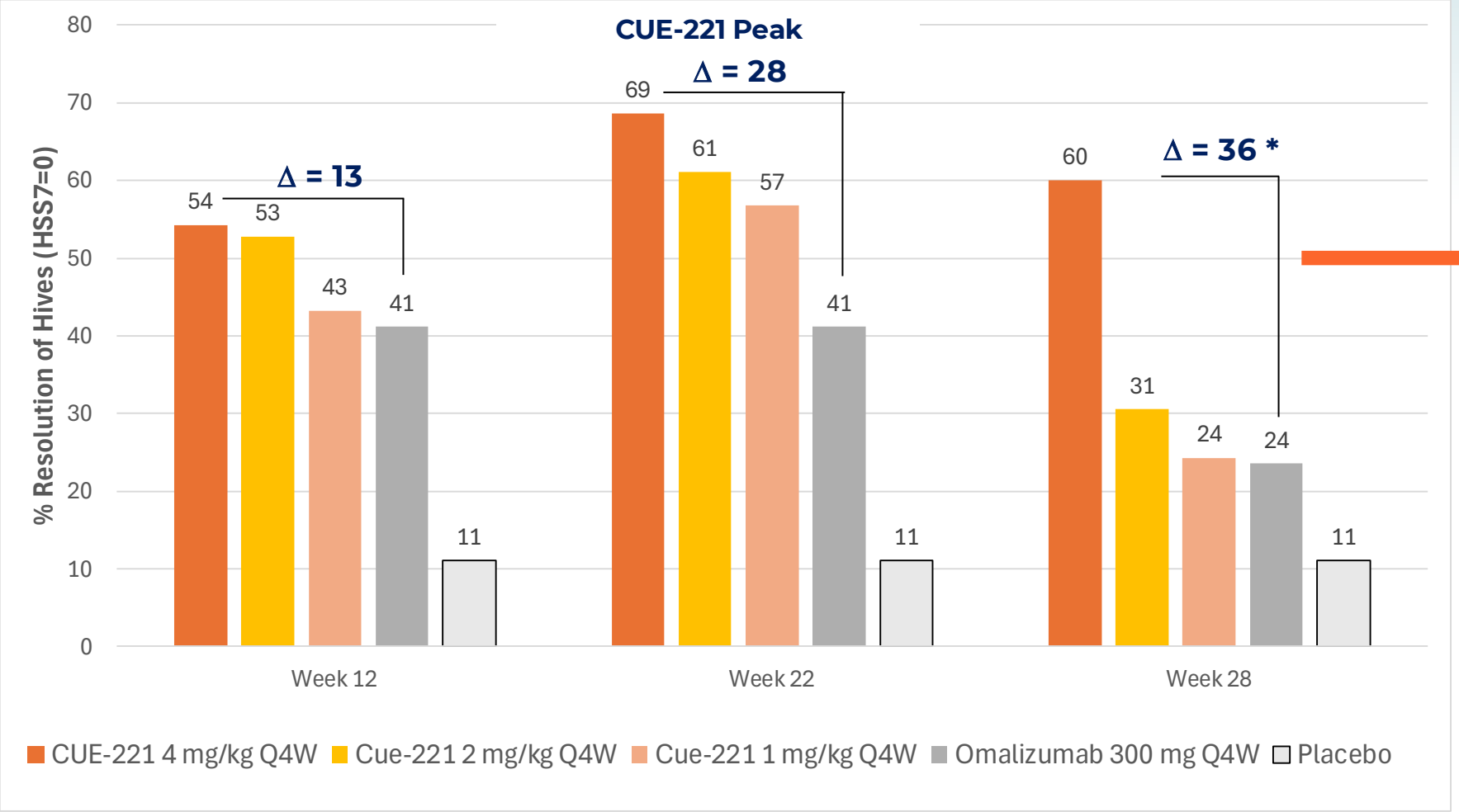
Sources: CUE-221 Data on File; Dupilumab: Mathur et al. J Allergy Clin Immunol 2024; Remibrutinib REMIX-1: Metz et al. NEJM 2025 and US Prescribing Information; RPT904: RAPT therapeutics PR 20Oct2025; Barzolvolimab: Metz et al. Allergy Clin Immunol 2026. Omalizumab ASTERIA I: Baseline UAS7 = 31.3 and change from baseline at week 12 = 21: Saini et al. J of Investigative Dermatol 2015 and US Prescribing Information.
Placebo (-37 to -39) is range across Dupilumab, Remibrutinib and Barzolvolimab trials; RPT904 P2 did not include placebo.

