P1540

KT-621, an Oral STAT6 Degrader, Improves Pruritus and Sleep in Patients With Moderate-to-Severe Atopic Dermatitis: Phase 1b Results

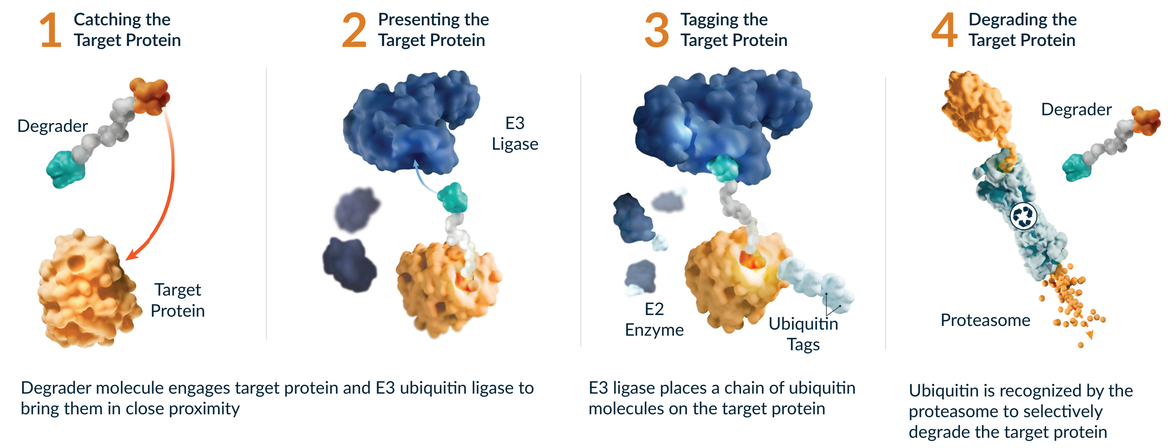
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INTRODUCTION

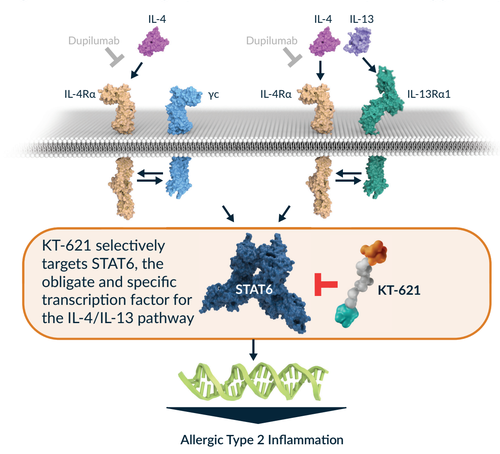
- Pruritus, driven largely by IL-31, a cytokine that is downstream of IL-4/IL-13/STAT6 signaling, and associated sleep disruption are among the most burdensome symptoms of atopic dermatitis (AD), substantially impairing patients' quality of life (QoL)[1]
- Although biologics targeting the IL-4/IL-13 pathway have transformed the treatment of Type 2 inflammatory diseases including AD, there remains a need for safe, well-tolerated oral therapies capable of delivering broad and consistent disease control[1]

Figure 1. Targeted Protein Degradation (TPD): Achieving Biologics-Like Activity With Oral Medicines[2]



Catalytic activity of degraders enables a single molecule to drive degradation of multiple copies of the target protein, delivering deep and continuous pathway blockade[2]

Figure 2. STAT6: Highly Validated, Historically Undrugged Target for Treatment of Type 2 Inflammatory Diseases[3]



STAT6 Transcription Factor

- STAT6 is the specific transcription factor in the IL-4/IL-13 pathway[3-5]
- IL-4/IL-13 is clinically validated by dupilumab across multiple Type 2 diseases:
  - AD, asthma, COPD, EoE, CRSwNP, CSU, PN, BP[1]
- While several therapies target the upstream IL-4/IL-13 receptors, there are no known drugs that selectively target this pathway with oral delivery[1]

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

- 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 placebo[6]

