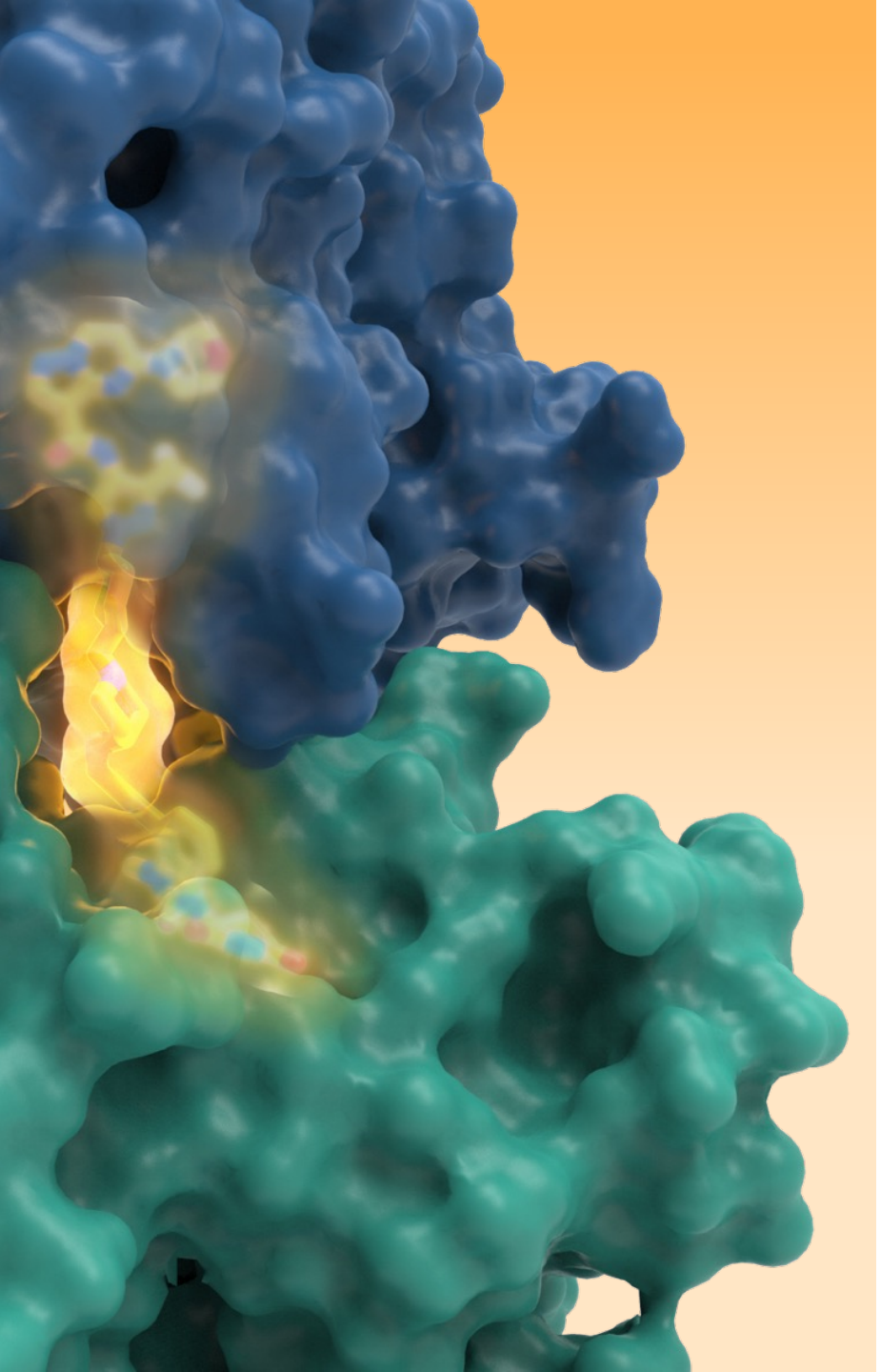


17 September 2025

KT-621, an Oral, Once Daily, Targeted STAT6 Degrader: First-in-Human Phase 1a Safety, Pharmacokinetics, Pharmacodynamics and Th2 Biomarker Effects

Mahta Mortezavi, MD

Senior Medical Director, Clinical Development

Kymera Therapeutics, Inc.

EADV Congress | Paris | 17-20 September 2025

KYMERA

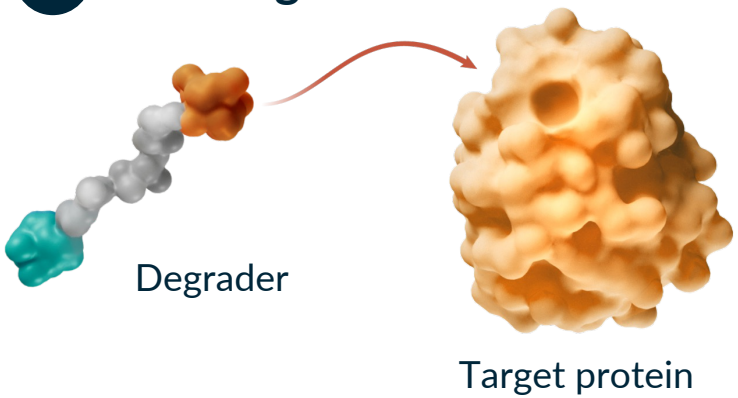
Conflict of Interest Disclosure

Arsalan Shabbir, Sagar Agarwal, Alice A. McDonald, Kelvin Shi, Annie L. Conery, Mahta Mortezavi, Nello Mainolfi, Jared Gollob, and Chad Nivens are employees with shares and stock options of Kymera Therapeutics, Inc.

Pioneering Targeted Protein Degradation for New Oral Medicines

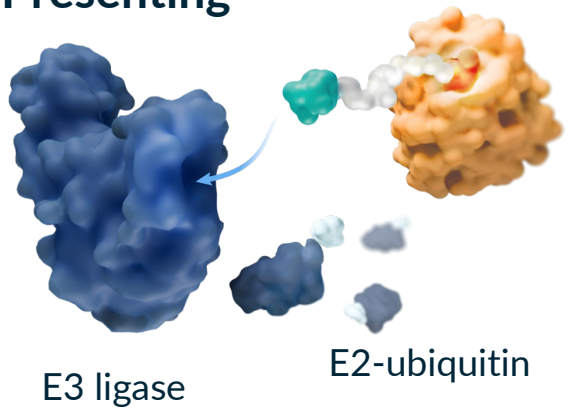
Targeted protein degradation (TPD) harnesses the natural cellular homeostasis and protein degradation system used to clear out misfolded or accumulated proteins to degrade disease causing proteins

1 Catching



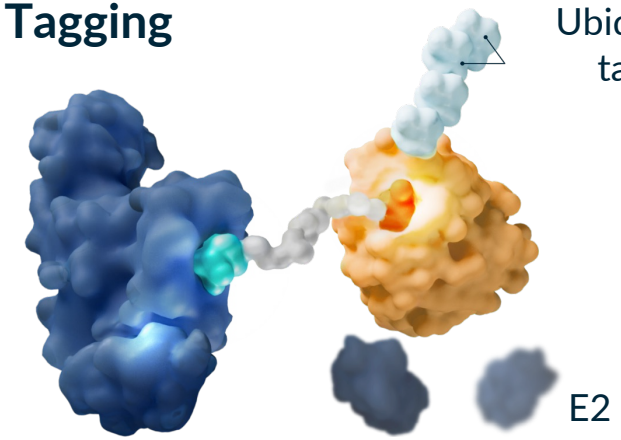
Heterobifunctional small molecules engage the target protein

2 Presenting



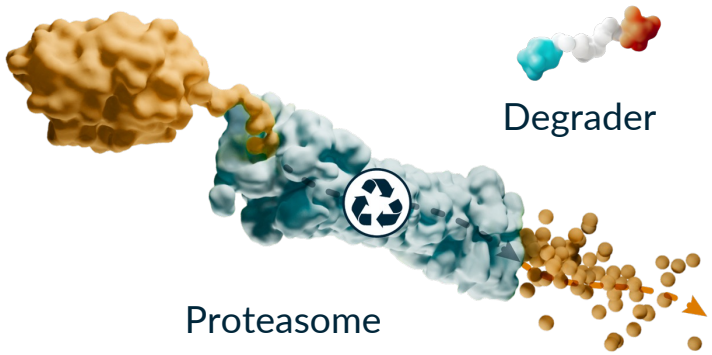
And recruits E3 ubiquitin ligase to bring target and E3 in close proximity

