Revolutionizing Immunology with Oral Medicines

Michael Feldman, MD, PhD
Executive Medical Director
Kymera Therapeutics

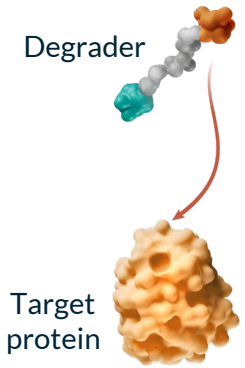
ATS Annual Meeting, Respiratory Innovation Summit | May 2026

Targeted Protein Degradation: Achieving Biologics-like Activity with Oral Medicines

Targeted Protein Degradation (TPD) Mechanism of Action

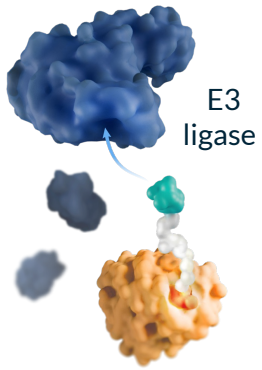
Harnessing the E3 Ubiquitin Proteasome System

1 Catching the Target Protein

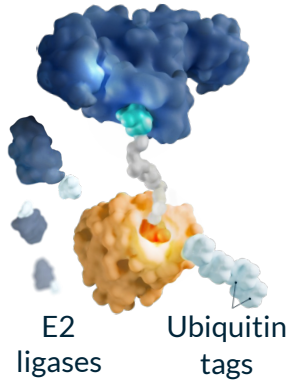


Degrader molecule engages target protein and E3 ubiquitin ligase to bring them in close proximity

2 Presenting the Target Protein

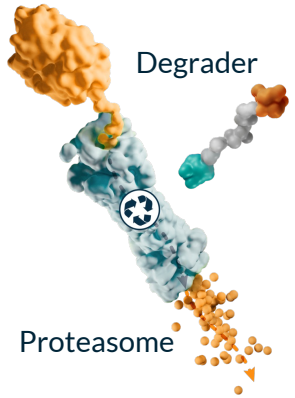


3 Tagging the Target Protein



E3 ligase places a chain of ubiquitin molecules on the target protein

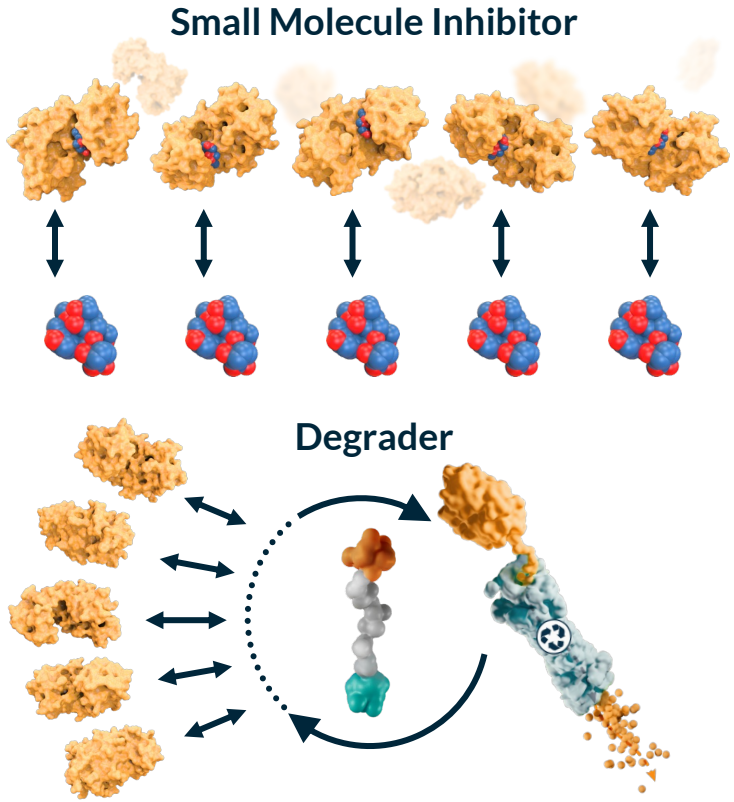
4 Degrading the Target Protein



Ubiquitin is recognized by the proteasome to selectively degrade the target protein