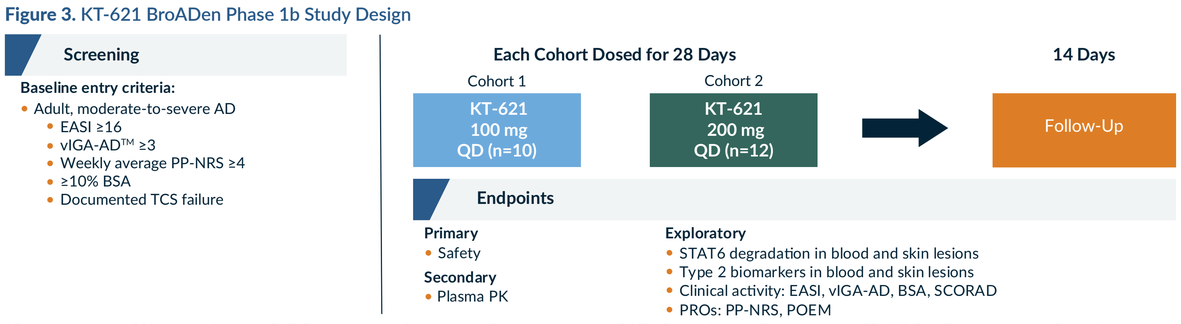
AD, atopic dermatitis; BP, bullous pemphigoid; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; CSU, chronic spontaneous urticaria; EoE, eosinophilic esophagitis; γc, gamma chain; IL, interleukin; PN, prurigo nodularis; STAT6, signal transducer and activator 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
- In this analysis, effects of KT-621 across Type 2 biomarkers and clinical endpoints, including patient-reported outcomes (PROs) assessing pruritus, sleep, and QoL were evaluated

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



AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; PK, pharmacokinetics; POEM, Patient Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; PRO, patient-reported outcome; QD, once daily; SCORAD, SCORing Atopic Dermatitis; STAT6, signal transducer and activator of transcription 6; TCS, topical corticosteroid; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.
Prior biologics were allowed, after washout, if patient had responded to treatment. Concurrent medications for AD not permitted.

RESULTS

Table 1. Baseline Characteristics Were Well Balanced Between Dose Cohorts

Patient Demographics	100 mg (n=10)	200 mg (n=12)	Overall (n=22)
Gender, n (%)			
Female	6 (60.0)	7 (58.3)	13 (59.1)
Male	4 (40.0)	5 (41.7)	9 (40.9)
Age, years, mean (SD)	30.1 (8.5)	33.0 (11.4)	31.7 (10.1)
BMI, kg/m², mean (SD)	32.8 (11.5)	30.8 (9.2)	31.7 (10.1)
Patient Baseline Characteristics			
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)
Other Disease Characteristics, mean (SD)			
PP-NRS*	7.4 (1.2)	7.6 (0.9)	7.5 (1.0)
SCORAD	55.7 (15.6)	63.8 (13.4)	60.1 (14.7)
POEM	16.1 (6.7)	20.8 (5.2)	18.6 (6.3)
DLQI	9.2 (6.63)	13.7 (8.66)	11.6 (7.96)

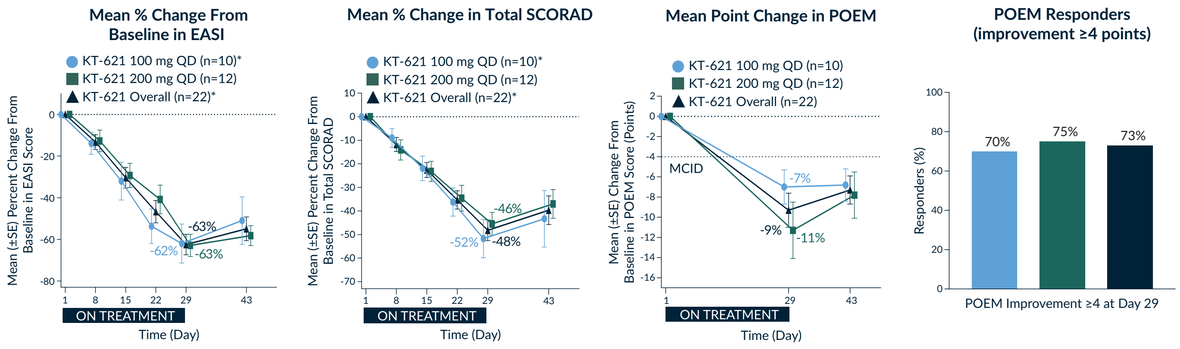
*Score ranging from 0 to 10.
AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; POEM, Patient Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

- In the overall cohort:
  - Mean baseline PP-NRS score of 7.5 indicated moderate-to-severe itch severity
  - Mean baseline POEM score of 18.6 indicated severe patient-reported disease
  - Mean baseline DLQI score of 11.6 indicated AD had a large impact on patients' QoL