- Across published trials, CUE-221 comes closest to providing full control of disease activity
- Residual disease activity estimated of minimal clinical relevance

Information in this slide is derived from publicly available sources. Cross-Trial comparisons cannot be made as no head-to-head clinical trials have been conducted. Cross trial comparisons are for illustrative purposes only and should not be interpreted as direct comparisons of efficacy

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Complete Hives Resolution (HSS7=0) Continued to Increase Beyond Week 12; Most subjects on CUE-221 responded and achieved complete resolution of hives

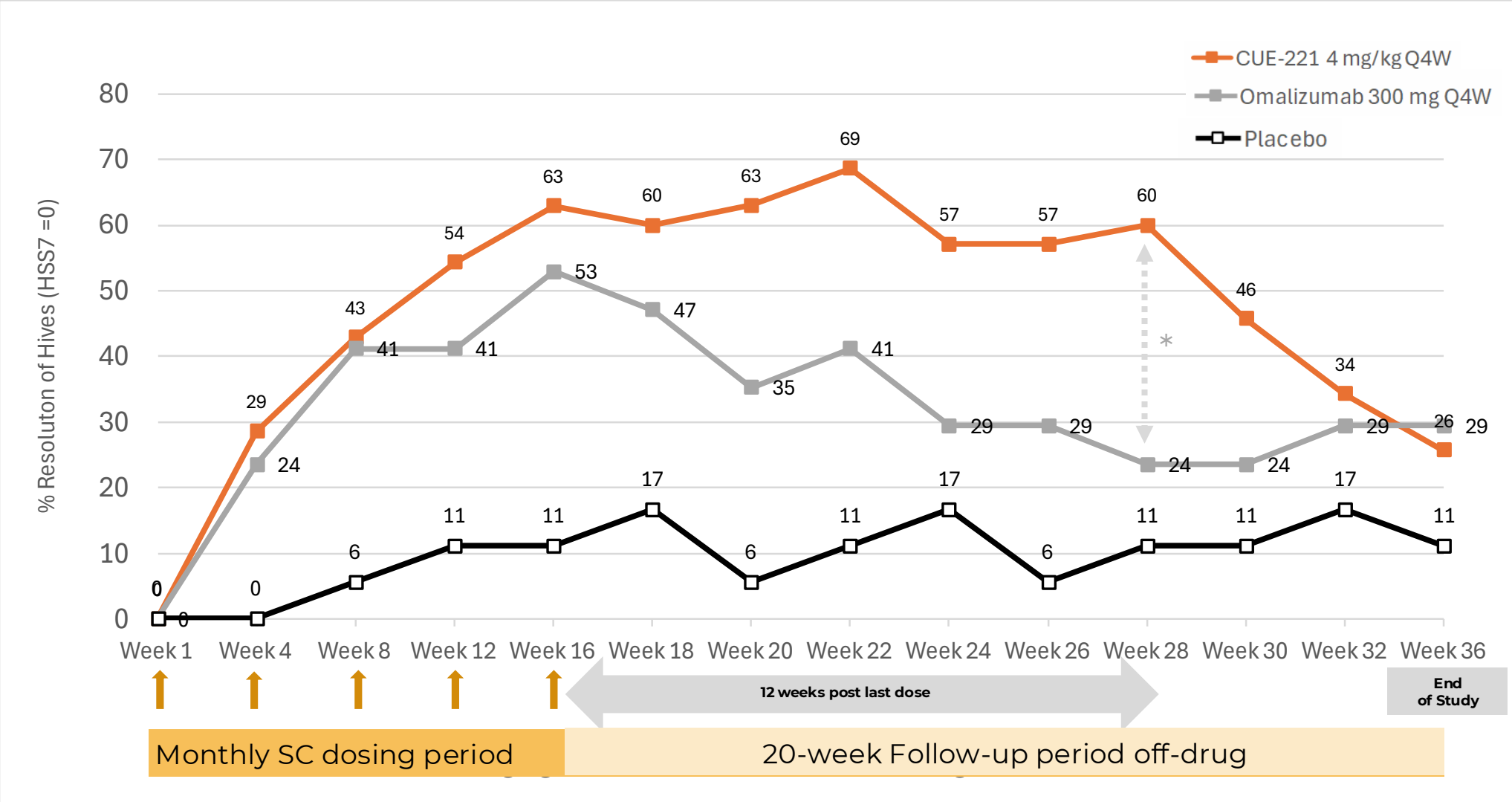


Suggests fundamental biological difference between omalizumab and CUE-221, supportive of its dual MoA design

- Completed resolution of hives peaked at week 22, which is 6 weeks after last dose
- Meaningful benefit persisted for the 4 mg/kg dose at week 28, which is 12 weeks off drug
- Week 28 rate of complete resolution of hives at the 4 mg/kg QW dose significantly higher than with omalizumab *(*; p<0.05, Fisher's exact test, post-hoc analysis)*

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Rapid and Sustained Complete Resolution of Hives Through 12 Weeks Post Last Dose (Week 28)

