Revolutionizing Immunology with Oral Medicines

January 2025

KYMERA

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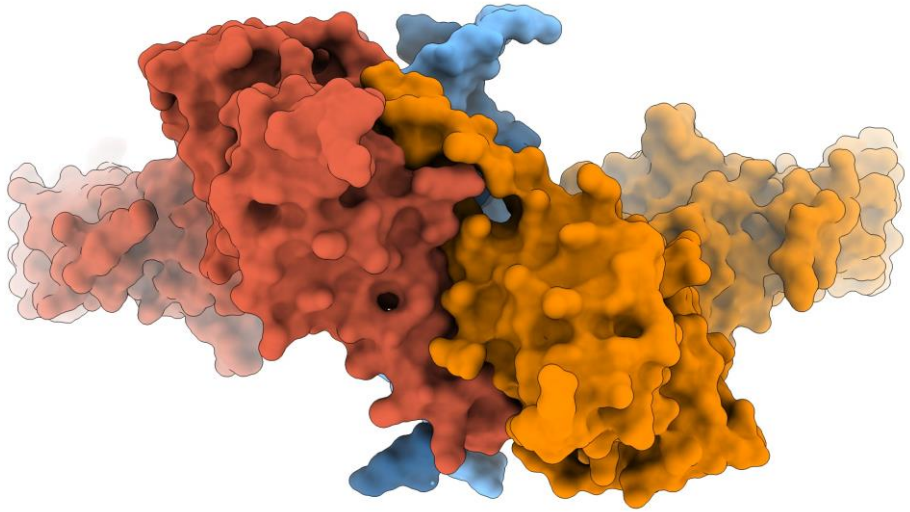
Revolutionizing Immunology: Oral Drugs with Biologics-Like Efficacy

Science-driven clinical stage organization with industry-leading oral immunology pipeline

- Targeted Protein Degradation (TPD) leader
- Best-in-industry capabilities in hit finding and optimization of oral degraders
- Unique target selection strategy pursuing traditionally undrugged targets
- Portfolio poised to disrupt conventional treatment paradigms



By combining the **"right target" with the disruptive potential of TPD, Kymera is delivering oral therapies with biologics-like profiles** for the first time in industry with the potential to expand access to millions of patients around the world

Clear Vision and History of Strong Execution

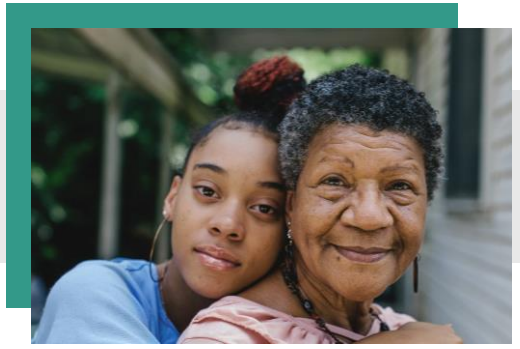
VISION

- *Reinventing the treatment of human disease* **as a fully integrated commercial global biotech**
  - Building a world-class immunology development team to execute on large Phase 2/3 trials
  - Raised **$1.7B** to date, with **$850M**[1] of cash on hand, providing a runway to mid-2027

EXECUTION

- Delivered **5 new investigational degrader drugs into the clinic since 2020**, and on path to deliver a total of **10 by 2026**

IMPACT

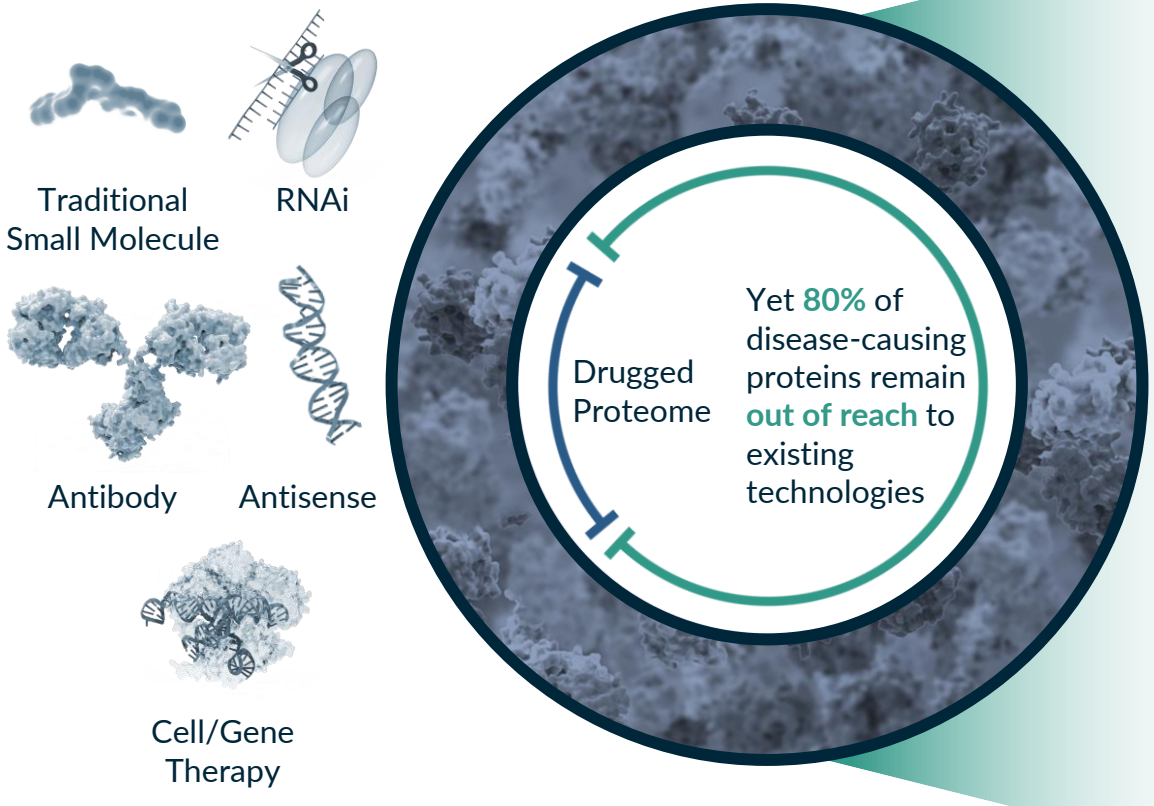


- Dosed over **300 healthy volunteers/patients** to date across clinical pipeline, demonstrating:
  - **>90% target degradation in all programs**
  - **Desired safety and efficacy profiles**

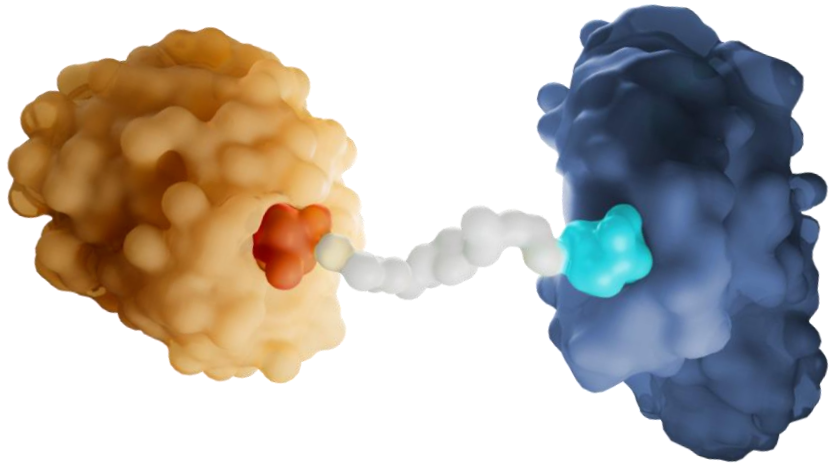
[1]Estimated, unaudited cash as of December 31, 2024

Targeted Protein Degradation: New Modality Expanding the Range of Treatable Disease

Existing modalities have limitations that restrict their application leaving millions of patients without adequate treatment options.



Targeted Protein Degradation



can unlock the undrugged proteome

- Small molecule-based modality with gene silencing power
- Not limited by delivery, target or tissue/organ type; disease agnostic
- Oral delivery
- Efficient development/manufacturing
- **Validated across multiple FDA-approved drugs** with >$17 billion in combined peak WW sales[1]

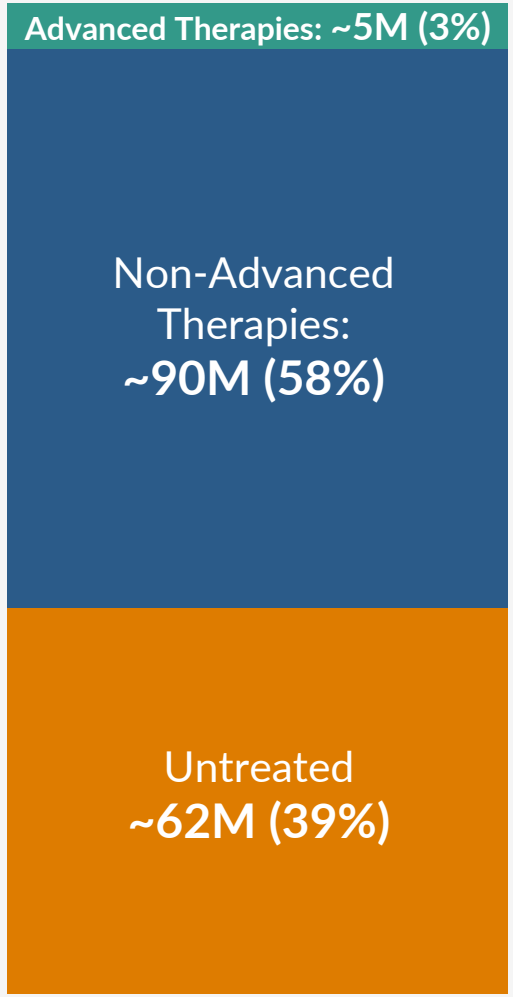
[1]Combined peak WW sales of FDA-approved degrader-based therapies (GlobalData)

Immunology: A Large, Underserved Market

~160M Total Patients Across Key Immunologic Diseases[1]

>$100B

- **~5M patients (3% of total diagnosed)** are on systemic advanced therapies with **>$100B** in annual sales for key I/I indications[2]
- **2/3 of those therapies are injectable biologics**



>$500B?

- ~ **97%** of the diseased population does not have access to advanced therapies
- Enormous untapped market potential

Oral Degraders with Biologics-Like Profiles Can Disrupt the Immunology Market

- **Displace injectable biologics**
- **Offer a convenient highly effective advanced therapy** to the 97% unserved and underserved patients

[1]Diagnosed prevalent patient population for US/EU5/JP (GlobalData; 2023); key immunologic diseases includes AD, Asthma, COPD, HS, MS, PsO, PsA, RA, SLE, UC, CD;
[2]Market Forecasts for US/EU5/JP (GlobalData; 2023)

Small Molecule Oral Degraders Can Transform Immunology

Potentially Superior Profile to Injectable Biologics and Traditional Small Molecule Inhibitors

Biologics have several limitations:

DUPIXENT® (dupilumab) Injection

Skyrizi® risankizumab-rzaa

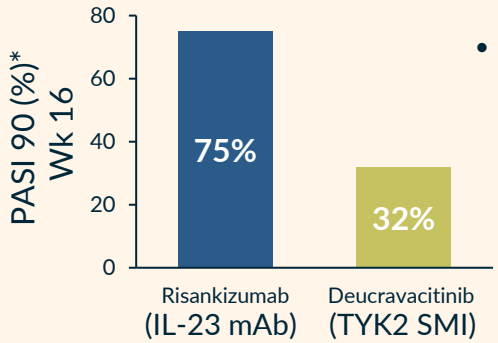
- Expensive, challenging to prescribe/reimburse
- Immunogenicity
- Cold storage
- Inconvenient and/or painful route of administration for patients

Orals preferred by most patients:

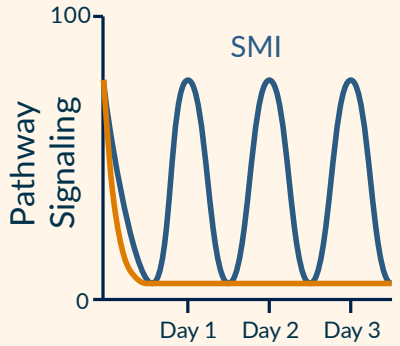
- In multiple surveys[1], **75%** of patients would switch from injectable biologics to oral with similar profile

Oral degraders have unique potential to provide **comparable pathway inhibition to biologics**, with the convenience of **oral dosing**, and potentially access **broader patient populations**

Traditional small molecule inhibitors (SMI) insufficiently block pathways, limiting efficacy:



- Anti IL-23 biologic dramatically more effective than TYK2 SMI in PsO[2]



- Traditional small molecule inhibitors do not allow continuous and complete pathway blockade

Oral Degrader

[1]J&J Business Review Dec '23 (survey of N=395 patients with moderate-to-severe psoriasis); [2]Skyrizi (IL-23 mAb) and Sotyktu (TYK2 SMI) package inserts

Unique Target Selection Strategy Drives Best-In-Class Pipeline

Undrugged or inadequately drugged targets

Strong genetic/clinical validation

Clear path to early clinical differentiation

Large clinical/ commercial opportunities

FOCUS ON FIRST- AND BEST-IN-CLASS OPPORTUNITIES

Industry Leader at Developing Oral Degrader Drugs

Hit Finding, Structural Biology and Chemistry

Comprehensive Proprietary Technologies to Identify Novel Ligands to Undrugged Proteins

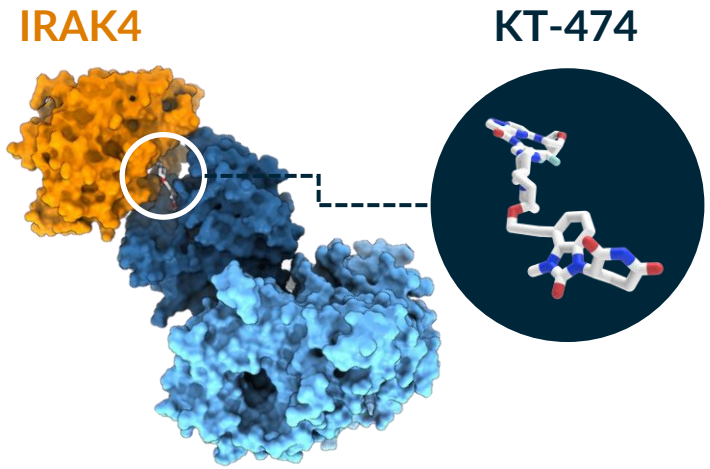
Virtual Screen	DEL	Fragment-Based Screen	Cysteine Covalent Screening	HTS	ASMS

- Transcription Factors
- Scaffolding Proteins
- E3 Ligases
- Others

Leading to:
>8 development candidates, including **>4** targeting **undrugged transcription factors**

Best-in-Industry Structural Biology Capabilities Across all Programs

Example: Cereblon-(KT-474)-IRAK4



Ternary complex Cryo-EM structures enable design of highly specific and potent degraders

World-Class Chemistry: Highly potent degraders (sub-nanomolar) with refined drug-like properties (orally bioavailable with systemic distribution to all target tissues), and comprehensive understanding of PK/PD, resulting in impeccable translation of our pipeline into the clinic across programs

Building the Best-in-Industry Oral Immunology Pipeline

	Potential Indications	IND-Enabling	Phase 1	Phase 2	Upcoming Milestones
Kymera Wholly-Owned					
STAT6	AD, Asthma, COPD, PN, CRSwNP, EoE, BP, others	KT-621			**Ph1 HV Data:** 2Q25 **Ph1b AD Data:** 4Q25 **Ph2b AD Start:** 4Q25 **Ph2b Asthma Start:** 1Q26
TYK2	Psoriasis, IBD, PsA, Lupus, others	KT-295			**Ph1 HV Start:** 2Q25 **Ph1 HV Data:** 4Q25
Transcription Factor	Lupus, Sjogren's, RA, IBD, others	Undrugged target to be disclosed in 1H25			**FIH:** Early 2026
Partnered with Sanofi (Kymera 50/50 US Opt-In Potential)[1]					
IRAK4	HS, AD, RA, Asthma, IBD, others[2]	KT-474 - HS KT-474 - AD			**Ph2b Completion:** **HS**: 1H26 **AD**: Mid-2026

Value Proposition: Combining the convenience of oral drugs and the efficacy of biologics to expand access to advanced therapies for millions of patients around the world

[1]KT-474 (SAR444656) partnered with Sanofi, with Kymera option to participate in the development and commercialization, and 50/50 profit split, in the United States. Double digit tiered royalties in ROW.
[2]Current indications: HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities.

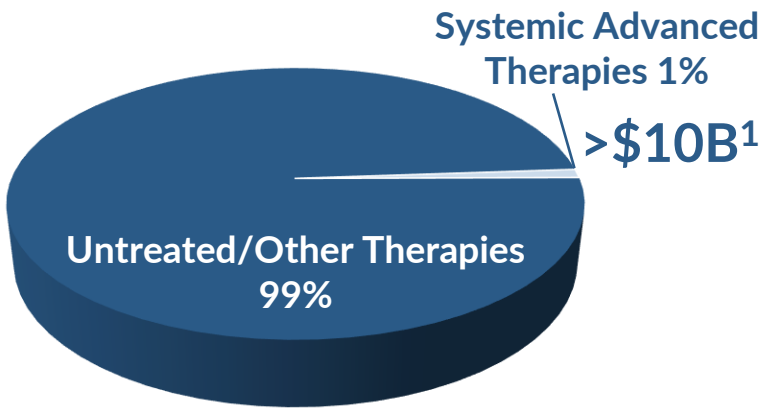
Oral Degraders in Immunology With Significant Market Potential

First-In-Industry: Orals with Biologics-Like Profiles Could Change the Commercial Landscape

STAT6
TRANSCRIPTION FACTOR

Key Indications: AD, Asthma, COPD, CRSwNP, EoE, CSU, PN

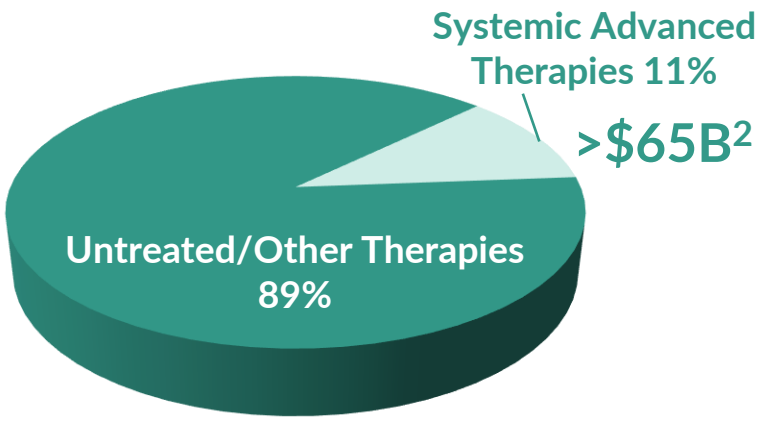
>130M[1] Diagnosed Patients



TYK2
SCAFFOLDING KINASE

Key Indications: PsO, PsA, SLE, UC, CD, MS

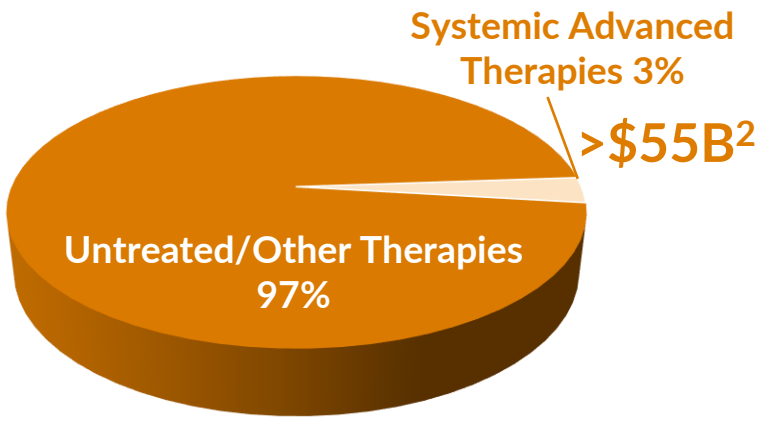
>20M[2] Diagnosed Patients



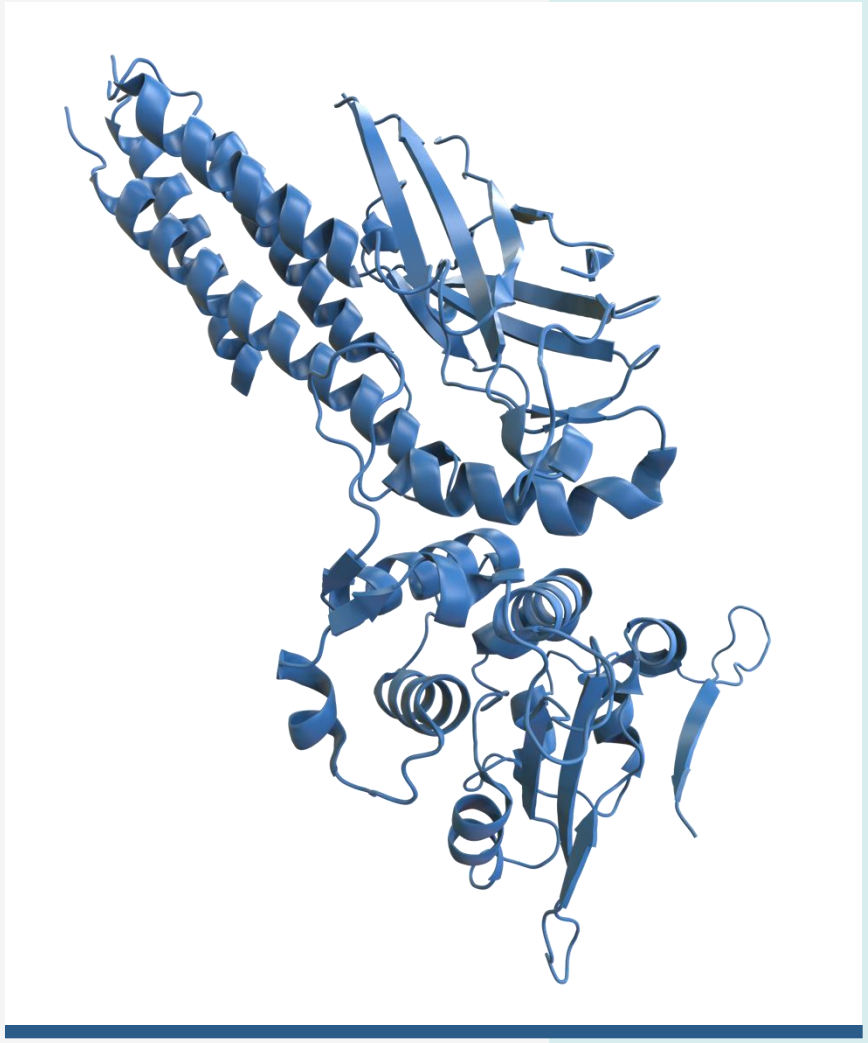
IRAK4
SCAFFOLDING KINASE

Key Indications[3]: HS, AD, Asthma, COPD, RA, SLE, UC, CD

>140M[2] Diagnosed Patients



[1]GlobalData (2023 diagnosed prevalent patient population and forecasted sales for approved systemic advanced therapies for AD, Asthma, and COPD only in US/EU5/JP)
[2]GlobalData (2023 diagnosed prevalent patient population and forecasted sales for approved systemic advanced therapies in US/EU5/JP)
[3]Current indications: HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities



First-in-Class Oral STAT6 Degrader Program

Dupilumab-like activity in a pill

STAT6 Biology and Target Rationale

Target Biology and Rationale

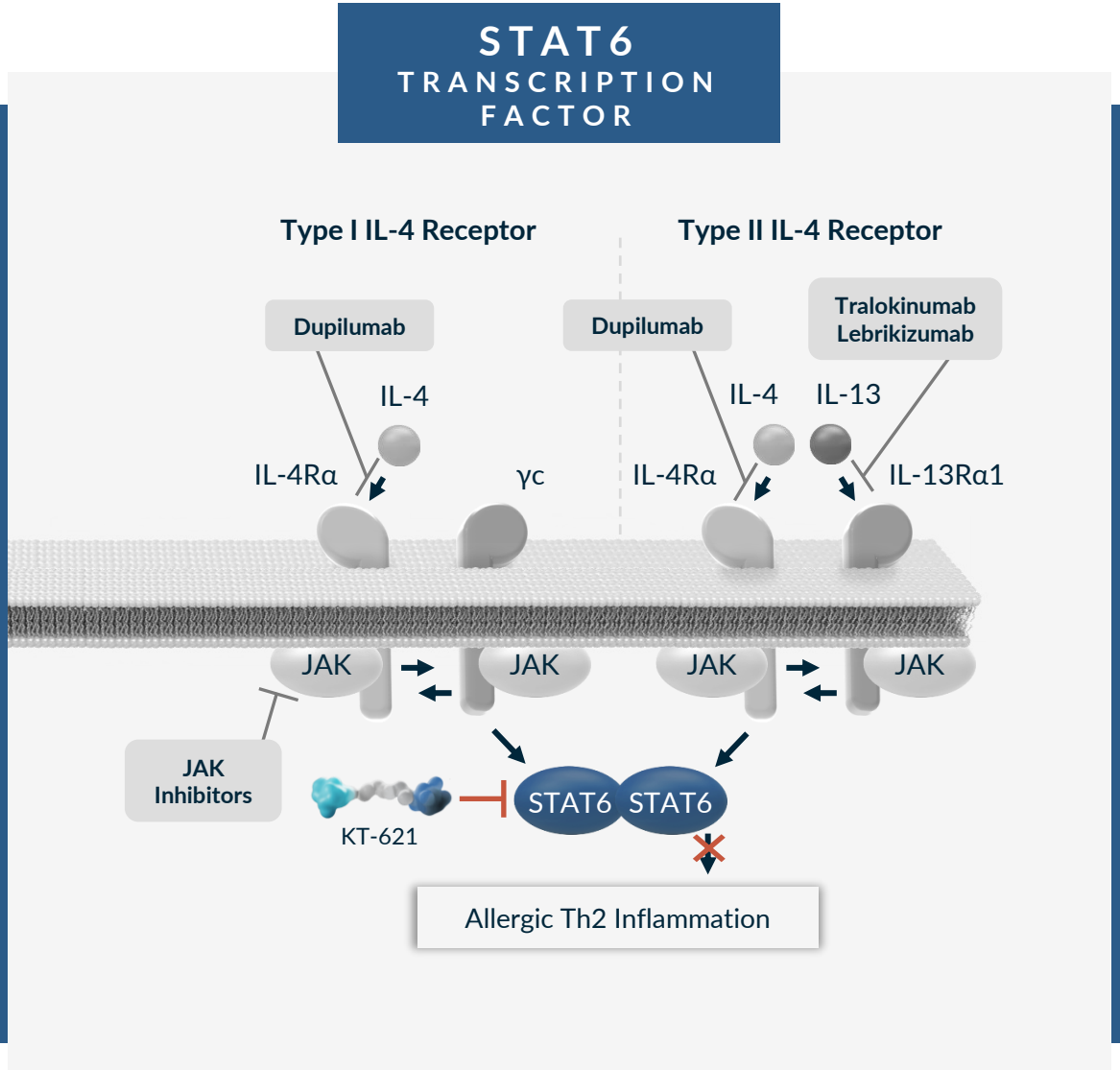
- STAT6 is the specific transcription factor required for IL-4 and IL-13 cytokine signaling
- STAT6 regulated cytokines are clinically validated targets for allergic diseases

Human and Mouse Genetics

- Gain of function (GOF) mutations of STAT6 cause severe allergic diseases in human
- STAT6 KO mice develop normally, are viable and fertile
- STAT6 partial loss-of-function, healthy, and protects from Th2-driven asthma

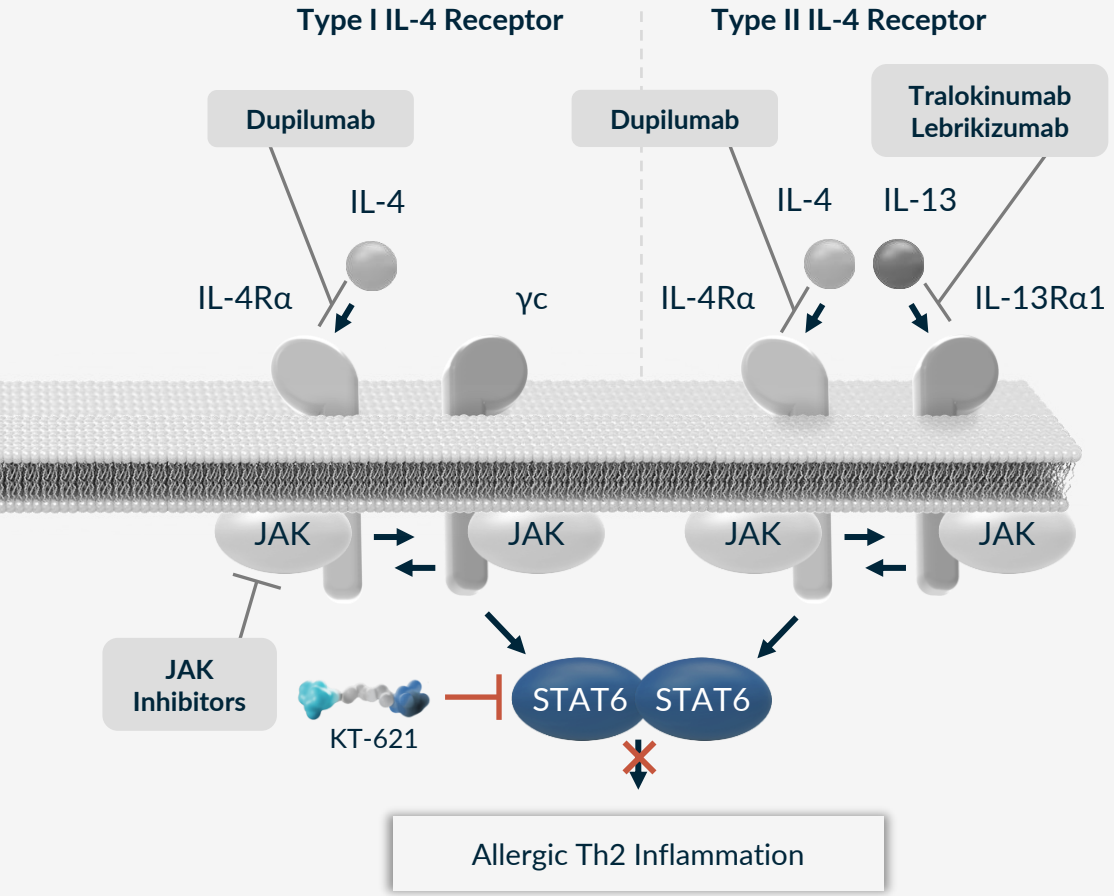
Clinical Pathway Validation

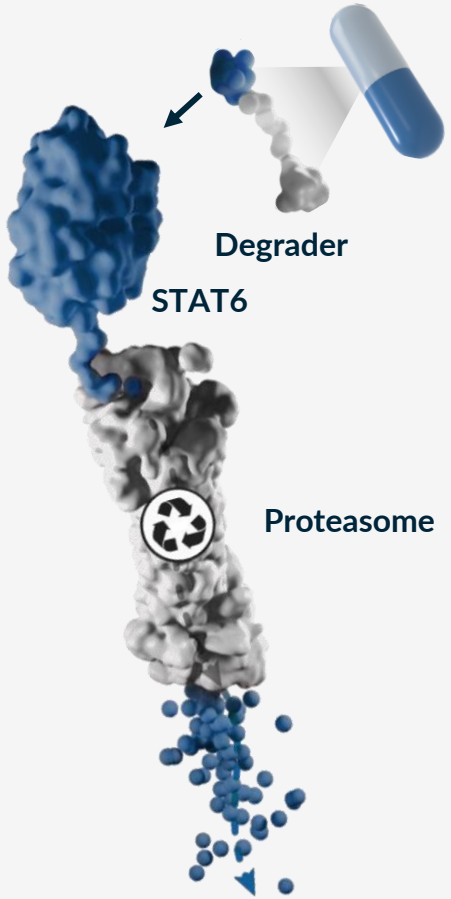
- Dupilumab, an IL-4Rα monoclonal Ab that blocks IL-4/IL-13 signaling, has been approved in: Atopic dermatitis, Asthma, COPD, CRSwNP, Eosinophilic Esophagitis, Prurigo Nodularis, and has positive Phase 3 data in Bullous Pemphigoid and is in development for multiple additional indications
- STAT6 degradation can fully block IL-4/IL-13 signaling*



Adapted from Junttila. *Front Immunol*. 2018; Sharma et al. *J Exp Med*. 2023; Suratannon et al. *J Allergy Clin. Immunol*. 2022; Takeuchi et al. *J Allergy Clin Immunol*. 2022; *Statements regarding STAT6 degrader biology throughout this presentation are based upon preclinical experiments in human cells and preclinical species conducted by Kymera

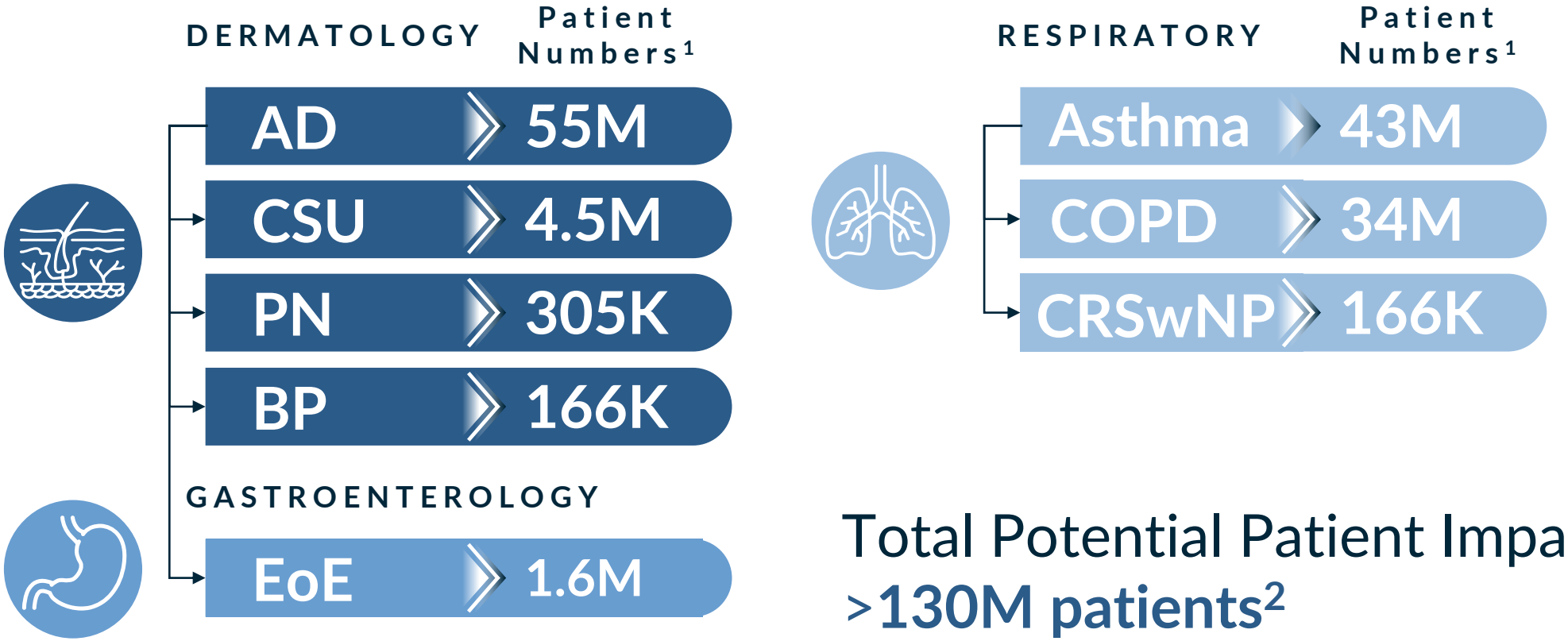
STAT6 Degrader Advantage





- STAT6 is the specific and essential transcription factor in the IL-4/13 pathway
- Occupancy based approaches (e.g., SMI) unlikely to block pathway fully in a pharmacologically relevant manner
- However, degradation of STAT6 can fully block IL-4/IL-13 signaling *in vitro* and *in vivo*

Oral STAT6 Degraders Can Transform the Treatment Paradigm in Multiple Indications De-risked by Dupilumab



Total Potential Patient Impact: >130M patients[2]

- Numerous indication opportunities across multiple therapeutic areas de-risked by dupilumab
- STAT6 degradation leading to full pathway inhibition has the potential to deliver dupilumab-like activity
- Oral degrader medicines offer opportunity to reach broader patient populations

1GlobalData (2023 diagnosed prevalent patient population in US/EU5/JP)
[2]GlobalData (2023 diagnosed prevalent patient population for AD, Asthma, and COPD only in US/EU5/JP)

Executive Summary: STAT6 Program

Vision: Develop an oral STAT6 degrader with dupilumab-like profile to provide a more convenient and broadly accessible treatment option for millions of patients suffering from Type 2 diseases (AD, asthma, CRSwNP, COPD, EOE, PN, etc.)

- STAT6 has human genetics and clinical pathway validation
- KT-621 is the first highly selective, potent and orally active STAT6 degrader in clinical development
- In preclinical testing, KT-621 fully degrades STAT6 across multiple species and in all tissues tested and is safe and well tolerated
- KT-621 was more potent than Dupilumab in blocking IL-4 and IL-13 driven Th2 inflammation in preclinical cellular and in vivo models
- The KT-621 Phase 1 trial is ongoing, with a goal of demonstrating robust STAT6 degradation in blood and skin with good tolerability. Results are expected in 2Q25
- Patient testing is planned for 2025, beginning with a Phase 1b trial in AD patients in 2Q25, followed by two parallel Phase 2 studies in AD and Asthma starting in 4Q25 and 1Q26, respectively

KT-621: A Picomolar Degrader of STAT6

Consistent Degradation Across All Disease Relevant Cell Types Evaluated

Blood

Skin

Lungs

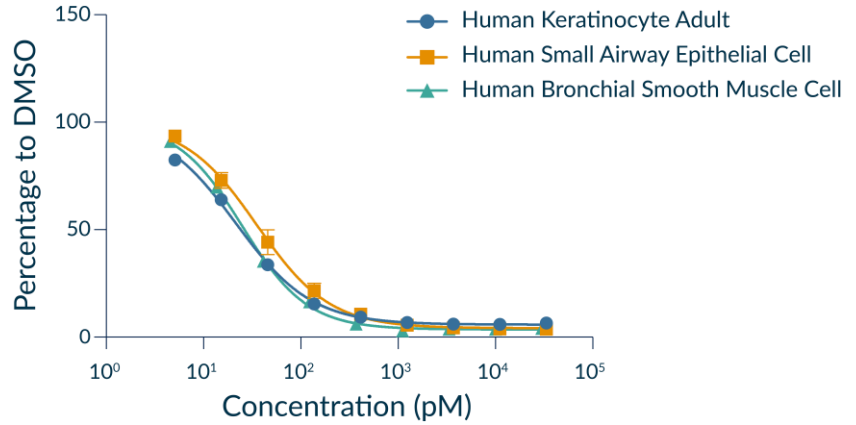
Throat/ Airway

Blood Vessels

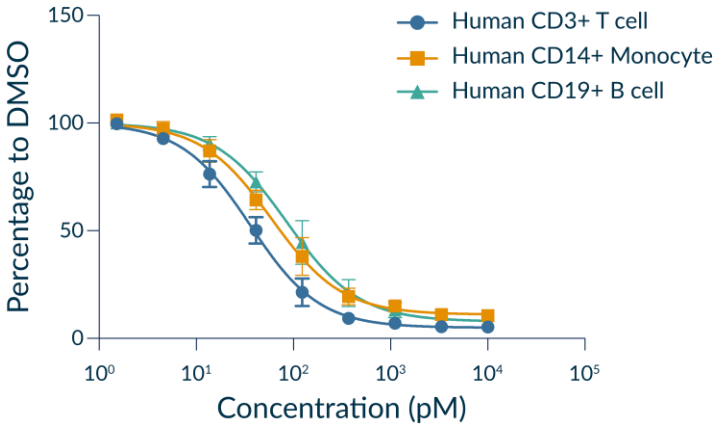
Neurons

Human Primary Cell Type	KT-621, DC_{50} (pM)
Hematopoietic cell (all Th2 diseases)	
Human PBMC	13
Human CD3 T cell	36
Human CD14 monocyte	60
Human CD19 B cell	86
Human eosinophil	99
Epithelial cell (AD, CSU, asthma, COPD)	
Human keratinocyte (adult)	22
Human keratinocyte (neonatal)	18
Human bronchial tracheal epithelial cell	33
Human small airway epithelial cell	35
Smooth muscle cell (asthma, COPD, EoE)	
Human bronchial smooth muscle cell	25
Human esophageal smooth muscle cell	33
Endothelial cell (all Th2 diseases)	
Human vascular endothelial cell	46
Neuron (AD, PN, CSU)	
Human iPSC derived sensory neuron	22

STAT6 Degradation in Hematopoietic Cells

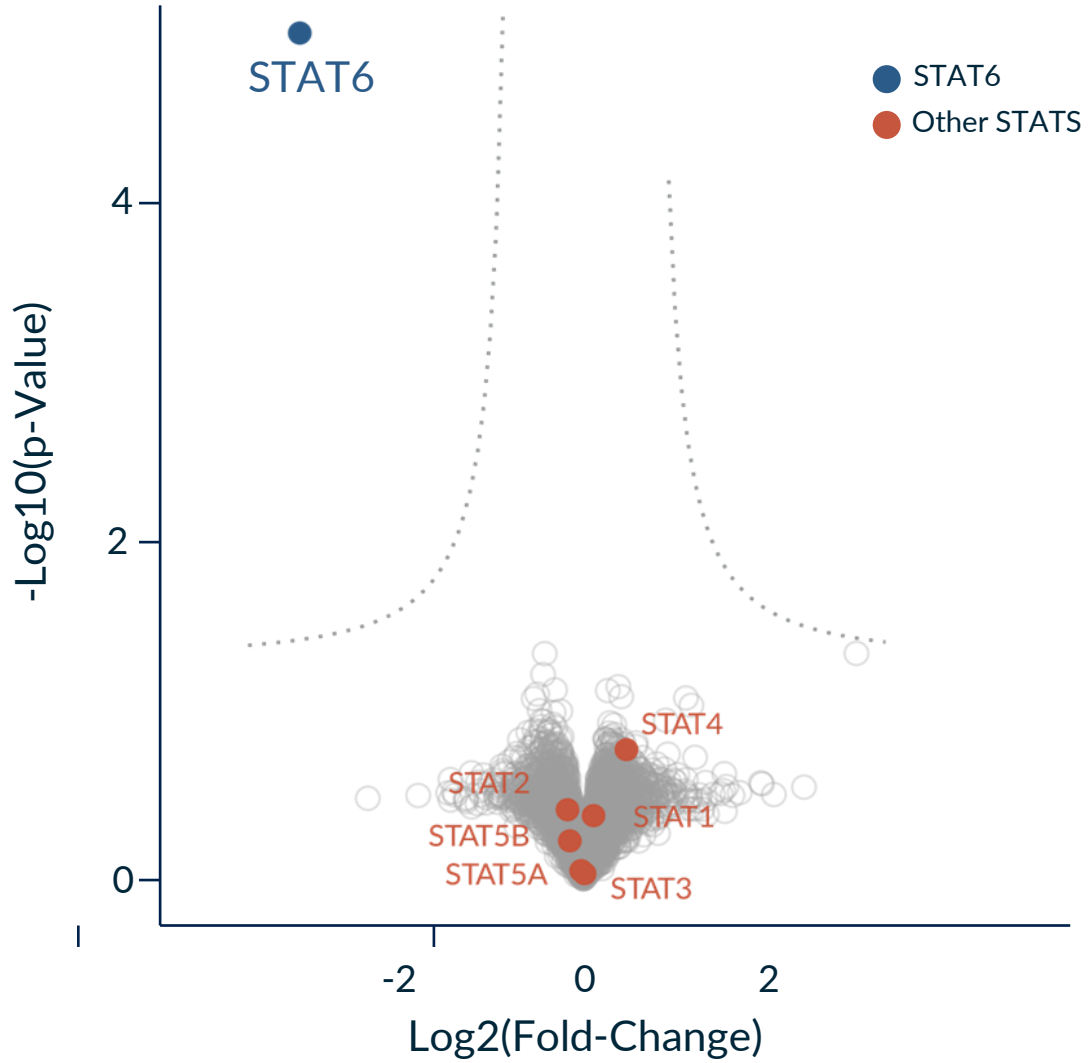


STAT6 Degradation in Tissue Cells



KT-621: Exquisite Degradation Selectivity for STAT6

- Complete STAT6 degradation selectivity in human PBMC proteome at 100 x DC_{90}
- No other STATs are degraded to any extent



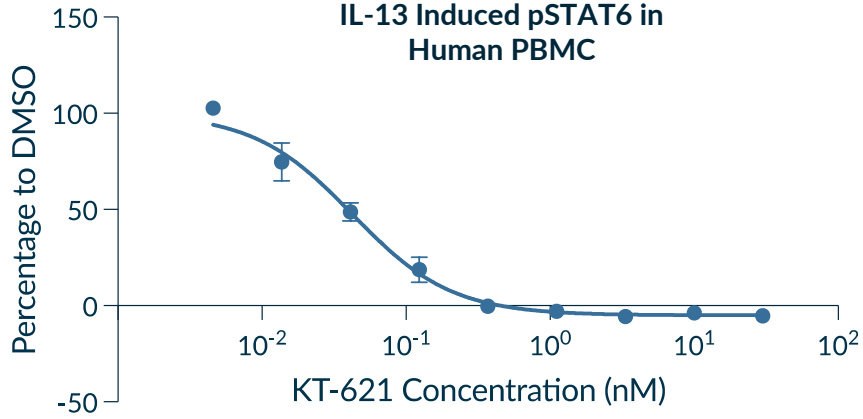
KT-621: Exquisite Pathway Selectivity for STAT6

No Impact on Any Other STAT Pathway Observed

STAT assays	KT-621, IC_{50} (nM)
IFN-α induced pSTAT1	> 1000
IFN-α induced pSTAT2	> 1000
IL-10 induced pSTAT3	> 1000
IL-12 induced pSTAT4	> 1000
IL-2 induced pSTAT5	> 1000
IL-13 induced pSTAT6	0.042

