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KT-621, an Oral STAT6 Degrader, Consistently Improves Moderate-to-Severe Atopic Dermatitis Across Body Regions: Phase 1b Results

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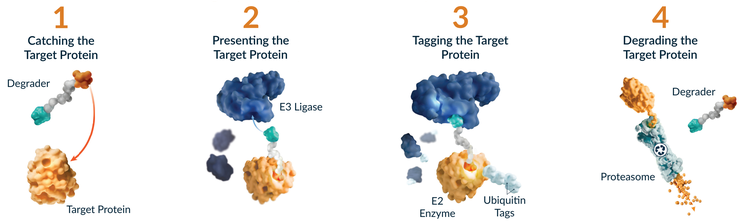
INTRODUCTION

- Although biologics targeting the IL-4/IL-13 pathway have transformed the treatment of atopic dermatitis (AD), a need remains for safe and well tolerated oral therapies capable of delivering broad and consistent disease control across clinically relevant body regions[1]
- KT-621 is a first-in-class, oral STAT6 degrader designed to selectively inhibit IL-4/IL-13 signaling through targeted protein degradation (TPD)[2-4]

Figure 1. TPD: Achieving Biologics-Like Activity With Oral Medicines[2]

TPD Mechanism of Action: Harnessing the E3 Ubiquitin Proteasome System



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

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

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

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[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[3,5,6]
- IL-4/IL-13 is clinically validated by dupilumab across multiple Type 2 diseases, including AD, asthma, COPD, EoE, CRSwNP, CSU, PN, BP[1,7]
- 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 (eotaxin-3 and thymus and activation-regulated chemokine [TARC]), and a safety profile undifferentiated from placebo[4]

BP, bullous pemphigoid; 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.

OBJECTIVE & METHODS

- AD is heterogeneous across body regions, and involvement of visible or difficult-to-treat areas such as the head/neck can disproportionately affect patient burden.[8,9] This analysis evaluated whether the rapid EASI improvement observed with KT-621 was consistent across EASI body regions after 4 weeks of once-daily oral treatment
- Reported here is a post hoc analysis of a Phase 1b open-label, multicenter, single-arm study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of oral KT-621 in adults with moderate-to-severe AD
- EASI subscores were assessed for the head/neck, upper extremities, trunk, and lower extremities. All analyses are based on observed cases

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

Screening

Baseline entry criteria:
- Adult, moderate-to-severe AD
  - EASI ≥16
  - vIGA-AD™ ≥3
  - Weekly average PP-NRS ≥4
  - ≥10% BSA
  - Documented TCS failure

Each Cohort Dosed for 28 Days — **14 Days**

Cohort 1: KT-621 100 mg QD (n=10)

Cohort 2: KT-621 200 mg QD (n=12)

→ Follow-Up

Endpoints

Primary
- Safety

Secondary
- Plasma PK

Exploratory
- STAT6 degradation in blood and skin lesions
- Type 2 biomarkers in blood and skin lesions
- Clinical activity: EASI, vIGA-AD, BSA, SCORAD
- PROs: PP-NRS, POEM

Prior biologics were allowed, after washout, if patient had responded to treatment. Concurrent medications for AD not permitted.
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.

RESULTS

Table 1. Baseline Characteristics Were Well Balanced Between Dose Cohorts

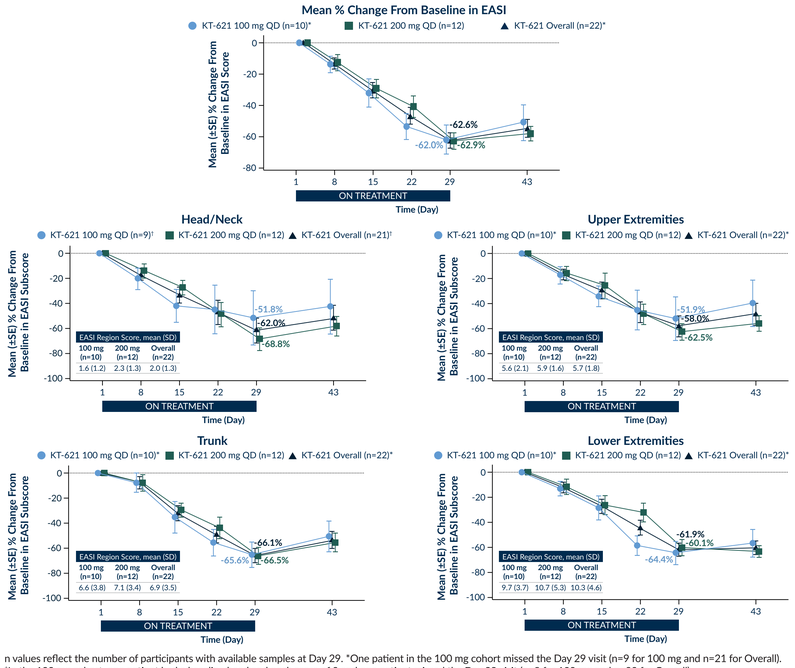
Patient Baseline Characteristics	100 mg (n=10)	200 mg (n=12)	Overall (n=22)
EASI Score, mean (SD)	23.5 (7.5)	26.1 (9.0)	24.9 (8.3)
vIGA-AD™, n (%)			
Moderate (3)	6 (60.0)	6 (50.0)	12 (54.5)
Severe (4)	4 (40.0)	6 (50.0)	10 (45.5)
Other Disease Characteristics, mean (SD)			
PP-NRS	7.4 (1.2)	7.6 (0.9)	7.5 (1.0)
SCORAD	55.7 (15.6)	63.8 (13.4)	60.1 (14.7)
BSA (%)	29.1 (9.8)	30.0 (15.1)	29.6 (12.7)
POEM	16.1 (6.7)	20.8 (5.2)	18.6 (6.3)

BSA, body surface area; 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.