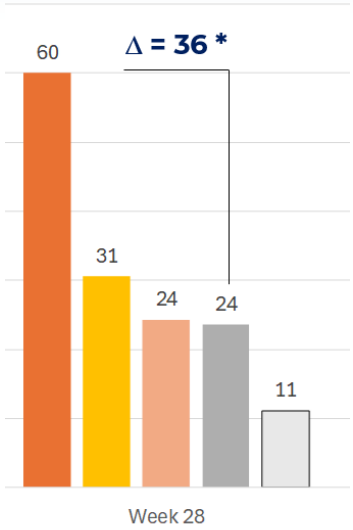


(p<0.05, Fisher's exact test, post-hoc analysis)*

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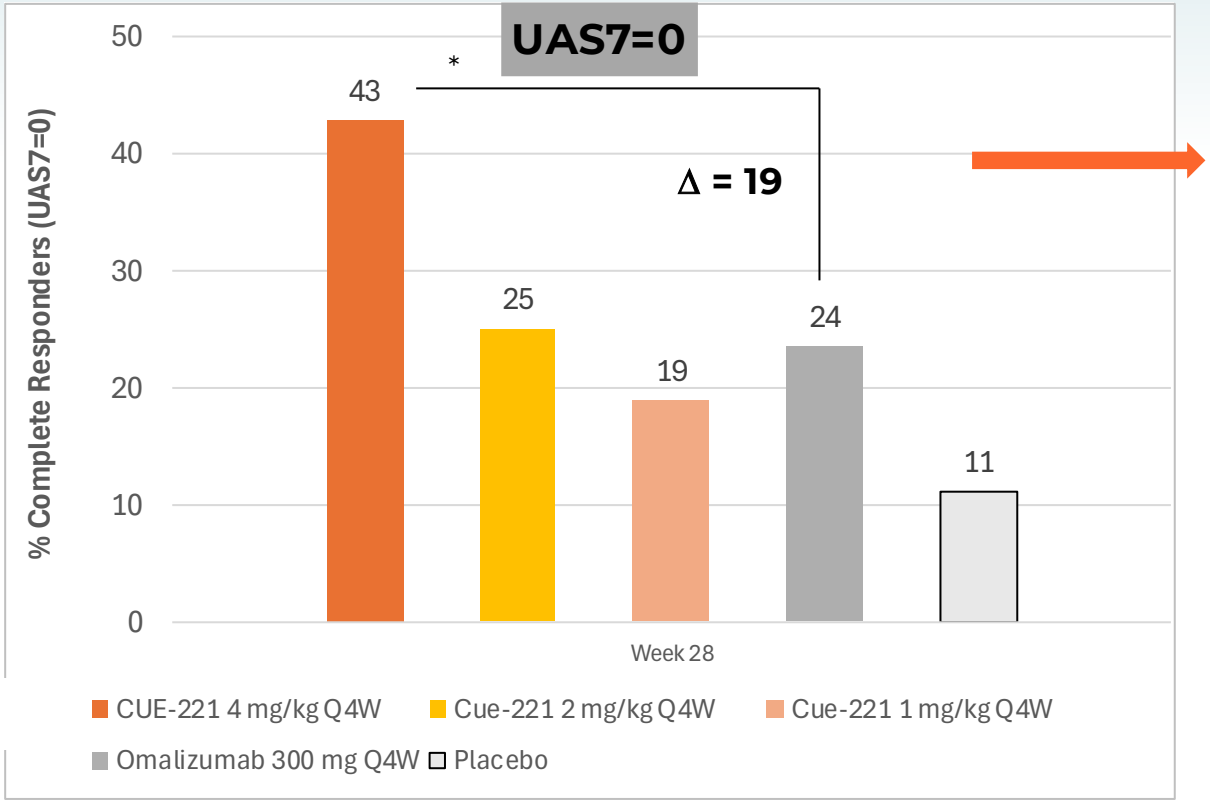
Complete Response (UAS7=0) is Also Sustained Over 12 Weeks Off Drug (Week 28) at the Highest Dose