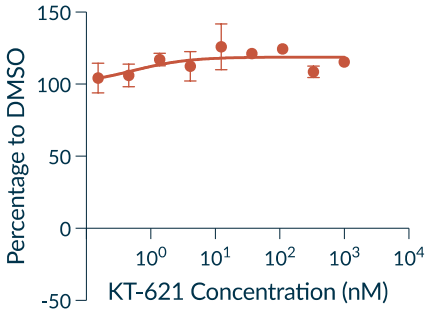
STAT6

IL-13 Induced pSTAT6 in Human PBMC



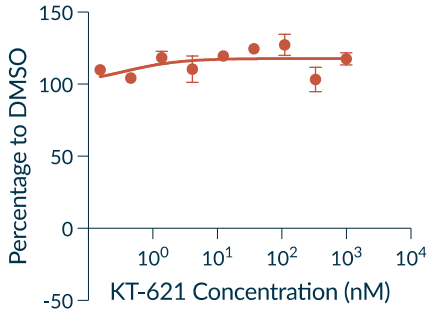
STAT1

IFN-α Induced pSTAT1 in Human CD19 Cell



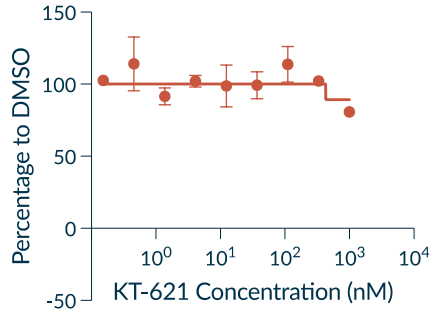
STAT2

IFN-α Induced pSTAT2 in Human CD19 Cell



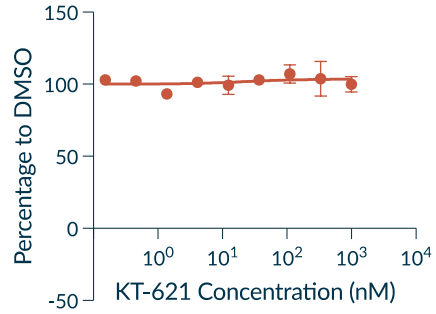
STAT3

IL-10 Induced pSTAT3 in Human CD14 Cell



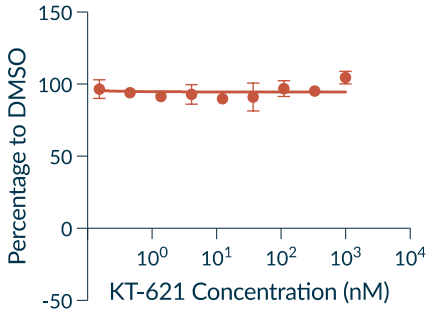
STAT4

IL-12 Induced pSTAT4 in Human PBMC



STAT5

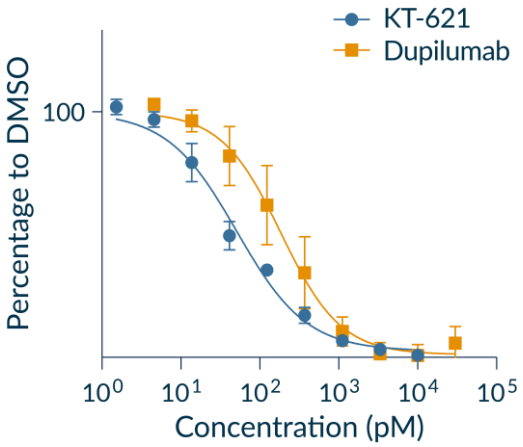
IL-2 Induced pSTAT5 in Human CD3 T Cell



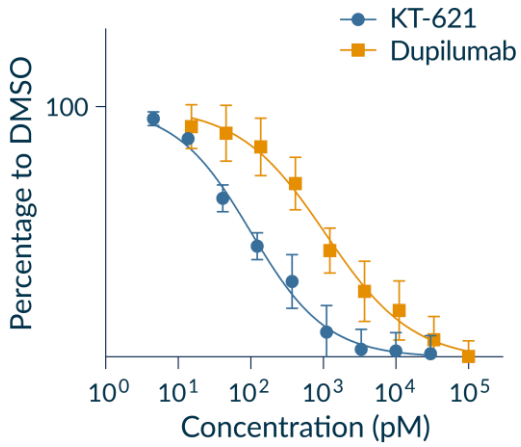
KT-621 Fully Blocks IL-4/13 Pathway in Human Th2 Functional Assays with IC_{50}'s Lower than Dupilumab

		Cellular Functional Assay	KT-621 IC_{50} (pM)	Dupilumab IC_{50} (pM)
TARC	Serum Th2 biomarker, chemoattractant for Th2 cell	IL-4 TARC release in human PBMC	**62**	194
		IL-13 TARC release in human PBMC	**43**	113
CD23	B cell activation marker, correlates with IgE class switch	IL-4 CD23 expression in human CD19 B cell	**125**	354
		IL-13 CD23 expression in human CD19 B cell	**98**	1070
PERIOSTIN	Serum Th2 biomarker and ECM protein associated with tissue remodeling in atopic diseases	IL-13 Periostin release in human bronchial smooth muscle cell	**24**	637
		IL-13 Periostin release in human esophageal smooth muscle cell	**39**	431
TAC1 NPPB	Neuropeptides related to itch transmission in sensory neurons	IL-13 TAC1 expression in iPSC derived human sensory neuron	**89**	1027
		IL-13 NPPB expression in iPSC derived human sensory neuron	**121**	5714

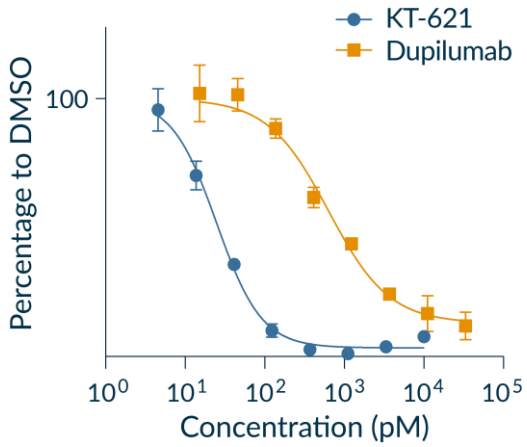
IL-4 Induced TARC Release in Human PBMC



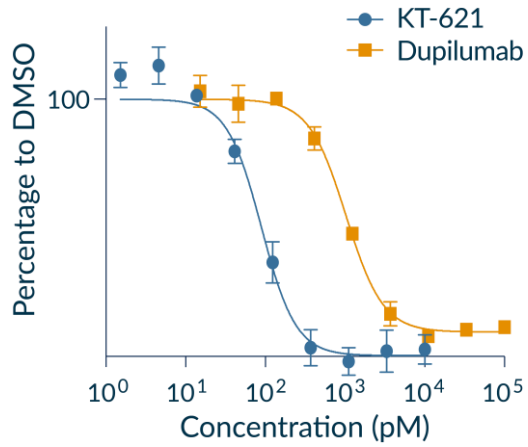
IL-13 Induced CD23 Expression in Human CD19 B Cell



IL-13 Induced Periostin Release in Human Bronchial Smooth Muscle Cell



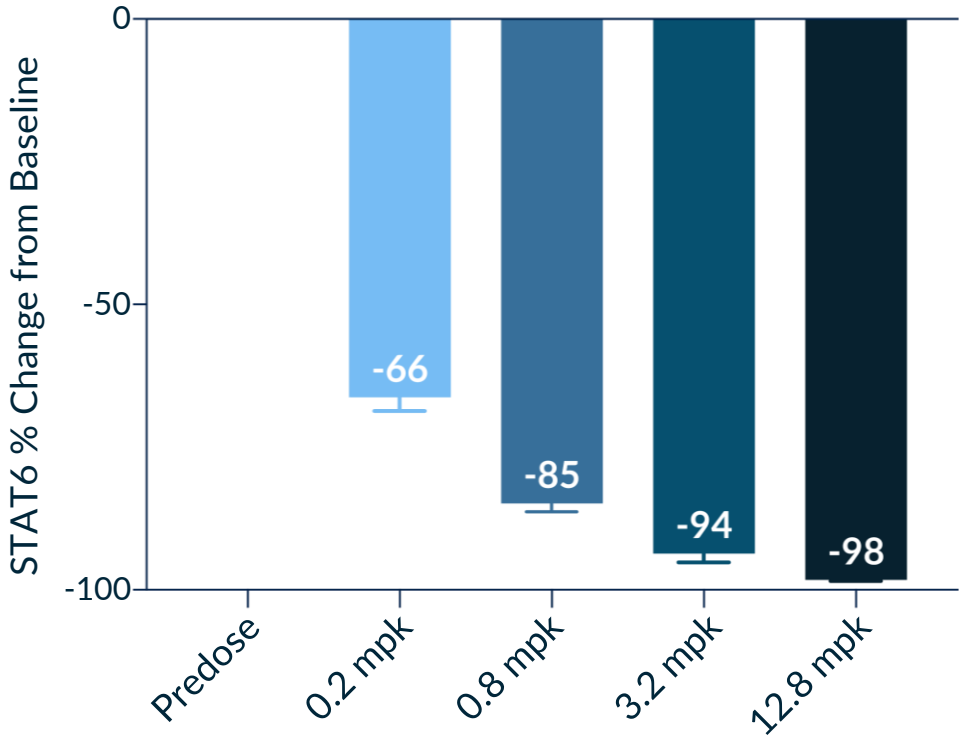
IL-13 Induced TAC1 Expression in iPSC Derived Human Sensory Neuron



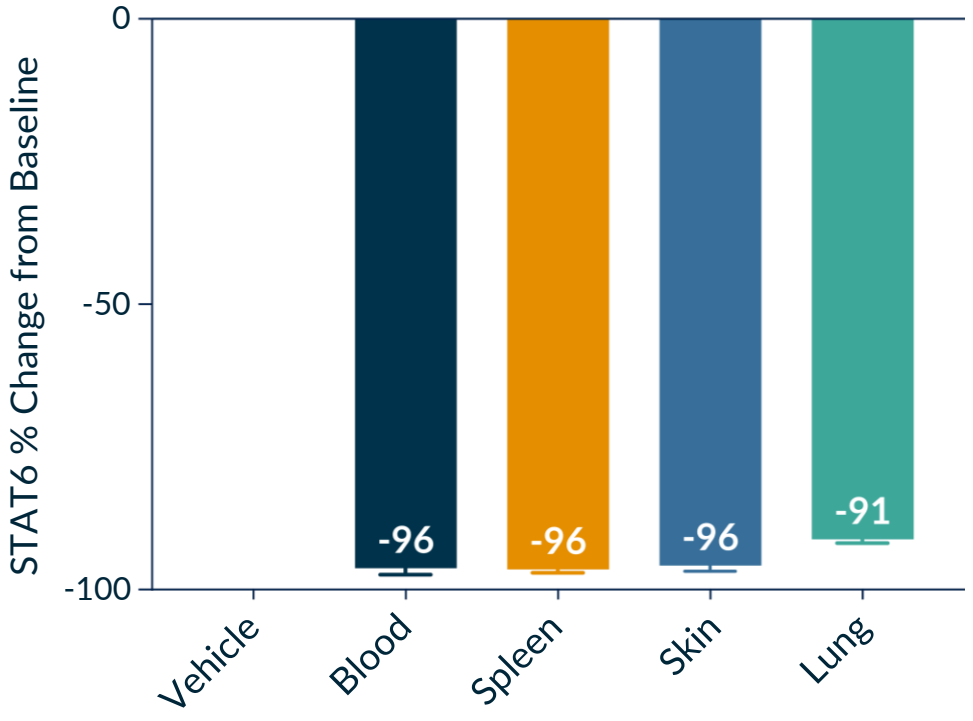
KT-621 Compelling Preclinical PK/PD and Safety Holds Promise for Positive Human Translation

KT-621 Potently Degrades STAT6 to Depletion with Low Oral Doses Across Multiple Preclinical Species and in Multiple Tissues

STAT6 Degradation in Dog Blood Post 7 Days of KT-621 QD Oral Dosing



STAT6 Degradation in NHP Tissues Post 14 Days of KT-621 10 mpk QD Oral Dosing

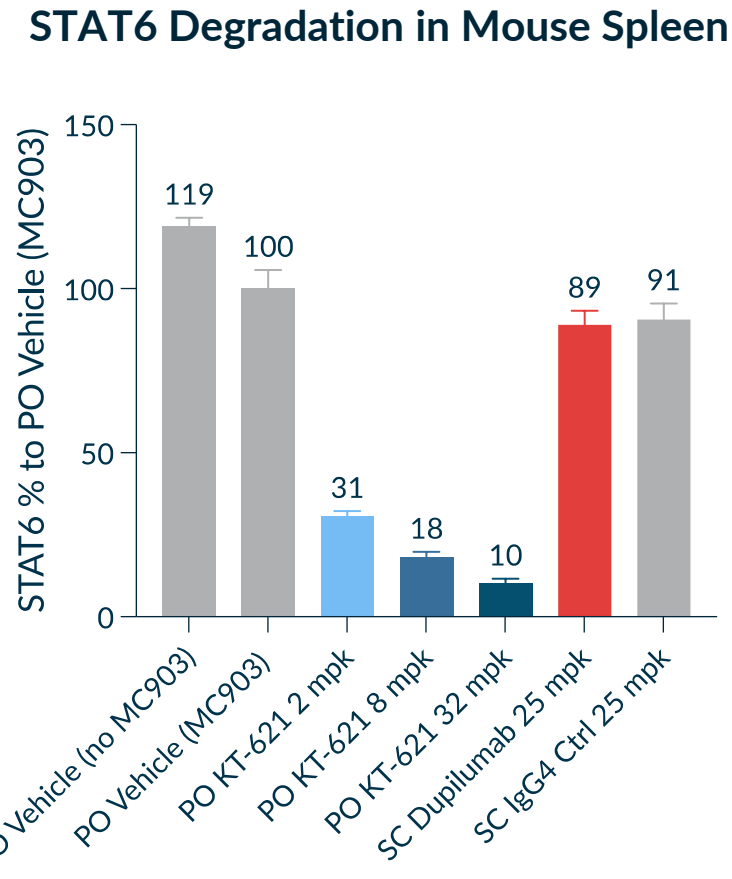


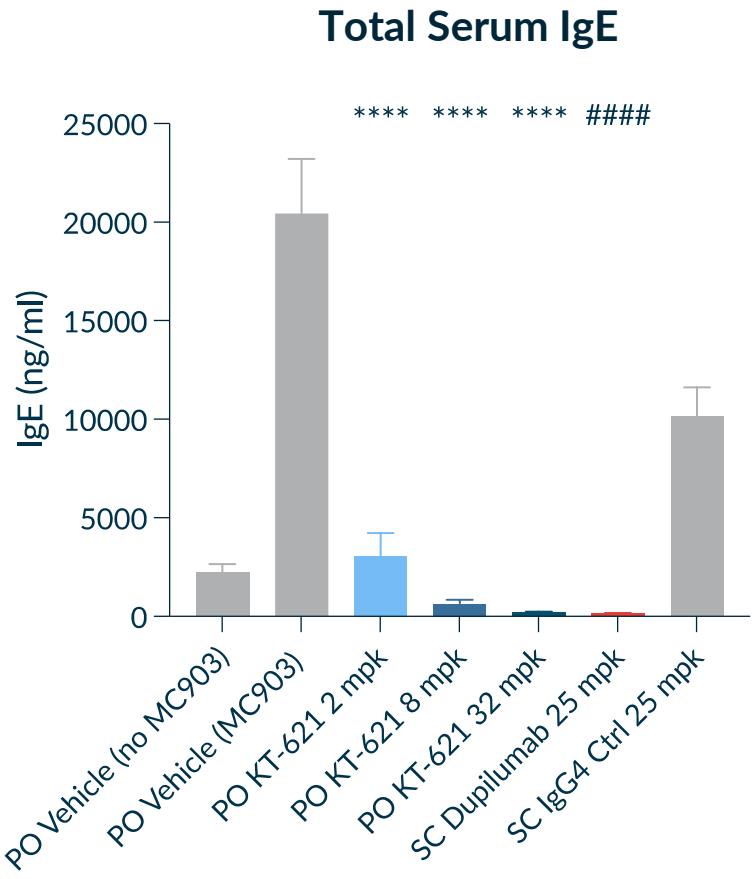
No adverse safety findings in any doses of GLP tox studies

KT-621 Has Comparable *In Vivo* Activity to IL-4Rα Saturating Dose of Dupilumab in the MC903 Atopic Dermatitis Model

An atopic dermatitis model induced by topical application of low-calcemic vitamin D3 analog MC903 with prominent Th2 inflammation in the IL4/IL4RA humanized mice:

- **KT-621 dosed QD orally for 11 days**
- **Dupilumab dosed 4 times subcutaneously**, 25 mpk twice a week (IL-4Rα saturating dose); **effect equivalent to 300 mg every other week in human**



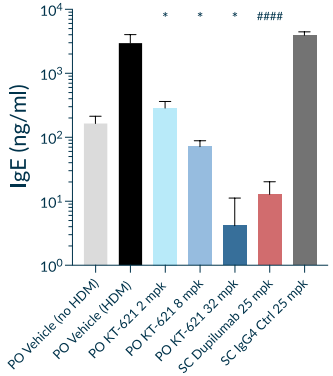


* Significance to PO vehicle (MC903); # Significance to SC IgG4 25 mpk BIW

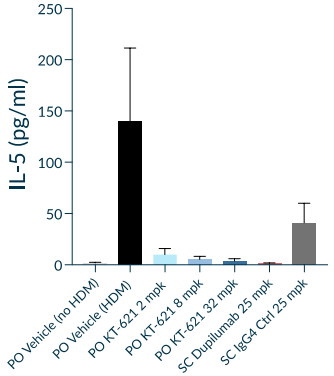
KT-621 Blocks Th2 Inflammation *In Vivo* Equally or Better than an IL-4Rα Saturating Dose of Dupilumab in the Intranasal HDM Asthma Model

Serum IgE and Lung Cytokine

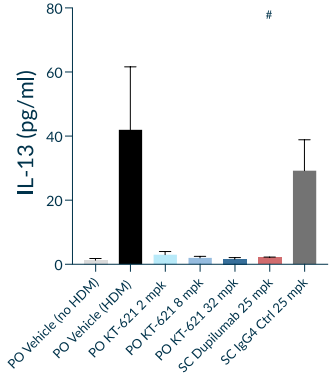
Total Serum IgE



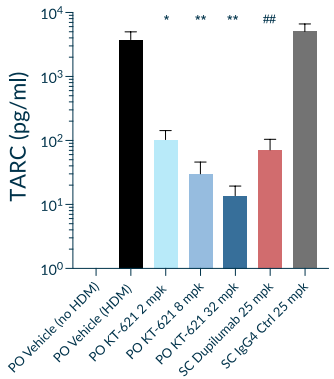
BAL IL-5



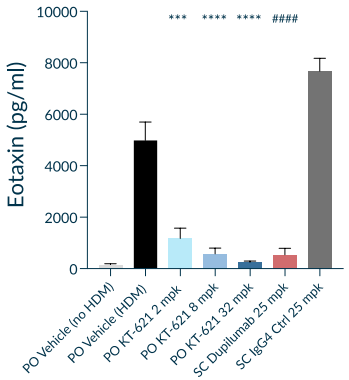
BAL IL-13



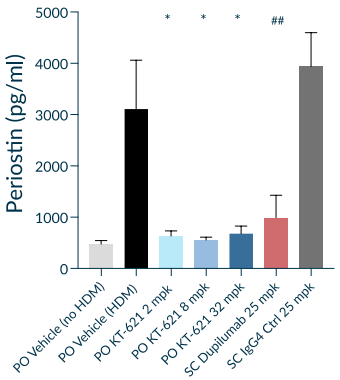
BAL TARC (CCL17)



BAL Eotaxin (CCL11)

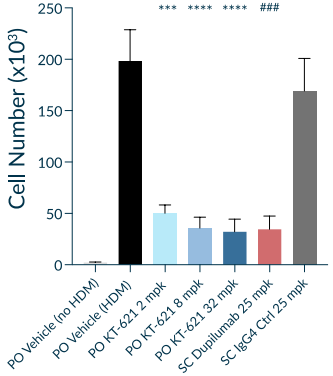


BAL Periostin

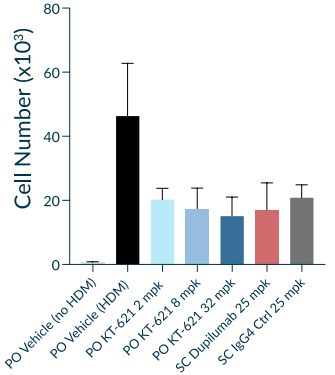


Inflammatory Infiltrate

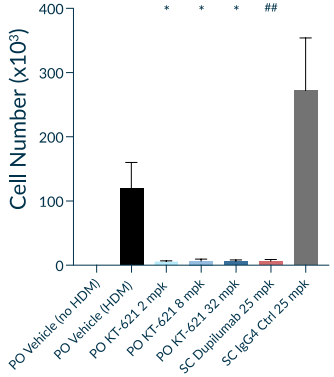
BAL CD4+ T Cell



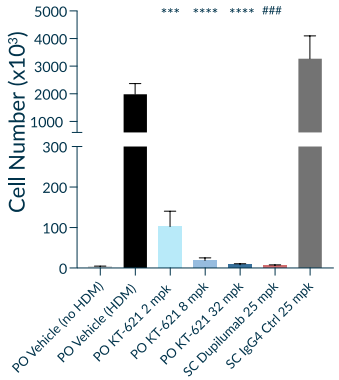
BAL CD8+ T Cell



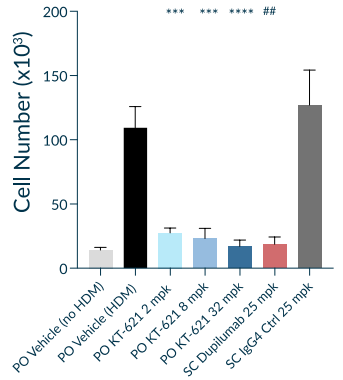
BAL Activated B Cell



BAL Eosinophil



BAL Dendritic Cell



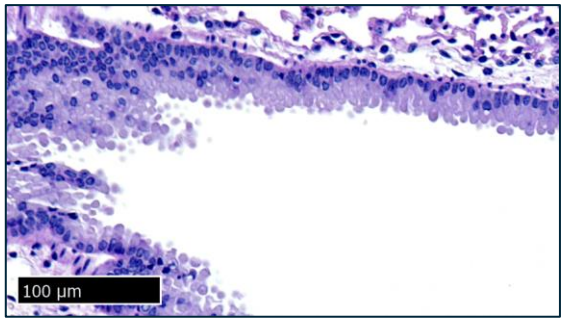
- **KT-621 dosed QD orally for 31 days. 2/8/32 mpk** doses showed **72/85/91% STAT6 degradation** respectively in mouse spleen
- **Dupilumab dosed 9 times subcutaneously**, 25 mpk BIW (IL-4Rα saturating dose), **effect equivalent to 300 mg every other week in human**

A lung inflammation model induced by intranasal house dust mite administration with dominant Th2 inflammation in the IL4/IL4RA humanized mice (Le Floc'h et al. Allergy. 2020); BAL – bronchoalveolar lavage; *Significance to PO vehicle (HDM); # Significance to SC IgG4 Ctrl 25 mpk.

