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Safety, Pharmacokinetics and Pharmacodynamics of KT-621, an Oral STAT6 Degrader, in Healthy Adults

Arsalan Shabbir, MD, PhD, Vice President, Clinical Development

Kymera Therapeutics, Inc.

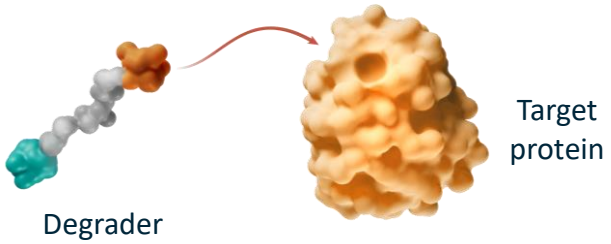
Conflict of Interest Disclosure

Arsalan Shabbir is an employee with shares and stock options of Kymera Therapeutics, Inc.

Pioneering Targeted Protein Degradation to Invent New Oral Medicines

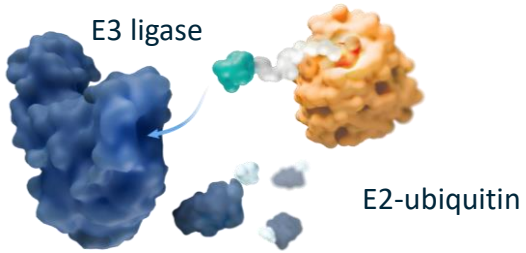
Targeted protein degradation (TPD) harnesses the natural cellular homeostasis and protein degradation system used to clear out misfolded or accumulated proteins to degrade disease causing proteins

1 Catching



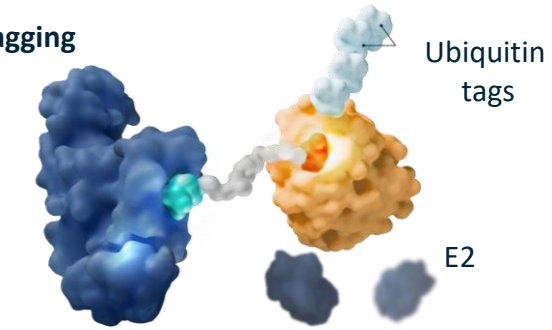
Heterobifunctional small molecules engage the target protein

2 Presenting



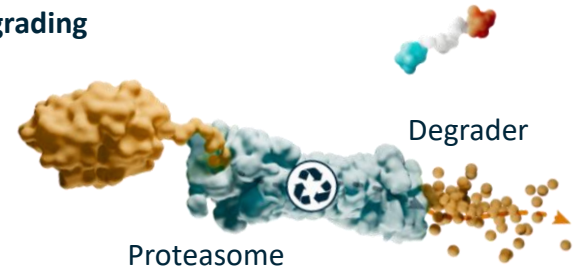
And recruits E3 ubiquitin ligase to bring target and E3 in close proximity

3 Tagging



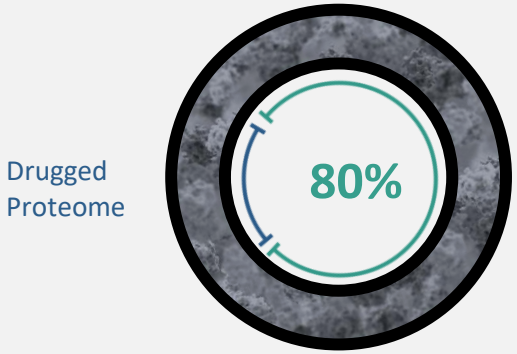
E3 ligase places a chain of ubiquitin molecules on the recruited protein

4 Degrading

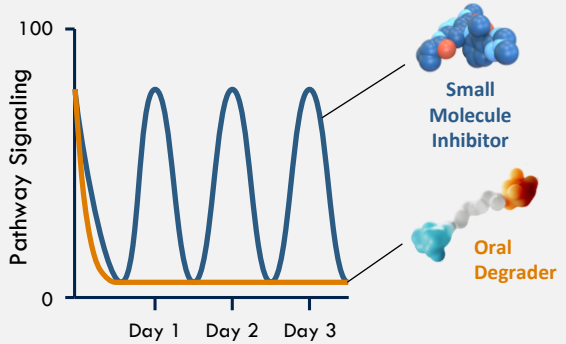


Ubiquitin tag is recognized by cell's recycling systems—the proteasome—to selectively break down the protein