HSS7=0



**; p<0.05, Fisher's exact test, post-hoc analysis*

UAS7=0

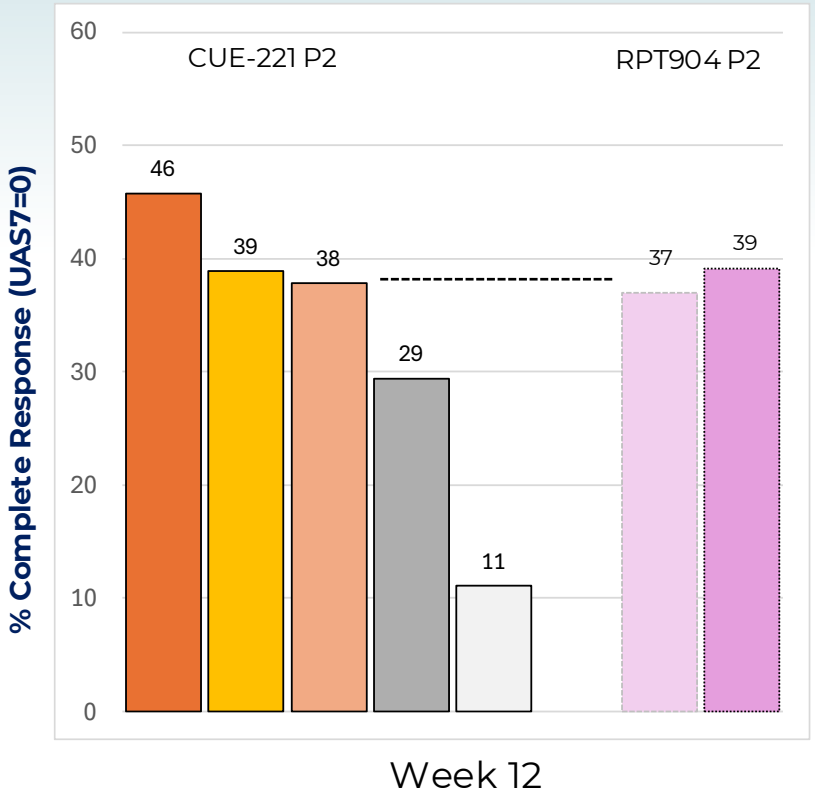


Suggests fundamental biological difference between omalizumab and CUE-221, supportive of its dual MoA design

