

KT-621, an Oral STAT6 Degradar, in Patients With Moderate-to-Severe Atopic Dermatitis and Comorbid Asthma or Allergic Rhinitis: Safety and Evidence of Clinical Activity Across Type 2 Inflammatory Diseases in a Phase 1b Trial

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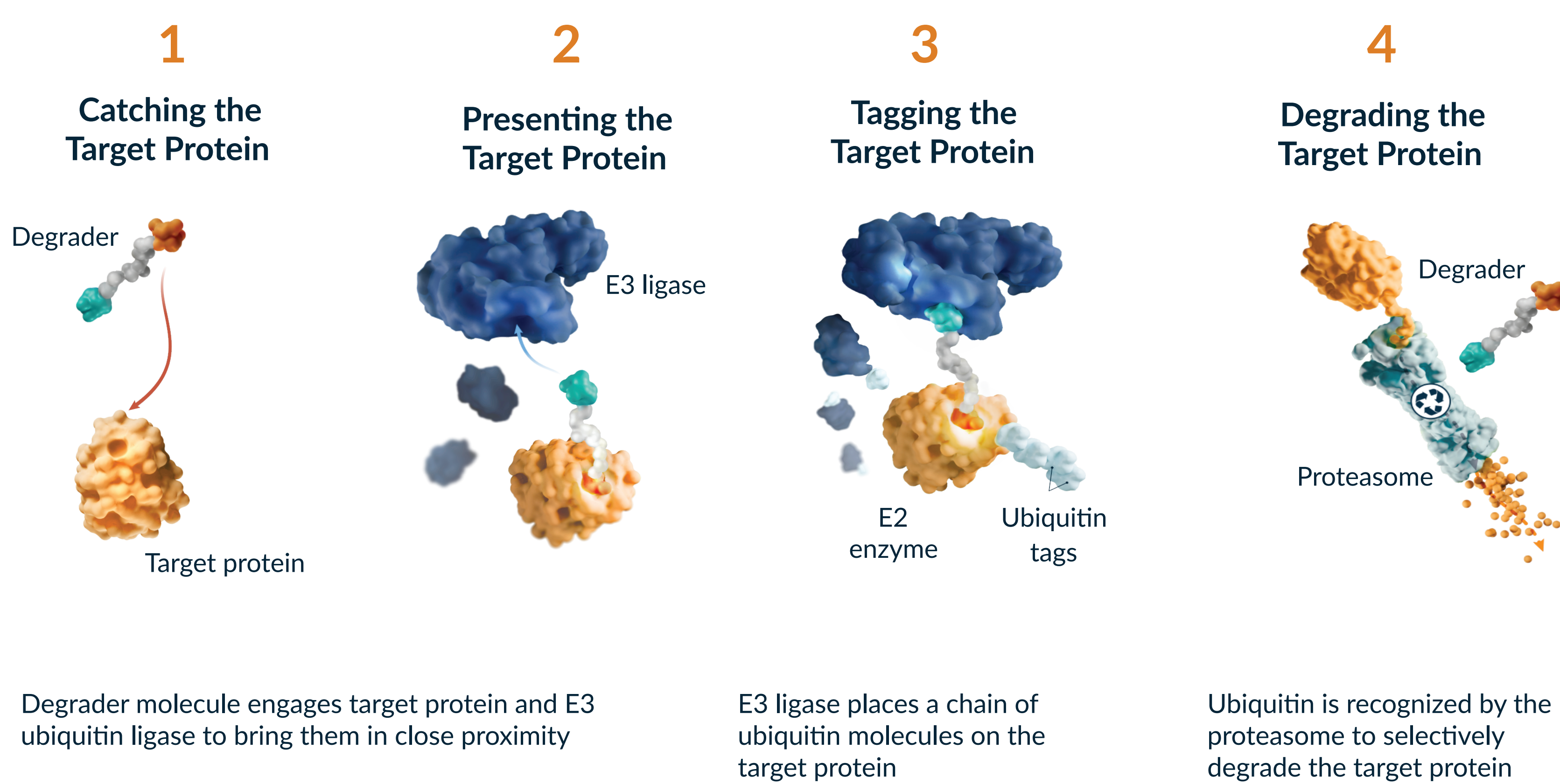
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INTRODUCTION

- Asthma and allergic rhinitis are common comorbidities in patients with atopic dermatitis (AD), driven by Type 2 inflammation and IL-4/IL-13-STAT6 signaling¹
- Although biologics targeting the IL-4/IL-13 pathway have transformed the treatment of Type 2 inflammatory diseases, a need remains for safe and well-tolerated oral therapies capable of delivering broad and consistent disease control¹