Degraders Enable Continuous, Complete Pathway Blockade

Superior to Traditional Small Molecule Inhibitors



STOICHIOMETRIC INHIBITION

Pharmacodynamic effect (PD) correlated to drug exposure pharmacokinetics (PK) (stoichiometric) requiring continuous high drug exposures to block protein function[1]

CONTINUOUS DEGRADATION

PD not directly correlated to PK (catalytic), allowing fast, complete protein elimination and continuous pathway blockade with low/short drug exposures

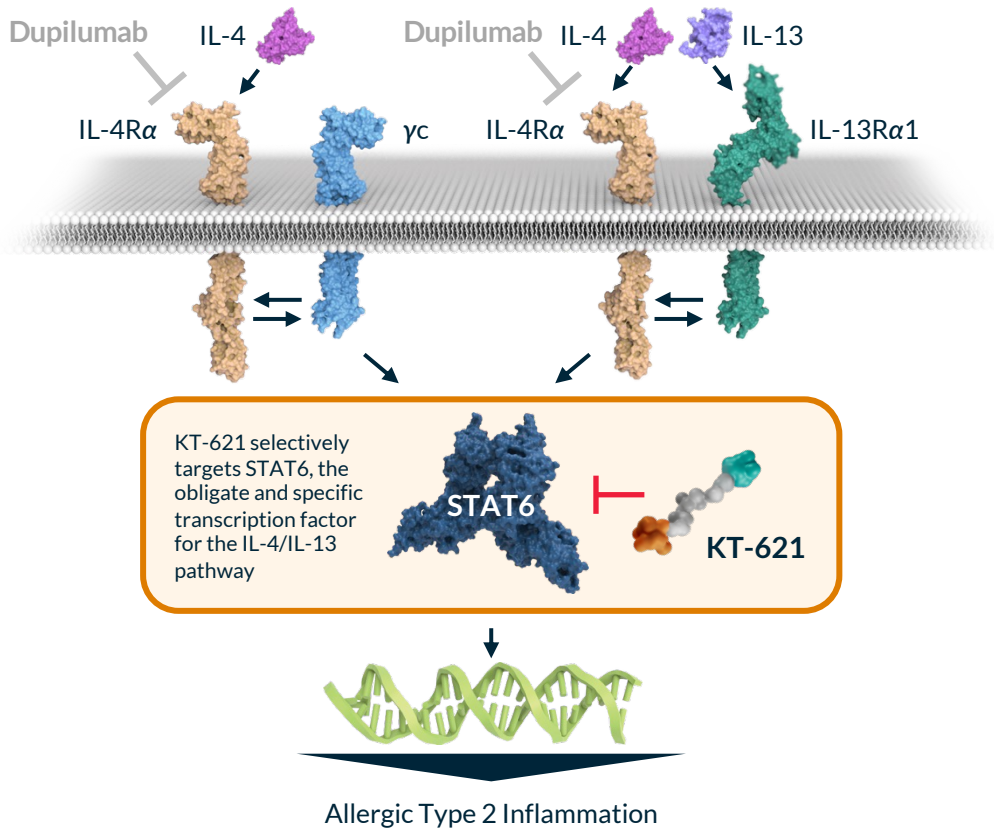
Catalytic activity of degraders enables a single molecule to drive degradation of multiple copies of the target protein, delivering deep and continuous pathway blockade with biologics-like activity in a pill

1. Mainolfi N, Rasmusson T. *Annual Reports Med Chem.* 2017;50:301-334; PD, pharmacodynamics; PK, pharmacokinetics; TPD, targeted protein degradation.

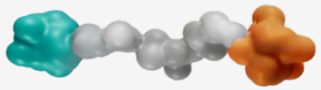
STAT6: Highly Validated, Historically Undrugged Target for the Treatment of Type 2 Inflammatory Diseases

STAT6
TRANSCRIPTION FACTOR

- STAT6 is the specific transcription factor in the IL-4/IL-13 pathway[1-3]
- IL-4/IL-13 is clinically validated by dupilumab across multiple Type 2 diseases[4]
- STAT6 is genetically validated by human GoF and heterozygous LoF alleles, and mouse knockout phenotype[1,5]
- There are no known approved drugs that selectively target this pathway with oral delivery[4]



KT-621
FIRST-IN-CLASS ORAL STAT6 DEGRADER[6]



- Provides complete STAT6 degradation selectivity in human PBMC proteome at 100 x DC_{90} and picomolar potency across all disease-relevant cell types
- Fully blocks IL-4/IL-13 pathway in human Type 2 functional assays and in vivo models
- Phase 1 healthy volunteer trial 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 placebo