3 Tagging



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

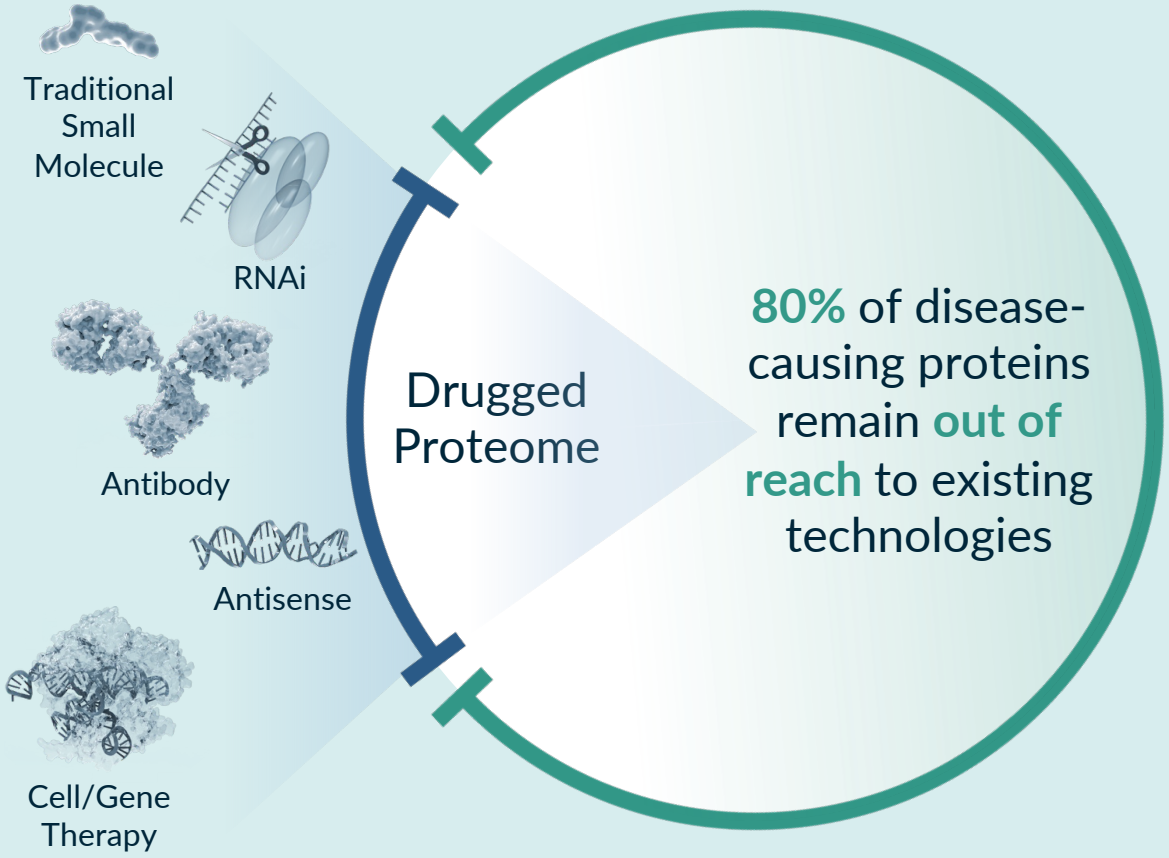
4 Degrading



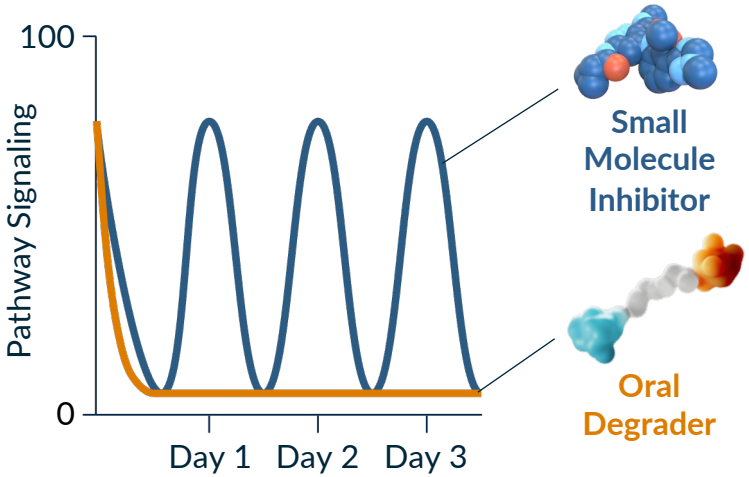
Ubiquitin tag is recognized by cell's recycling systems — the proteasome — to selectively break down the protein

Small Molecule Oral Degraders Can Transform Drug Development

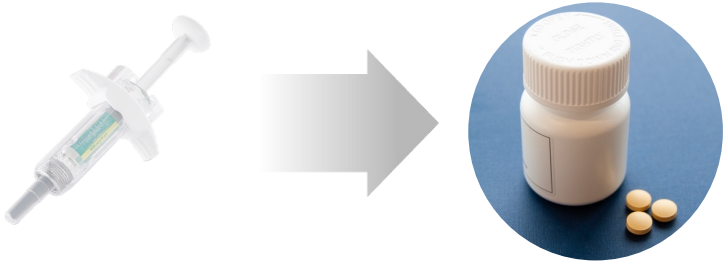
TPD Allows Drugging of Previously Undrugged Targets



Oral Degraders Allow for Continuous, Complete Pathway Blockade

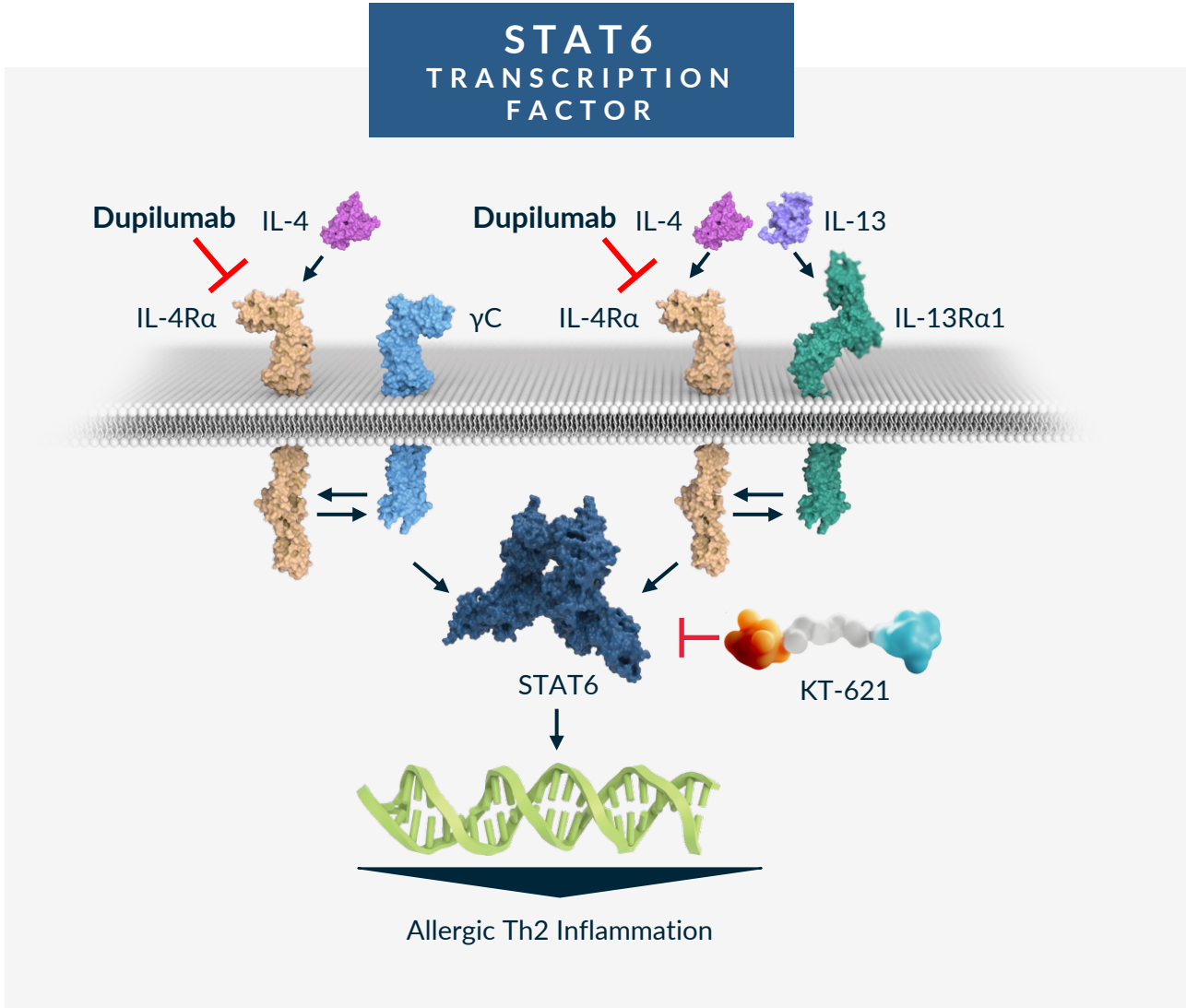


Oral Degraders Provide a Convenient Route of Administration Preferred by Patients