Figure 1. Targeted Protein Degradation (TPD): Achieving Biologics-Like Activity With Oral Medicines²

TPD Mechanism of Action: Harnessing the E3 Ubiquitin Proteasome System



Catalytic activity of degraders enables a single molecule to drive degradation of multiple copies of the target protein, delivering deep and continuous pathway blockade with biologics-like activity²

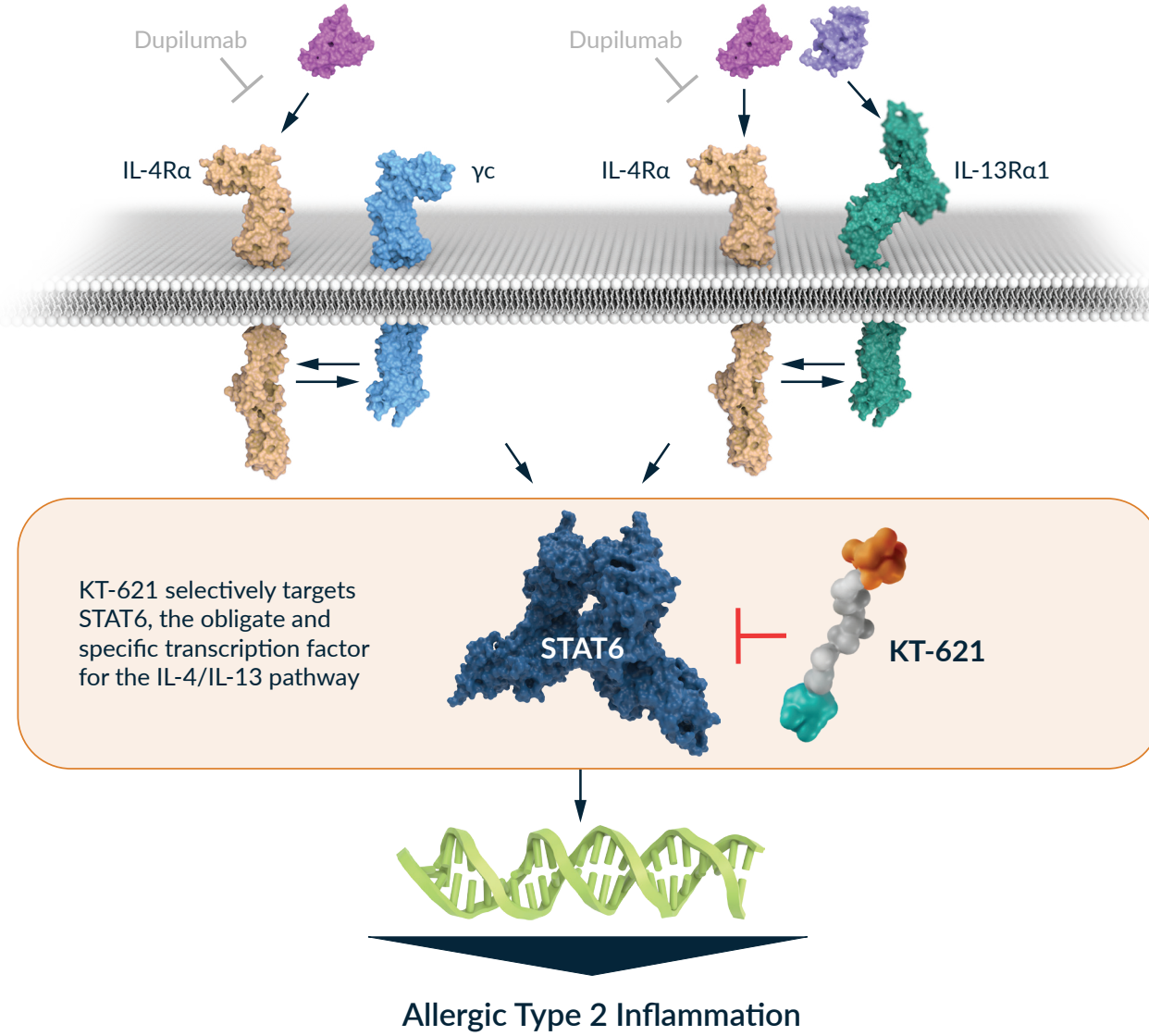
Figure 2. STAT6: Highly Validated, Historically Undrugged Target for Treatment of Type 2 Inflammatory Diseases³