1. Kaplan MH, et al. *Immunity.* 1996;4:313-319; 2. Takeda K, et al. *J Immunol.* 1996;157(8):3220-3222; 3. Junttila IS. *Front Immunol.* 2018;9:888; 4. Kolkhir P, et al. *Nat Rev Drug Discov.* 2023;22(9):743-767; 5. Sharma M, et al. *J Exp Med.* 2023;220(5):e20221755; 6. Shabbir A, et al. European Academy of Dermatology and Venereology Congress; Sept 17–20, 2025; Paris, France; γc, gamma chain; GoF, gain of function; IL, interleukin; LoF, loss of function; PBMC, peripheral blood mononuclear cells; STAT6, signal transducer and activator of transcription 6.

KT-621 Achieved Deep STAT6 Degradation in Blood and Skin

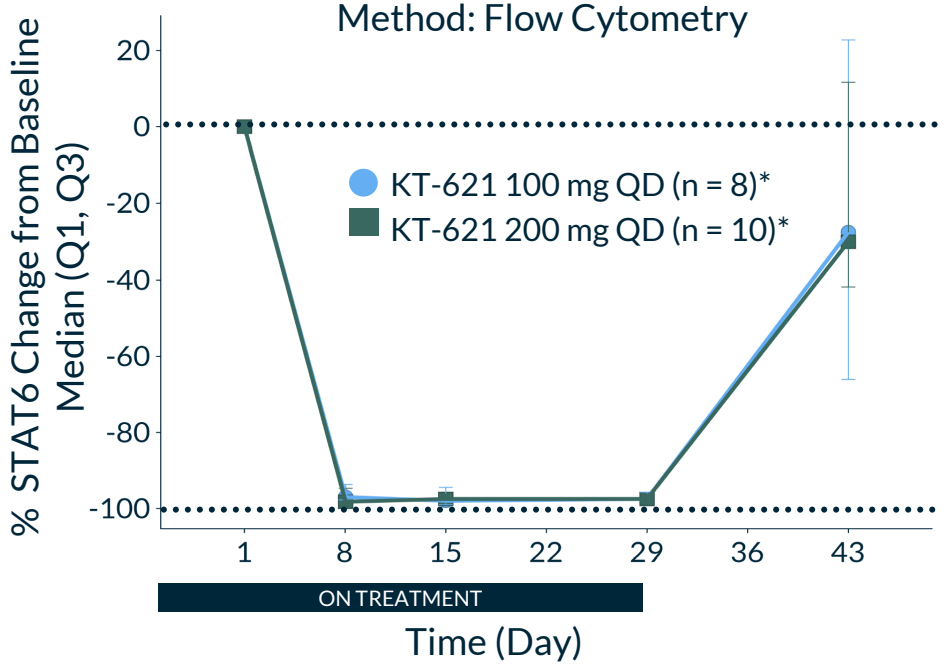
Degradation Maintained for 28 Days Across Both Dose Cohorts

BROADEN STUDY

- **KT-621 Phase 1b AD Study:** Open-label, multicenter, single-arm study to evaluate the safety, tolerability, PK, PD, and clinical activity of oral KT-621 in adults with moderate-to-severe AD
- **Two sequential dose cohorts:** 100 mg (10 patients), 200 mg (12 patients)