STAT6 Transcription Factor, Highly Validated but Undrugged Target

- Signal transducer and activator of transcription 6 (STAT6) is an essential transcription factor in the interleukin (IL)-4 and IL-13 pathway
- IL-4/IL-13 pathway is clinically validated by dupilumab across multiple respiratory, dermatologic and gastrointestinal T helper 2 (Th2) allergic diseases, such as AD and asthma
- STAT6 is genetically validated by human gain-of-function and heterozygous loss-of-function alleles, and mouse knockout phenotype
- While several therapies target the upstream IL-4/IL-13 receptors, there are no drugs that selectively target IL-4/IL-13 within the cell with oral delivery potential

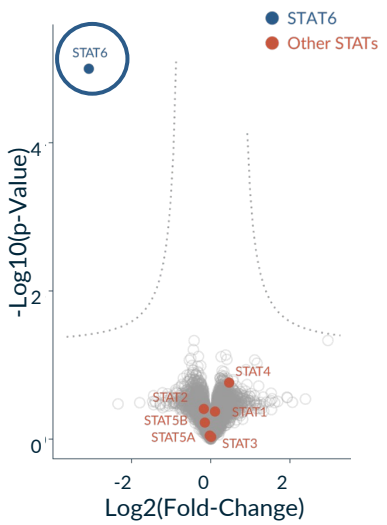


Sharma et al. 2023. Takeda et al. 1996. Kaplan et al. 1996. Junttila. 2018. Kolkhir et al. 2023.

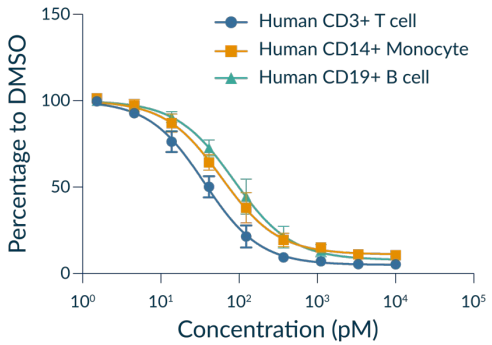
KT-621: First STAT6-targeted Drug in Clinical Development

Compelling KT-621 Preclinical Package Provides Potential for Dupilumab-like Activity in a Pill

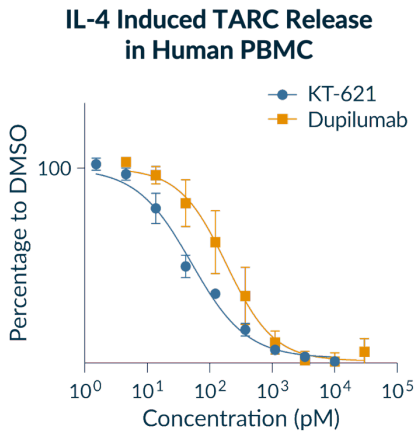
Exquisite Selectivity

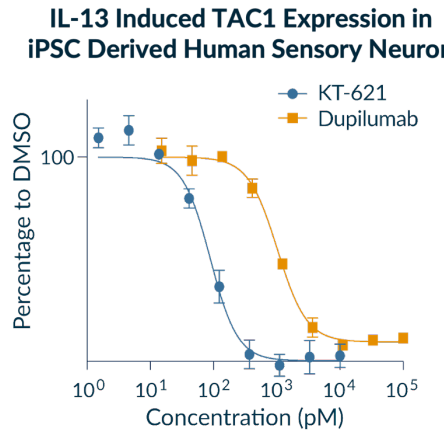


Robust Degradation in Relevant Cell Types



Full Inhibition of IL-4/IL-13 Pathways, More Potent than Dupilumab





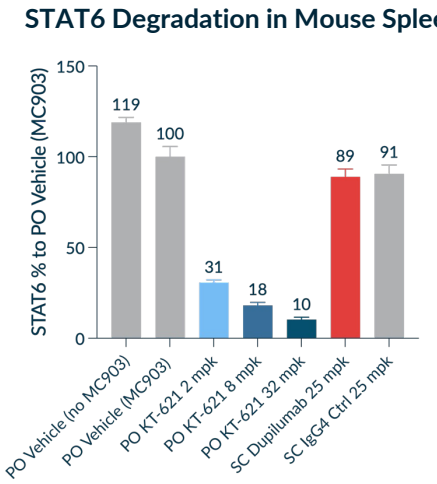
Favorable Safety Profile

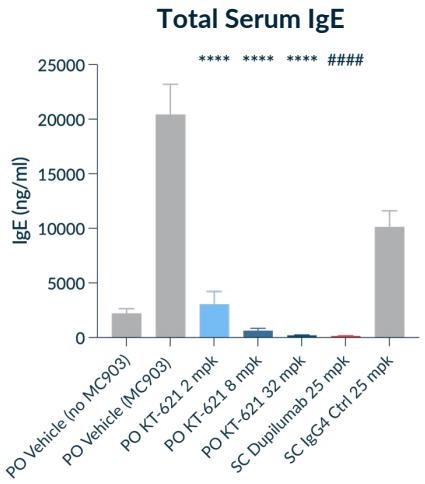
Well tolerated in multiple preclinical species and safety studies at concentrations 40-fold above efficacious dose with up to 4 months of dosing

Excellent Preclinical Efficacy

KT-621 has comparable *in vivo* efficacy to IL-4Rα saturating dose of dupilumab in the MC903 atopic dermatitis model