DISCLOSURES

Eric L. Simpson reports grants and fees for participation as a consultant or principal investigator from AbbVie, Acrotech, Aclaris Therapeutics, Almirall, Amgen, Arcutis, ASLAN, Astria Therapeutics, Attovia Therapeutics Inc., Bambusa Therapeutics Inc., Castle, CorEvitas, Dermavant, Dermira, Eli Lilly, Evommune, FIDE, Genentech, Inc., Impetus Healthcare, Incyte, Innovaderm Research/Indero, Inmagene Biopharmaceuticals, Janssen, Khanda UK Employco Ltd., Kymera Therapeutics, Inc., La Fonderie Ressources, LEO Pharma, Nektar/PPD Development, L.P., Numab Therapeutics AG, Pfizer, Recludix Pharma, Regeneron, Roche Products Ltd., Sanofi-Genzyme, SITRYX Therapeutics, Target, UCB Biopharma SRL, and VeriSki. **Alan Irvine** reports fees for participation as a consultant from AbbVie, Eli Lilly, LEO Pharma, Novartis, Pfizer, Quoin, Regeneron Pharmaceuticals Inc., Sanofi, Sitryx, and UCB; fees for participation as a speaker from AbbVie, Eli Lilly, Kymera Therapeutics, Inc., LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., and Sanofi; participation as an investigator for AbbVie, Novartis, and Sanofi–Regeneron Pharmaceuticals Inc.; and is a patent holder with Regeneron Pharmaceuticals Inc. **Jared Gollob, Nello Mainolfi, Neil Graham, Anna Tallman, Kelvin Shi**, and **Sagar Agarwal** are employees with shares and stock options of Kymera Therapeutics, Inc. **Joyoti Dey** is a former employee of Kymera Therapeutics, Inc.

Figure 4. KT-621 Produced Rapid and Consistent Improvements in Clinician- and Patient-Reported Disease Severity



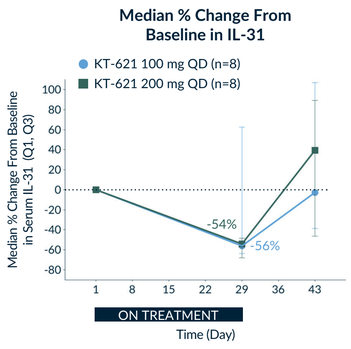
Analysis based on observed cases at each visit.
EASI, Eczema Area and Severity Index; MCID, minimum clinically important difference; POEM, Patient Oriented Eczema Measure; QD, once daily; SCORAD, SCORing Atopic Dermatitis; SE, standard error.
*One patient in the 100 mg cohort missed the Day 29 visit (n=9 for 100 mg and n=21 for Overall at Day 29).

- Rapid reductions in EASI and SCORAD were observed as early as Day 8 and continued through Week 4
- All patients achieved clinically meaningful improvements in SCORAD, exceeding the 8.7-point MCID
- POEM improvements exceeded the MCID, with the majority of patients achieving clinically meaningful responses (≥4-point improvement) by Week 4

KT-621 Substantially Improved Disease Burden as Measured by EASI-50, EASI-75, and vIGA-AD™ 0 or 1 at Week 4

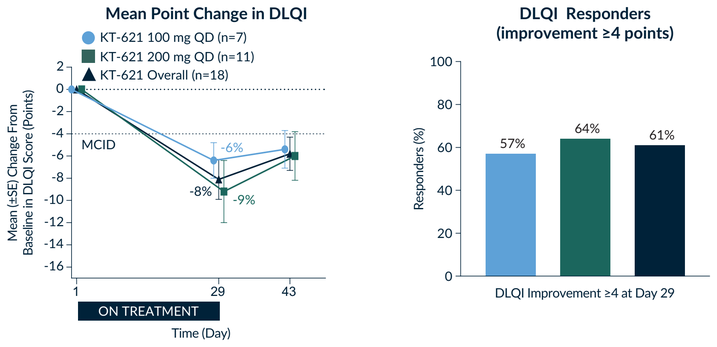
- At week 4, 76.2% and 28.6% of patients in the overall cohort achieved EASI-50 and EASI-75, respectively
- Overall, 19.0% of patients achieved a vIGA-AD response at Week 4

Figure 5. KT-621 Achieved Rapid and Deep STAT6 Degradation in Blood and Skin and Marked Reductions in Type 2 Biomarkers in Blood, Including Pruritogenic Cytokine IL-31