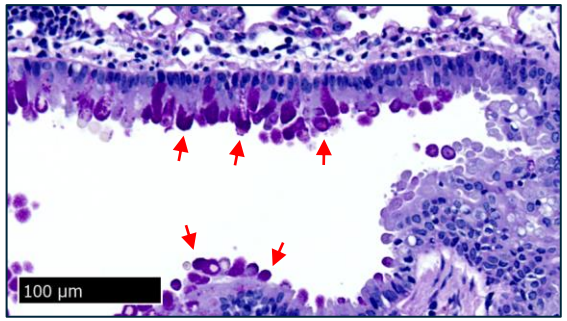
KT-621 Reduced Disease Severity in the Lung in the Intranasal HDM Asthma Model

Lung Remodeling: Goblet Cell Metaplasia (Arrow)

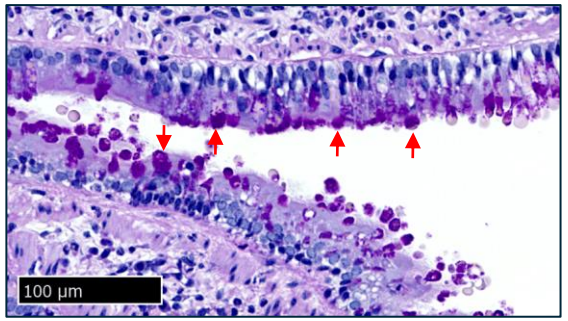
PO Vehicle (no HDM)



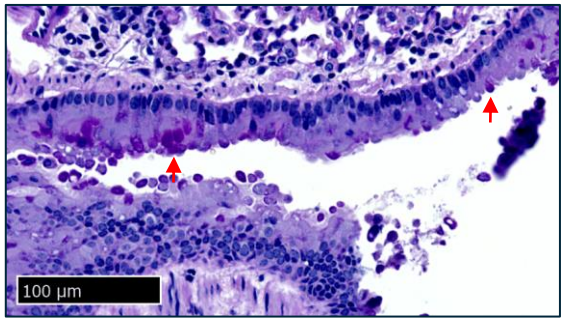
PO Vehicle (HDM)



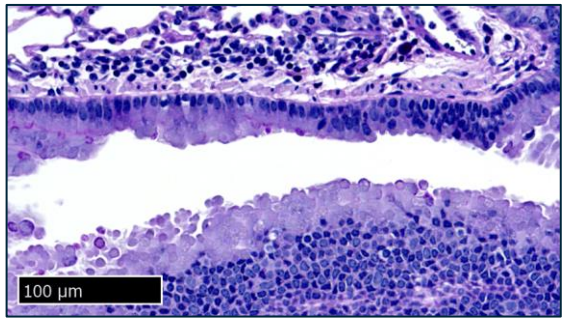
SC IgG4 Ctrl 25 mpk



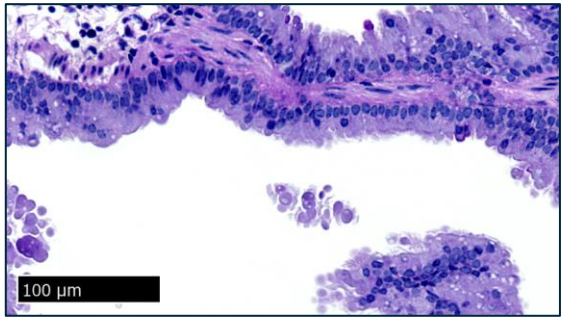
PO KT-621 2 mpk



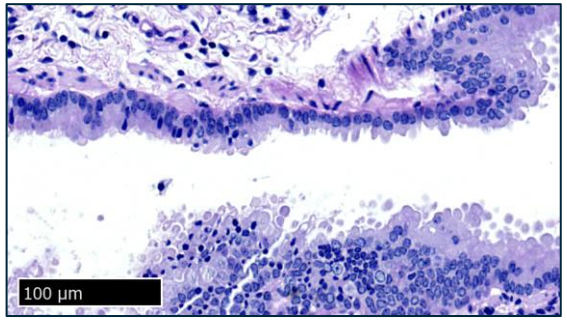
PO KT-621 8 mpk



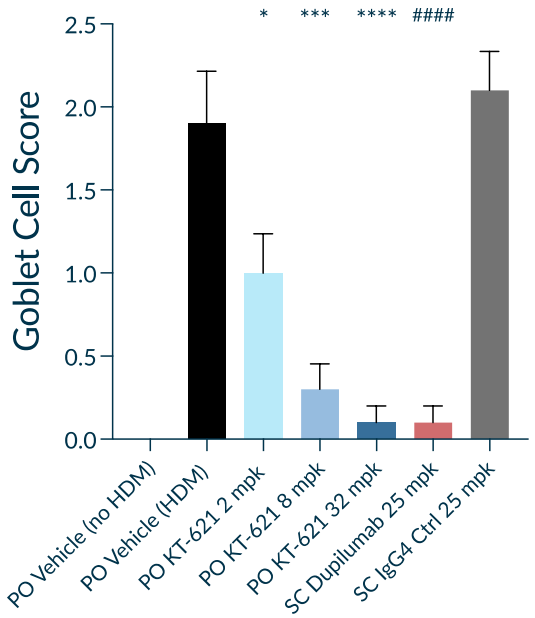
PO KT-621 32 mpk



SC Dupilumab 25 mpk



Lung Goblet Cell Metaplasia

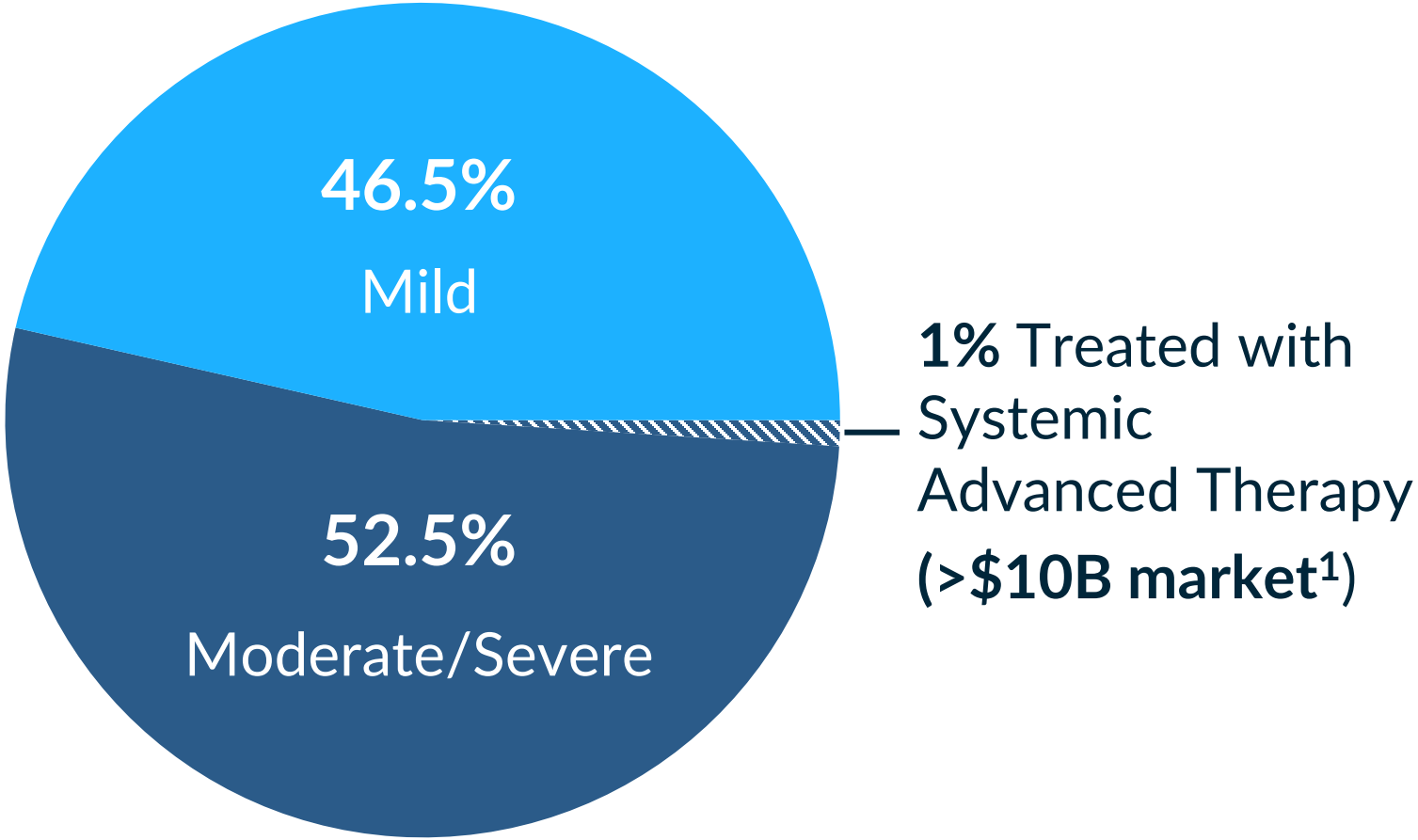


Amelioration of lung remodeling seen after low daily oral doses of KT-621 comparable to dupilumab

A lung inflammation model induced by intranasal house dust mite administration with dominant Th2 inflammation in the IL4/IL4RA humanized mice (Le Floc'h et al. Allergy. 2020); *Significance to PO vehicle (HDM); # Significance to SC IgG4 Ctrl 25 mpk.

Kymera's Goal is to Build a STAT6 Franchise That Will Serve ALL Patients with Th2 Inflammation

>130 million diagnosed mild and moderate/severe patients across the seven major markets[1]



Kymera is the leader in the STAT6 target space (with multiple molecules as needed) poised to deliver transformative treatments for ALL patients with Th2 diseases: AD, Asthma, COPD, CRSwNP, CSU, EoE, BP, PN, others

[1]GlobalData (2023 diagnosed prevalent patient population and forecasted sales for approved systemic advanced therapies for AD, Asthma, and COPD only in US/EU5/JP)

Opportunity to Transform Treatment Paradigm in Th2 Inflammation

Examples: Atopic Dermatitis and Asthma

Atopic Dermatitis[1]

Non-Rx. Management
(Emollients, salt baths, trigger avoidance)

Topicals Therapy
(Corticosteroids, Calcineurin, PDE4, JAK inhibitors)

Systemic Advanced Therapy
(Biologic: IL-4/13, IL-13, SMI: JAK)

KT-621

Asthma[2]

Inhaled Corticosteroids (ICS)
(As needed → Maintenance)

ICS ± LABA ± LAMA ± LTRA

ICS + LABA + LAMA ± Biologic
(Biologic: IgE, IL-5, TSLP, IL-4/13)

[1]AD Clinical Guidelines (AAD, 2024); [2]Global Strategy for Asthma Mgmt and Prevention (GINA, 2024): ICS inhaled corticosteroid, LD low dose, HD high dose, LABA long-acting beta agonist, LAMA long-acting muscarinic antagonist, LTRA leukotriene receptor antagonist

KT-621: First STAT6 Agent to Enter Clinical Evaluation

Phase 1 Trial: Double-blind, Placebo-controlled SAD and MAD in Healthy Volunteers

Part A
Single Ascending Dose
(SAD)

Part B
Multiple Ascending Dose
(MAD)
14x daily doses

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

Secondary
- Pharmacokinetic measures

Exploratory
- STAT6 protein levels in blood and skin (MAD)
- Th2 biomarkers

2Q 2025

Phase 1 Healthy Volunteer Data

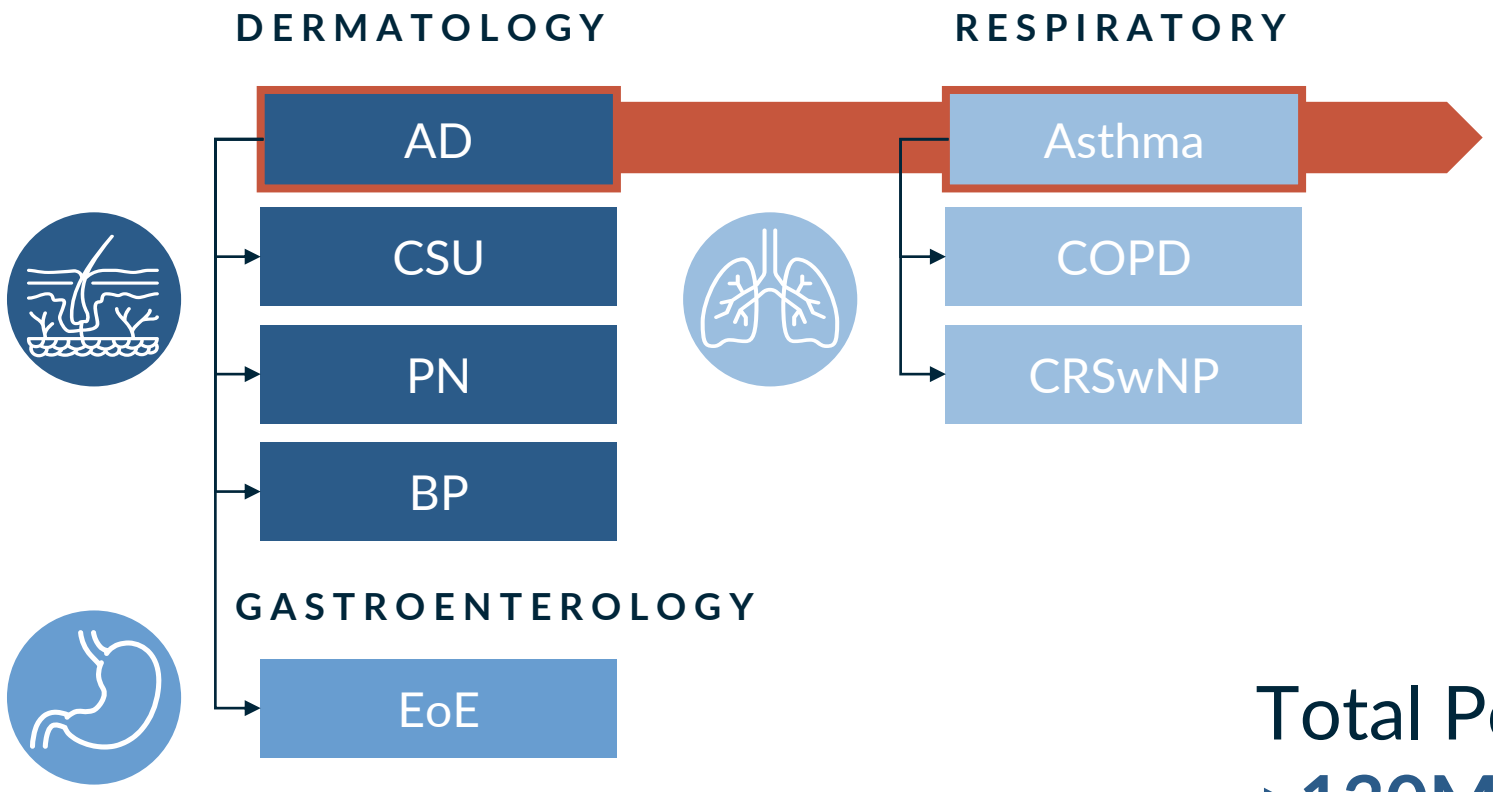
Key trial aim is to show that **KT-621 can robustly degrade STAT6 in blood and skin** at doses that are safe and well-tolerated

Phase 1 trial status update:

Recruitment ongoing with multiple SAD/MAD cohorts completed

KT-621 on Track for Full Development Across at Least Eight Dupilumab Established Indications

Initial Parallel Development in Moderate/Severe Atopic Dermatitis (AD) and Asthma is Expected to Enable Accelerated Late Parallel Development Across All Other Dermatology/GI and Respiratory indications



Near-Term Planned Trials

- Phase 1b in AD (2Q25)
- Parallel Phase 2b in AD (4Q25) and Asthma (1Q26)

Total Potential Patient Impact:
>130M patients[1]

[1]GlobalData (2023 diagnosed prevalent patient population for AD, Asthma, and COPD only in US/EU5/JP)

KT-621 Development Path to Key Proof-of-Concept Inflection Points

	Trial Goal / Key New Data
Phase 1 Healthy Volunteers	Safety and tolerability and robust STAT6 degradation in blood and skin measured over 14 days
Phase 1b Atopic Dermatitis Patients	Impact on Th2 biomarkers, with dupilumab-like signature measured over 28 days
Parallel Phase 2b Trials in Atopic Dermatitis & Asthma Patients	Clinical activity in two initial Th2 diseases to support registrational studies in multiple indications

Once daily, oral pill: KT-621 is the first STAT6 directed medicine in clinical development with the potential to shift the treatment paradigm for multiple Th2 diseases

Oral STAT6 Degrader: KT-621

Dupilumab-like Activity in a Pill

Validated Biology

- Historically undrugged, essential transcription factor in IL-4 and IL-13 signaling pathways
- Central driver of Th2 inflammation
- STAT6 validated by human genetics
- Pathway validated by human genetics and FDA-approved dupilumab across multiple indications

Opportunity

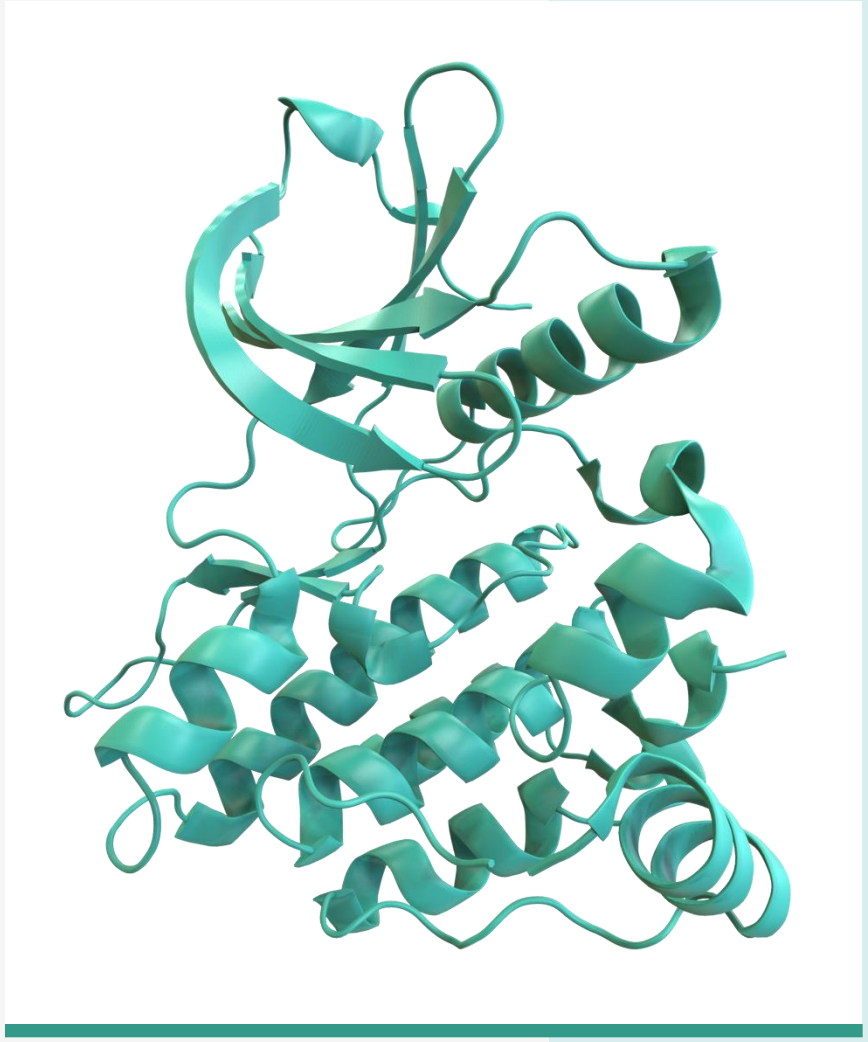
- Total potential patient impact >130M patients[1]
- Potential to access beyond biologics-eligible patients and address patients across all disease severities
- WW IL-4/IL-13 biologic market currently $10B+ annually[2]
- Estimated to grow to $23B+ with expanded indications and new entrants[2]
- Mega-blockbuster potential for oral degraders in allergic diseases

KT-621 Profile

- Full IL-4 and IL-13 functional inhibition with picomolar IC50's superior to dupilumab
- Robust activity shown in *in vivo* preclinical models of AD and lung inflammation equal or superior to dupilumab
- STAT6 degradation was well-tolerated in multiple preclinical safety studies (including GLP-tox) at >40x efficacious concentration
- Phase 1 Healthy Volunteer Clinical Study ongoing

Upcoming Milestones
Phase 1 HV Data: 2Q 2025
Phase 1b AD Data: 4Q 2025
Phase 2b Starts: 4Q 2025 (AD)/1Q 2026 (Asthma)

[1]GlobalData (2023 diagnosed prevalent patient population for AD, Asthma, and COPD only in US/EU5/JP)
[2]GlobalData Consensus Forecast



First-in-Class Oral TYK2 Degrader Program

TYK2-LOF profile to deliver biologics (i.e., anti-IL-23)-like activity in a pill

TYK2 Biology and Target Rationale

Target Biology and Rationale

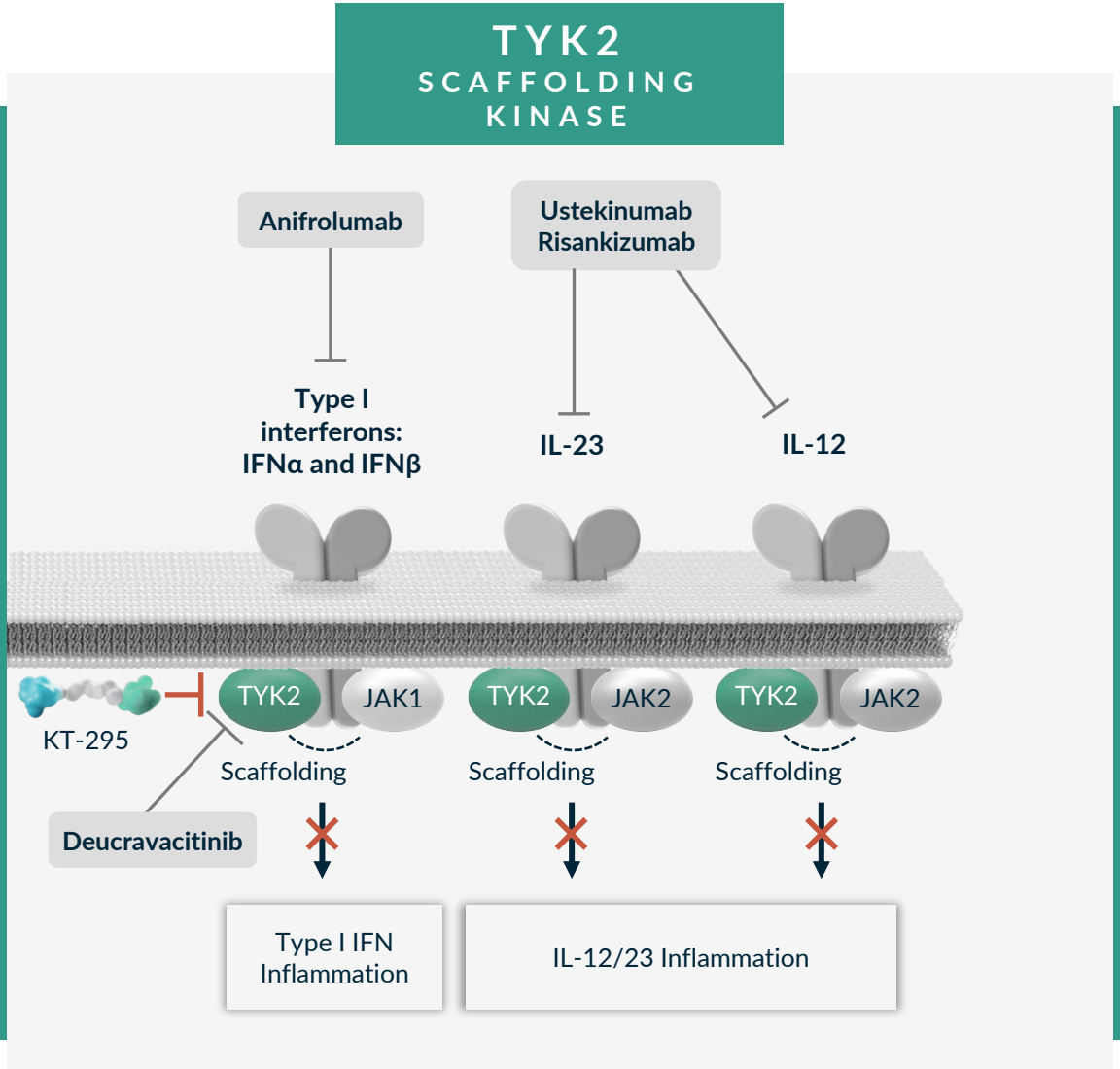
- TYK2 is a member of the JAK family required for Type I IFN, IL-12 and IL-23 cytokine signaling
- TYK2 regulated cytokines are clinically validated targets for autoimmune and inflammatory diseases