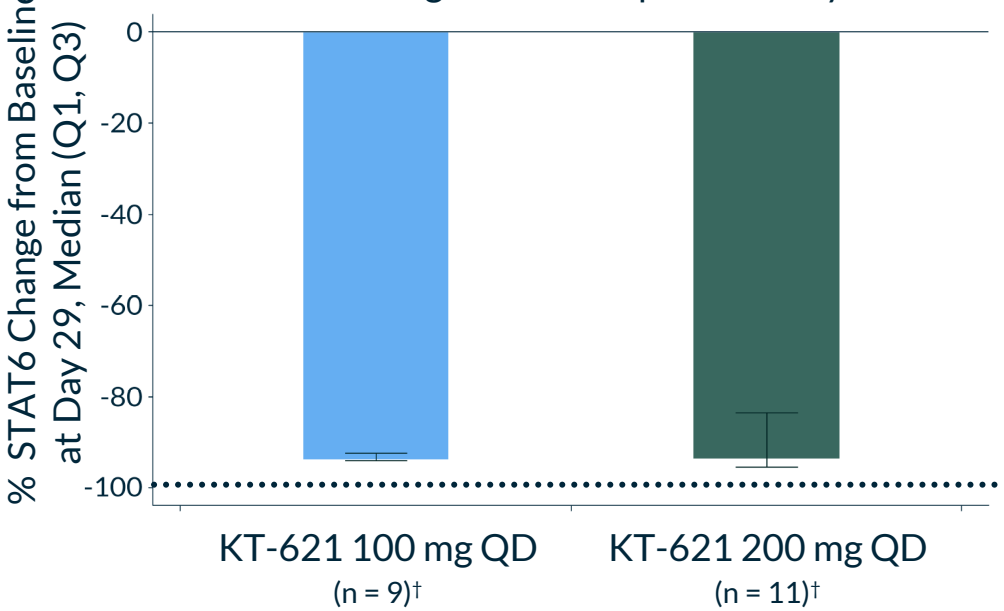
Median STAT6 Degradation in Blood

Method: Flow Cytometry



Median STAT6 Degradation in Skin

Method: Targeted Mass Spectrometry



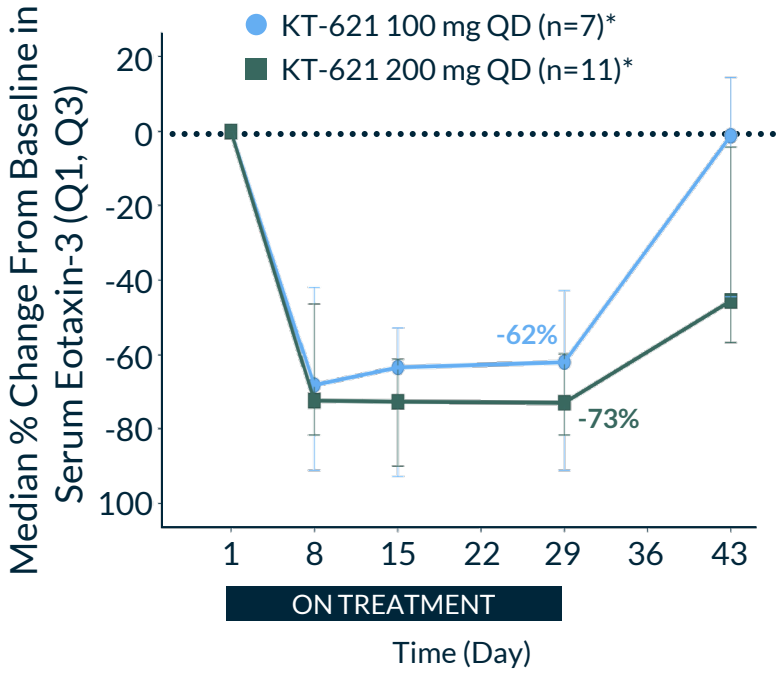
- Median STAT6 degradation of 98% in blood in both dose groups maintained throughout the treatment period
- Deep skin degradation of 94% in both dose groups with multiple patients' STAT6 levels below the LLOQ

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 D29 samples (one in each dose group) were unevaluable due to shipping issues that led to loss of stability; †Two patients (one in each dose group) did not consent to D29 biopsies.
AD, atopic dermatitis; LLOQ, lower limit of quantification; QD, once daily; PD, pharmacodynamics; PK, pharmacokinetics; STAT6, signal transducer and activator of transcription 6.

