KT-474 HS and AD Clinical Data and Oncology Pipeline Update

Company Webcast

December 14, 2022

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PRESENTATION AGENDA

1. **Welcome**

2. **Oncology Update** 15’
   - IRAKIMiD (KT-413)
   - STAT3 (KT-333)

3. **IRAK4 Update** 35’
   - KT-474 HS and AD Patient Cohort

4. **Q&A** 40’

Introduction to Kymera

Kymera is a **leader in Targeted Protein Degradation** (TPD)

Building a **fully-integrated**, global biotech company

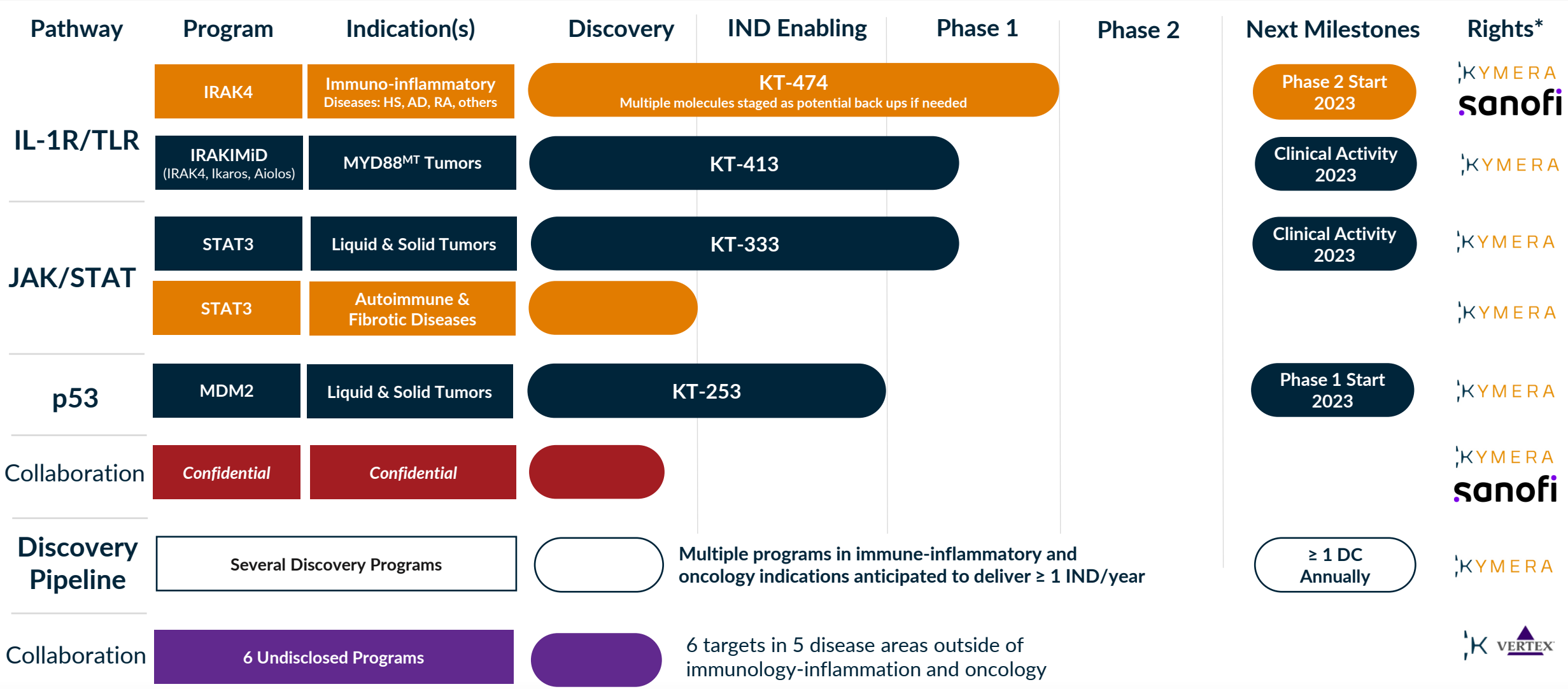
Initial focus in Immunology/ Inflammation and Oncology, but already a **disease-agnostic platform**

Accelerating **forward integration** through key strategic **partnerships**

Key accomplishments to date:

- Since 2016 founding, advanced **4 clinical stage programs** and developed a deep pipeline **positioned to deliver ≥1 IND/year**
- Unique **target selection strategy** based on using TPD to unlock high value, undrugged targets
- First to advance degraders (**KT-474**) in **healthy volunteers and patients with HS and AD**, demonstrating **degrader vs. small molecule inhibitors (SMI) biological differentiation**, and potential **best in class profile in I/I**
- Demonstrated **fidelity of translation of PK, PD and safety** across three clinical programs in I/I and oncology patients
- Well capitalized with **$596 million of cash** as of 9/30/22 positioning Kymera to accelerate and **expand clinical impact in areas with large clinical and commercial opportunities**

Kymera's Pipeline of Novel Protein Degraders



*Option to participate equally in the development and commercialization of Sanofi-partnered programs in the US.
RA: Rheumatoid arthritis, AD: Atopic Dermatitis, HS: Hidradenitis suppurativa

Presentation Summary

Oncology

- KT-333 and KT-413 Phase 1 trials in dose escalation phase
- Both molecules demonstrating PK/PD consistent with pre-clinical models
- No dose-limiting toxicities observed to date
- KT-253 IND cleared; Phase 1 trial expected to commence in early 2023

KT-474

- Part C cohort complete: data supportive of promising clinical and market opportunities in HS and AD
  - PK/PD in patients in line with healthy volunteers with broad impact on disease relevant cytokines in blood and skin of HS and AD patients
  - KT-474 generally well-tolerated; QTc spontaneously returned to normal baseline during the dosing period
  - Clinical endpoints suggest promising potential in both HS and AD, supporting targeting IRAK4 and clear differentiation of degrader versus small molecule inhibitors
  - Sanofi officially committed to advance KT-474 into Phase 2 clinical trials, initially in HS and AD

STAT3 (KT-333)

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STAT3 Degraders In Oncology: KT-333

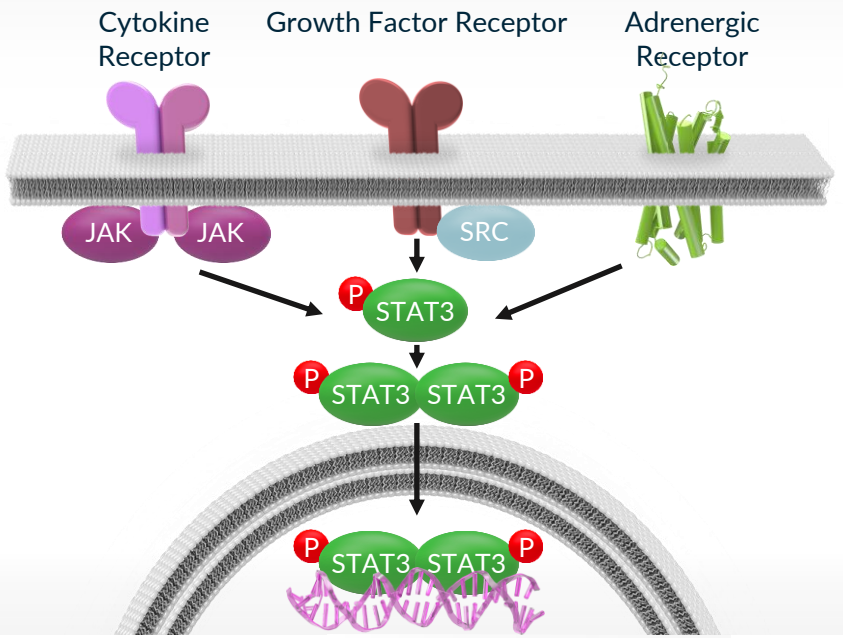
- High degree of validation of JAK-STAT pathway in oncology and immuno-oncology supported by >25k publications
- Traditionally undrugged target
- First-in-class opportunity to address STAT3 driven pathology across large and diverse indications

	U.S.		R.O.W.	
	Prevalence	Incidence	Prevalence	Incidence
Peripheral T-cell lymphoma (PTCL)	~13k	~6.5k	~27k	~15k
Cutaneous T-cell lymphoma (CTCL)	~30k	~2.6k	~67k	~6k
Large granular lymphocyte leukemia (LGL-L)	~4.5k	<1k	~24k	~3k
Solid Tumors, PD-1 Combo (e.g. Stage IV MSI-H CRC)	~30k	~5k	~78k	~20k

Source: Bionest, SEER. GlobalData; ROW includes EU, UK, Japan and China.