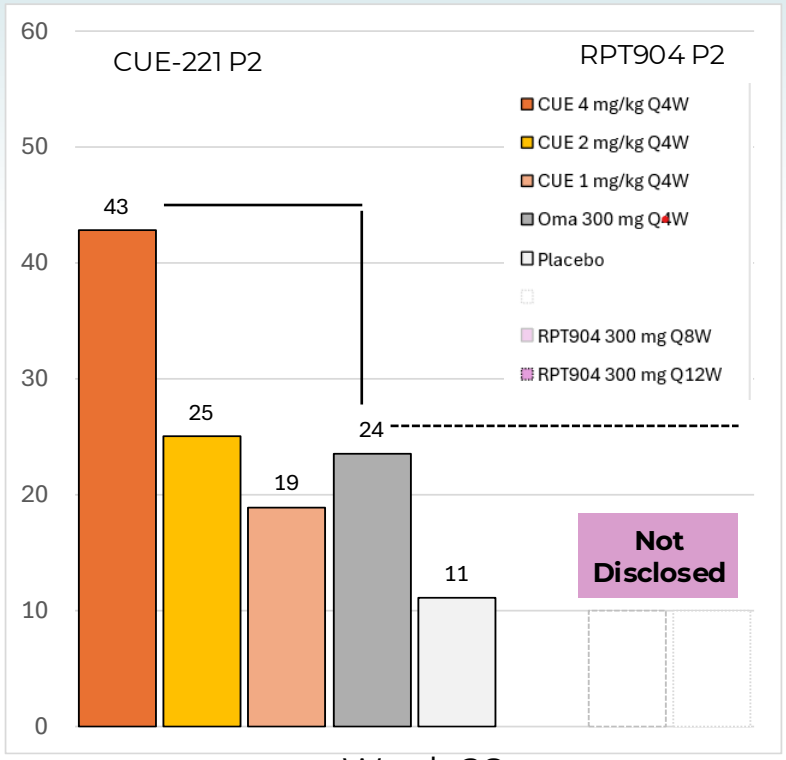
Over 90% of CUE-221 complete response by week 12 was maintained after 12 weeks off-drug at week 28

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Contrasting Features of Targeted IgE Therapies



Week 12



Week 28

- The IgE neutralizers (omalizumab/RPT904) share binding epitopes and MOA and appear to perform closer to CUE-221 low doses rather than high dose

- Impact of RPT904 at timepoints Week 28 & beyond has not been disclosed
- Week 28 data for CUE-221 support fundamental biological difference with therapeutics that are only blocking IgE

Source: CUE-221 Data on File; RPT904: RAPT therapeutics PR 20Oct2025; RPT904 P2 CSU study did not include a placebo group.

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CUE-221 Was Well Tolerated

No treatment related SAEs

No adverse events of anaphylaxis

Treatment group n (%)	CUE-221 Q4W 4 mg/kg N=35	CUE-221 Q4W 2 mg/kg N=36	CUE-221 Q4W 1 mg/kg N=37	Omalizumab Q4W 300 mg N=17	Placebo N=18
Any TEAE					
Treatment Related	15 (42.9%)	17 (47.2%)	12 (32.4%)	4 (23.5%)	11 (61.1%)
Treatment-related SAE	0(0)	0(0)	0(0)	0(0)	0(0)
Treatment-related AESI					
Anaphylaxis	0(0)	0(0)	0(0)	0(0)	0(0)
Serum Sickness	0(0)	0(0)	0(0)	0(0)	0(0)
Injection Site Reactions	0(0)	1 (2.8%)[1]	0(0)	0(0)	0(0)
Treatment-related AE leading to study discontinuation	0(0)	1 (2.8%)[2]	1 (2.7%)[3]	0(0)	0(0)
TEAE leading to death	0(0)	0(0)	0(0)	0(0)	0(0)

TEAE: treatment-emergent adverse event; SAE = Serious adverse event; AESI: Adverse event of special interest.
[1] ISR > Grade 1; [2] Worsening of urticaria; [3] Insomnia.