*Significance to PO vehicle (MC903);
#Significance to SC IgG4 25 mpk BIW

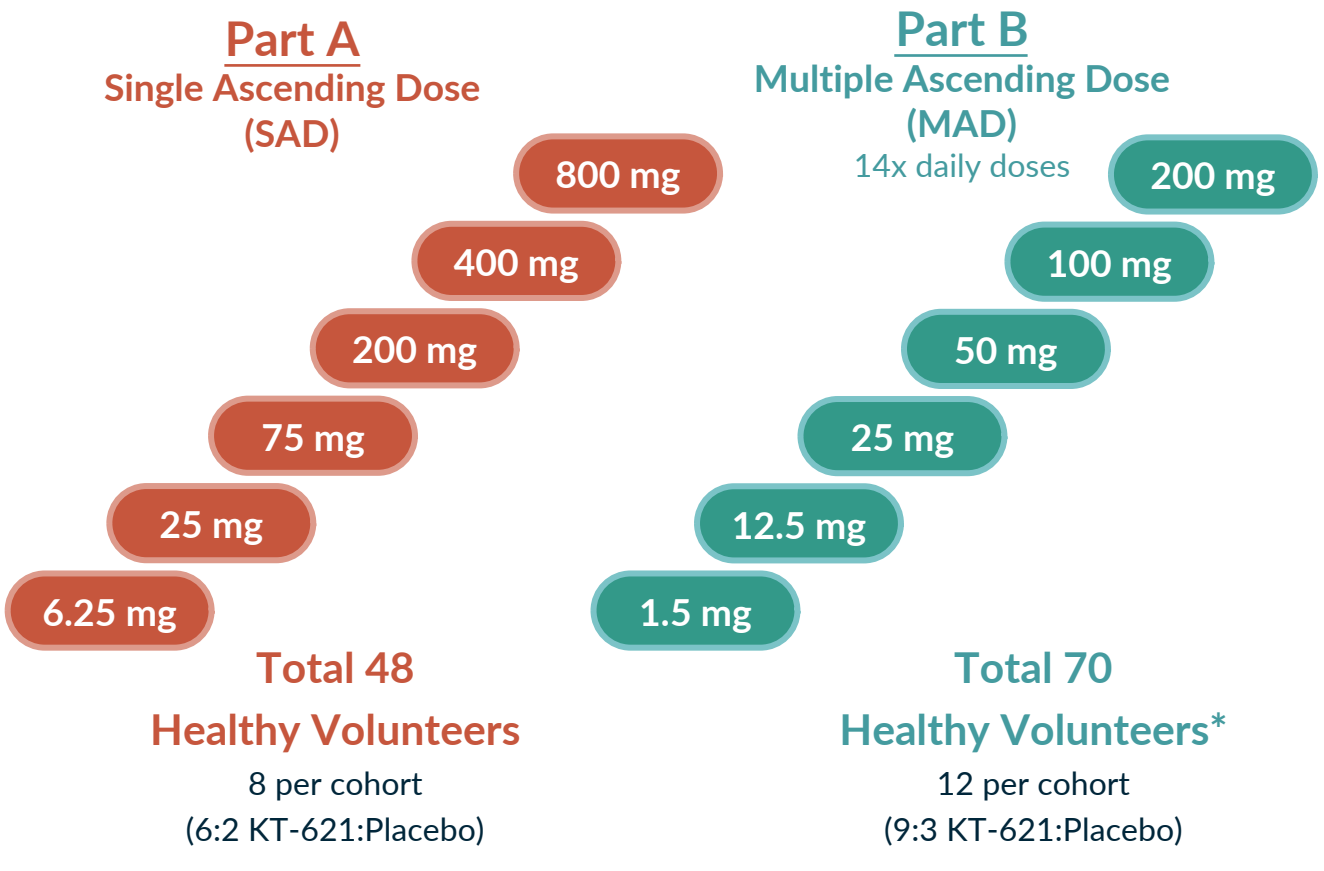




KT-621: First-in-Human, Phase 1a Healthy Volunteer Study

Randomized, Double-blind, Placebo-controlled, Single Ascending Dose (SAD), Multiple Ascending Dose (MAD)

118 Healthy Volunteers Were Enrolled in Parts A and B



Endpoints

Primary

- Safety & tolerability of escalating single and multiple doses of KT-621

Secondary

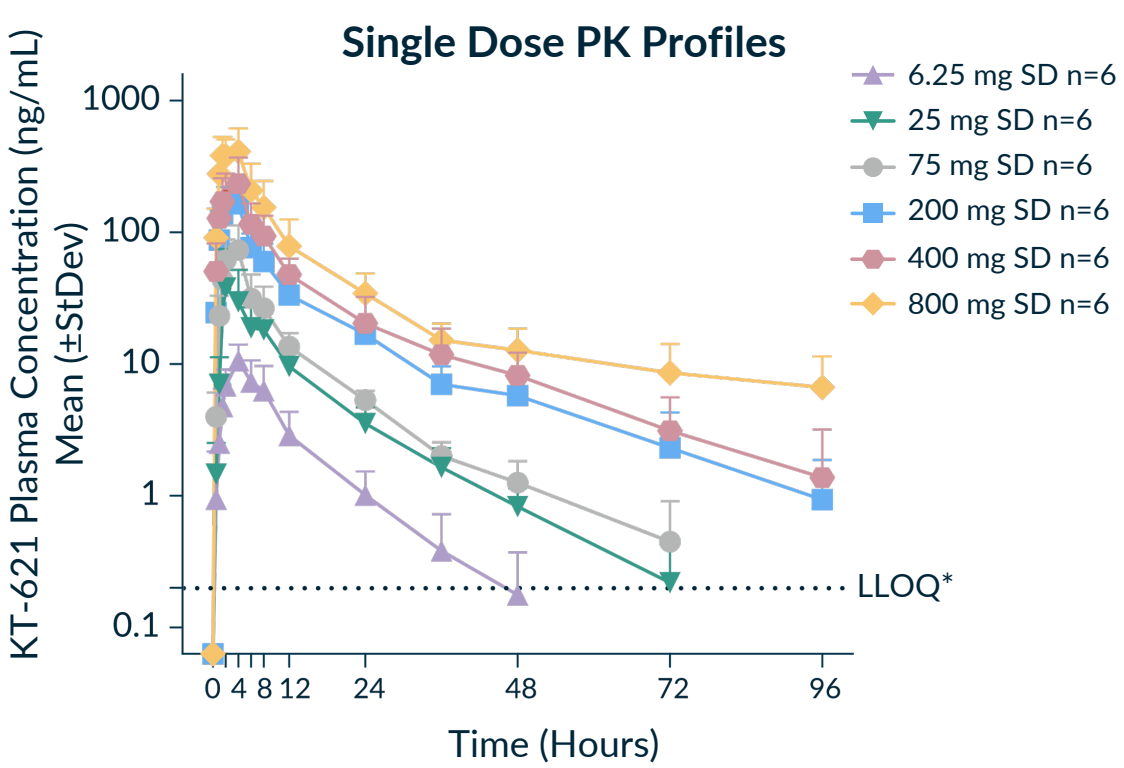
- Pharmacokinetic measures

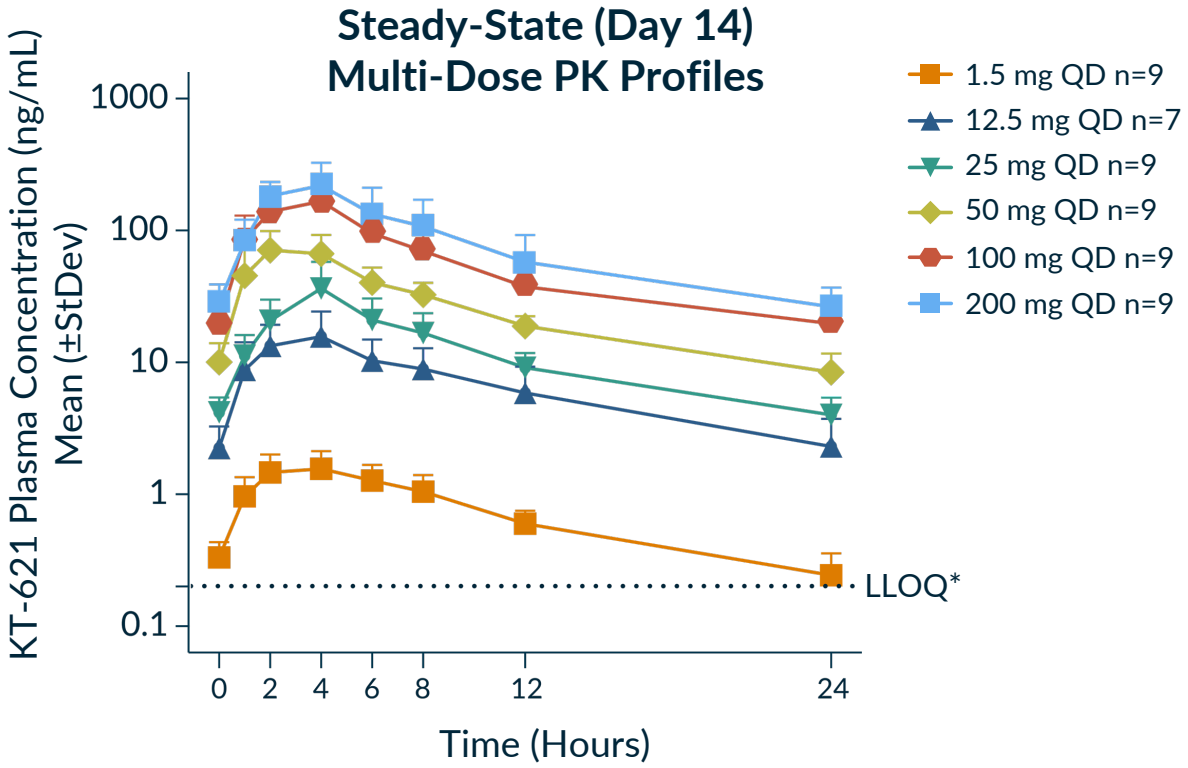
Exploratory

- STAT6 protein levels in blood (SAD/MAD) and skin (MAD)
- T helper 2 (Th2) biomarkers in blood (MAD)

*Part B: 10 subjects were enrolled onto 12.5 mg (7 KT-621 and 3 placebo). Additional information on the trial is available on https://clinicaltrials.gov/: NCT06673667.
mg: milligrams