KT-621 Achieved Rapid and Deep STAT6 Degradation in Blood and Skin and Marked Reductions in Type 2 Biomarkers in Blood

- 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 up to 56% median reduction by Week 4

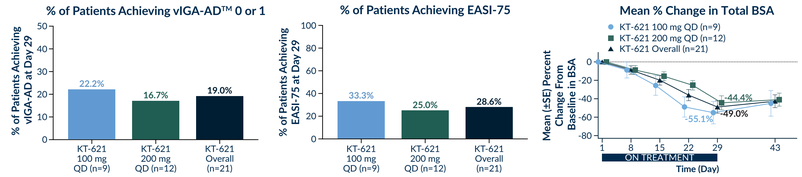
Figure 4. KT-621 Achieved Uniform Reductions in EASI Across Body Regions at Week 4



n values reflect the number of participants with available samples at Day 29. *One patient in the 100 mg cohort missed the Day 29 visit (n=9 for 100 mg and n=21 for Overall). †In the 100 mg cohort, one patient had a baseline head and neck score of 0 and one patient missed the Day 29 visit (n=8 for 100 mg and n=20 for Overall).
EASI, Eczema Area and Severity Index; QD, once daily; SE, standard error.

- Marked and early improvements in mean EASI scores across both dose cohorts, with responses evident by Day 8 and continuing through Week 4 without apparent plateau
- In this post hoc analysis, improvements in EASI scores by body region were observed as early as Day 8
- At Week 4, EASI scores decreased consistently across all body regions, with reductions ranging from 58% to 66% (62% for head/neck, 58% for upper extremities, 66% for trunk, and 62% for lower extremities)

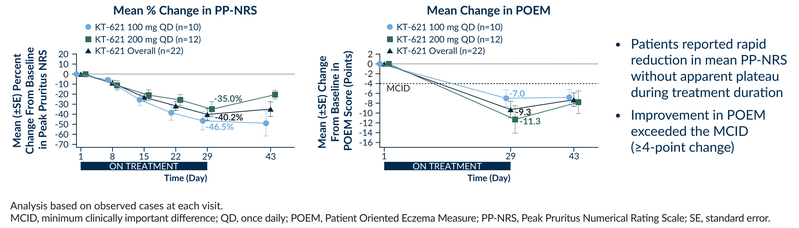
Figure 5. KT-621 Demonstrated Strong vIGA-AD™ and EASI-75 Responses at Week 4 and Robust Improvement in BSA



n values reflect the number of participants with available samples at Day 29. BSA, body surface area; EASI, Eczema Area and Severity Index; QD, once daily; SE, standard error; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

- At Week 4, vIGA-AD 0 or 1 was achieved by 19% of patients overall
- EASI-75 response was achieved in 29% of patients overall at Week 4
- Reductions in BSA seen as early as Day 8 without apparent plateau during treatment duration

Figure 6. KT-621 Achieved Robust and Consistent Improvements in Peak Pruritus and POEM



Analysis based on observed cases at each visit.
MCID, minimum clinically important difference; QD, once daily; POEM, Patient Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; SE, standard error.

- Patients reported rapid reduction in mean PP-NRS without apparent plateau during treatment duration
- Improvement in POEM exceeded the MCID (≥4-point change)

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 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

CONCLUSIONS

- KT-621 demonstrated rapid and consistent improvements in EASI across all body regions after 4 weeks of once-daily oral treatment, including difficult-to-treat areas such as the head and neck, supporting broad clinical activity throughout the body
- Uniform improvements across body regions were accompanied by deep STAT6 degradation in blood and skin and broad suppression of Type 2 inflammatory biomarkers, consistent with the proposed mechanism of action
- KT-621 also produced rapid improvements in skin lesion burden, clinically meaningful improvements in pruritus and patient-reported outcomes, and 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. Shabbir A, et al. European Academy of Dermatology and Venereology Congress; Sept 17–20, 2025; Paris, France.
5. Kaplan MH, et al. *Immunity*. 1996;4:313-319.
6. Takeda K, et al. *J Immunol*. 1996;157(8):3220-3222.
7. Hamilton JD, et al. *Clin Exp Allergy*. 2021;51(7):915-931.
8. Lio PA, et al. *J Drugs Dermatol*. 2020;19:943–948.
9. Lauletta G, et al. *Antibodies (Basel)*. 2025;14(4):104.

DISCLOSURES

Jonathan I. Silverberg has received grants and/or personal fees from AbbVie, AFYX Therapeutics, Almirall, Arena Pharmaceuticals, Asana BioSciences, Bluefin Biomedicine, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly and Company, Galderma, GlaxoSmithKline, Incyte Corporation, Kiniksa Pharmaceuticals, LEO Pharma, Luna Pharma, Menlo Therapeutics, Novartis, Pfizer, RAPT Therapeutics, Regeneron, and Sanofi. Jared Gollob, Neil Graham, Kelvin Shi, Anna M. Tallman, Joyoti Dey, Mahta Mortezavi, Sagar Agarwal, and Nello Mainolfi are employees with shares and stock options of Kymera Therapeutics, Inc.

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2026 AAD Innovation Academy • July 16-19, 2026 • New York, NY