Human Genetics

- Loss-of-function variant of TYK2 is protective in autoimmune and inflammatory diseases

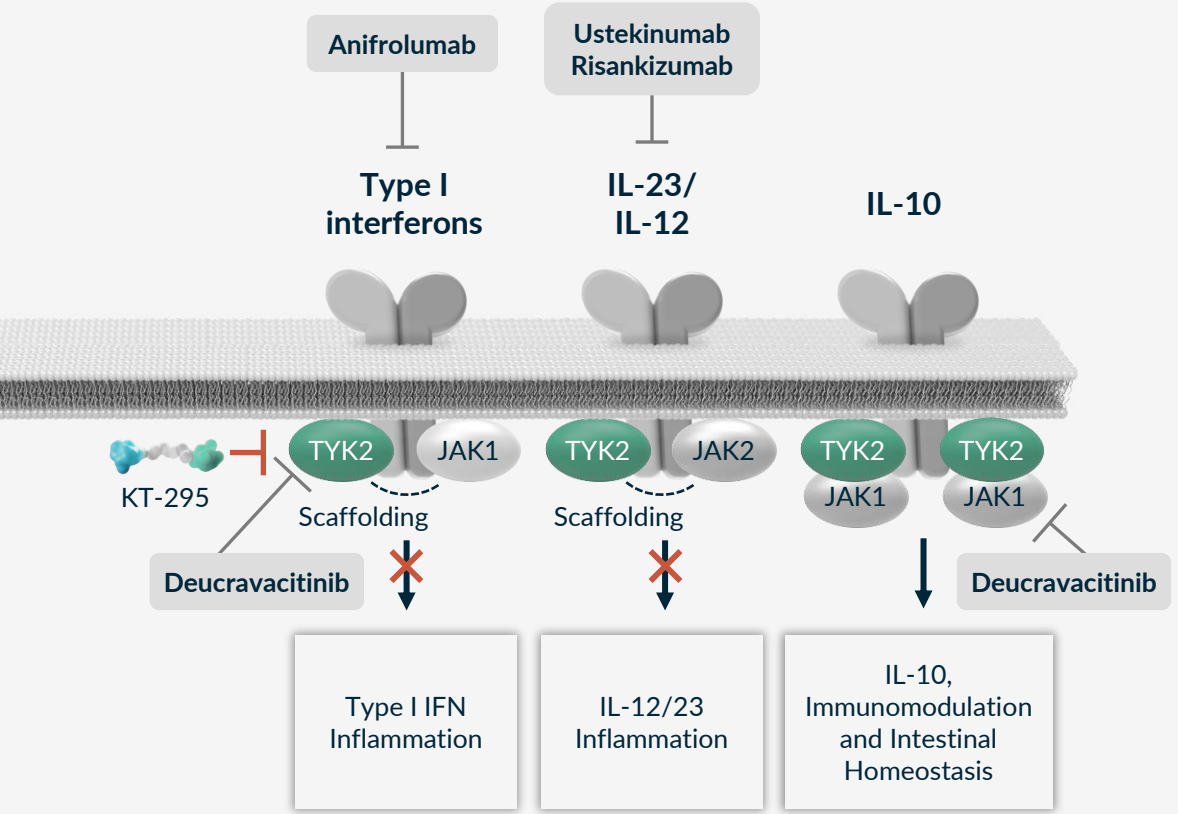
Clinical Pathway Validation

- IL-23 (± IL-12)-targeting agents include ustekinumab, risankizumab, guselkumab, and tildrakizumab, with approvals in PsO, PsA, CD, UC
- Type I IFN-targeting agents include anifrolumab with approval in SLE
- TYK2 SMI deucravacitinib recently approved in PsO



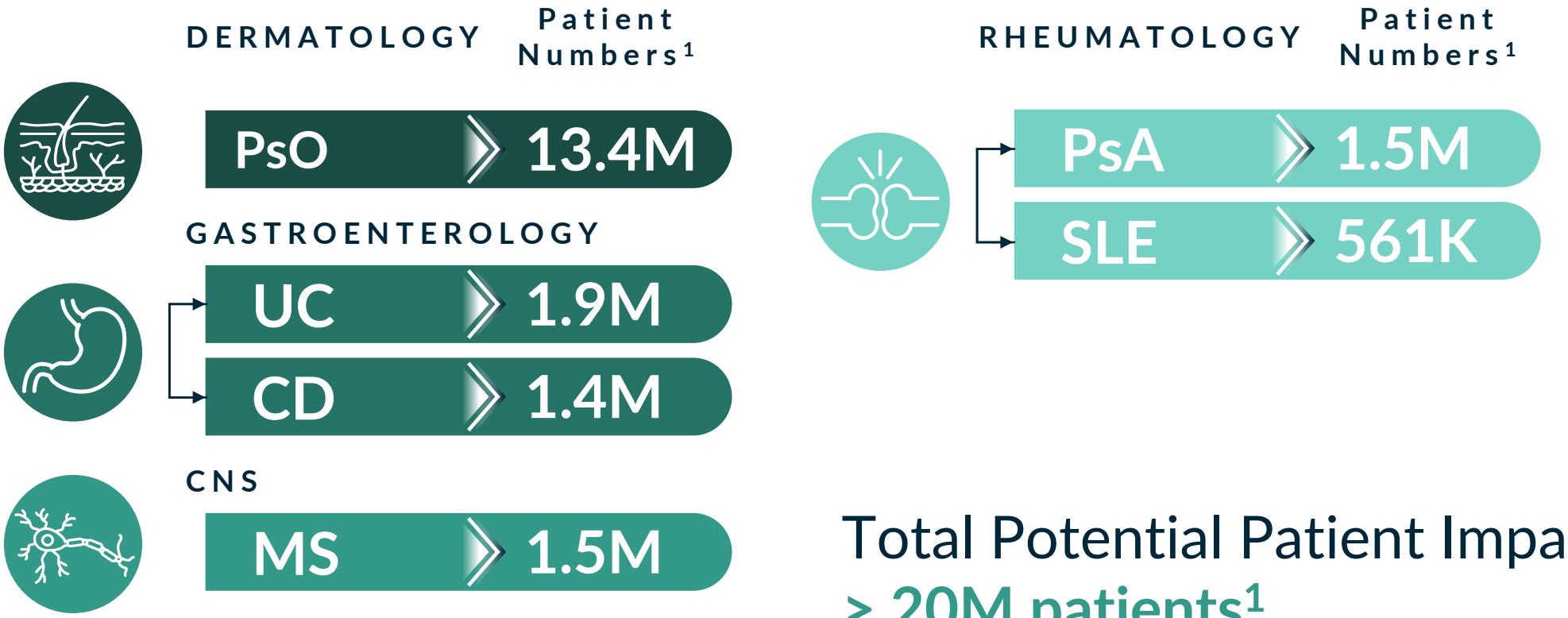
TYK2 Degrader Advantage

Only TYK2 Degraders Can Achieve Biologics-like Activity



- TYK2 has a well-established scaffolding function that is responsible for cytokine receptor surface expression and activation
- Unlike SMIs, only TYK2 degradation recapitulates the human LOF phenotype of full pathway inhibition of Type I IFN, IL-12 and IL-23 and sparing of IL-10
  - Unlike deucravacitinib, which inhibits IL-10 through JAK1, TYK2 degradation does not inhibit IL-10, which is important in IBD
  - Compared to Zasocitinib (TAK-279), TYK2 degradation fully inhibits Type I IFN
- Full TYK2 degradation leads to pathway inhibition superior to existing SMIs with potential for biologics-like activity

Patient Impact of TYK2: Potential Best-In-Class Opportunity in I&I



Total Potential Patient Impact:
> 20M patients[1]

- Numerous indication opportunities across multiple therapeutic areas de-risked by biologics and deucravacitinib
- TYK2 degradation, differentiated from inhibition, leads to full pathway inhibition with potential to deliver biologic-like activity*
- Oral degrader medicines offer opportunity to reach broader patient populations

[1]GlobalData (2023 diagnosed prevalent patient population for US/EU5/JP);
[2]Statements regarding TYK2 degrader biology throughout this presentation are based upon preclinical experiments in human cells and preclinical species conducted by Kymera

Executive Summary: TYK2 Program

Vision: Develop an oral TYK2 degrader with biologics-like profile as a preferred option for patients suffering from Th17 (Psoriasis, Psoriatic Arthritis, IBD) and interferon related disorders (SLE)

- TYK2 has human genetics and clinical validation
- KT-295 is the first highly selective, potent and orally active TYK2 degrader about to enter clinical development
- KT-295, unlike small molecule inhibitors approved or in the clinic, is able to replicate the TYK2 genetic LOF profile of full blockade of IL-23, IL-12 and Type-1 Interferon while sparing IL-10
- In preclinical testing, KT-295, fully degrades TYK2 across multiple species and in all tissues tested and is safe and well tolerated
- The KT-295 IND/Phase 1 trial is expected to start in 2Q 2025 with data in 4Q 2025

TYK2 Has Well-Established Scaffolding Function

- TYK2 complete deficiency severely impairs IL-23, Type I IFN, and IL-12 signaling but spares IL-10 in humans
- TYK2 scaffolding functions are demonstrated by differential pathway inhibitions in complete TYK2 deficiency vs a kinase dead variant in humans
- TYK2 deficient humans are generally healthy with only increased risk of some mycobacteria and viral infections that are relatively mild, curable and tend not to recur, de-risking safety for TYK2 degradation

Cytokine Pathway	IL-23	Type I IFN	IL-12	IL-10
WT TYK2	++++	++++	++++	++++
Complete deficiency TYK2 -/-	+	+	+	+++
TYK2 Kinase dead P1104A/P1104A	+	++++	++++	++++

TYK2 Degrader (LOF Phenotype) Opportunity

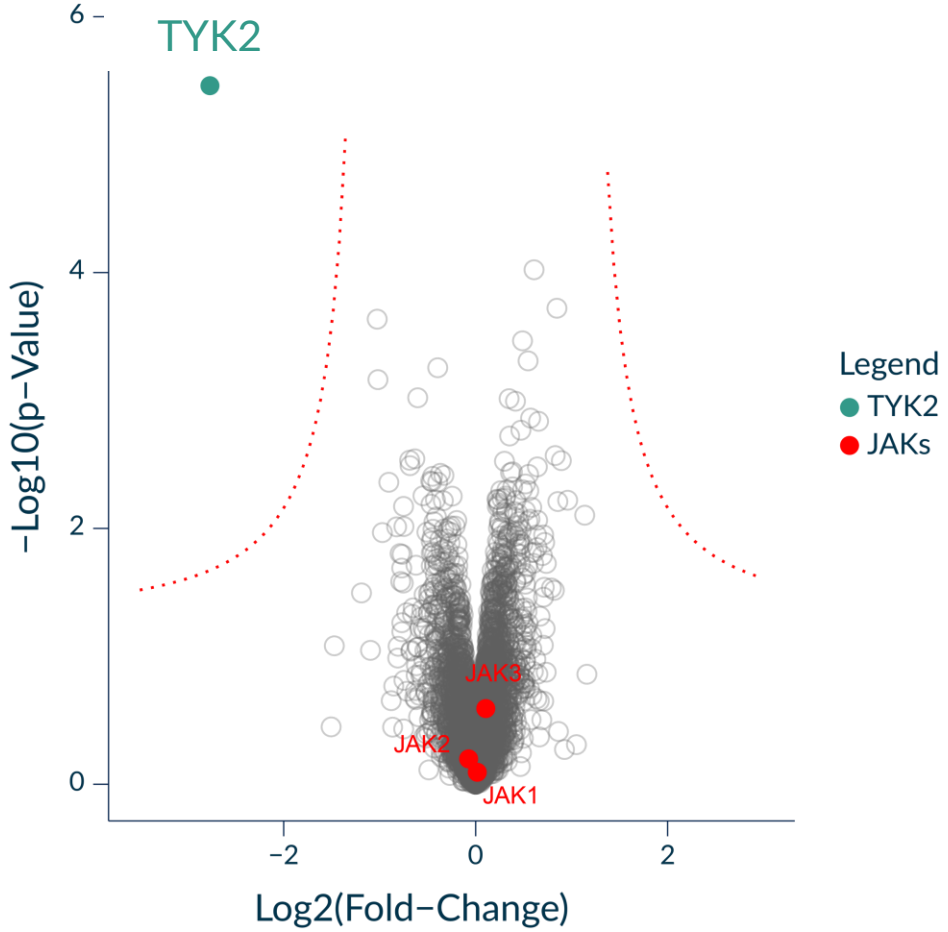
Degrading TYK2 is the only small molecule approach to potentially eliminate all scaffolding and catalytic functions of TYK2, fully recapitulating the human TYK2-/- biology

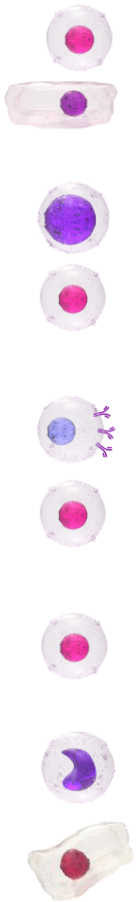
Ogishi et al. JEM. 2022

KT-295, a Highly Selective Picomolar TYK2 Degrader, Recapitulates TYK2 Human Deficiency Biology

Fully Inhibits Type I IFN and IL-12/23 and Spares IL-10/22

Selective TYK2 Degradation by KT-295 in hPBMC Proteome at 10x DC_{90}



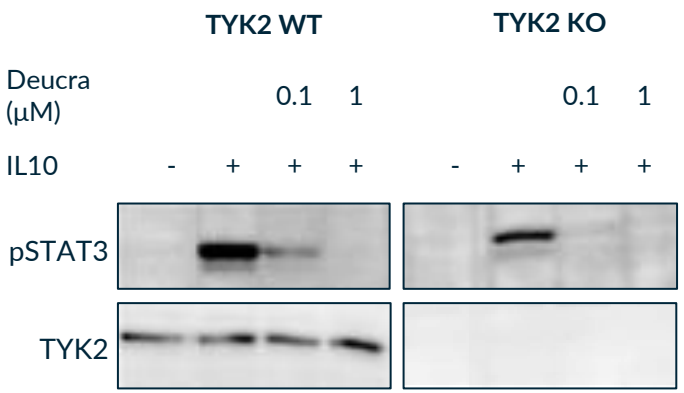


Cellular Degradation/Functional Assay	KT-295 DC_{50}/IC_{50} (nM)
Human PBMC degradation	**0.08**
Human keratinocyte	**0.06**
IL-23 pathway	
IL-23 pSTAT3 in human CD3+CD161high TH17 cell	**1.3**
IL-23/IL-1β IFN-γ release in human PBMC	**3.6**
Type I IFN pathway	
IFN-α pSTAT1 in human CD19 B cell	**10**
IFN-α pSTAT2 in human CD19 B cell	**14**
IFN-α IP10 release in human PBMC	**37**
IL-12 pathway	
IL-12/IL-18 pSTAT4 in human PBMC	**1.1**
IL-12/IL-18 IFN-γ release in human PBMC	**14**
IL-10 and IL-22 pathways	
IL-10 pSTAT3 in human CD14 monocyte	**> 1000**
IL-22 pSTAT1 in HT29 cell	**> 1000**
IL-22 pSTAT3 in HT29 cell	**> 1000**

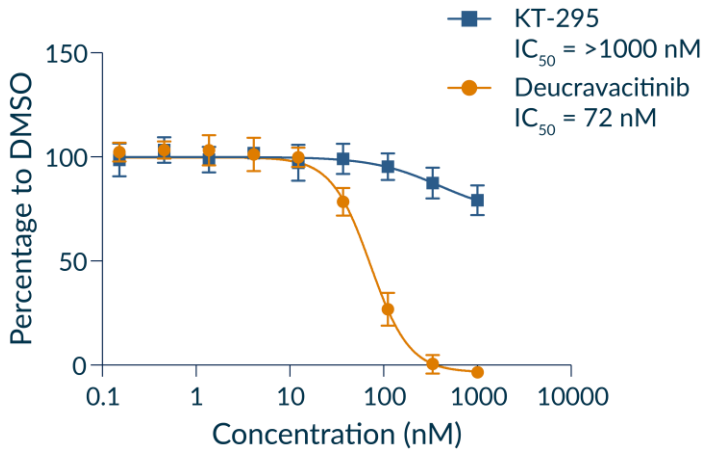
Unlike Allosteric TYK2 Inhibitor Deucravacitinib, KT-295 Does Not Inhibit IL-10

- IL-10 has essential roles in intestinal homeostasis
  - Loss of function mutations of the IL-10 pathway cause early onset refractory colitis in humans
- Deucravacitinib inhibits IL-10 because of its anti-JAK1 activity; KT-295 spares IL-10 as a result of TYK2 selectivity

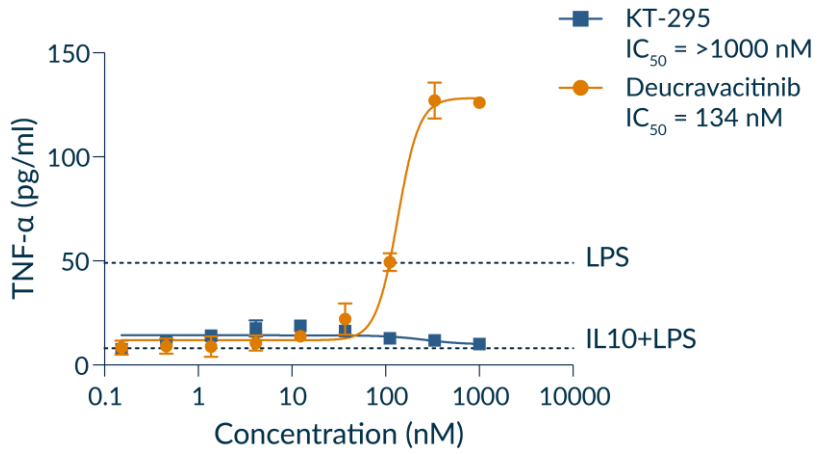
Deucravacitinib Inhibited IL-10-induced pSTAT3 in TYK2 KO EBV B Cell



Deucravacitinib Inhibited IL-10-induced pSTAT3 in Human CD14 Monocyte

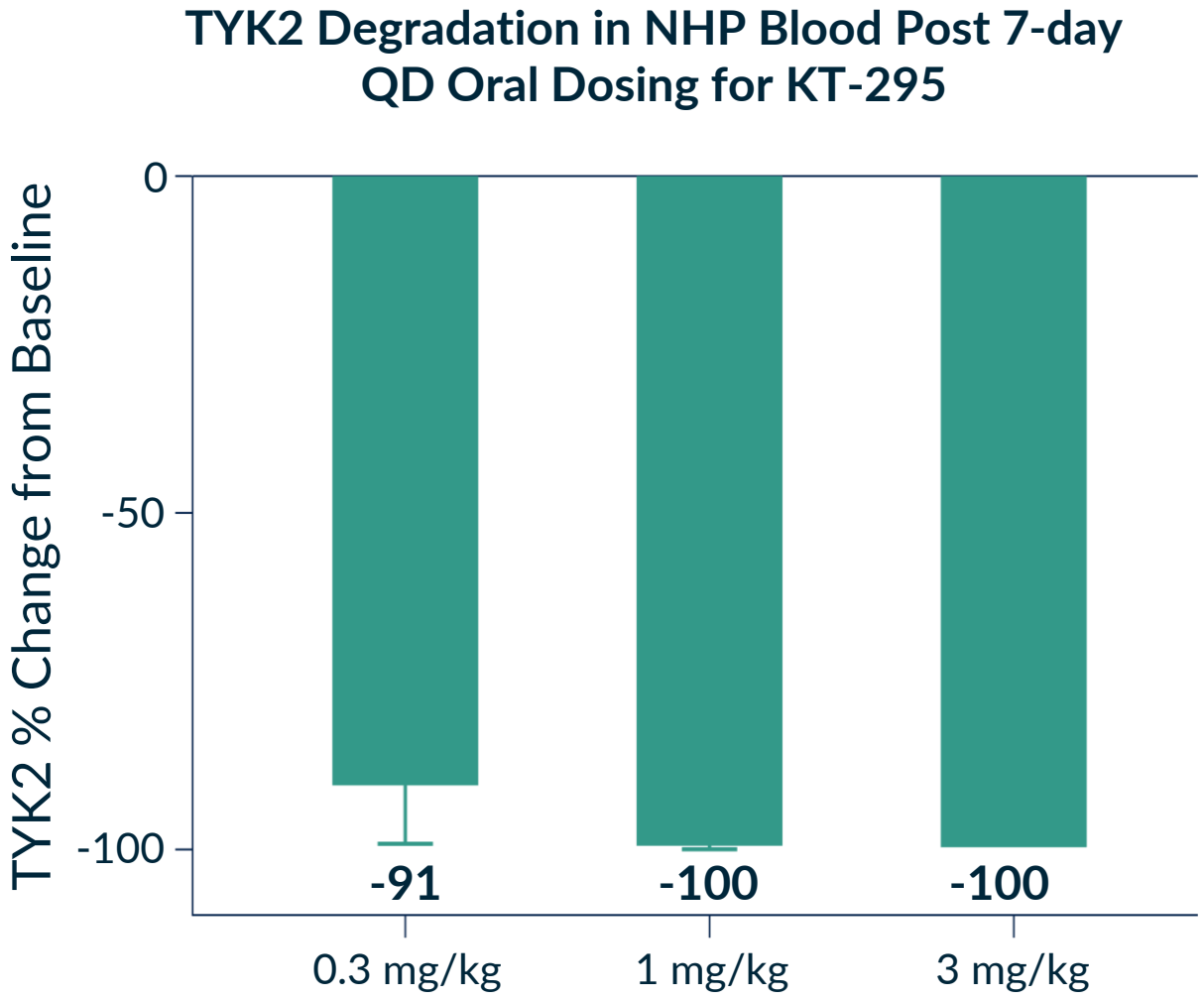


Deucravacitinib Inhibits IL-10's Function of Suppressing LPS-induced TNF-α Release in Human CD14 Monocyte