TPD allows drugging of previously undruggable targets



TPD allows for continuous and complete pathway blockage

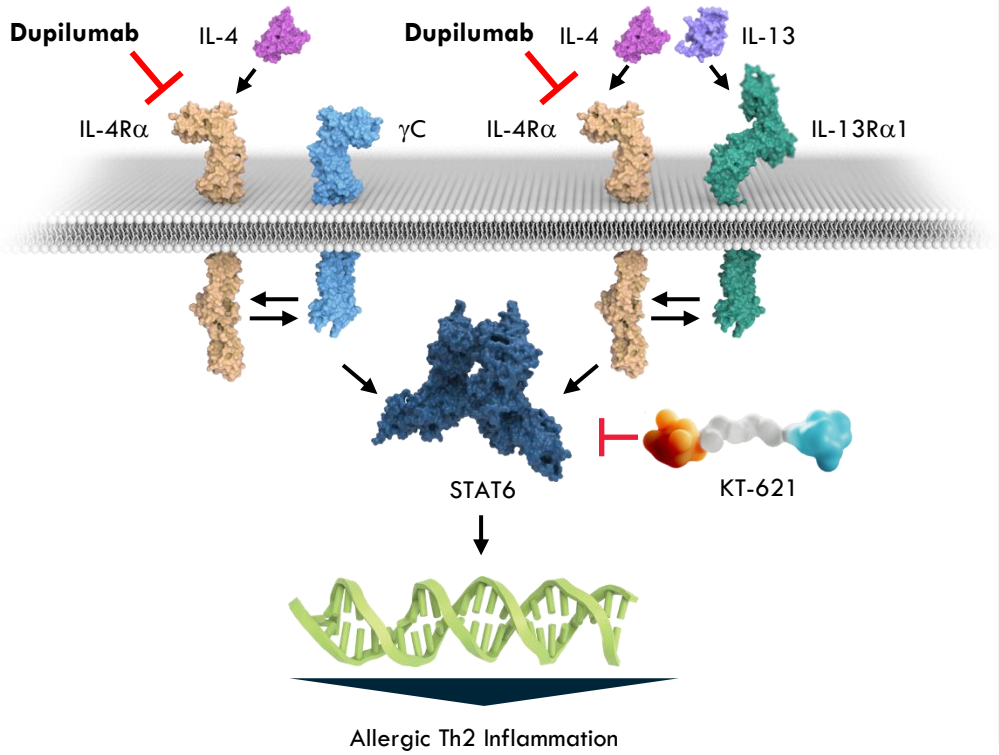


KT-621: First STAT6-targeted Drug in Clinical Development

STAT6
TRANSCRIPTION FACTOR

- 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 Th2 allergic diseases
- STAT6 is genetically validated by human gain-of-function and heterozygous loss-of-function alleles, and mouse knockout phenotype