STAT6 Transcription Factor

- STAT6 is the clinically validated transcription factor in the IL-4/IL-13 pathway³⁻⁵
- IL-4/IL-13 is clinically validated by dupilumab across multiple Type 2 diseases:
 - AD, asthma, COPD, EoE, CRSwNP, CSU, PN, BP¹
- While several therapies target the upstream IL-4/IL-13 receptors, there are no known drugs that selectively target this pathway with oral delivery¹

KT-621: First-In-Class, Oral, Once-Daily, STAT6 Degradar

- In a first-in-human Phase 1a study in healthy volunteers, KT-621 demonstrated deep STAT6 degradation in blood and skin following low daily oral doses, reductions of multiple disease-relevant Type 2 biomarkers, and a safety profile undifferentiated from placebo⁶



AD, atopic dermatitis; BP, bullous pemphigoid; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; CSU, chronic spontaneous urticaria; EoE, eosinophilic esophagitis; yc, gamma chain; IL, interleukin; PN, prurigo nodularis; STAT6, signal transducer and activator of transcription 6.

METHODS

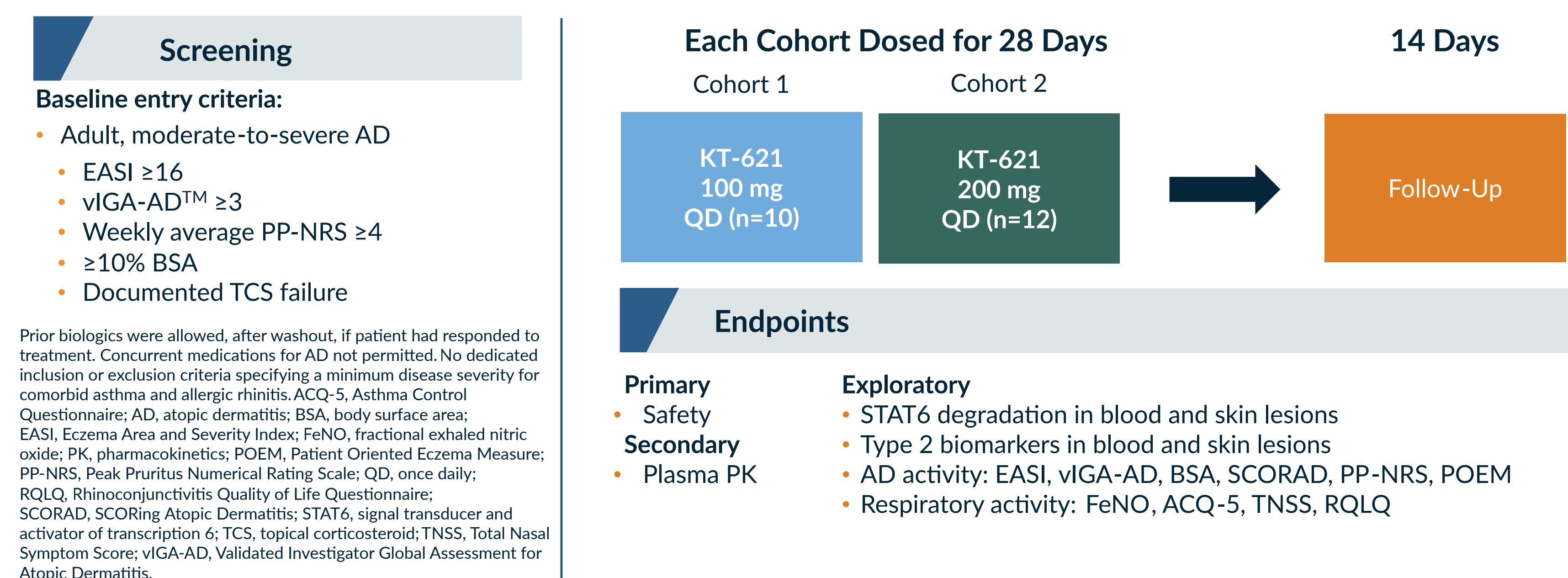
Study Design and Population

- This open-label, multicenter, single-arm Phase 1b study evaluated the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of oral KT-621 in adults with moderate-to-severe AD
- Relevant biomarker and clinical endpoints were evaluated in the subgroup of patients with AD and comorbid asthma or allergic rhinitis

DISCLOSURES

Michael B. Feldman, Jared Gollob, Kelvin Shi, Sagar Agarwal, Neil Graham, and Nello Mainolfi are employees with shares and stock options of Kymera Therapeutics, Inc. Joyoti Day is a former employee of Kymera Therapeutics, Inc.