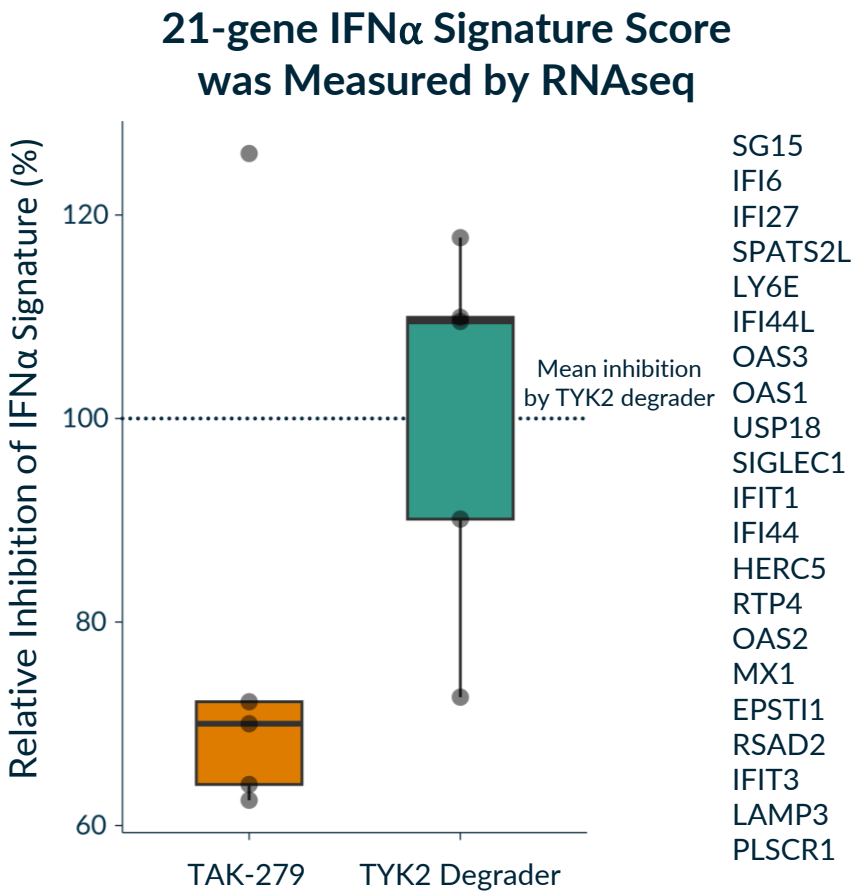


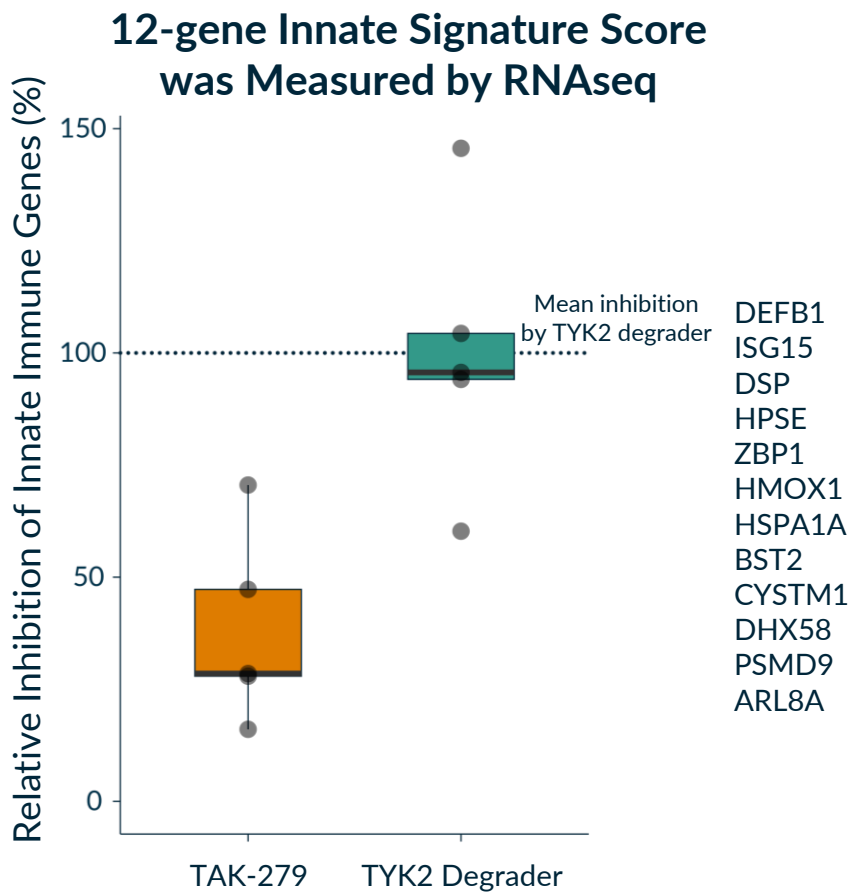
KT-295 Achieved Dose Dependent Deep Degradation of TYK2 *In Vivo* with Low Oral Doses

- KT-295 potently degrades TYK2 across multiple preclinical species
- In NHP, KT-295 can degrade TYK2 to depletion with low oral doses



Superior Inhibition of Type I IFN Pathway and Innate Immunity by Degrader vs. Inhibitor





Doses Used:

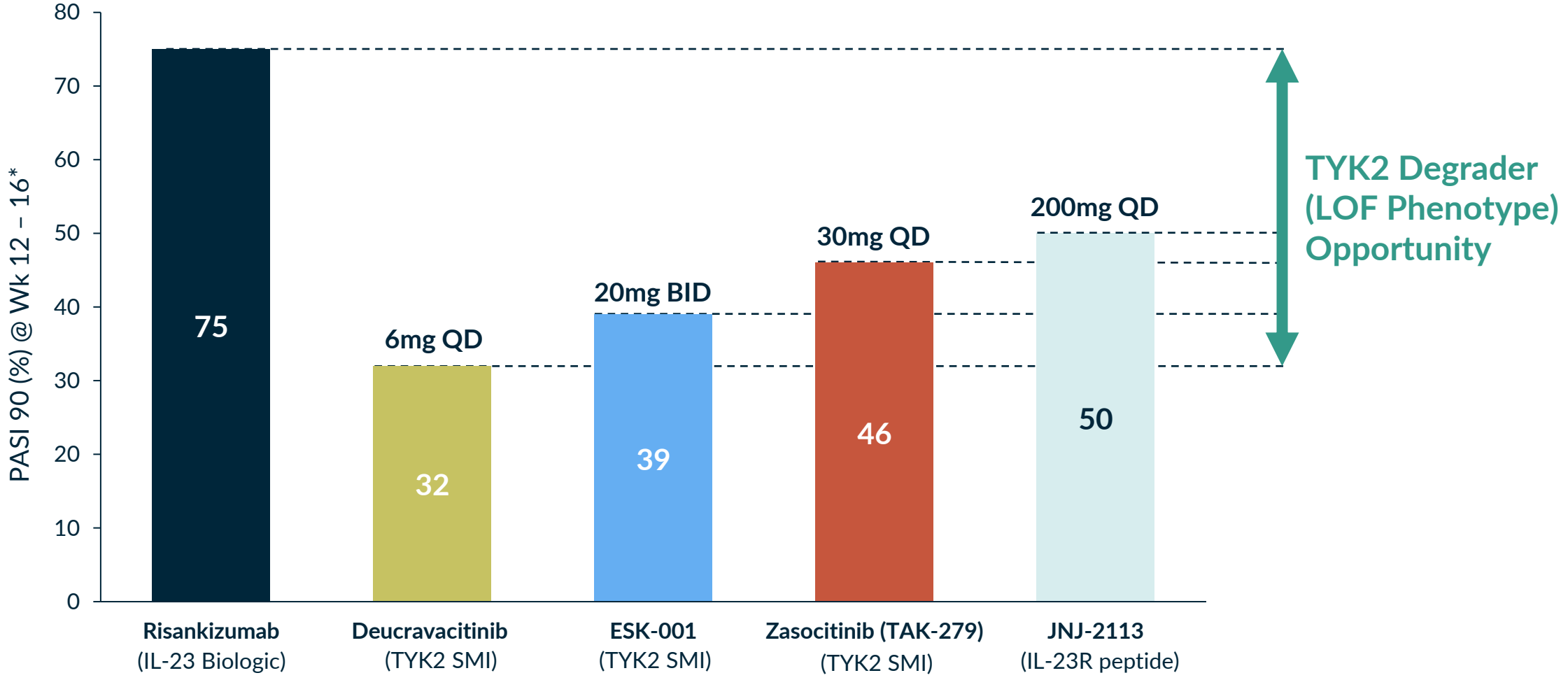
- TYK2 Inhibitor Zasocitinib (TAK-279) = 422nM (IFNα stimulated pSTAT2 IC_{95}). Clinical exposure Cmax (free) at 35mg[1] = ~ 77 nM
- TYK2 Degrader = 56nM (IFNα stimulated pSTAT2 IC_{95})

At concentrations where SMI and degrader block pathway 95%, degrader demonstrates superior biological effect. Zasocitinib (TAK-279) does not reach these exposures in clinic

[1]Gangolli et al., SID 2022

Traditional SMI's Do Not Reach Maximal Target Engagement and Have Limited Clinical Activity vs. Biologics

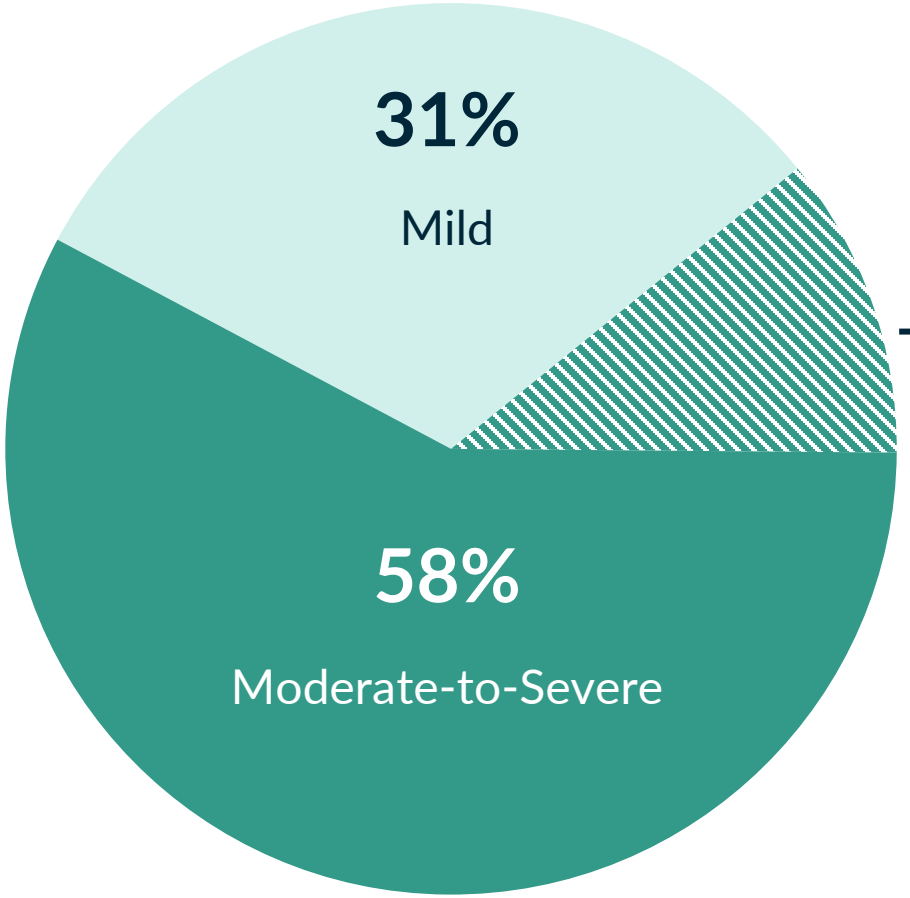
Clinical Efficacy in Psoriasis is Target Engagement Dependent



Sources: Company presentations and package inserts; *Timepoint for measure of PASI90 ranges from Week 12 to Week 16 depending on therapy/trial.

KT-295 Has the Potential to Bring Biologics-Like Efficacy in an Oral Daily Pill to All Addressable Patients

>20 million diagnosed mild and moderate/severe patients across the 7 major markets (2023)



— **11%** Treated with Systemic Advanced Therapy **(>$65B market)**[1]

Potential to address patients across all disease severities

[1]GlobalData (2023 diagnosed prevalent patient population and forecasted sales for approved systemic advanced therapies in US/EU5/JP)

Oral TYK2 Degrader: KT-295

TYK2-LOF Profile to Deliver Biologics (i.e., IL-23)-like Activity in a Pill

Validated Biology

- TYK2 is a member of the JAK family required for Type I IFN, IL-12 and IL-23 cytokine signaling
- TYK2 has a well-established scaffolding function that plays a key role in cytokine receptor surface expression and activation
- TYK2 validated by human genetics
- Pathway validated by upstream biologics (i.e., ustekinumab) and TYK2 SMIs across many diseases

Opportunity

- Total potential patient impact[1]: >20M patients
- IL-23 and Type 1 IFN-based biologic market currently ~$18B annually[2]
- Estimated to grow to ~$27B with expanded indications and new entrants[2]
- TYK2 SMIs have limitations due to selectivity (deucravacitinib) or lack of potent IFN-α activity (Zasocitinib/TAK-279) and limited clinical target engagement (both)
- Mega-blockbuster potential for oral degrader with biologics-like activity that is superior to TYK2 SMI with potential for TYK2 franchise to address patients across all disease severities

KT-295 Profile

- Degrades TYK2 in human cells with pM potency
- Recapitulates the phenotype of TYK2 human deficiency showing potent IFN-α, IL-12 and IL-23 inhibition and sparing IL-10
- Dosed orally, shows complete TYK2 degradation in NHP providing a path to full target engagement in clinic, unlike current SMIs
- IND enabling studies ongoing

Upcoming Milestones
Phase 1 HV Start: 2Q 2025
Phase 1 HV Data: 4Q 2025

[1]GlobalData (2023 diagnosed prevalent patient population for US/EU5/JP)
[2]GlobalData Consensus Forecast

First-in-Class Oral IRAK4 Degrader Program

Combined activity of upstream biologics (anti-IL-1/18/33/36) in a pill

IRAK4 Biology and Target Rationale

Target Rationale

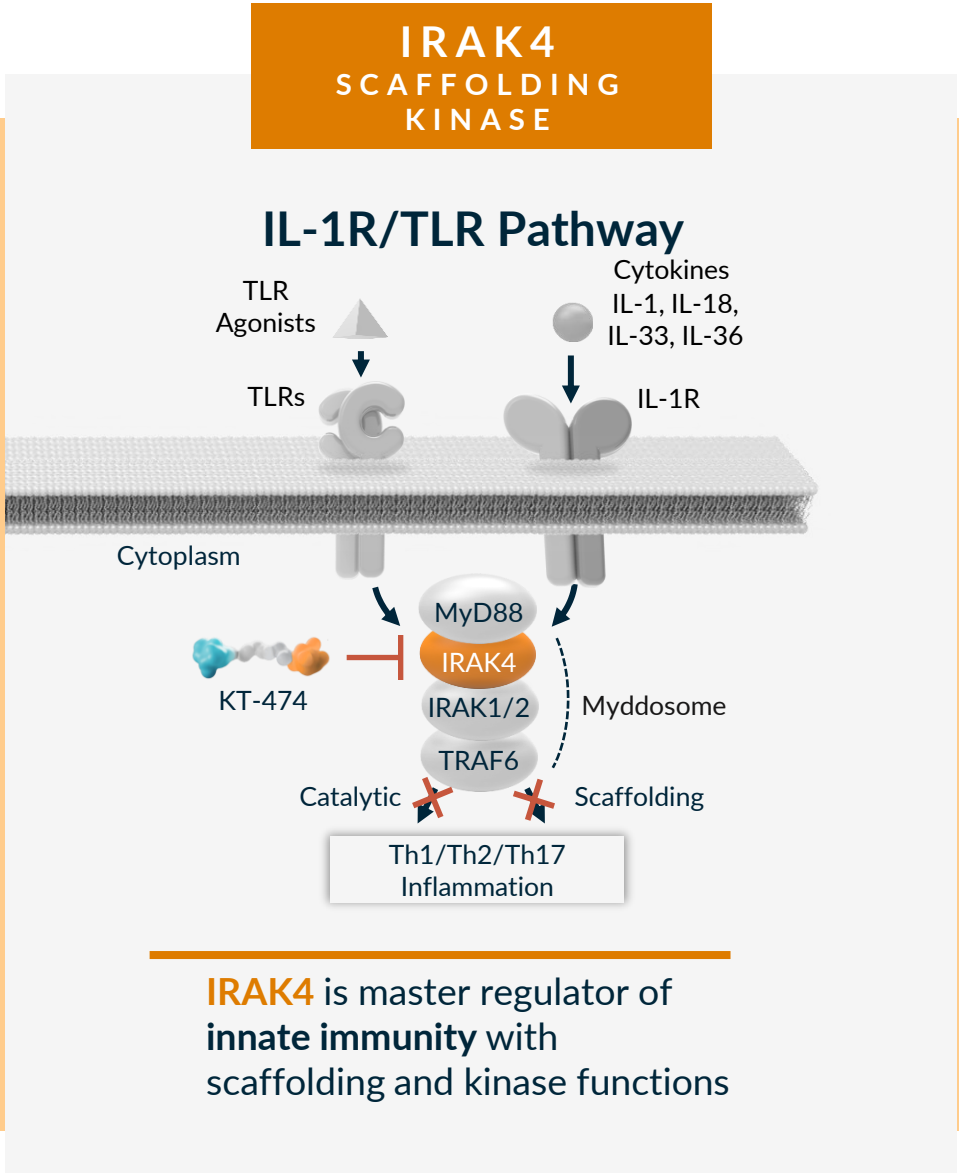
- IRAK4 is an obligate node in IL-1R/TLR signaling, and its degradation is the only approach to fully block the pathway

Human Genetics

- Adult humans with IRAK4 null mutation are healthy

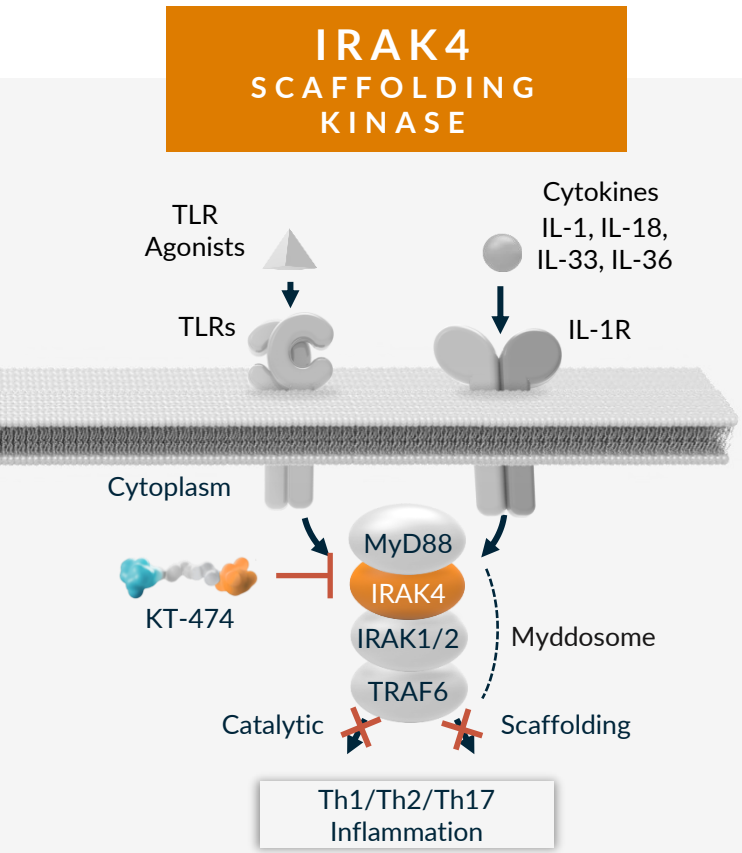
Clinical Pathway Validation

- IRAK4 degradation has the potential to achieve a broad, well-tolerated anti-inflammatory effect
- Multiple development opportunities in immune-inflammatory diseases which signal through MyD88/IRAK4 have been validated[1]:
  - IL-1α/IL-1β : RA, CAPS, HS, AD, Gout
  - IL-18: AD, Macrophage Activation Syndrome
  - IL-36: Generalized Pustular Psoriasis, AD
  - IL-33: Asthma, COPD
  - IRAK4 SMI: RA



[1]Current indications; HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities.
Figure adapted from West NT. *Front Immunol* 2019.

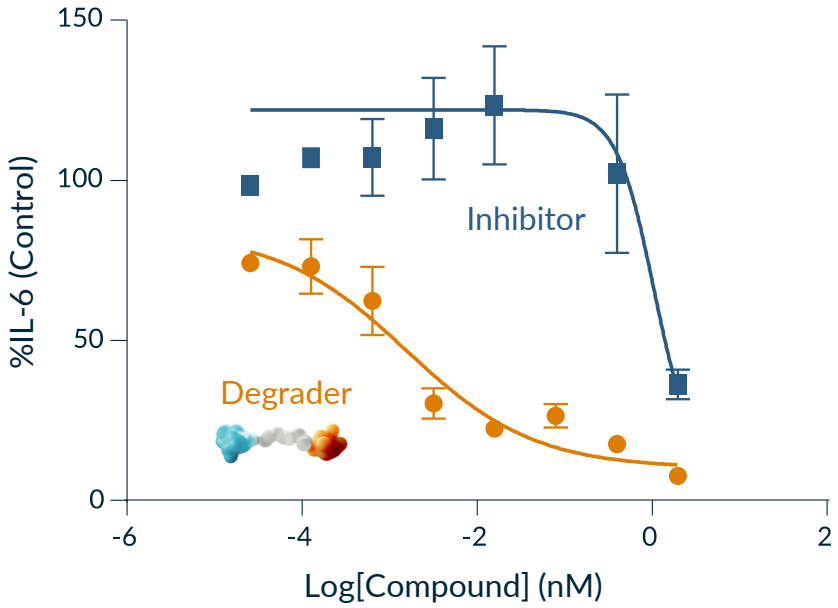
IRAK4 Degrader Advantage



IRAK4 caps the oligomer size of MYD88 to trigger myddosome formation

Only Degrader Can Fully Block Inflammation

LPS + IL-1β → IL-6



Preclinical Data *(Kymera IRAK4 Backgrounder)*

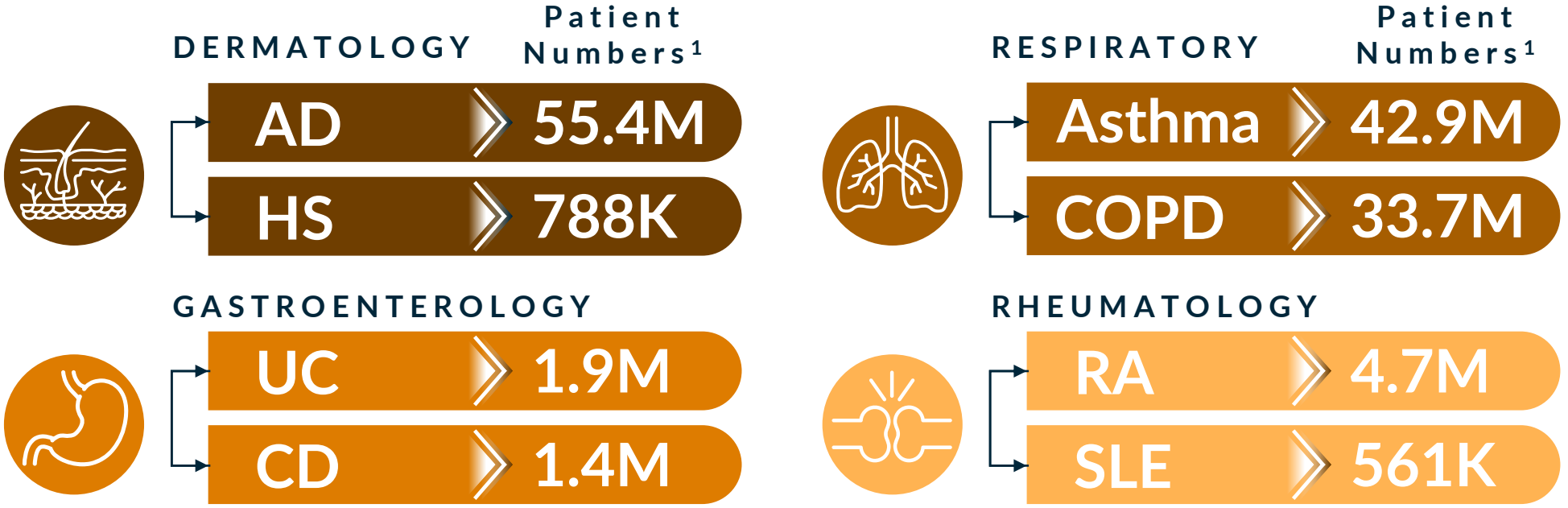
- IRAK4 KO is able to block TLR activation unlike the kinase dead rescue
- IRAK4 **scaffolding function** is critical in Myddosome formation and pathway signaling
- IRAK4 degradation, but not kinase inhibition, can **block TLR induced NF-κB translocation** and **IL1R+TLR activation**
- IRAK4 degradation is superior to kinase inhibition at **blocking downstream phosphoproteome**
- IRAK4 degradation is superior to inhibition in a **variety of preclinical efficacy models**

Clinical Data *(Nature Medicine*)*

- IRAK4 degradation **reduces signs and symptoms of HS and AD**, while IRAK4 SMI inactive in Phase 2 HS trial
- IRAK4 blocks inflammation in blood and skin of HS and AD patients

*Ackerman, et al., *Nature Medicine* (2023).