Potential for Dupilumab-like Activity in a Pill



KT-621
FIRST-IN-CLASS ORAL STAT6 DEGRADER

Preclinical Highlights

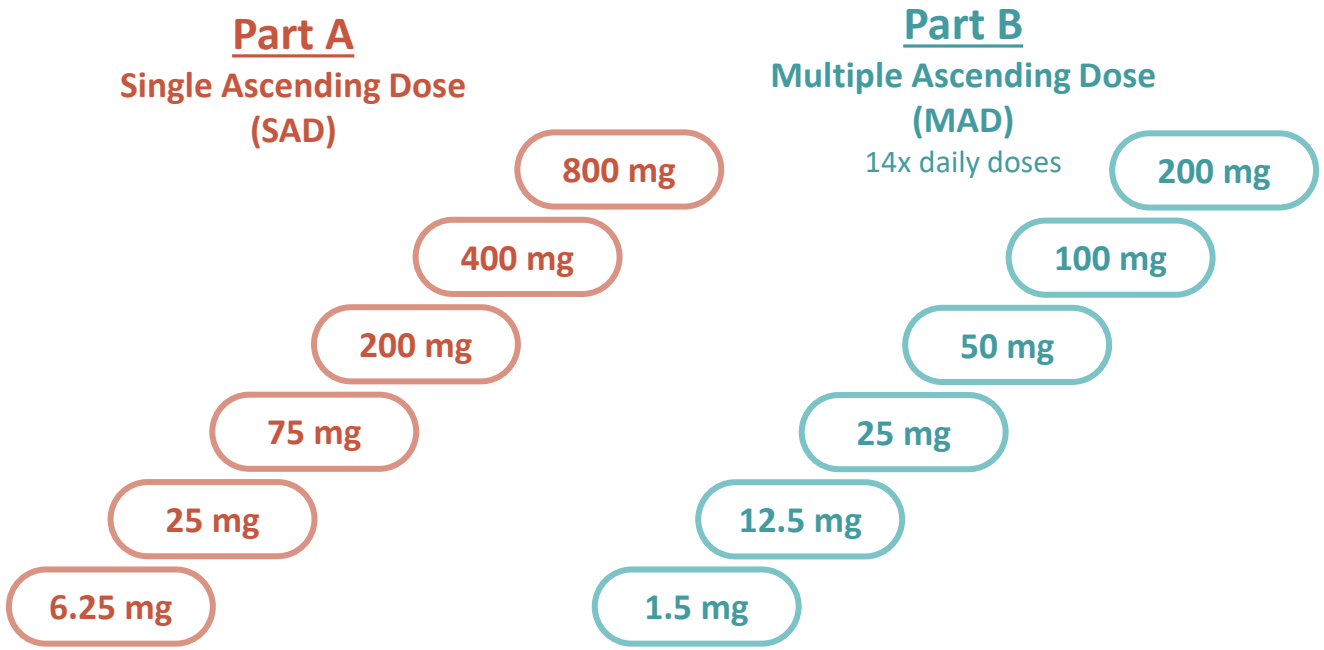
- Fully degrades STAT6 at picomolar concentrations in human cells with complete selectivity at concentrations well above that required for STAT6 degradation
- Fully blocks IL-4/IL-13 pathway in human Th2 functional assays at concentrations lower than dupilumab
- Blocks Th2 inflammation and prevents/reverses disease progression in intranasal HDM Asthma Model with activity comparable or superior to dupilumab
- Well tolerated with no adverse findings in preclinical safety studies with up to 4 months of dosing

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

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



Total 48 Healthy Volunteers

8 per cohort

(6:2 KT-621:Placebo)

Total 70 Healthy Volunteers*

12 per cohort

(9:3 KT-621:Placebo)

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.