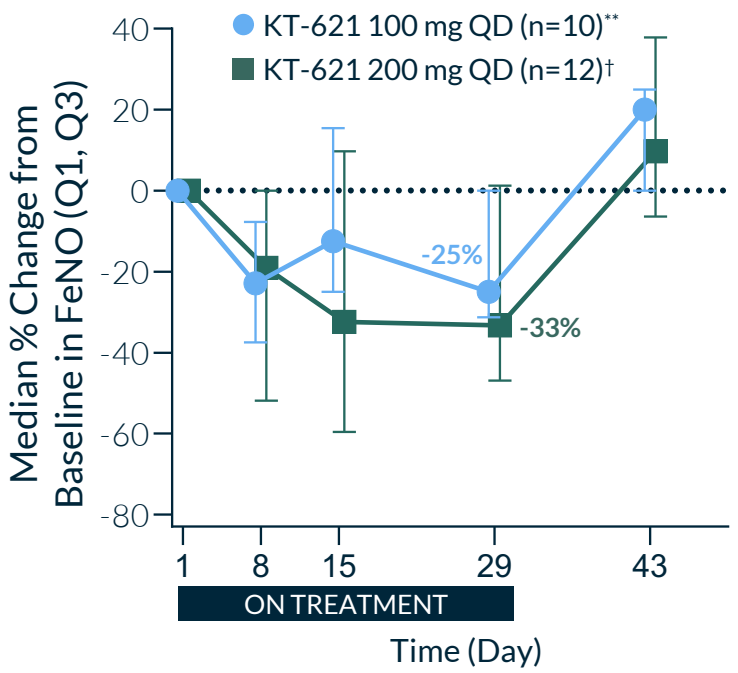
KYMERA 10

KT-621 Achieved Robust Reductions in Type 2 Inflammatory Biomarkers in Blood and Lungs (FeNO)

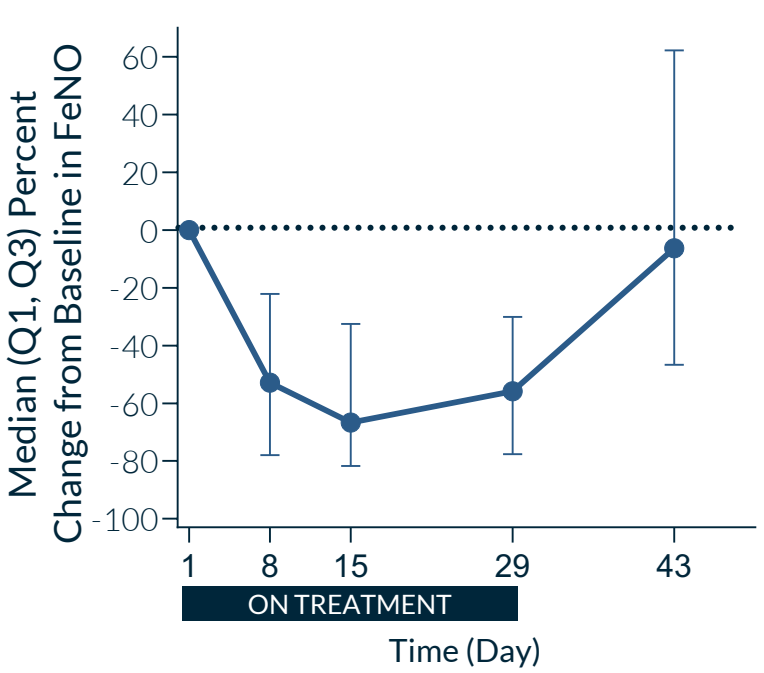
Median % Change From Baseline in Eotaxin-3



Median % Change from Baseline in FeNO



Median % Change from Baseline in FeNO (n=4)‡



- Rapid and robust median serum Eotaxin-3 reduction across both dose groups
- In AD patients, KT-621 achieved up to 33% median reduction in FeNO; first known demonstration of FeNO reduction in AD patients
- In AD patients with comorbid asthma, KT-621 achieved 56% median FeNO reduction at Day 29, exceeding dupilumab (31%) in asthma studies at week 4[1]

N values reflect the number of participants with available samples at Day 29; *Four patients had baseline levels below the lower limit of quantification (LLOQ) of assay, hence change could not be calculated at D29; **Median FeNO baseline for 100 mg = 13 ppb, one patient missed the D29 visit, n=9 at D29; †Median FeNO baseline for 200 mg = 20 ppb; ‡Mean baseline FeNO of 49 ppb; 1. Pavord et al. *JACI.* 2024; AD, atopic dermatitis; FeNO, fractional exhaled nitric oxide; QD, once daily; STAT6, signal transducer and activator of transcription 6.