KT-621: Favorable PK Profile After Single and Multiple Dosing



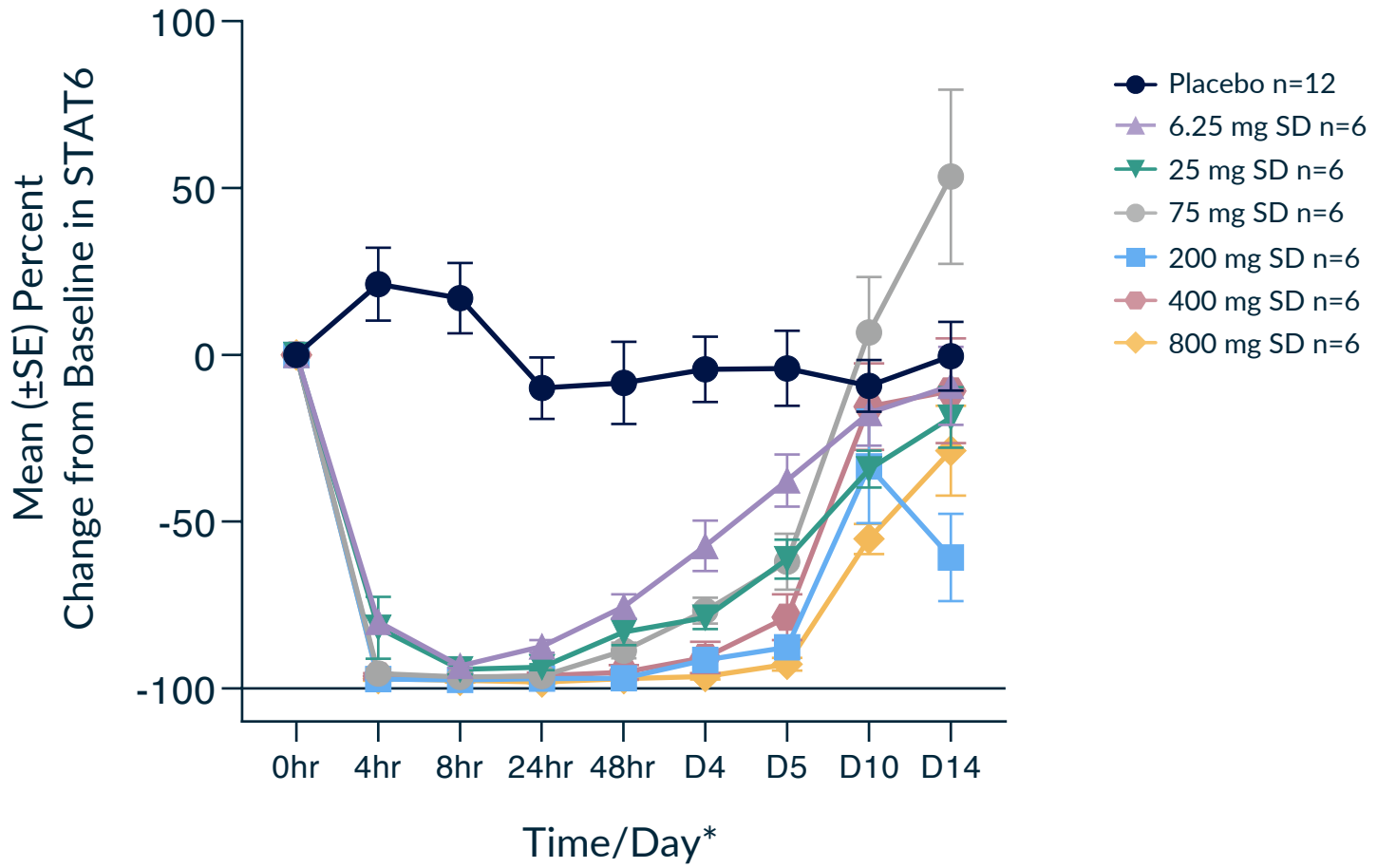


- Rapid absorption with median t_{max} of 2-4 hours and mean half-life of 9-36 hours
- Generally dose-proportional increase in exposure after single and multiple doses with low-moderate variability
- Steady-state achieved by Day 4 of once daily dosing

*Lower Limit of Quantification (LLOQ): below this level, value is assumed to be zero for calculation of summary statistics.
PK: pharmacokinetics, ng: nanograms, mL: milliliter, StDev: standard deviation, SD: single dose, SSE: standard error, hr: hour, D: Study Day, QD: once daily, n: # participants, mg: milligram, t_{max}: time to peak drug concentration

Single Doses of KT-621 Achieved Rapid, Deep and Prolonged STAT6 Degradation in Blood

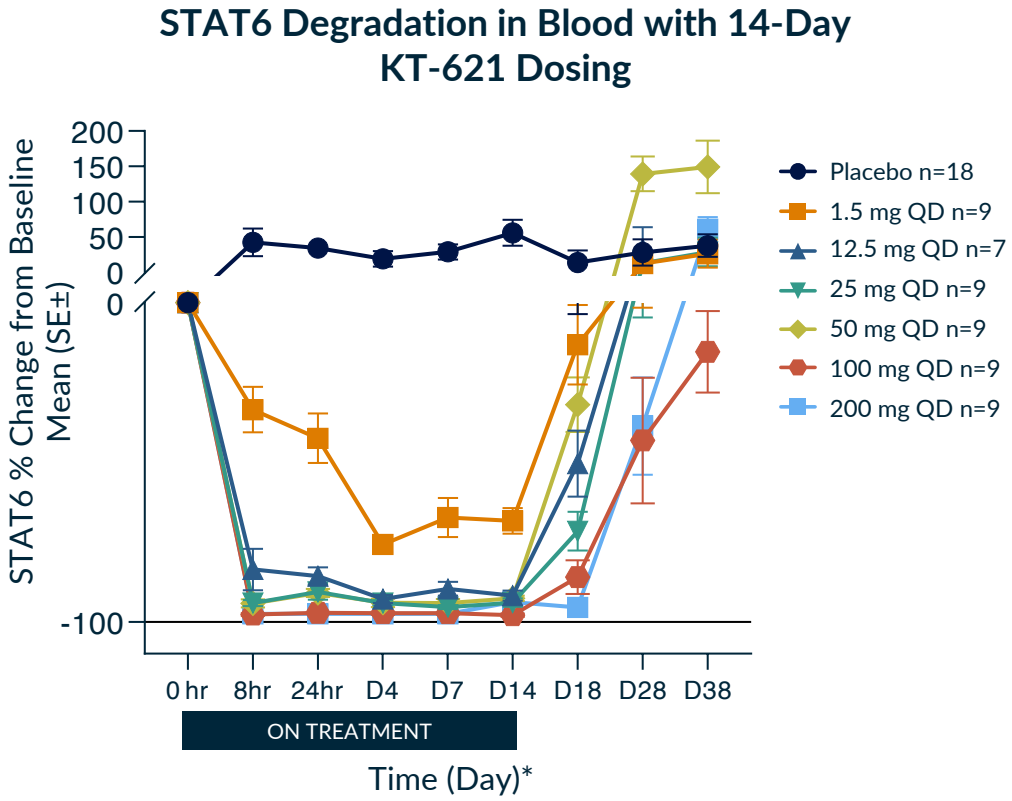
Mean Percent Change from Baseline in STAT6[1]

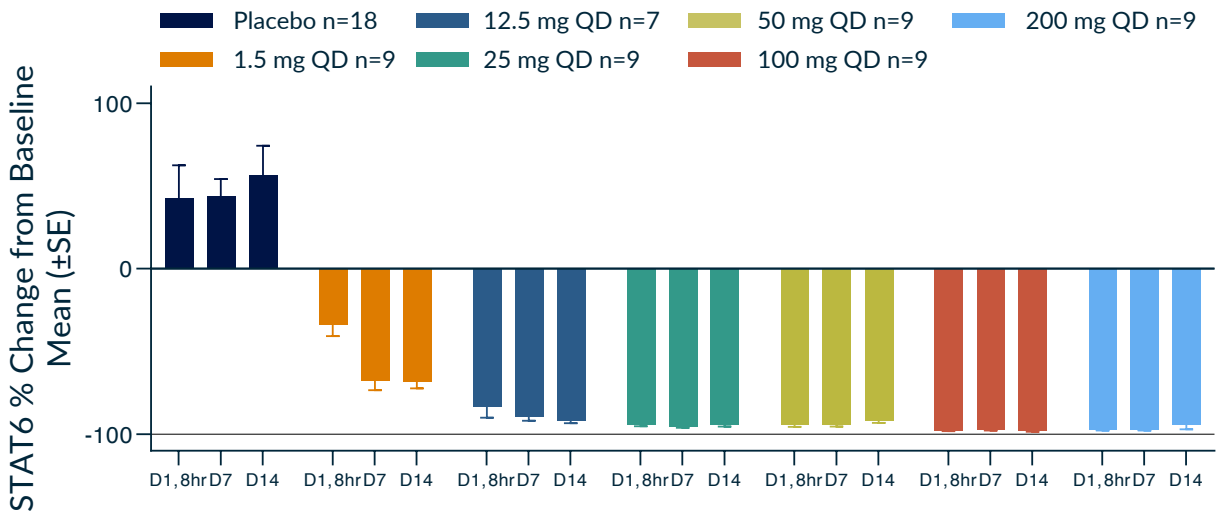


- Maximal degradation seen as quickly as 4 hours after a single dose of KT-621
- Robust degradation maintained as long as 4 days after single dose with recovery by Day 14
- Multiple subjects with STAT6 levels below LLOQ at doses of 75 mg or greater

[1]STAT6 levels measured in isolated PBMC using targeted mass spectrometry; *Compound dosed on Day 1.