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Risk/Benefit Considerations Across Different MOAs

	XOLAIR® (omalizumab)	DUPIXENT® (dupilumab)	RHAPSIDIO® (remibrutinib)	Barzolvolimab (investigational)
MOA	Anti-IgE mAb	Anti-IL4/IL13 mAb	Oral selective BTK inhibitor	Anti-KIT mAb
Key Warnings/ Precautions	Anaphylaxis (boxed warning) Malignancy	Hypersensitivity reactions	Risk of bleeding; Avoid live attenuated vaccines	n/a
Notable mechanism related safety	--	Conjunctivitis/keratitis, eosinophilic conditions; helminth infection	Bleeding risk; CYP3A4 drug interactions	Hair and skin hypopigmentation ; Decrease in sperm count (preclinical studies)

Sources: Omalizumab: US Prescribing Information; Dupilumab US Prescribing Information; Remibrutinib US Prescribing Information; Barzolvolimab: Metz et al. Allergy Clin Immunol 2026.

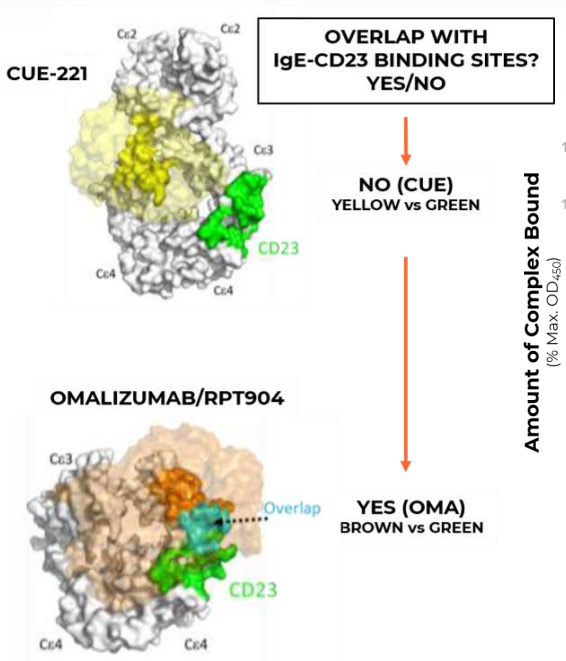
Broad Interest For the Field of Allergy and IgE-Mediated Disease
Additional MOAs in Earlier Stage Development without Validated Safety and Efficacy Profiles

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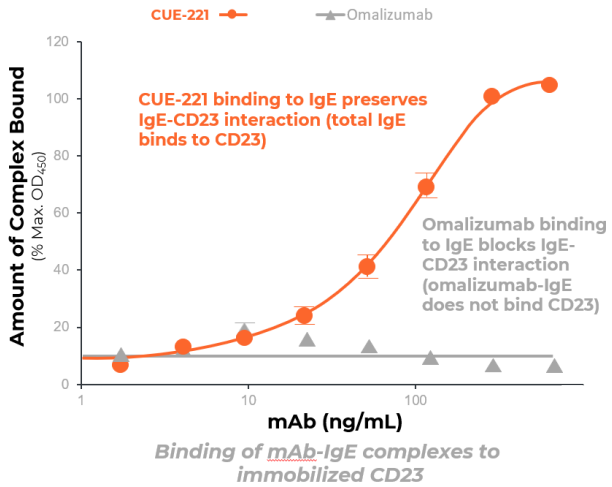
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Targeting Potential for Functional Cure of IgE-Mediated Disease