Figure 3. KT-621 BroADen Phase 1b Study Design



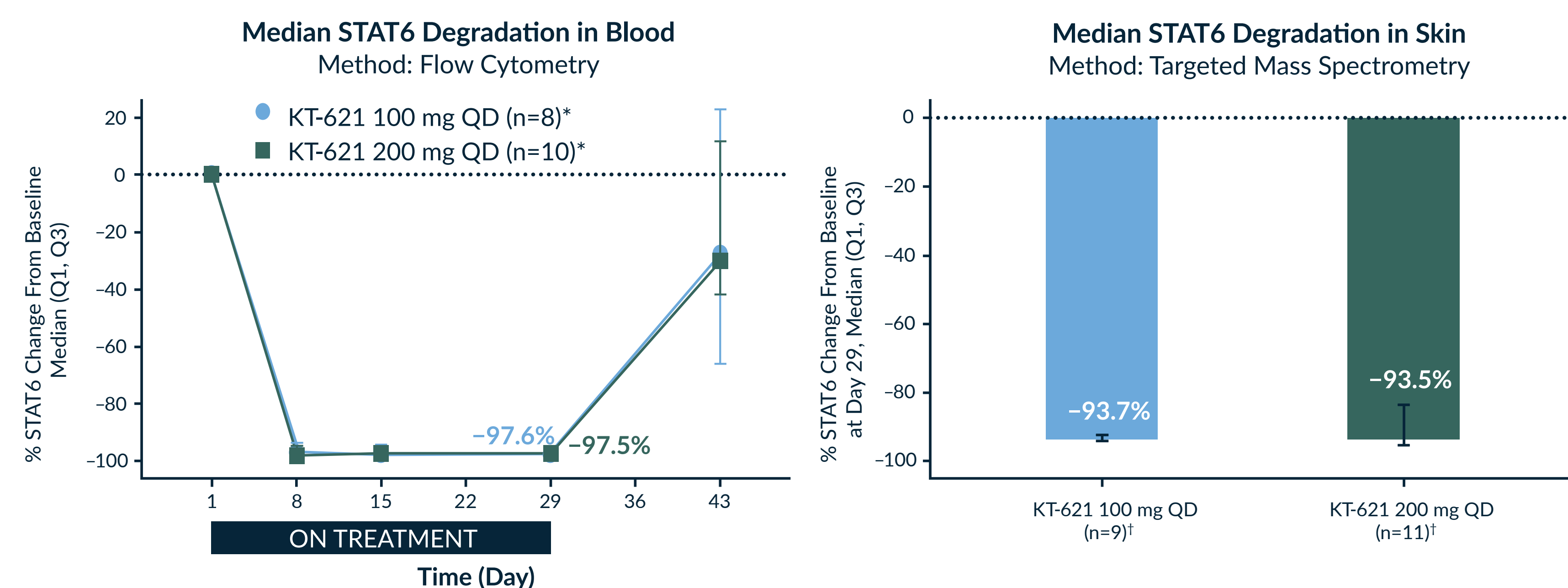
RESULTS

Table 1. Baseline Characteristics Were Well Balanced Between Dose Cohorts

Patient Baseline Characteristics	100 mg (n=10)	200 mg (n=12)	Overall (n=22)
vIGA-AD™, n (%)			
Moderate (3)	6 (60.0)	6 (50.0)	12 (54.5)
Severe (4)	4 (40.0)	6 (50.0)	10 (45.5)
EASI Score, mean (SD)	23.5 (7.5)	26.1 (9.0)	24.9 (8.3)
Comorbid Type 2 Diseases, n (%)			
Asthma	1 (10.0)	3 (25.0)*	4 (18.2)
Allergic Rhinitis	2 (20.0)	7 (58.3)	9 (40.9)
Comorbid Asthma Baseline Clinical Characteristics	100 mg (n=1)	200 mg (n=3)	Overall (n=4)
Baseline FeNO (ppb), median (range)	12.0 (-)	47.0 (37.0-98.0)	42.0 (12.0-98.0)
Baseline ACQ-5, mean (SD)	3.00 (-)	2.33 (0.81)	2.50 (0.74)
Comorbid Allergic Rhinitis Baseline Clinical Characteristics	100 mg (n=2)	200 mg (n=7)	Overall (n=9)
Baseline TNSs, mean (SD)	2.00 (2.83)	3.86 (3.08)	3.44 (2.96)
Baseline RQLQ, mean (SD)	1.29 (1.72)	1.71 (1.59)	1.62 (1.52)

ACQ-5, Asthma Control Questionnaire; BMI, body mass index; BSA, body surface area; EASI, Eczema Area and Severity Index; FeNO, fractional exhaled nitric oxide; POEM, Patient Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; TNSs, Total Nasal Symptom Score; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.
*The three patients also had comorbid allergic rhinitis. *All patients were on an inhaled β -agonist; 1 patient was also on an inhaled corticosteroid.