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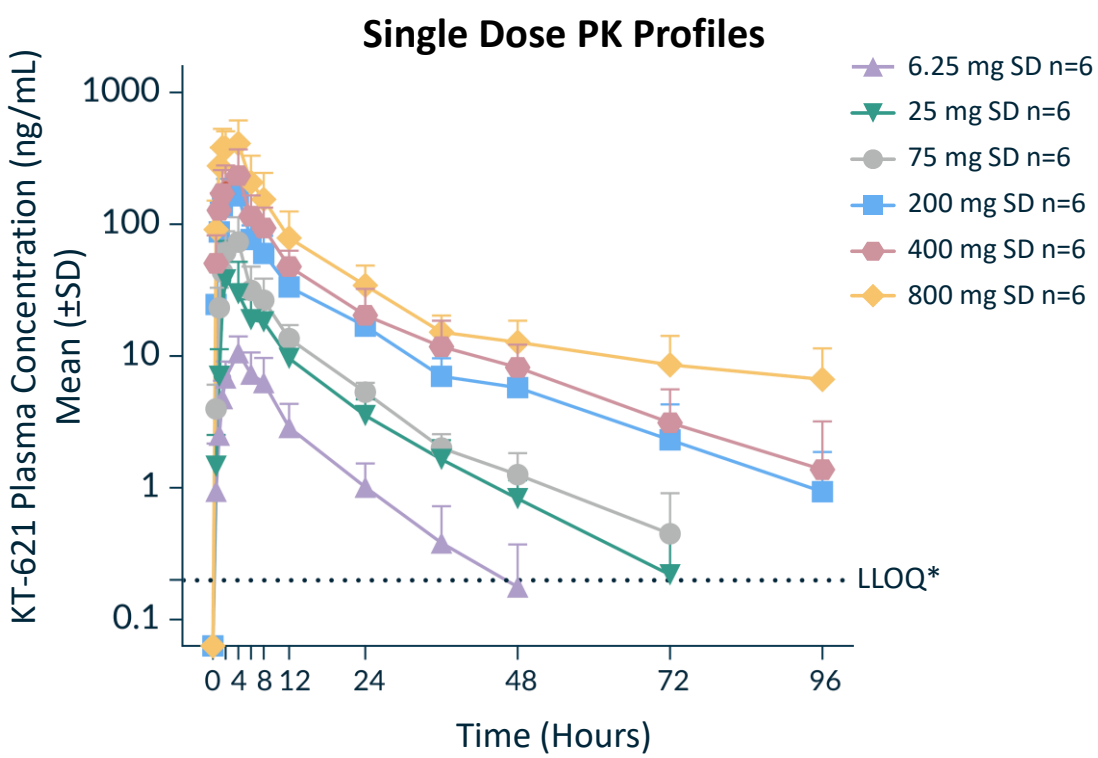
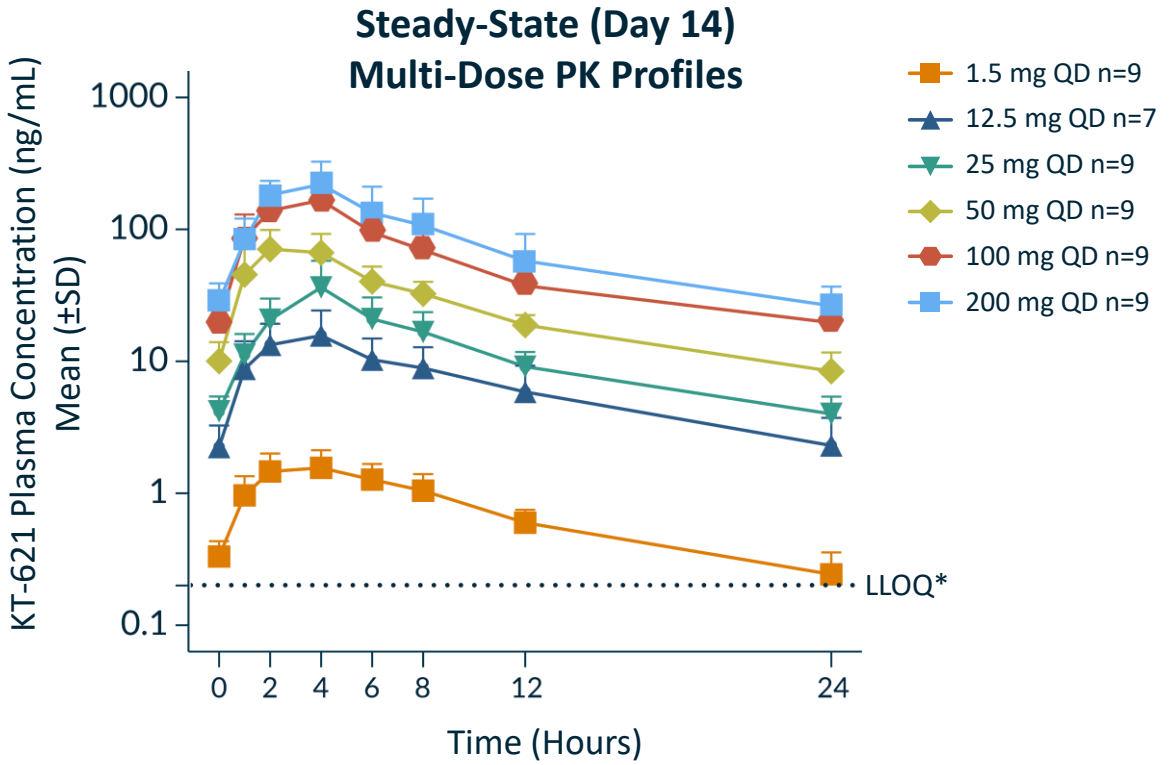
KT-621: Favorable PK Profile After Single and Multiple Dosing





- 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.