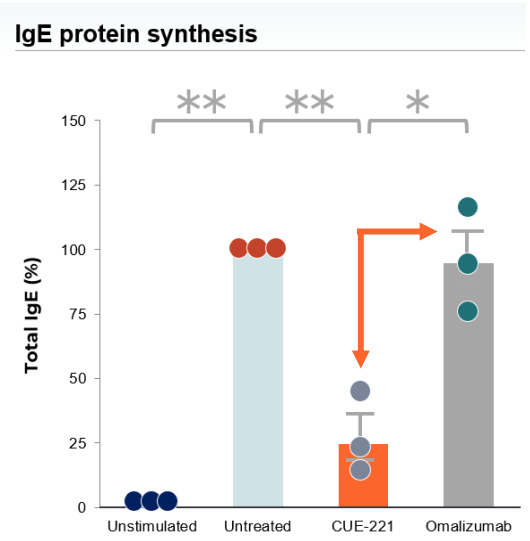
CUE-221 BINDING SITE DIFFERS FROM OMALIZUMAB



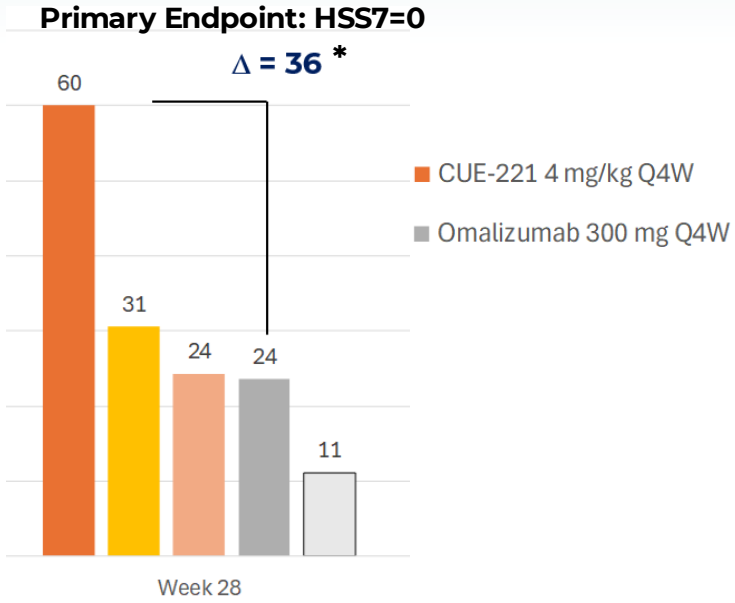
CUE-221 DOES NOT PREVENT IgE:CUE-221 COMPLEXES FROM BINDING CD23



MAINTAINED CD23 NEGATIVE FEEDBACK LOOP RESULTS IN REDUCED IgE SYNTHESIS



CONTRASTING CLINICAL IMPACT 3-MONTH OFF DRUGS POINTS TO FUNDAMENTAL BIOLOGICAL DIFFERENCE



- The P2 CSU trial results provide the first clinical evidence supportive of CUE-221's engineered dual MOA and indicates mechanism(s) beyond IgE neutralization
- If reduced IgE synthesis is demonstrated, disease modification and functional cure could follow IgE eradication
- Active investigation of PK/PD relationships is ongoing with plans to present complete results at future medical conferences

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Positive Results from CUE-221 Phase 2 CSU Study Demonstrate Robust and Durable Clinical Benefit

- **Robust Dose-Responsive Results** supported by primary endpoint and key secondary endpoint met with statistical significance
- **Favorable Safety and Tolerability** without hypersensitivity reactions (anaphylaxis)
- **Clinical evidence Supportive of Dual MOA** indicative of both IgE blocking and prevention of new IgE production
- **Path to IgE Eradication** can be envisioned which could result in functional cure for IgE-mediated disease
- **Demonstrated Differentiated Clinical Effects** supports implementing a broad approach to IgE mediated disease, starting with registration-enabling trials in CSU and P2 in food allergy

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