- 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
- Rapid and robust reductions of TARC (48% with 100 mg; 55% with 200 mg) and Eotaxin-3 (62% with 100 mg; 73% with 200 mg)
- First known demonstration of serum IL-31 reduction in patients with AD in response to IL-4/IL-13 pathway inhibition, with median reductions of 56% and 54% by Week 4 in the 100 mg and 200 mg cohorts, respectively

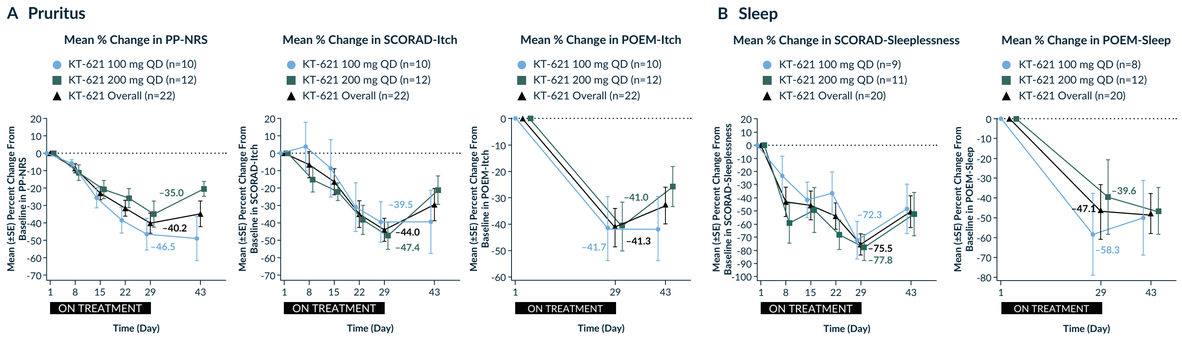
Figure 6. KT-621 Achieved Clinically Relevant Improvement in Patient Quality of Life (DLQI)



- Mean improvement in DLQI exceeded the established MCID by Week 4, with most patients achieving clinically meaningful responses (≥4-point improvement)

Analysis based on observed cases at each visit. Only patients with baseline DLQI score ≥4 included.
DLQI, Dermatology Life Quality Index; MCID, minimum clinically important difference; QD, once daily; SE, standard error.

Figure 7. KT-621 Achieved Robust and Consistent Reductions in Pruritus and Sleep Across Independent Clinical Measures



Outcomes by dose group and overall, with once-daily dosing for 28 days starting on Day 1.
POEM, Patient Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; SCORAD, SCORing Atopic Dermatitis; QD, once daily; SE, standard error.

- Rapid and consistent reductions in pruritus and sleep were observed in both dose cohorts across multiple validated outcome measures
- Concordant improvements across independent patient- and clinician-reported assessments support a broad treatment effect on these key symptoms of AD

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

- KT-621 produced rapid and consistent improvements in pruritus and sleep across multiple independent patient- and clinician-reported assessments, addressing two of the most burdensome symptoms of AD
- Clinical improvements were accompanied by rapid and deep STAT6 degradation and broad suppression of Type 2 inflammatory biomarkers, including marked reductions in IL-31, supporting the proposed mechanism of action
- Patients experienced clinically meaningful improvements in patient-reported disease severity and QoL, with POEM and DLQI exceeding the MCID
- KT-621 demonstrated a favorable safety and tolerability profile at both 100 mg and 200 mg dose levels

KT-621 CLINICAL DEVELOPMENT PROGRAM

- BROADEN2 is a randomized, double-blind, placebo-controlled Phase 2b trial in approximately 200 patients with moderate-to-severe AD
- Patients randomized 1:1:1:1 to one of three KT-621 dose groups or placebo for 16 weeks, with a 52-week open-label extension
- The primary endpoint is percent change from baseline in EASI score at week 16. Enrollment has been completed, and topline results are expected by year-end 2026

REFERENCES

1. Kolkhir P, et al. *Nat Rev Drug Discov*. 2023;22(9):743-767.
2. Mainolfi N, Rasmusson T. *Annual Reports Med Chem*. 2017;50:301-334.
3. Junttila IS. *Front Immunol*. 2018;9:888.
4. Kaplan MH, et al. *Immunity*. 1996;4:313-319.
5. Takeda K, et al. *J Immunol*. 1996;157(8):3220-3222.
6. Shabbir A, et al. European Academy of Dermatology and Venereology Congress; Sept 17–20, 2025; Paris, France.

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