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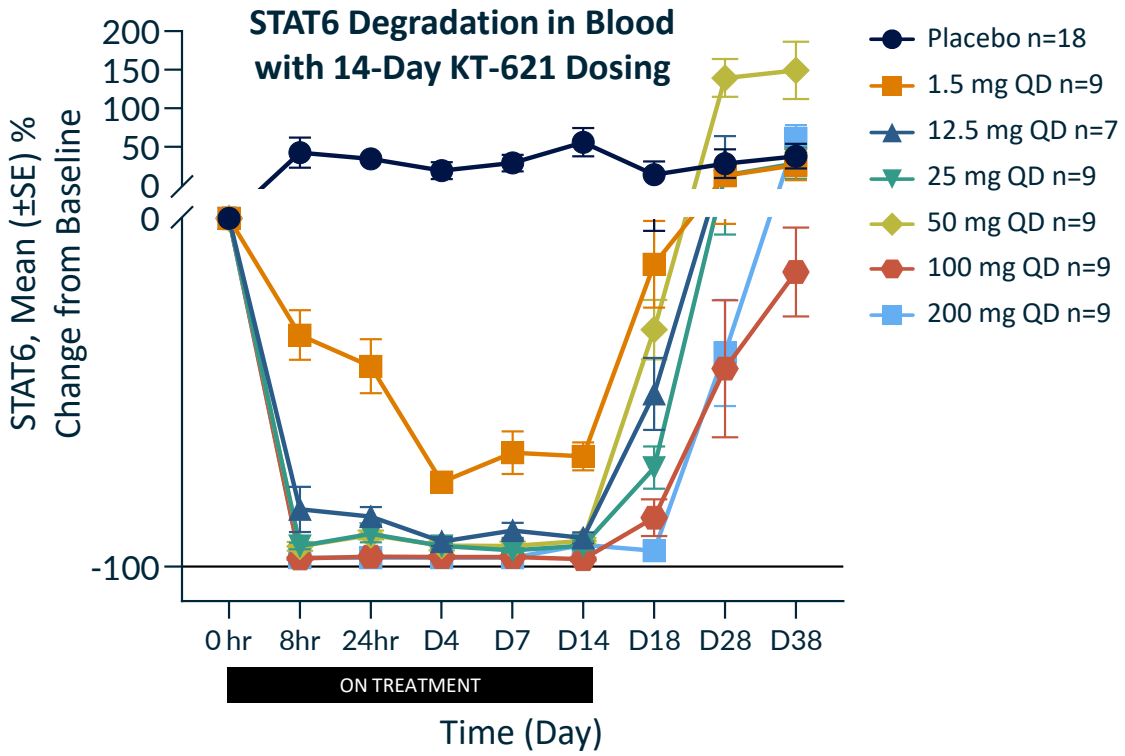
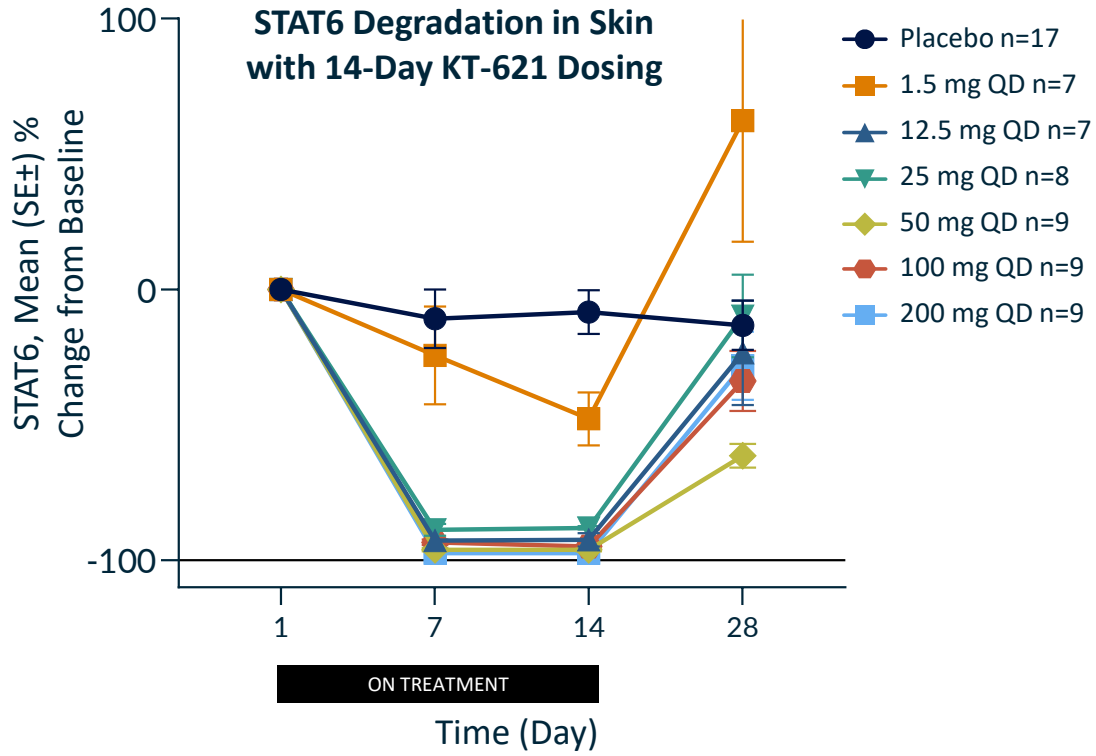
KT-621: Daily Doses Over 14 Days Rapidly Achieve Complete STAT6 Degradation in Blood and Skin