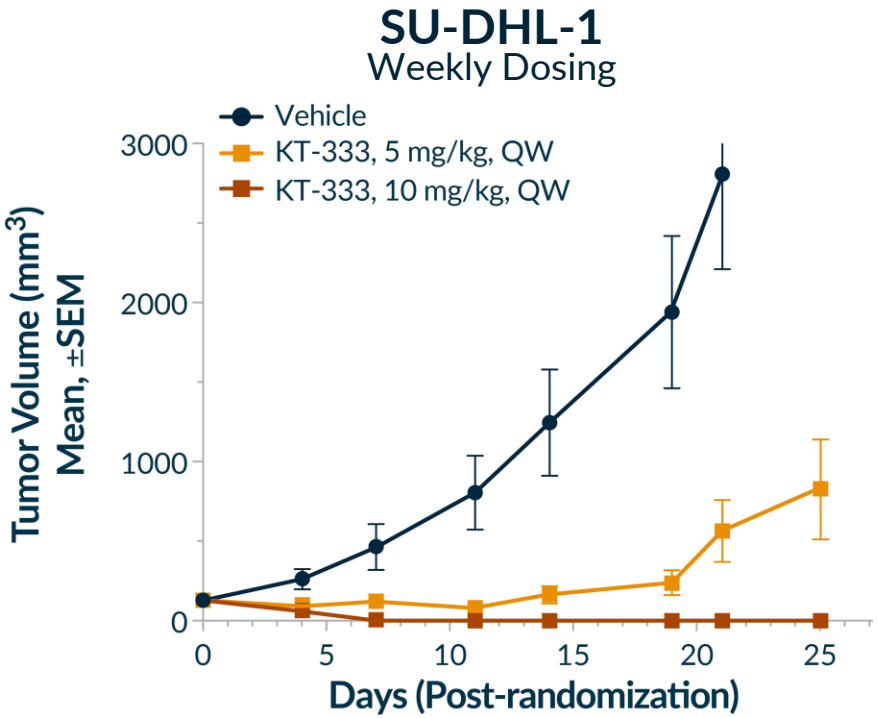
STAT3 Has Unique Tumor Cell Intrinsic and Extrinsic Mechanisms

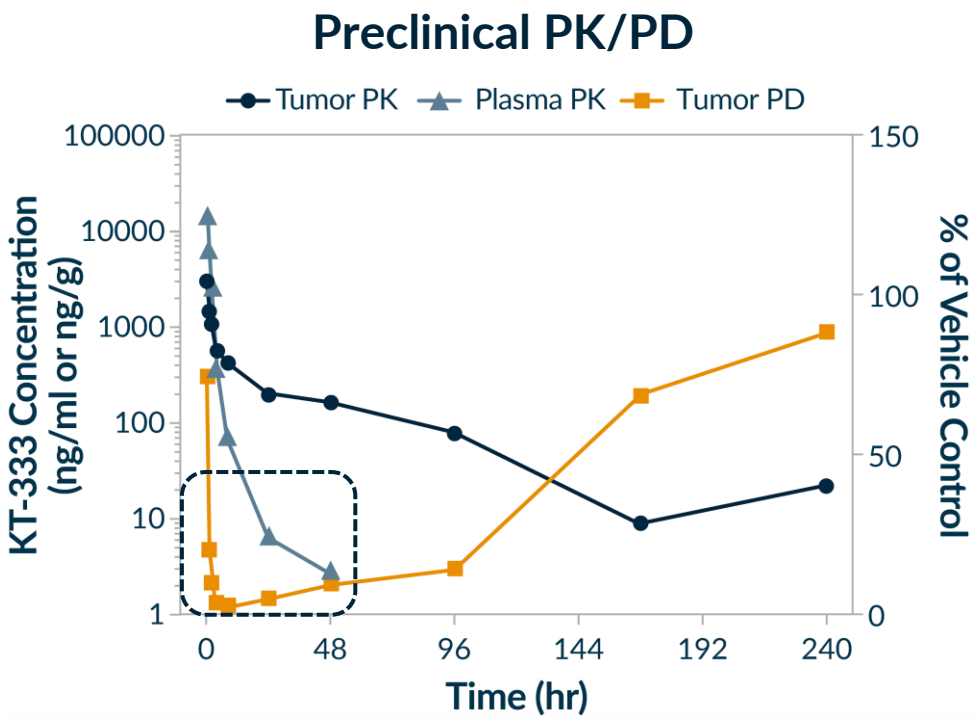
- **Intrinsic**: Hyperactivation of STAT3 via either receptor signaling, or hotspot mutations promotes gene expression programs involved with survival, proliferation, stemness and metastasis of tumor cells
- Opportunities in STAT3-dep. malignancies (e.g., T cell maligs., DLBCL, AML) and drug resistant tumors (e.g., TKI res. oncogene-driven solids)
- **Extrinsic**: STAT3 promotes the differentiation and activity of immunosuppressive and endothelial cells, resulting in an immunosuppressive tumor microenvironment
- Opportunities in multiple heme and solid tumor indications that are not responsive to immune checkpoint inhibitors