KT-621 Phase 1b Safety Summary

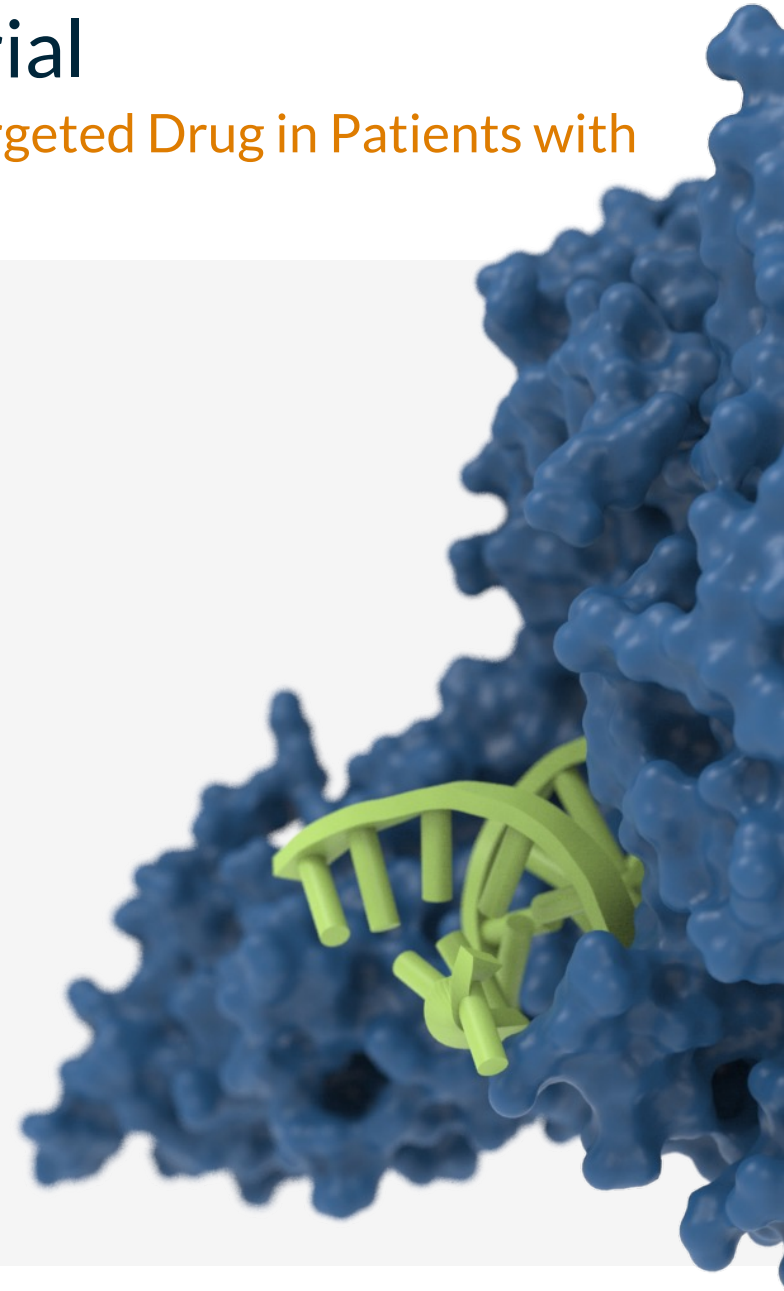
- Well-tolerated with favorable safety at both 100 mg and 200 mg
- No SAEs or Severe AEs
- No dose-dependent pattern in the TEAEs
- No related TEAEs or TEAEs leading to discontinuation
- No AEs of conjunctivitis (or of any ocular disorder), herpes infections, or arthralgias
- No clinically relevant changes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

AE, adverse event; ECG, electrocardiogram; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

KT-621 Phase 1b BroADen Atopic Dermatitis Trial

First Evidence Demonstrating Clinical Activity and Safety of a STAT6-targeted Drug in Patients with Atopic Dermatitis

- Deep STAT6 degradation in blood and lesional skin
- Robust suppression of Type 2 inflammation
- Robust impact on AD clinical endpoints
- Early evidence of activity in asthma based on improvement in biomarkers and patient-reported outcome in AD patients with comorbid asthma
- Favorable safety profile and tolerability at both 100 mg and 200 mg doses



AD, atopic dermatitis; STAT6, signal transducer and activator of transcription 6.

KT-621: BREADTH Phase 2b Trial

Randomized, Double Blind, Placebo-controlled, Parallel-group, Multicenter Dose-ranging

BREADTH TRIAL

Adult, Moderate to Severe Eosinophilic Asthma Patients

Baseline entry criteria:
Blood eosinophils ≥300 cells/uL
FeNO ≥25 ppb
Pre-bronchodilator FEV1 40-80% of predicted normal

Design

- Randomized, double-blind, placebo-controlled
- ~264 patients
- Daily dose for 12-weeks

Dosing

- Three KT-621 doses + one placebo (1:1:1:1)