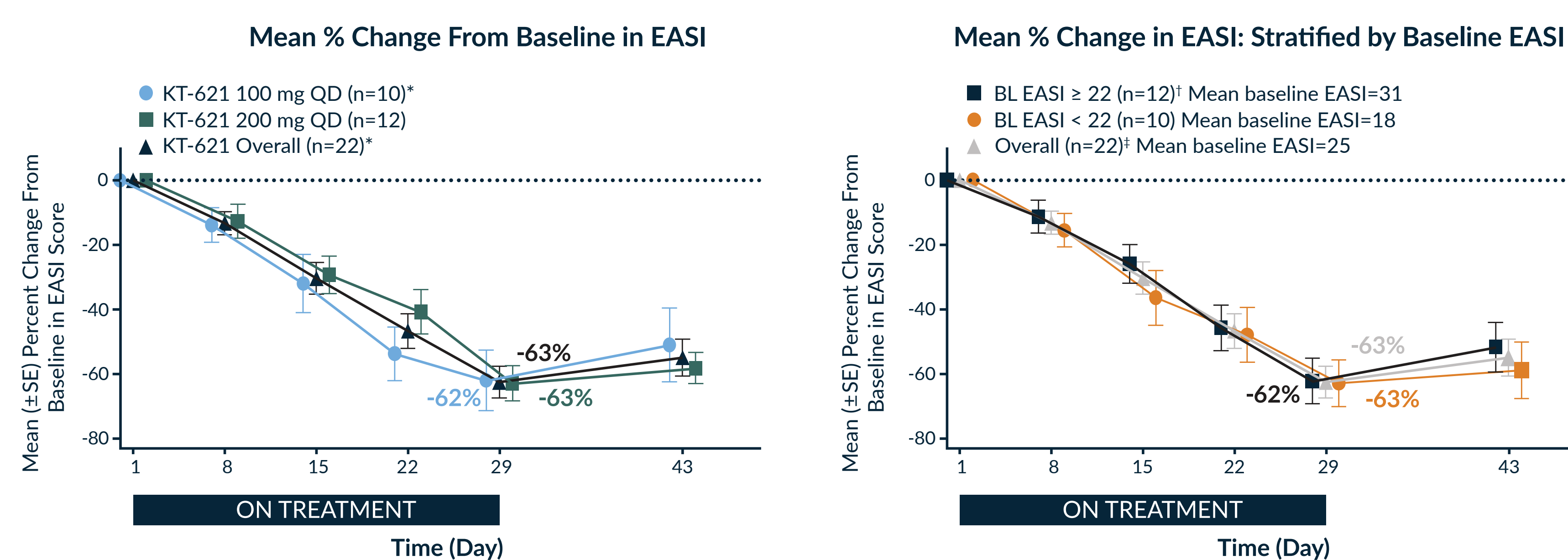
Figure 4. KT-621 Achieved Deep STAT6 Degradation in Blood and Skin



Q1, lower quartile; Q3, upper quartile; QD, once daily; STAT6, signal transducer and activator of transcription 6, n values reflect the number of participants with available samples at Day 29. *Two patients (one each in 100 mg and 200 mg dose groups) did not have baseline samples collected, and two Day 29 samples (one in each dose group) were unavailable due to shipping issues that led to loss of stability. *Two patients (one in each dose group) did not consent to Day 29 biopsies.

- Median STAT6 degradation of 98% in blood was maintained through Day 29 in both dose cohorts
- Median STAT6 degradation of 94% in skin was observed in both dose cohorts, with STAT6 levels below the lower limit of quantification in multiple patients