KT-621: Daily Doses Over 14 Days Rapidly Achieve Complete STAT6 Degradation in Blood



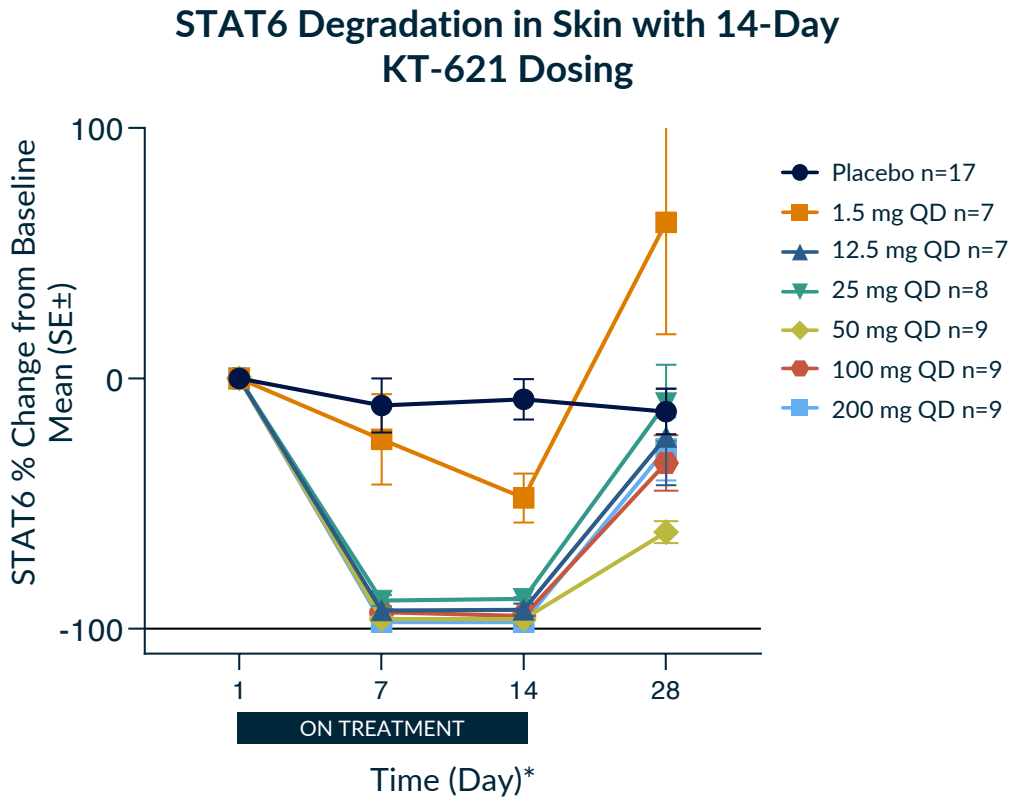


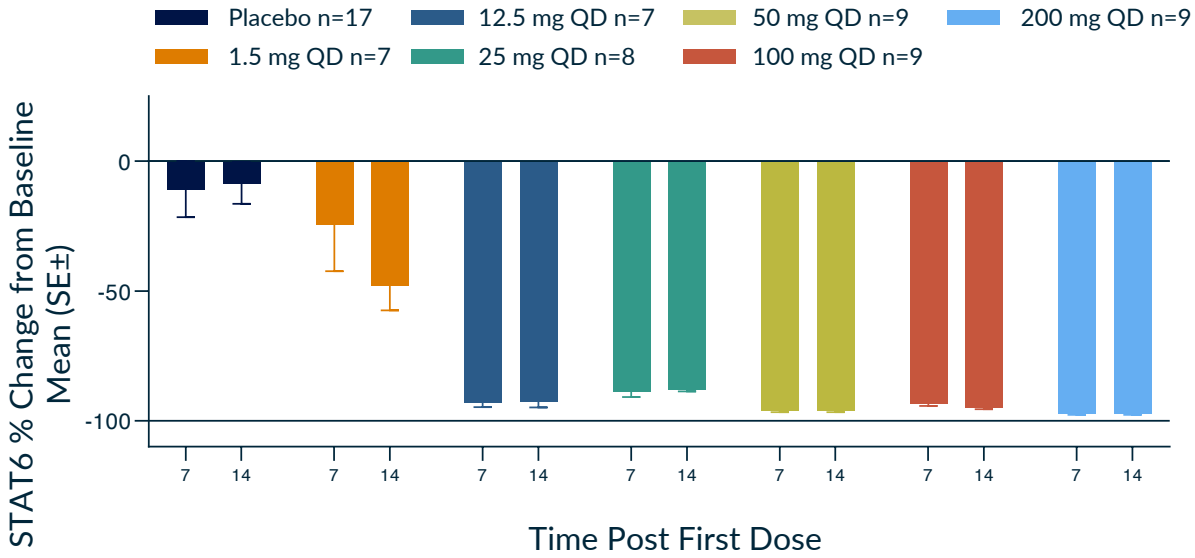
	Mean % STAT6 Change Day 1, 8hr	Mean % STAT6 Change Day 7	Mean % STAT6 Change Day 14
Placebo	43%	44%	56%
1.5 mg	-34%	-67%	-68%
12.5 mg	-84%	-90%	-92%
25 mg	-94%	-95%	-94%
50 mg	-94%	-94%	-92%
100 mg	-98%	-97%	-98%
200 mg	-97%	-97%	-94%

- Steady-state maximum degradation in blood achieved as early as 8hr post-first dose with recovery starting at 4 days post-last dose
- Complete STAT6 degradation, characterized by ≥95% decrease from baseline and/or undetectable levels in most participants, was achieved at doses ≥50 mg

*Compound dosed on Day 1. SE: standard error, hr: hour, D: Study Day, QD: once daily, n: # participants, mg: milligram

KT-621: Daily Doses Over 14 Days Rapidly Achieve Complete STAT6 Degradation in Skin





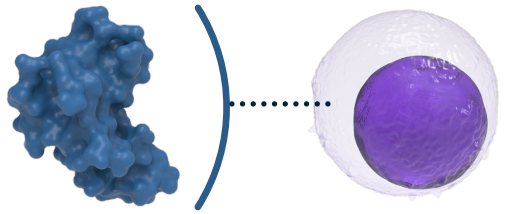
	Mean % STAT6 Change Day 7	Mean % STAT6 Change Day 14
Placebo	-11%	-8%
1.5 mg	-24%	-48%
12.5 mg	-93%	-92%
25 mg	-89%	-88%
50 mg	-96%	-96%
100 mg	-93%	-95%
200 mg	-97%	-97%

- Steady-state maximum degradation in skin achieved by Day 7 at doses >1.5 mg with recovery observed 14 days post-last dose
- Complete STAT6 degradation was achieved at doses ≥50 mg at Day 14, showing correlation between degradation in skin and blood

*Compound dosed on Day 1. SE: standard error, hr: hour, D: Study Day, QD: once daily, n: # participants, mg: milligram