Endpoints

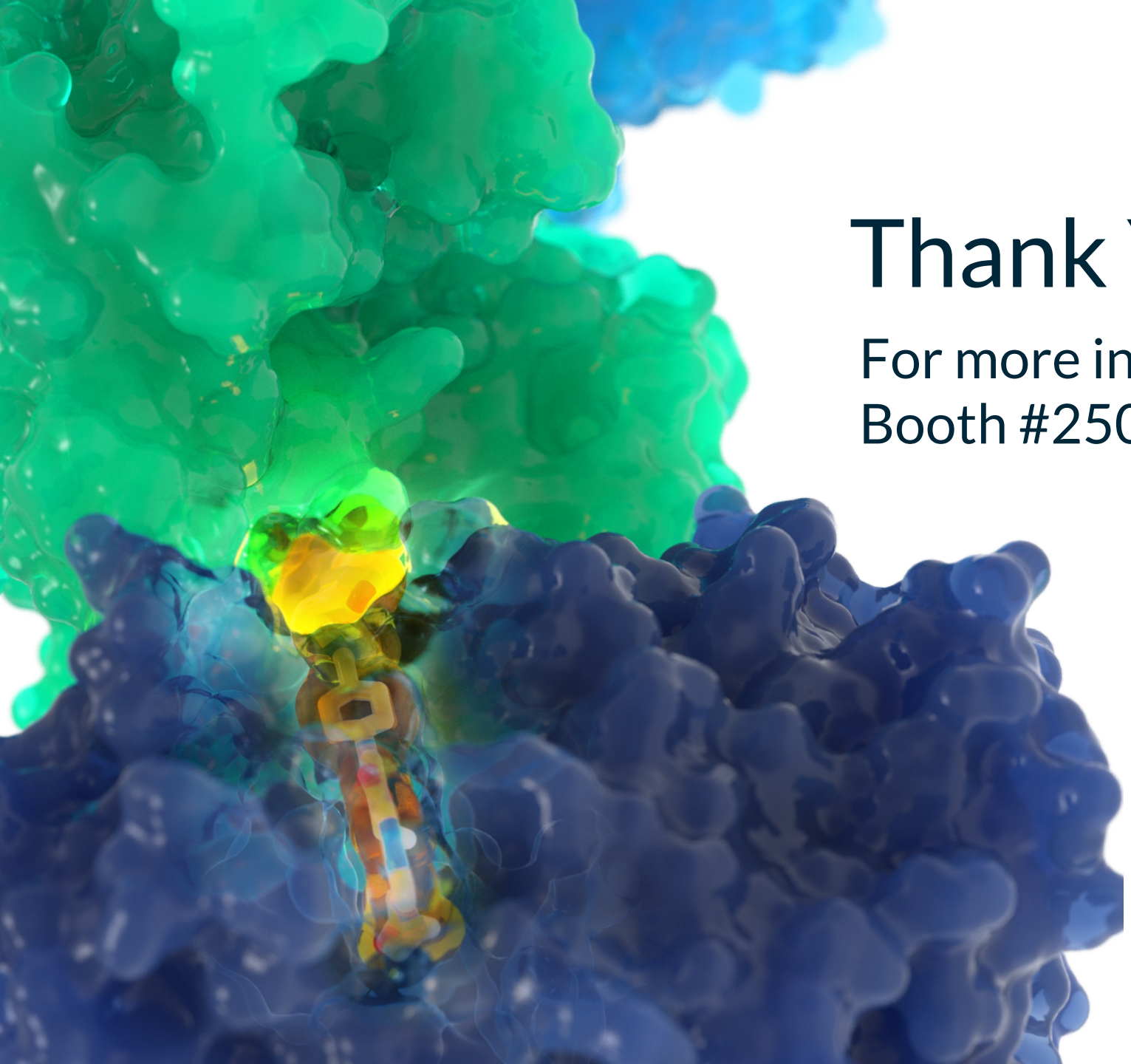
- Primary endpoint: Change from baseline in pre-bronchodilator FEV1 at week 12
- Secondary endpoints include:
  - Change from baseline in ACQ-5, AQLQ

Key Trial Aim

Establish clinical activity and safety in **asthma to select Phase 3 dose to support registrational studies** in multiple respiratory indications

Status update:
Ongoing;
Data expected late 2027

ACQ-5, asthma control questionnaire-5; AQLQ, asthma quality of life questionnaire; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in the first second.



Thank You

For more information, please visit our Booth #2501 or www.kymeratx.com

ATS Annual Meeting | May 2026