Figure 5. KT-621 Achieved Mean EASI Reduction of Up to 63% by Week 4



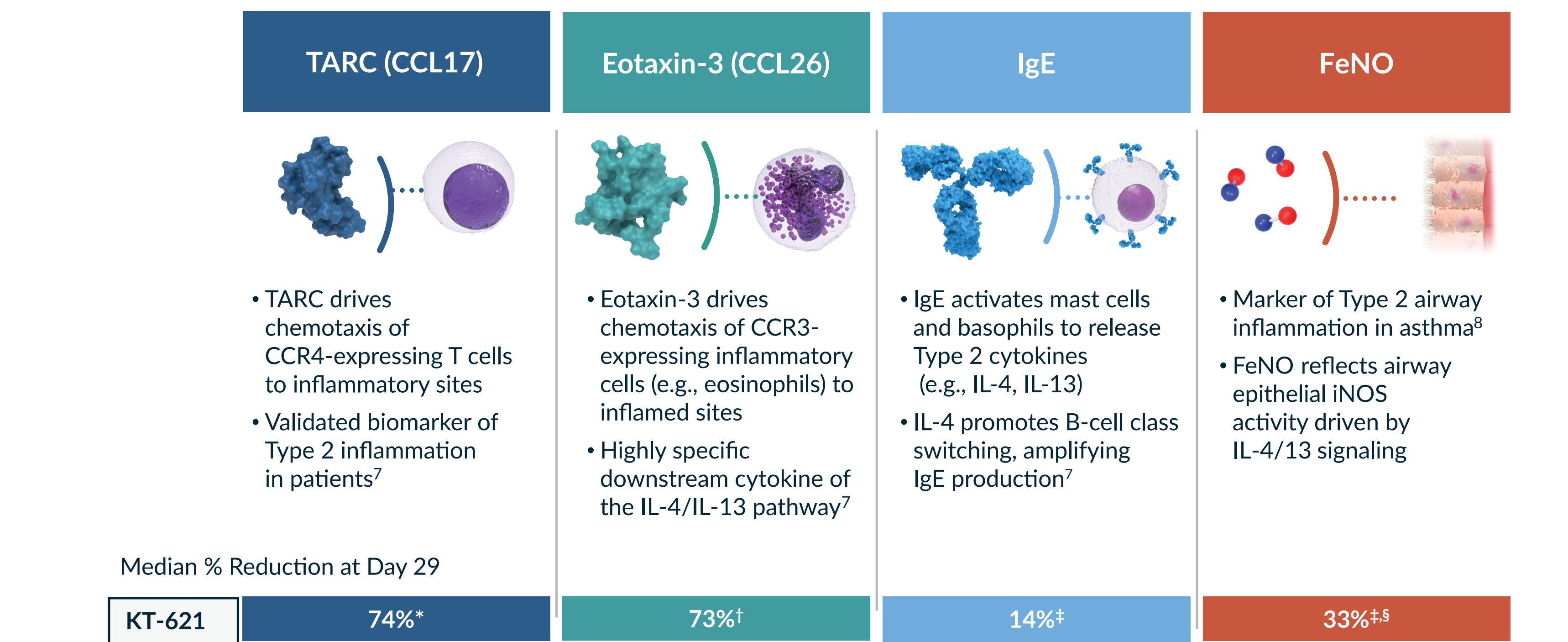
BL, baseline; EASI, Eczema Area and Severity Index; QD, once daily; SE, standard error.

Analysis based on observed cases at each visit.

*One patient in the 100 mg cohort missed the Day 29 visit (n=9 for 100 mg and n=21 for Overall at Day 29). *n=11 at Day 29. *n=21 at Day 29.

- Rapid and robust mean EASI reductions were observed in both dose cohorts without apparent plateau after 4 weeks
- Magnitude of EASI reduction was similar across the full range of baseline EASI scores