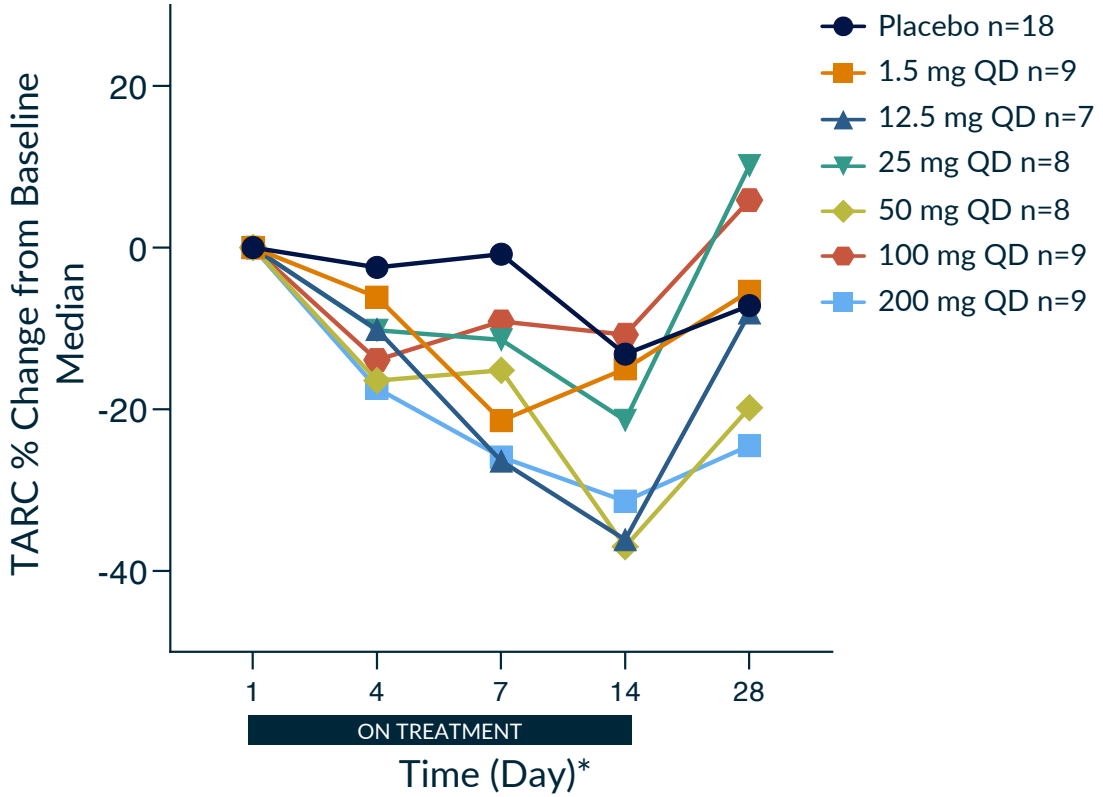
KT-621: Daily Doses Over 14 Days Achieved Median TARC Reduction of Up to 37%

Thymus and Activation-regulated Chemokine (TARC) [CCL17]



- TARC is the chemokine responsible for chemotaxis of CCR4-expressing T cells (e.g., Th2) to sites of inflammation
- **TARC is a validated biomarker in patients** for suppression of Th2 driven inflammatory responses

Serum TARC[1] with 14-Day KT-621 Dosing



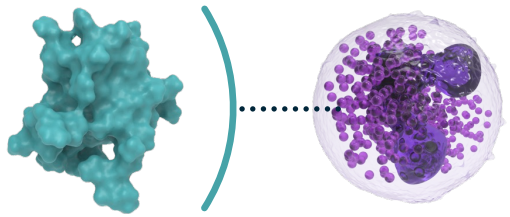
Arm	Day 14 TARC (% Change From Baseline Median)
Placebo	-13%
1.5 mg	**-15%**
12.5 mg	**-36%**
25 mg	**-21%**
50 mg	**-37%**
100 mg	**-11%**
200 mg	**-31%**

- TARC reduction comparable to what has been reported for dupilumab in healthy subjects[2,3]

[1]TARC levels measured in serum using MSD VPLEX; [2]Hamilton et al. Clinical & Experimental Allergy. 2021.[3]No head-to-head trials have been conducted comparing KT-621 to dupilumab. Phase 1 clinical data for KT-621 may not be directly comparable to dupilumab's clinical data due to differences in molecule composition, trial protocols, dosing regimens, and patient populations and characteristics. Accordingly, cross-trial comparisons may not be reliable.;CCL17: C-C motif chemokine ligand 17, CCR4: C-C motif chemokine receptor 4, Th2: T helper 2, QD: once daily, n: # participants, mg: milligram. *Compound dosed on Day 1.

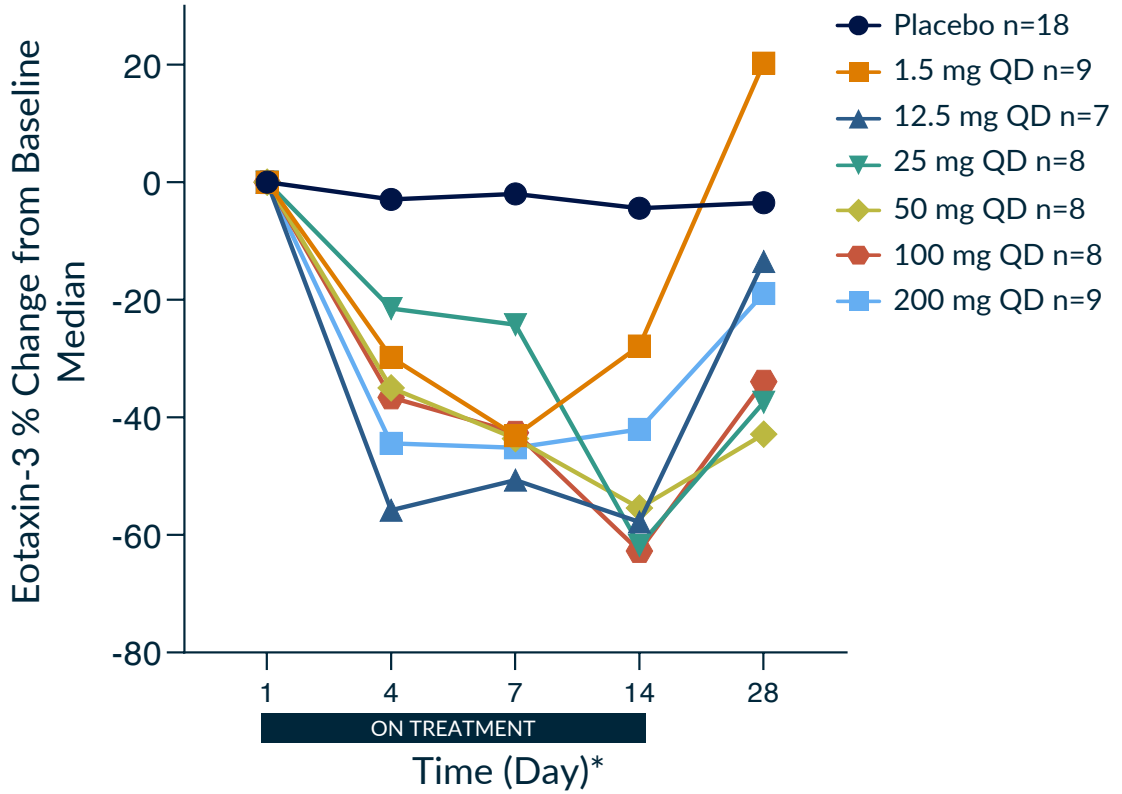
KT-621: Daily Doses Over 14 Days Achieved Median Eotaxin-3 Reduction of Up to 63%

Eotaxin-3 (CCL26)



- The chemokine responsible for chemotaxis of CCR3-expressing inflammatory cells (e.g., eosinophils) to sites of inflammation
- **Eotaxin-3 is a highly specific downstream cytokine of IL-4/IL-13 pathway**

Serum Eotaxin-3[1] with 14-Day KT-621 Dosing



Arm	Day 14 Eotaxin-3 (% Change From Baseline Median)
Placebo	-4%
1.5 mg	**-28%**
12.5 mg	**-58%**
25 mg	**-62%**
50 mg	**-55%**
100 mg	**-63%**
200 mg	**-42%**

- Eotaxin-3 reduction comparable or superior to what was reported with dupilumab in asthma or CRSwNP at 52 weeks[2,3]

[1]Eotaxin-3 levels measured in serum using MSD VPLEX; [2]Hamilton et al. Clinical & Experimental Allergy. 2021.[3]No head-to-head trials have been conducted comparing KT-621 to dupilumab. Phase 1 clinical data for KT-621 may not be directly comparable to dupilumab's clinical data due to differences in molecule composition, trial protocols, dosing regimens, and patient populations and characteristics. Accordingly, cross-trial comparisons may not be reliable; CCL26: C-C motif chemokine ligand 26, CCR3: C-C motif chemokine receptor 3, IL: interleukin, QD: once daily, n: # participants, mg: milligram. *Compound dosed on Day 1.