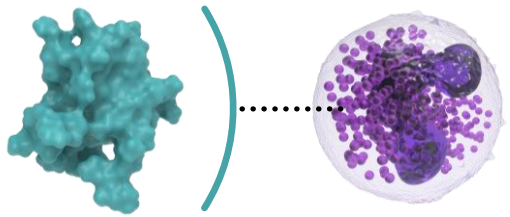




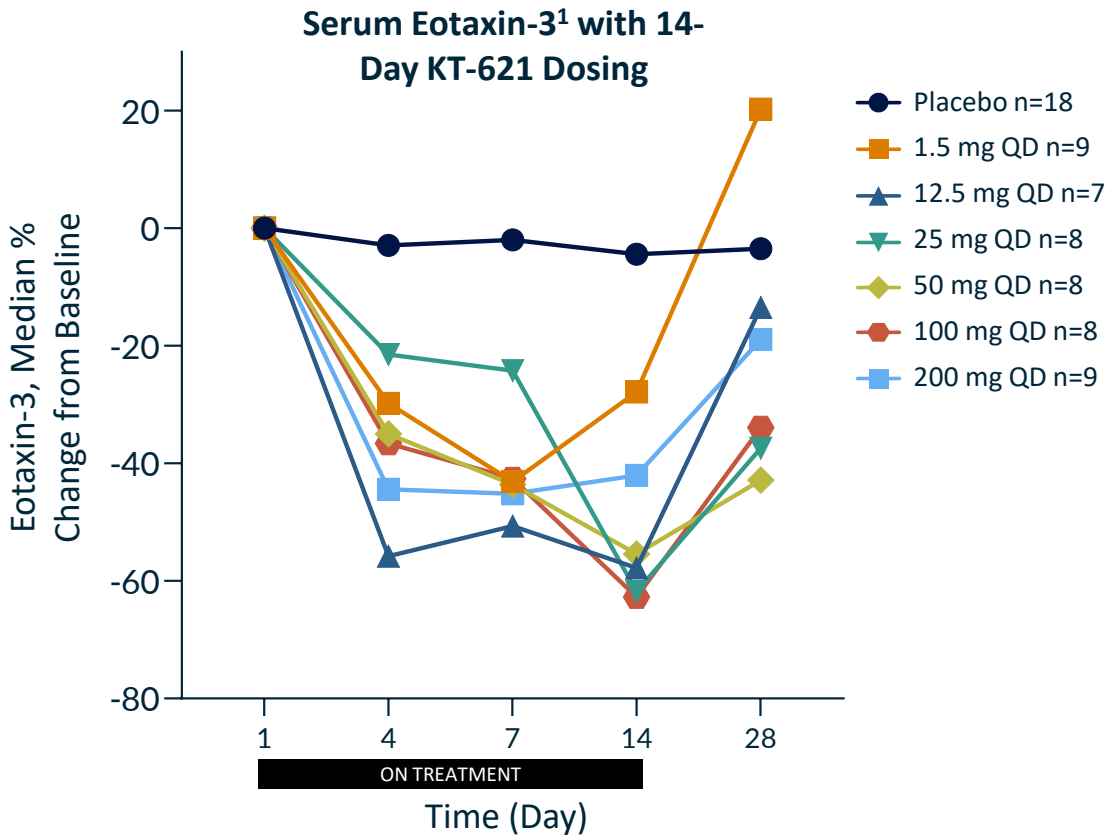
- Steady-state maximum degradation in blood achieved as early as 8hr post-first dose with recovery starting at 4 days post-last dose
- Steady-state maximum degradation in skin achieved by Day 7 at doses >1.5 mg with recovery observed 14 days post-last dose
- Complete STAT6 degradation, characterized by ≥95% decrease from baseline and/or undetectable levels in most participants, was achieved in both blood and skin at doses ≥50 mg at Day 14