IL-1R/TLR Pathway Potential Impact Across Multiple Immune-Inflammatory Diseases



Total Potential Patient Impact:
>140M patients[1]

- Numerous indication opportunities across multiple therapeutic areas validated by sub-optimal pathway inhibitors
- IRAK4 degradation leading to full pathway inhibition has the potential to deliver superior profile to upstream biologics
- Oral degrader medicines offer opportunity to reach broader patient populations

[1]GlobalData (2023 diagnosed prevalent patient population for US/EU5/JP)

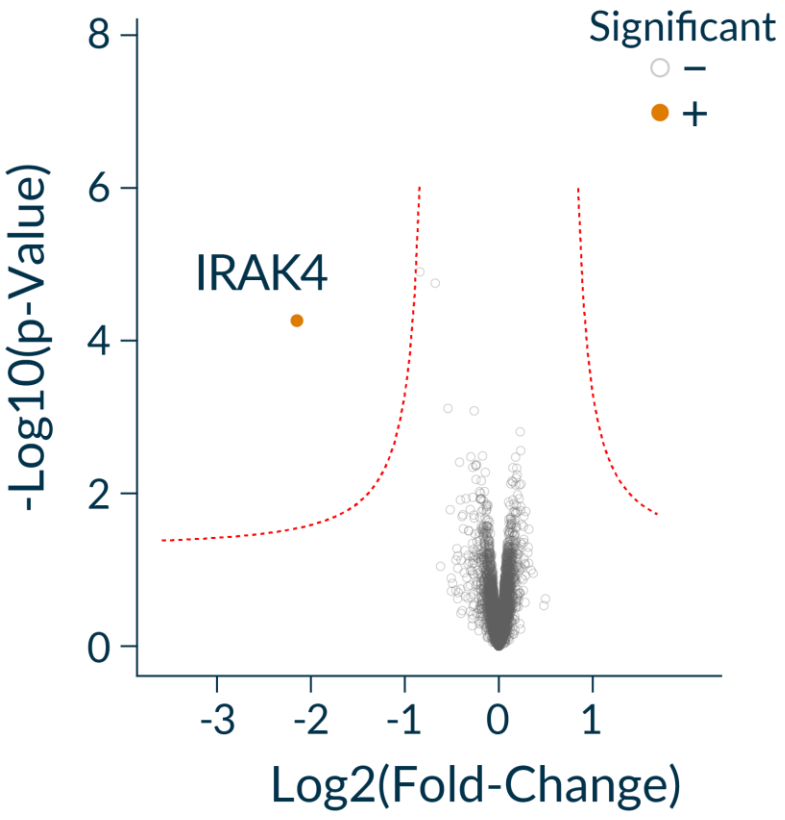
Executive Summary: IRAK4 Program

Vision: Develop an oral IRAK4 degrader with superior activity to upstream pathway biologics to address debilitating diseases driven primarily by innate immunity (TLR, IL-33, IL-36 and IL-1) for AD, HS and other diseases such as COPD, Asthma, IBD, Lupus, RA, others

- IRAK4 has both genetic and clinical validation, although it has been insufficiently drugged with small molecule inhibitors
- Fully blocking the IRAK4 pathway has the unique potential to combine the activity of multiple upstream biologics (anti-IL-1/18/33/36) in an oral pill
- KT-474 is the first, highly selective, potent and orally active IRAK4 degrader in clinical development
- In preclinical testing, KT-474 fully degraded IRAK4 across multiple species and was safe and well tolerated and was biologically differentiated and more potent than IRAK4 SMI's in blocking IL-1R/TLR driven inflammation
- In Phase 1 (healthy volunteers and AD/HS patients), KT-474 demonstrated robust degradation in blood and skin, impacting disease relevant biomarkers and disease measures (EASI and pruritus in AD and HiSCR and pain in HS)
- KT-474 is in Phase 2b trials in AD and HS, led by partner Sanofi, with data in 2026

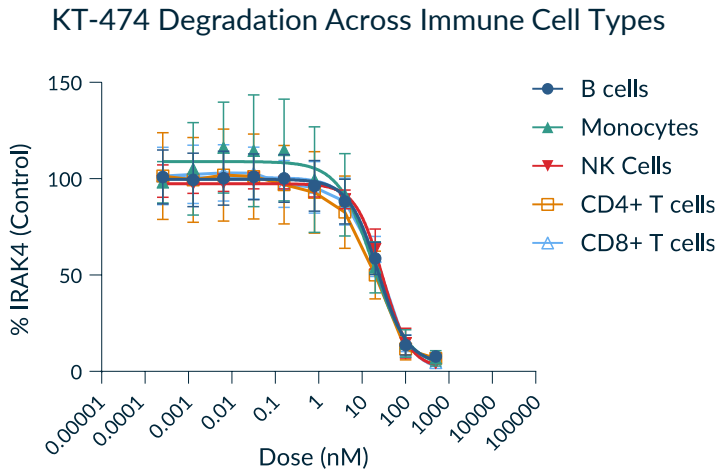
KT-474: Selective and Potent IRAK4 Degrader Active in Multiple Cell Types

Selectivity in PBMC



- KT-474 selectively degrades IRAK4 in human immune cells at concentration 10-fold above the DC_{90}
- Potent degradation in PBMC subsets and skin cells including fibroblasts, with single-digit nM DC_{50}
- Associated with functional inhibition of TLR- and IL-1β-stimulated cytokine production
- Comprehensive understanding of degradation kinetics across cell types to enable human translation

Potency in Blood and Skin Cells

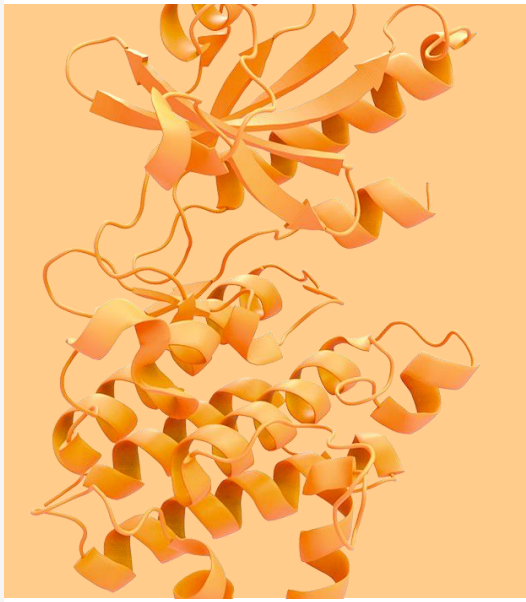


Cell type (Human)	Source	KT-474 DC_{50} (nM)
Monocytes	Blood	2.6
B cells	Blood	2.7
CD4 T cells	Blood	1.5
CD8 T cells	Blood	1.5
NK cells	Blood	1.8
Fibroblasts	Skin	1.5
Keratinocytes	Skin	7.8

KT-474 Phase 1: Compelling Data and Early POC in HS and AD

Healthy Volunteers (HV): SAD and MAD

- Evaluated safety, tolerability and pharmacokinetics in 105 healthy volunteers
  - SAD: Oral doses of 25-1600 mg
  - MAD: Escalating doses up to 200 mg were administered for 14 consecutive days
- Robust (>95%) and sustained IRAK4 degradation with single and multiple daily doses
- Broad inhibition of *ex vivo* TLR-mediated cytokine induction
- Generally well-tolerated across all dose groups



HS and AD Patient Cohort

- Open label study in 21 patients with HS and AD
- Dose: 75 mg QD with food (equivalent exposure to 100 mg fasted), administered for 28 consecutive days
- Safety, PK and PD comparable to healthy volunteers
- Robust IRAK4 degradation in blood and skin with associated systemic anti-inflammatory effect in HS and AD patients
- Promising clinical activity observed in HS and AD

nature medicine

Article https://doi.org/10.1038/s41591-023-02635-7

IRAK4 degrader in hidradenitis suppurativa and atopic dermatitis: a phase 1 trial

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Accepted: 6 October 2023
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Check for updates

Lindsay Ackerman[1], Gerard Acloque[2], Sandro Bacchelli[3], Howard Schwartz[4], Brian J. Feinstein[5], Phillip La Stella[6], Afsaneh Alavi[7], Ashwin Gollerkeri[8], Jeffrey Davis[8], Veronica Campbell[8], Alice McDonald[8], Sagar Agarwal[8], Rahul Karnik[8], Kelvin Shi[8], Aimee Mishkin[8], Jennifer Culbertson[8], Christine Klaus[8], Bradley Enerson[8], Virginia Massa[8], Eric Kuhn[8], Kirti Sharma[8], Erin Keaney[8], Randy Barnes[8], Dapeng Chen[8], Xiaozhang Zheng[8], Haojing Rong[8], Vijay Sabesan[8], Chris Ho[8], Nello Mainolfi[8], Anthony Slavin[8] & Jared A. Gollob[8]

News & views

Targeted therapy https://doi.org/10.1038/s41591-023-02622-y

PROTACs reach clinical development in inflammatory skin disease

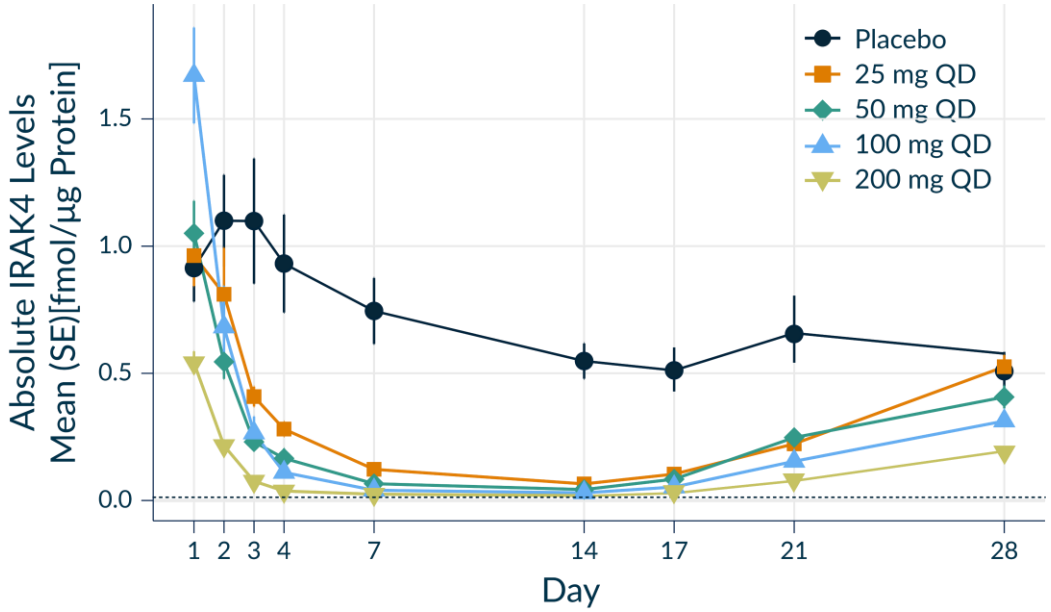
Fleur M. Ferguson

Check for updates

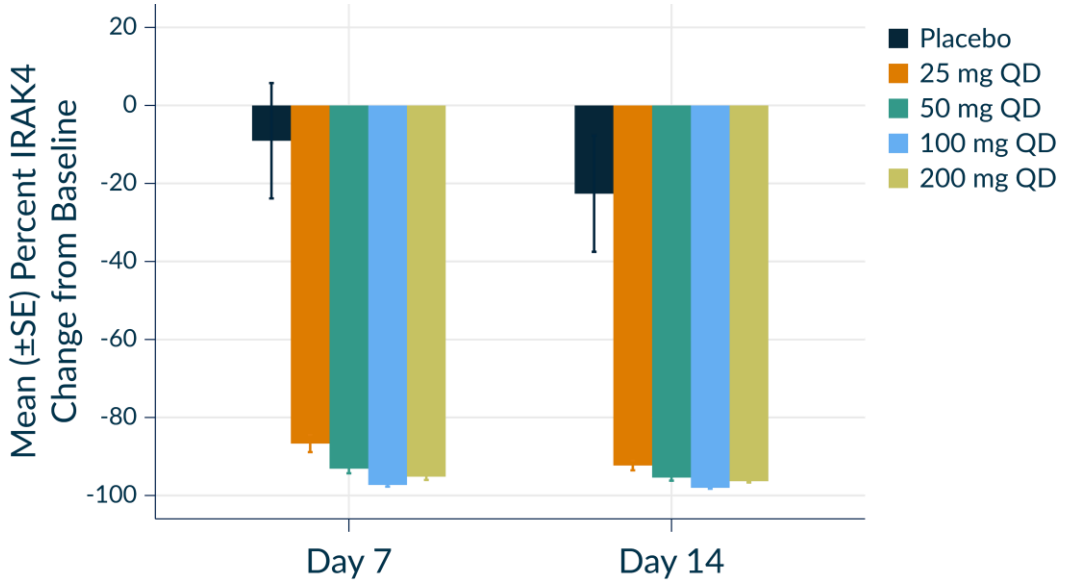
A phase 1 trial of an IRAK4-targeted protein degrader in patients with chronic inflammatory skin diseases hits an important milestone for the safe application of this drug class beyond oncology.

Phase 1 MAD HV: KT-474 Achieved Robust and Sustained IRAK4 Degradation with Multiple Daily Oral Doses (14 Days)

Absolute IRAK4 Levels



Percent IRAK4 Reduction at Steady State



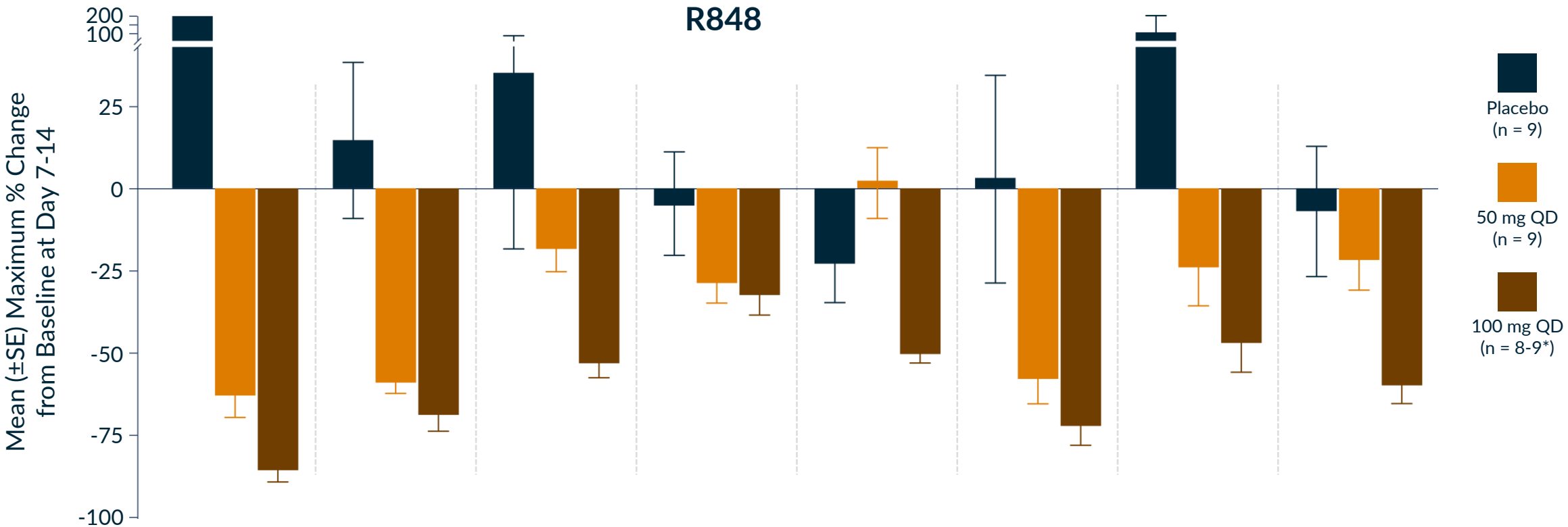
- Detected by mass spectrometry in circulating PBMC
- Steady state IRAK4 reduction achieved between Days 7 and 14
- Recovery towards baseline by Day 28 (2 weeks after last dose)
- MAD 2 through 4 approached Lower Limit of Quantitation (LLOQ)

	Placebo (n=12)	25 mg QD (n=9)	50 mg QD (n=9)	100 mg QD (n=9)	200 mg QD (n=9)
Mean Day 7	-9%	-87%	-93%	-97%	-95%
Mean Day 14	-23%	-92%	-95%	-98%	-96%
P value		<0.0001	<0.0001	<0.0001	<0.0001

* p-values relative to placebo

Deep and Broad Inhibition of Th1/Th17 Cytokines Ex Vivo

Results through MAD3 Showed Dose-Dependent Effect Tracking with Extent of Monocyte IRAK4 Degradation



	IFNγ	IL1β	IL6	IL8	IL10	IL12	IL17	TNFα
Pbo	>500%	15%	35%	-5%	-23%	3%	107%	-7%
50 mg QD	-62%	-59%	-18%	-28%	2%	-58%	-24%	-21%
100 mg QD	-85%	-68%	-53%	-32%	-50%	-72%	-46%	-59%

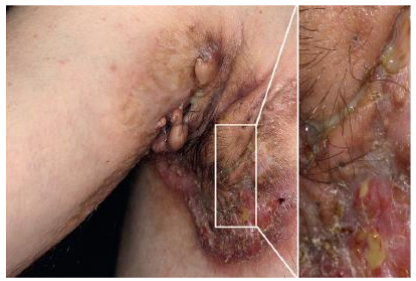
50 mg QD: 93-95% PBMC degradation at Day 7-10; 87-90% Monocyte degradation at Day 7-14. 100 mg QD: 97-98% PBMC degradation at Day 7-10; 92-93% Monocyte degradation at Day 7-14. *n=8 for LPS, n=9 for R848. Mean values > 200% have been replaced by 200 for visualization purposes.

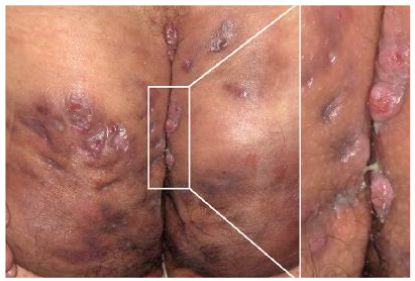
Initial Clinical Focus for KT-474: Moderate to Severe HS and AD

Hidradenitis Suppurativa (HS)

Chronic and debilitating skin disease with painful nodules, abscesses and draining fistulae/tunnels

Major QoL impact: Pain, itching, depression, social isolation



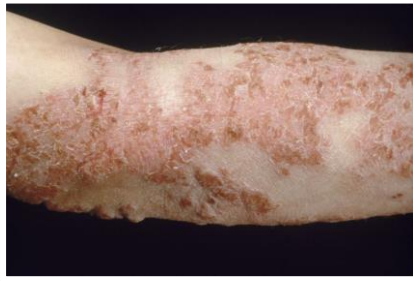


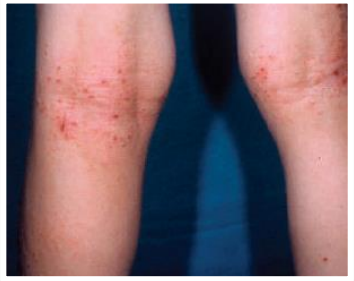
- Many diagnosed in their 20s/30s; more common in females (~3:1); prevalence estimated to be up to 1-3% of population in US and EU
- Lesions characterized by pleotropic inflammation with Th1/Th17 skewing; bacterial infection and tissue destruction leading to TLR activation; IL-1 and IL-36 production
- Active agents approved or in development target TNF-α, IL-17 and JAK/STAT pathways

Atopic Dermatitis (AD)

Chronic inflammatory skin disease with scaly, dry, erythematous lesions; intense itching/scratching, predisposition to infections