KT-621: Safety Summary

Well Tolerated Across All Doses Evaluated and Safety Profile Undifferentiated from Placebo

- No Serious Adverse Events
- No Severe Adverse Events
- No dose dependent pattern in Treatment Emergent Adverse Events (TEAEs)
- No Treatment Related AE (TRAE) reported in >1 participant
- No related TEAEs leading to discontinuation
- No clinically relevant changes in vital signs, laboratory tests, and ECGs

TRAEs by Preferred Term: SAD Cohorts

AE Term (severity)	SAD Placebo (n=12)	SAD KT-621 (n=36)
Headache (mild)	1 (8.3%)	0

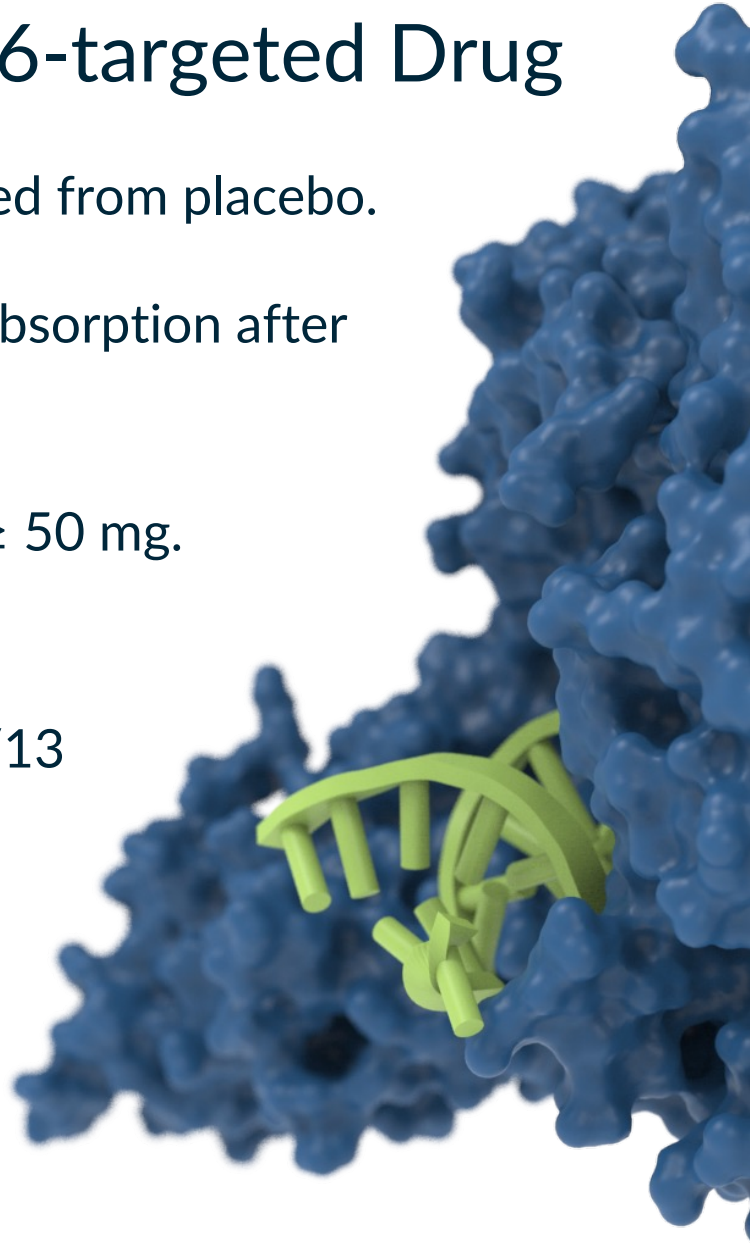
TRAEs by Preferred Term: MAD Cohorts

AE Term (severity)	MAD Placebo (n=18)	MAD KT-621 (n=52)
Nausea (mild)	1 (5.6%)	0
Asthenia (mild)	0	1 (1.9%)

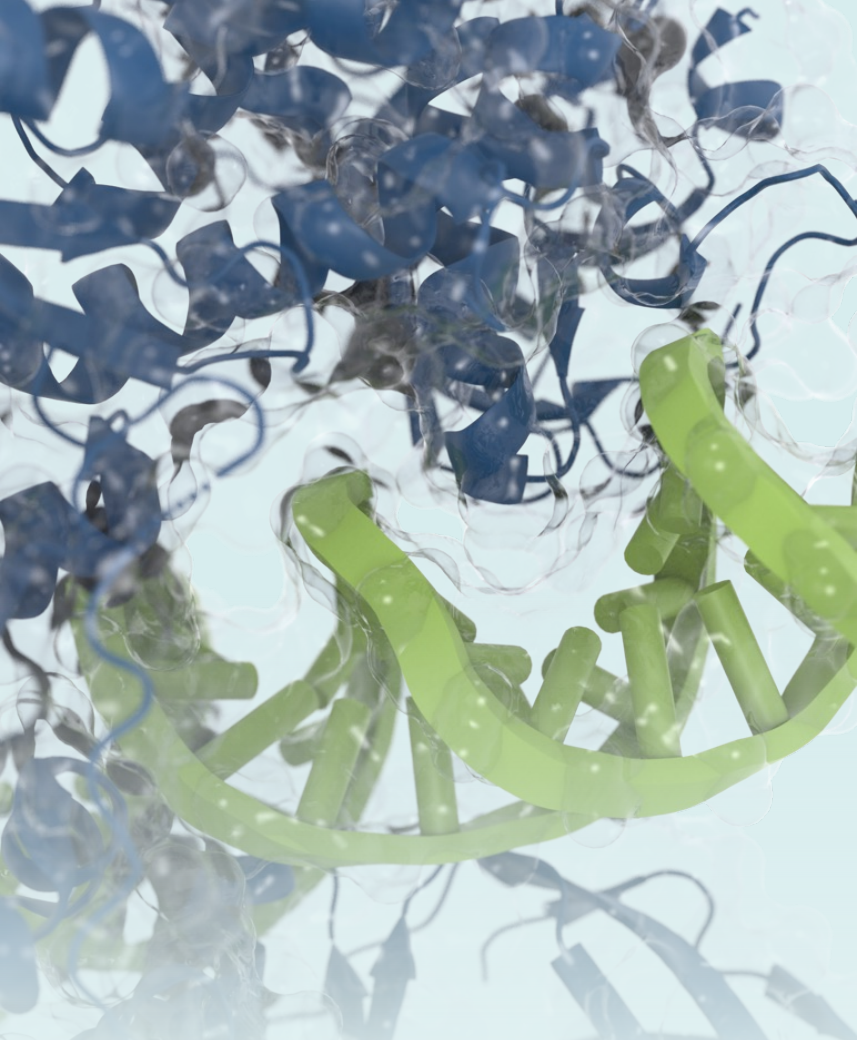
SAD: Single Ascending Dose, MAD: Multiple Ascending Dose, ECG: electrocardiogram, n: # participants

KT-621: First Clinical Proof of Concept for STAT6-targeted Drug

- Well-tolerated across all dose levels with safety profile undifferentiated from placebo.
- Favorable PK profile after single and multiple daily doses, with rapid absorption after oral dosing and dose-proportional increase in exposure.
- Complete STAT6 degradation in blood and skin with oral daily doses ≥ 50 mg.
- STAT6 degradation associated with suppression of blood Th2 biomarkers Eotaxin-3 and TARC, demonstrating inhibition of the IL-4/13 pathway comparable or superior to dupilumab.
- Phase 1b study in atopic dermatitis ongoing (patient data expected 4Q25)
- Phase 2b studies in atopic dermatitis and asthma planned to start in 4Q25 and 1Q26, respectively.



PK: pharmacokinetics, STAT6: Signal transducer and activator of transcription 6, mg: milligram, Th2: T helper 2, TARC: thymus and activation-regulated chemokine, IL: interleukin, Q: quarter



EADV Congress

Paris | 17-20 September 2025

KYMERA THERAPEUTICS
500 North Beacon Street, 4th Floor
Watertown, MA 02472

Thank You

For more information,
please visit our Booth #B14
or www.kymeratx.com

KYMERA