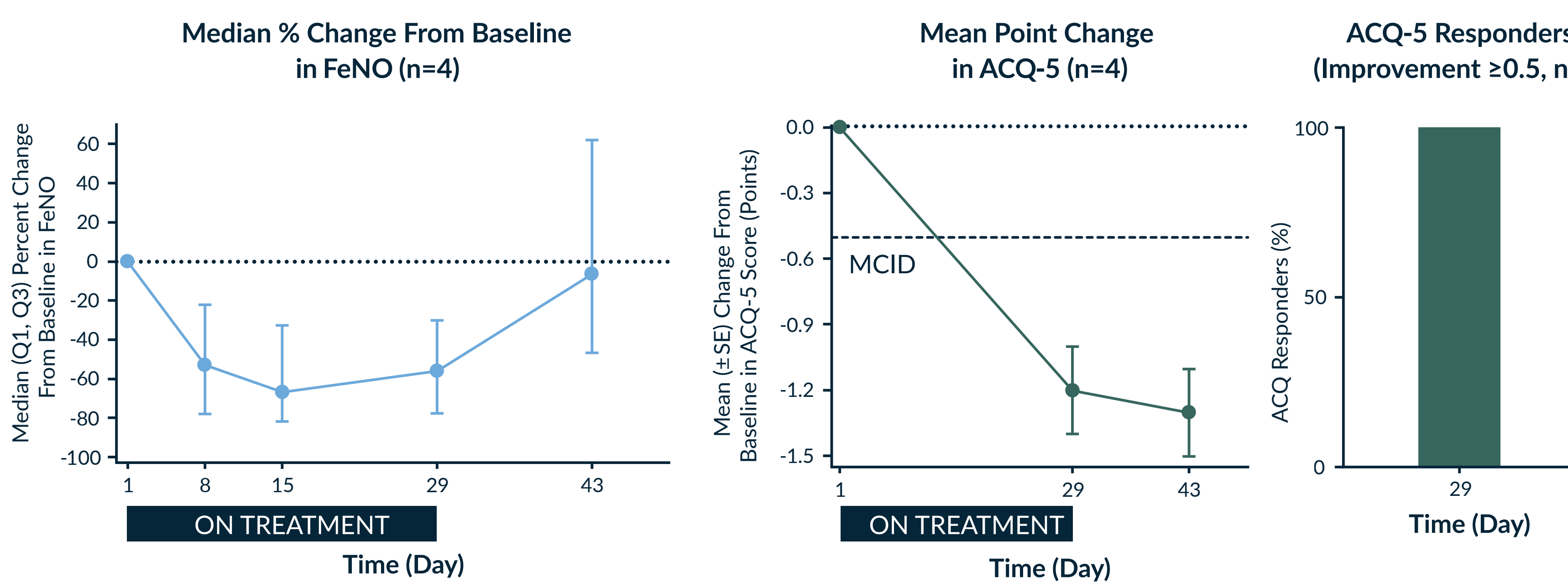
Figure 6. Impact on All Disease-Relevant Biomarkers of Type 2 Inflammation in BroADen Phase 1b AD Trial (total study population)



AD, atopic dermatitis; CCL, C-C motif chemokine ligand; CCR, C-C chemokine receptor; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; iNOS, inducible nitric oxide synthase; TARC, thymus and activation-regulated chemokine.
*Represents TARC reduction in patients with elevated baseline TARC levels, defined as the lower bound of the 95% confidence interval for median baseline TARC levels from the dupilumab SOLO1 and 2 AD studies. *KT-621 200 mg (n=11). *KT-621 200 mg (n=12). *Median (range) baseline FeNO=20.0 (6.0-98.0).

- Broad suppression of disease-relevant Type 2 inflammatory biomarkers, consistent with systemic STAT6 pathway blockade

