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

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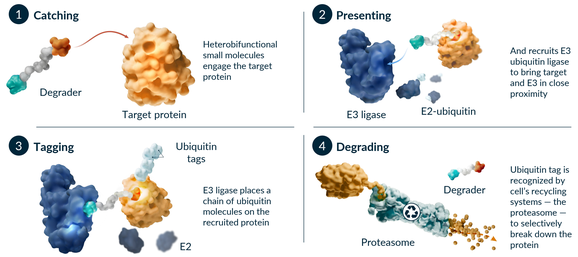
INTRODUCTION

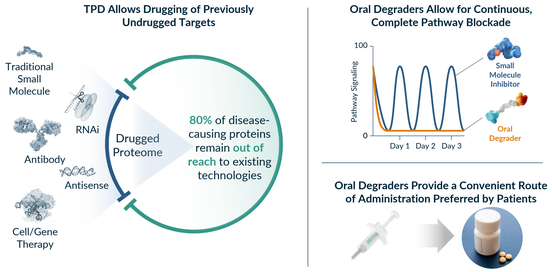
STAT6 is an essential transcription factor in the IL-4/IL-13 signaling pathways and the central driver of Th2 inflammation in allergic/atopic diseases. Multiple gain of function mutations of STAT6 have been identified to cause severe atopic/allergic diseases in humans. Dupilumab, an injectable monoclonal antibody that blocks IL-4/IL-13 signaling, is an approved therapy for multiple atopic/allergic diseases therefore targeting STAT6 in these diseases is supported by both human genetics and dupilumab's clinical activity. STAT6 functions through protein-protein and protein-DNA interactions. It has been challenging to selectively and potently inhibit STAT6 with traditional small molecule inhibitors. However, STAT6 is well suited for a novel targeted protein degradation approach, where a simple binding event is sufficient to drive degradation of the protein and fully block its functions.

Pioneering Targeted Protein Degradation for New Oral Medicines

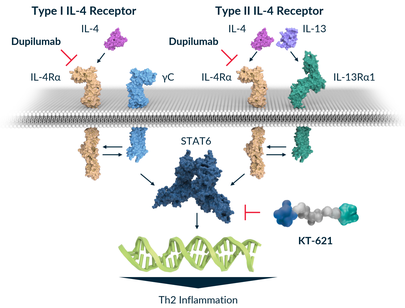
- Targeted protein degradation (TPD) harnesses the natural cellular homeostasis and protein degradation system used to clear out misfolded or accumulated proteins to degrade disease causing proteins



Small Molecule Oral Degraders Can Transform Drug Development



STAT6 Transcription Factor, Highly Validated but Undrugged Target



- STAT6 is the specific transcription 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.

RESULTS

Figure 1. KT-621: First STAT6-targeted Drug in Clinical Development

- Compelling KT-621 preclinical package provides potential for Dupilumab-like activity in a pill

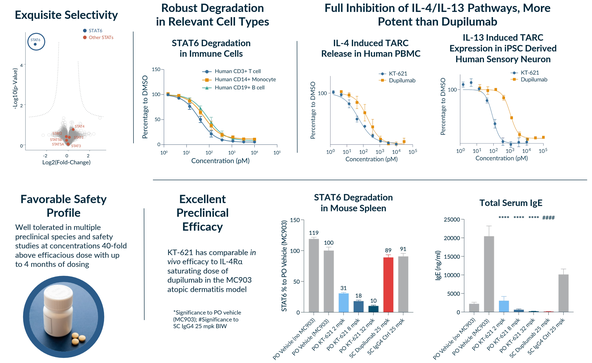
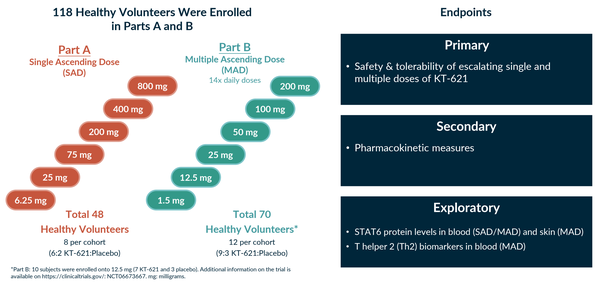


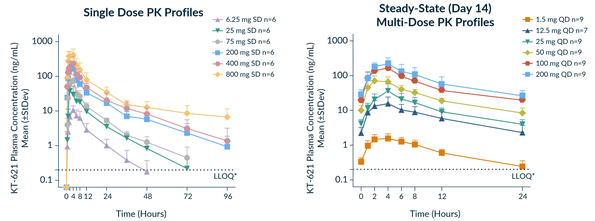
Figure 2. KT-621: First-in-Human, Phase 1a Healthy Volunteer Study

- Randomized, double-blind, placebo-controlled, single ascending dose (SAD), multiple ascending dose (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.