Major QoL impact: Itching, pain, sleep disturbance



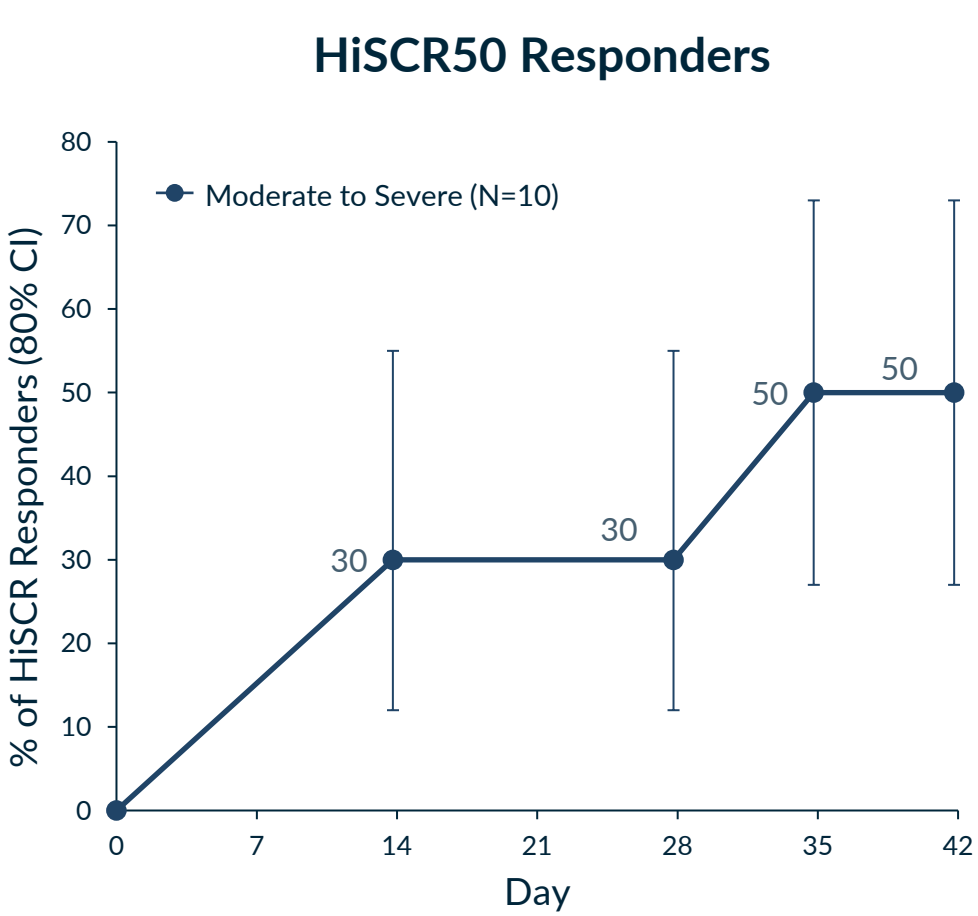


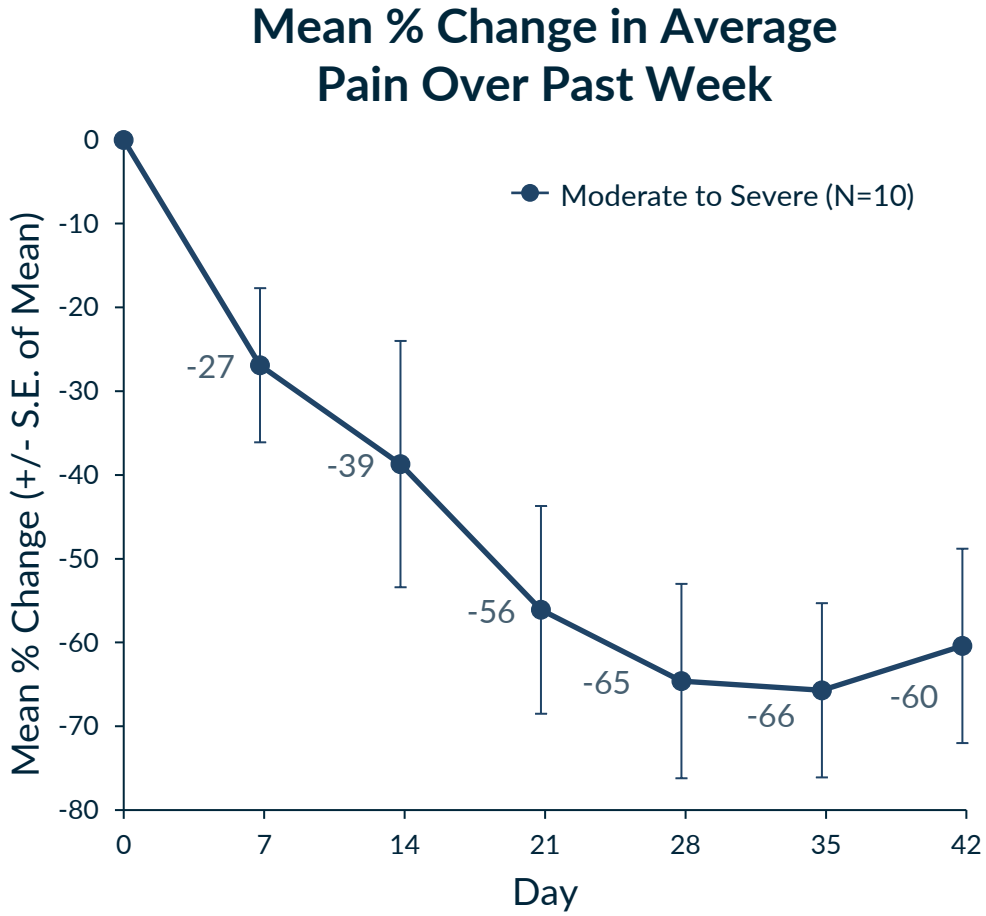
- Onset usually in early childhood; affects an estimated 98 million adults in US/EU5/JP[1]
- Lesions characterized by pleotropic inflammation with Th2 skewing; bacterial infection and skin barrier breakdown leading to TLR activation; IL-33 and IL-1 production
- Active agents approved or in development target IL-4/IL-13, JAK/STAT and OX40/OX40-L pathways

KT-474 Opportunity: Potential for broad anti-inflammatory effect, competitive efficacy vs. pathway biologics and convenience of once-daily oral dosing

[1]GlobalData (2022 undiagnosed, all-age prevalence)

Robust Clinical Impact in HS After Only 28 Days of Dosing





HiSCR50 response rate of up to 50% and pain reduction of up to 66% in moderate to severe HS patients

KT-474 Showed Meaningful Signs of Clinical Activity in HS, Comparing Favorably to Placebo Benchmarks and SOC

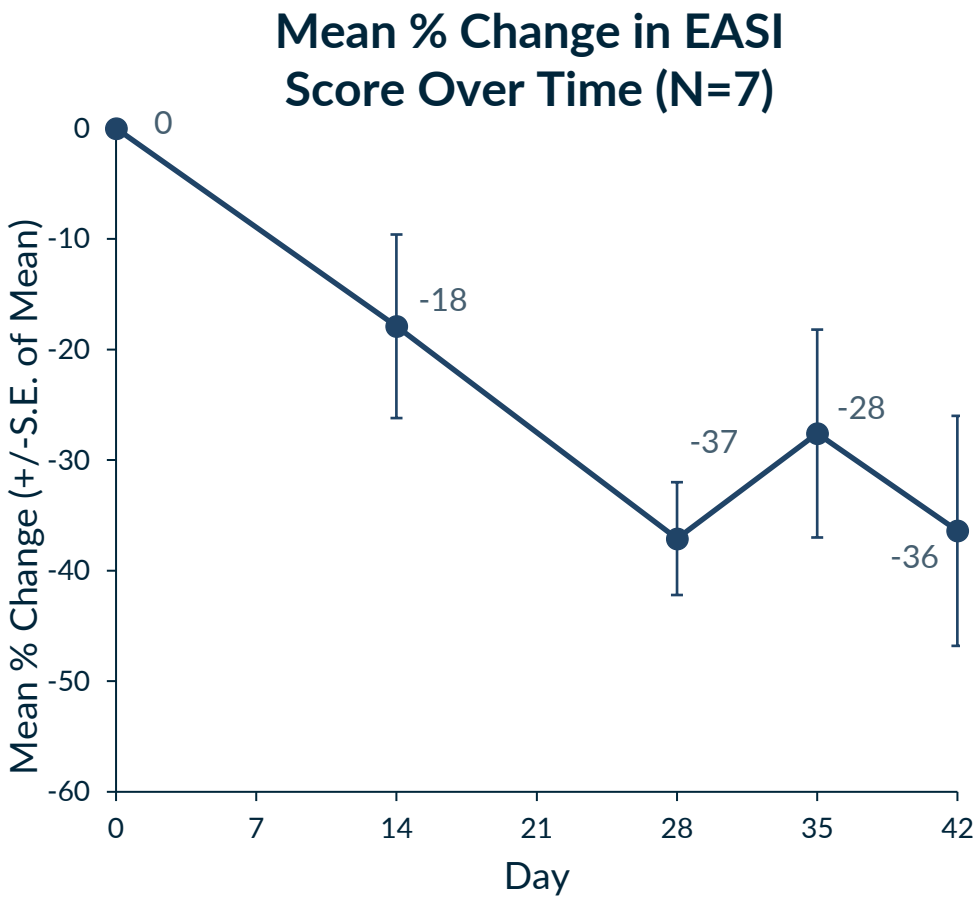
Summary Results

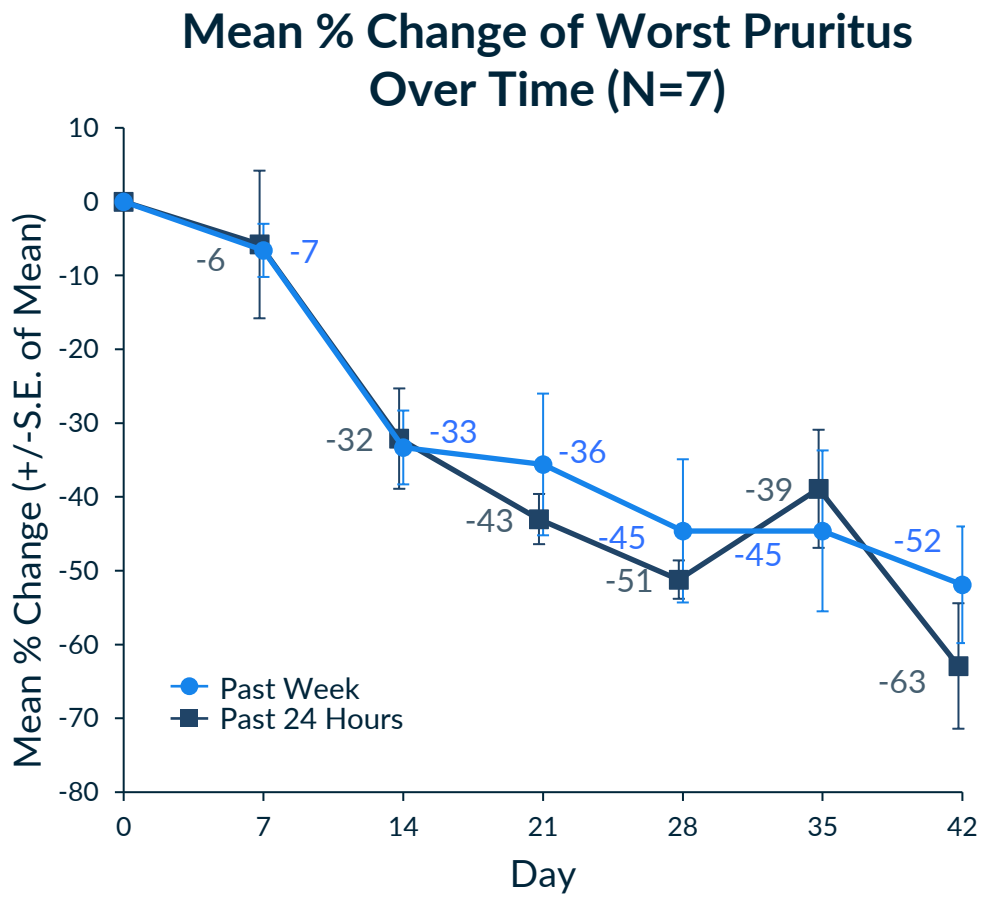
- Mean total AN count reduction of **46** to **51%**, with maximum reduction up to **100%**
- AN count of 0/1/2 response rate of **42** to **50%**
- HiSCR50 response rate of **42** to **50%**
- HiSCR75 response rate of **25** to **30%**
- Pain NRS30 response in **50** to **60%** and mean peak pruritis reduction of **62** to **68%**
- Physician Global Assessment (PGA) scores improved in **5** of **12** patients, including 1 moderate disease patient with full disease clearance, and stable in the others

	KT-474 Part C	**Placebo Benchmarks** Week 4	**Adalimumab Phase 2 and 3** Week 4
ΔAN Count	**-46 to -51%**	-15%[1]	-31%[1]
AN Count 0/1/2	**42 to 50%**	24 to 26%[3]	28 to 47%[2,3]
HiSCR50	**42 to 50%**	19 to 30%[3,4]	29 to 51%[3,4]
HiSCR75	**25 to 30%**	5%[4]	20%[4]
Pain NRS30	**50 to 60%**	18 to 23%[3,5]	39 to 58%[2,3,5]
ΔPeak Pruritus NRS	**-62 to -68%**	N/A	N/A

[1]Kimball AB, et al. *Ann Intern Med* 2012;157:846-55; [2]Morita A, et al. *J Dermatol* 2021;48:3-13; [3]Kimball AB, et al. *NEJM* 2016;375:422-434; [4]Glatt S et al. *JAMA Dermatol* 2021;157:1279-88; [5]Scheinfeld, et al. *Derm Online J* 2016:22; The Adalimumab clinical trial was conducted by other parties in a similar patient population with different enrollment criteria from Part 1C of our Phase 1 clinical trial evaluating KT-474. Results do not reflect a head-to-head trial and are shown for illustrative purposes only

Robust Clinical Impact in AD After Only 28 Days of Dosing





EASI score reduction of up to 36% and pruritus reduction of up to 63% in moderate to severe AD patients

KT-474 Showed Meaningful Signs of Clinical Activity in AD, Comparing Favorably to Placebo Benchmarks and SOC

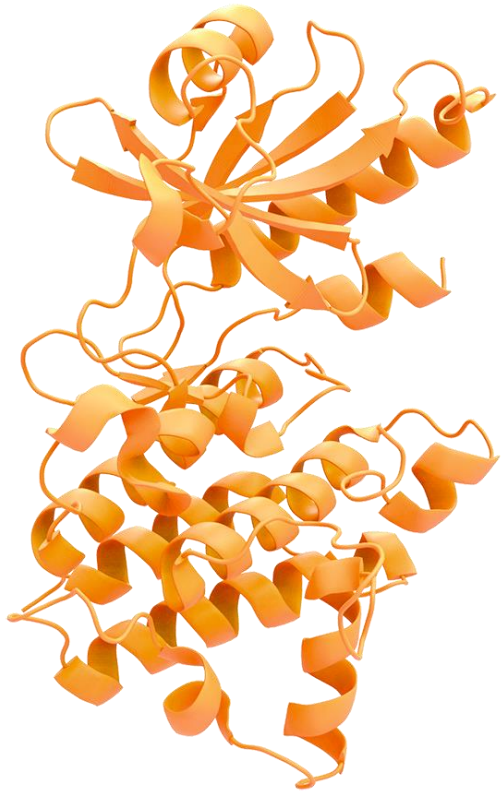
Summary Results

- Mean EASI score reduction up to **37%,** with maximum reduction of up to **76%**
- Mean peak pruritus NRS reduction of **52** to **63%**
- Peak pruritus NRS Responder rate of **57** to **71%**
- Investigator Global Assessment (IGA) scores improved in **2** of **7** patients and remained stable in the others

	KT-474 Part C	**Placebo Benchmarks** Week 4	**Dupilumab Phase 3** Week 4
ΔEASI	**-37%**	-12 to -25%*	-52%[1]
ΔPeak Pruritus NRS	**-52 to -63%**	-11%[1]	-34%[1]
Peak Pruritus NRS Responder	**57 to 71%**	4 to 17%**	23 to 40%[1,2]

*Range from 7 different Phase 2 and Phase 3 trials; **Range from 10 different Phase 2 and Phase 3 trials; [1]Simpson EL, et al. *NEJM* 2016;375:2335-2348; [2]Bieber T, et al. *NEJM* 2021;384:1101-1112; The Dupilumab clinical trial was conducted by other parties in a similar patient population with different enrollment criteria from Part 1C of our Phase 1 clinical trial evaluating KT-474. Results do not reflect a head-to-head trial and are shown for illustrative purposes only

KT-474/SAR444656: Positioned for Clinical Success



Phase 2b HS Trial
(ZEN)

- Double-blind, placebo-controlled
- Up to 156 patients, dosed for 16 weeks
- 2 KT-474 dose arms, 1 placebo arm
- Primary endpoint: % Change in AN Count
- Additional endpoints (select):
  - HiSCR50, IHS4, HS-Skin Pain-NRS30
- Primary completion (est.): 1H 2026

Phase 2b AD Trial
(ADVANTA)

- Double-blind, placebo-controlled
- Up to 200 patients, dosed for 16 weeks
- 3 KT-474 dose arms, 1 placebo arm
- Primary endpoint: % Change in EASI
- Additional endpoints (select):
  - EASI 50/75/90, vIGA-AD, PP-NRS
- Primary completion (est.): Mid-2026

Sanofi, following a safety/efficacy IA, has expanded the ongoing Phase 2 trials by adding additional doses to more rapidly progress toward pivotal trials

Additional information on the Phase 2 studies can be found at www.clinicaltrials.gov; identifier NCT06028230 (HS) and NCT06058156 (AD); Study Sponsor: Sanofi

Oral IRAK4 Degrader: KT-474

Combined Activity of Upstream Biologics (anti-IL-1/18/33/36) in a Pill

Validated Biology

- Mediates signaling through IL-1 and toll-like receptors
- Upstream cytokine blockers with proven clinical activity across many diseases
- Scaffolding kinase at the interface of innate and adaptive immune responses with a variety of functions

Opportunity

- Total potential patient impact[1]: >140M patients
- >$55B in combined global drug sales[2] opportunity
- Large potential for oral degraders with best in pathway efficacy across Th1-Th17 and Th2 Diseases

KT-474 Profile

Phase 1 complete:

- Robust IRAK4 degradation
- Favorable safety profile
- Systemic suppression of proinflammatory cytokines and chemokines
- Early signs of strong clinical activity

Upcoming Milestones
Phase 2b Completion:
1H 2026 (HS) and mid-2026 (AD)

[1]GlobalData (2023 diagnosed prevalent patient population for US/EU5/JP)
[2]GlobalData (2023 sales for AD, HS, Asthma, COPD, UC, CD, RA, SLE)

Pipeline with Clear Line of Sight to Large Value Creation

	Potential Indications	2025	1H 2026	Upcoming Milestones
Immunology – Oral QD Small Molecule Degraders				
STAT6 **KT-621**	AD, Asthma, COPD, PN, CRSwNP, EoE, BP, others	Ph1 HV → Ph1b AD → Ph2b AD; Ph2b Asthma Safety, STAT6 degradation in blood & skin Biomarkers in blood & skin, 28-day efficacy		Ph1 HV Data: 2Q25 Ph1b AD Data: 4Q25 Ph2b Starts: 4Q25/1Q26
TYK2 **KT-295**	Psoriasis, IBD, PsA, Lupus, others	IND Enabling → Ph1 HV → Patient Studies IND Safety, TYK2 degradation in blood & skin		Ph1 HV Start: 2Q25 Ph1 HV Data: 4Q25
Transcription Factor	Lupus, Sjogren's, RA, IBD, others	IND Enabling → Ph1 Program & data disclosure IND Safety, degradation in blood & skin		FIH: Early 2026
Partnered with Sanofi / Kymera Opt-In Potential				
IRAK4 **KT-474**[1]	HS, AD, RA, Asthma, IBD, others[2]	Ph2b HS Ph2b AD		Ph2b Completion: HS: 1H26 AD: Mid-2026

[1]KT-474 (SAR444656) partnered with Sanofi, with Kymera option to participate in the development and commercialization, and 50/50 profit split, in the United States. Double digit tiered royalties in ROW.
[2]Current indications: HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities.

An Unmatched Strategy for Millions of Patients

Advancing Multiple First-in-Class Oral Degraders That Address Significant Market Opportunities in Immunology

Unlocking high value targets to **revolutionize immunology with oral degrader medicines**

KT-621, the first oral STAT6-targeted agent in clinical development, with dupilumab-like activity in preclinical models, has the potential to transform treatment paradigms for the >130 million patients (across ages and severities) suffering from Th2 diseases.

- **Phase 1 HV data to be shared in 2Q25 followed by Ph1b AD data and start of the first Ph2b clinical trial in 4Q25**

KT-295 has the potential to be the **first oral TYK2 therapy to deliver biologics-like activity** in multiple diseases by replicating loss-of-function human genetics.

- **Initiation of Phase 1 HV study expected in 2Q25 with data in 4Q25**

Sanofi progressing **KT-474, the first IRAK4 oral degrader with potential of combined activity of upstream biologics.**

- **Phase 2b studies in HS and AD expected to complete by mid-2026**

Kymera advancing **additional novel immunology programs** in validated pathways for areas of significant patient need.

- **New program against an undrugged transcription factor to be shared in 1H25**

Thank You

NASDAQ: KYMR

www.kymeratx.com
@KymeraTX

For additional information contact:
investors@kymeratx.com
media@kymeratx.com
inquiries@kymeratx.com

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

KYMERA

Abbreviations

Ab	Antibody
AD	Atopic Dermatitis
ASMS	Affinity Selection Mass Spectrometry
AN Count	Abscess and Inflammatory Nodule Count
BID	Twice a day
BP	Bullous Pemphigoid
CAPS	Cryopyrin-Associated Periodic Syndrome
CD	Crohn's Disease
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
Cryo-EM	Cryo-Electron Microscopy
Ctrl	Control
CSU	Chronic Spontaneous Urticaria
$DC_{\#}$	Degradation Concentration
DEL	DNA-Encoded Library
DMSO	Dimethyl Sulfoxide
EASI	Eczema Area and Severity Index
EBV	Epstein-Barr Virus
EoE	Eosinophilic Esophagitis
EU	European Union
FDA	Food and Drug Administration
FIH	First-in-Human
GLP	Good Laboratory Practice
GOF	Gain of Function
HD	High Dose
HDM	House Dust Mite
HiSCR	Hidradenitis Suppurativa Clinical Response
hPBMC	Human Peripheral Blood Mononuclear Cells
HS	Hidradenitis Suppurativa
HTS	High Throughput Screening
HV	Healthy Volunteers
I&I	Immunology and Inflammation
IA	Interim Analysis
IBD	Inflammatory Bowel Disease
$IC_{\#}$	Inhibitory Concentration
ICS	Inhaled Corticosteroid
IFN	Interferon
IGA	Investigator Global Assessment
IgE	Immunoglobulin E
IHS4	International Hidradenitis Suppurativa Severity Score
IL	Interleukin
IND	Investigational New Drug Application
IRAK4	Interleukin 1 Receptor Associated Kinase 4
JAK	Janus Kinase
JP	Japan
KO	Knockout
LABA	Long-Acting Beta Agonist
LAMA	Long-Acting Muscarinic Antagonist
LD	Low Dose
LOF	Loss of Function
LPS	Lipopolysaccharide Solution
LTRA	Leukotriene Receptor Antagonist
MAD	Multiple Ascending Dose Study
MS	Multiple Sclerosis
NF-kB	Nuclear Factor Kappa B
NHP	Nonhuman Primate
nM	Nanomolar
NRS	Numerical Rating Scale
PASI	Psoriasis Area and Severity Index
PBMC	Peripheral Blood Mononuclear Cells
Pbo	Placebo
PGA	Physician Global Assessment
Ph	Phase
PK/PD	Pharmacokinetics/Pharmacodynamics
pM	Picomolar
PN	Prurigo Nodularis
POC	Proof-of-Concept
PP-NRS	Peak Pruritus Numerical Rating Scale
PsA	Psoriatic Arthritis

Abbreviations

PsO	Psoriasis
pSTAT	Signal Transducer and Activator of Transcription
QD	Once a day
QoL	Quality of Life
R&D	Research and Development
RA	Rheumatoid Arthritis
RNAseq	Ribonucleic Acid Sequencing
ROW	Rest of World
SAD	Single Ascending Dose study
SLE	Systemic Lupus Erythematosus
SMI	Small Molecule Inhibitor
SOC	Standard of Care
STAT	Signal Transducer and Activator of Transcription
STAT6	Signal Transducer and Activator of Transcription 6
TARC	Thymus and Activation-Regulated Chemokine
Th1	Type 1
Th2	Type 2
Th17	Type 17
TLR	Toll-like Receptors
TPD	Targeted Protein Degradation
TYK2	Tyrosine Kinase 2
UC	Ulcerative Colitis
US	United States
vIGA	Validated Investigator Global Assessment for AD
WW	Worldwide