Figure 7. KT-621 Reduced FeNO and ACQ-5 in Patients With AD and Comorbid Asthma

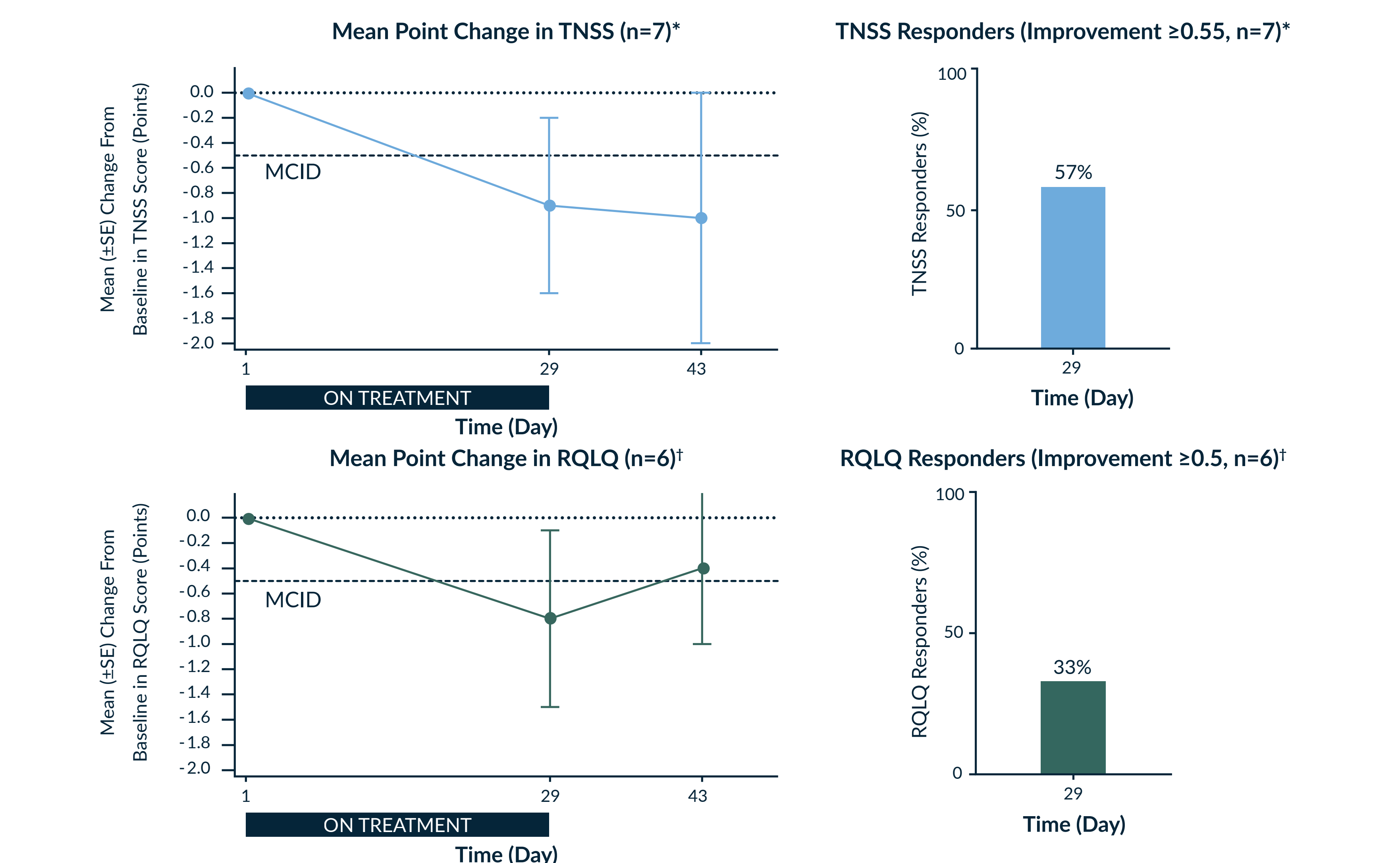


AD, atopic dermatitis; ACQ-5, Asthma Control Questionnaire; FeNO, fractional exhaled nitric oxide.

Note: Analysis based on observed cases at each visit for the overall cohort: Mean baseline FeNO of 49 ppb and ACQ-5 of 2.5.

- KT-621 achieved 56% median FeNO reduction at Day 29, exceeding dupilumab (31%) in asthma studies at week 4⁷
- All 4 patients had a clinically meaningful reduction in ACQ-5 (mean change of -1.2 points) and a 100% responder rate

Figure 8. KT-621 Improved TNSs and RQLQ in Patients With AD and Comorbid Allergic Rhinitis



AD, atopic dermatitis; MCID, minimum clinically important difference; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; TNSs, Total Nasal Symptom Score.
Note: Analysis based on observed cases at each visit for the overall cohort.
*Only patients with baseline TNSs score ≥0.55 are included. *Only patients with baseline RQLQ score ≥0.5 are included; Mean baseline TNSs and RQLQ of 4.4 and 2.4, respectively.

- At Day 29, KT-621 achieved mean changes of -0.9 and -0.8 points in TNSs and RQLQ, respectively, surpassing the MCID
- TNSs and RQLQ responder rates were 57% and 33%, respectively

KT-621 Phase 1b Safety Summary

- Well-tolerated with favorable safety at both 100 mg and 200 mg doses
- No serious adverse events (AEs) or severe AEs
- No dose-dependent pattern in TEAEs
- No related TEAEs or TEAEs leading to discontinuation
- No AEs of conjunctivitis (or of any ocular disorder), herpes infections, or arthralgias
- No clinically relevant changes in vital signs, laboratory tests, or ECGs

CONCLUSIONS

- Patients with AD and comorbid asthma or allergic rhinitis showed evidence of improved disease control, with clinically meaningful improvements in FeNO and ACQ-5 (asthma) and TNSs and RQLQ (allergic rhinitis) after 4 weeks of KT-621 treatment
- Clinical improvements were accompanied by deep STAT6 degradation in blood and skin and broad suppression of Type 2 inflammatory biomarkers, consistent with the proposed mechanism of action
- KT-621 was well tolerated at both dose levels, supporting further evaluation of STAT6 degradation as a potential therapeutic approach across Type 2 inflammatory diseases

KT-621 CLINICAL DEVELOPMENT PROGRAM

- BREADTH is an ongoing randomized, double-blind, placebo-controlled, parallel-group, dose-ranging Phase 2b trial in patients with moderate-to-severe eosinophilic asthma
 - Approximately 264 patients will be randomized 1:1:1 to three KT-621 dose groups or placebo for 12 weeks, with a 52-week open-label extension
 - The primary endpoint is the change from baseline in forced expiratory volume in 1 second (FEV₁); data are expected late 2027

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