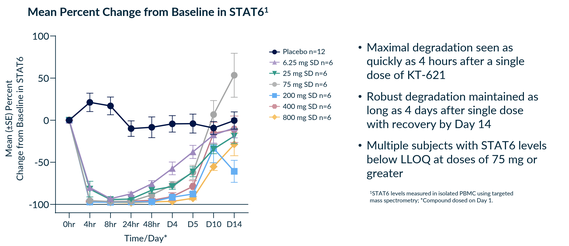
Figure 3. KT-621: Favorable PK Profile After Single and Multiple Dosing



*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, tmax: time to peak drug concentration. Additional information on the trial is available on https://clinicaltrials.gov/: NCT06673667. mg: milligrams.

- 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.

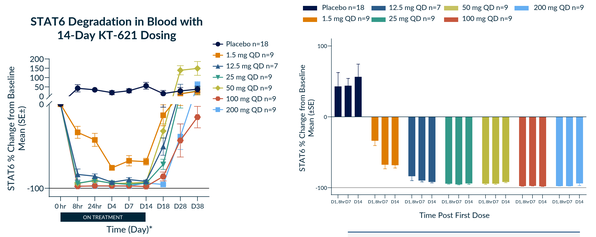
Figure 4. Single Doses of KT-621 Achieved Rapid, Deep and Prolonged STAT6 Degradation in Blood



- 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

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

Figure 5. KT-621: Daily Doses Over 14 Days Rapidly Achieve Complete STAT6 Degradation in Blood

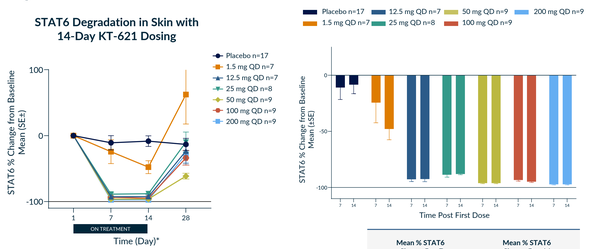


*Compound dosed on Day 1. SE: standard error, hr: hour, D: Study Day, QD: once daily, n: # participants, mg: milligrams

- 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.

	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%

Figure 6. KT-621: Daily Doses Over 14 Days Rapidly Achieve Complete STAT6 Degradation in Skin

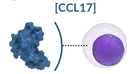


*Compound dosed on Day 1. SE: standard error, hr: hour, D: Study Day, QD: once daily, n: # participants, mg: milligrams

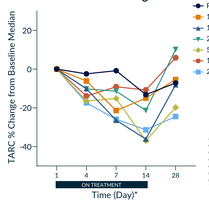
- Steady-state maximum degradation in skin achieved by Day 7 at doses >1.5 mg with recovery observed 14 days post-last dose.
- Complete STAT6 degradation was achieved at doses ≥50 mg at Day 14, showing correlation between degradation in skin and blood.

	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%

Figure 7. KT-621: Daily Doses Over 14 Days Achieved Median TARC Reduction of Up to 37%



- 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

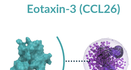


Arm	Day 14 TARC (% Change From Baseline Median)
Placebo	-13%
1.5 mg	-15%
12.5 mg	-36%
25 mg	-21%
50 mg	-37%
100 mg	-11%
200 mg	-31%

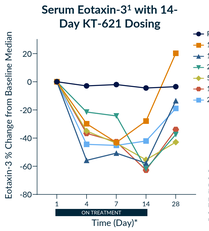
¹TARC levels measured in serum using MSD VPLEX; ²Hamilton et al. Clinical & Experimental Allergy, 2021. ³No head-to-head trials have been conducted comparing KT-621 to dupilumab. Phase 1 clinical data for KT-621 may not be directly comparable to dupilumab's clinical data due to differences in molecule 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.

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

Figure 8. KT-621: Daily Doses Over 14 Days Achieved Median Eotaxin-3 Reduction of Up to 63%



- 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 (% 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%

¹Eotaxin-3 levels measured in serum using MSD VPLEX; ²Hamilton et al. Clinical & Experimental Allergy, 2021. ³No 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.

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

Figure 9. 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

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

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%)

CONCLUSIONS

- 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.