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**



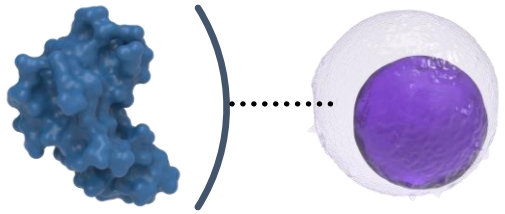
Arm	Day 14 Eotaxin-3, (Median % Change from Baseline)
Placebo	-4%
1.5 mg	**-28%**
12.5 mg	**-58%**
25 mg	**-62%**
50 mg	**-55%**
100 mg	**-63%**
200 mg	**-42%**

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

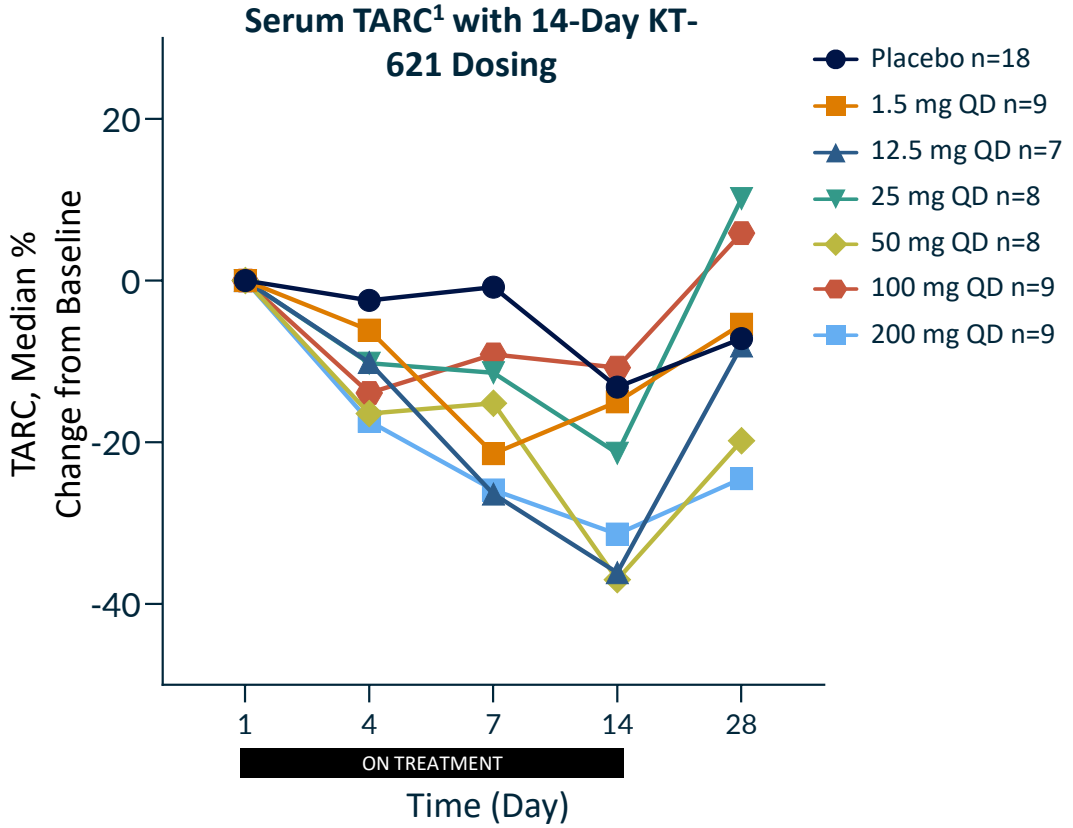
[1]Eotaxin-3 levels measured in serum using MSD VPLEX; [2]Hamilton et al. Clinical & Experimental Allergy. 2021.[3]No head-to-head trials have been conducted comparing KT-621 to dupilumab. Phase 1 clinical data for KT-621 may not be directly comparable to dupilumab's clinical data due to differences in molecule composition, trial protocols, dosing regimens, and patient populations and characteristics. Accordingly, cross-trial comparisons may not be reliable.

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



Arm	Day 14 TARC (Median % Change From Baseline)
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]

[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.

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%)

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.

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Q&A

THANK YOU!

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