KT-333 Highly Active on Intermittent Dosing Regimens

Complete Tumor Regressions Associated with Robust STAT3 KD for ~48h in Preclinical Models

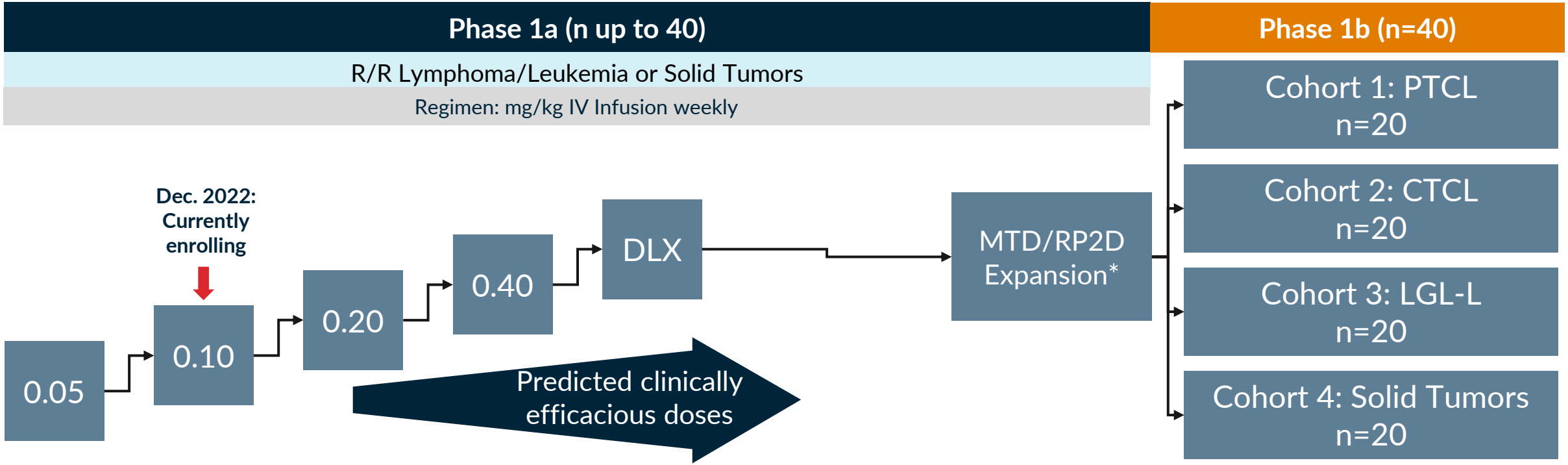




- Dose- and degradation-dependent tumor growth inhibition observed with once-weekly dosing in ALK+ ALCL
- 10 mg/kg sufficient to drive full tumor regression in SU-DHL- 1 that was durable for multiple weeks after the last dose (on day 14)

- Based on preclinical model (STAT3 dependent ALK+ ALCL), target PD >90% STAT3 KD for ~48 hours to achieve robust anti-tumor activity

KT-333: Phase 1, Multicenter, Dose-Escalation and Expansion Trial to Evaluate KT-333 in Adult Patients with PTCL, CTCL, LGL-L, and Solid Tumors



Key Objectives	Phase 1a	Phase 1b
Primary	• Safety/Tolerability and MTD and RP2D	• Safety/Tolerability at RP2D in Patients with Lymphoma/Leukemia and Solid Tumors
Secondary	• PK Parameters of KT-333 • Preliminary Estimates of Activity	• Preliminary Clinical Activity (ORR, DoR, PFS, DCR, OS) • PK Parameters of KT-333
Exploratory	• PD Effects of KT-333	• PD Effects of KT-333

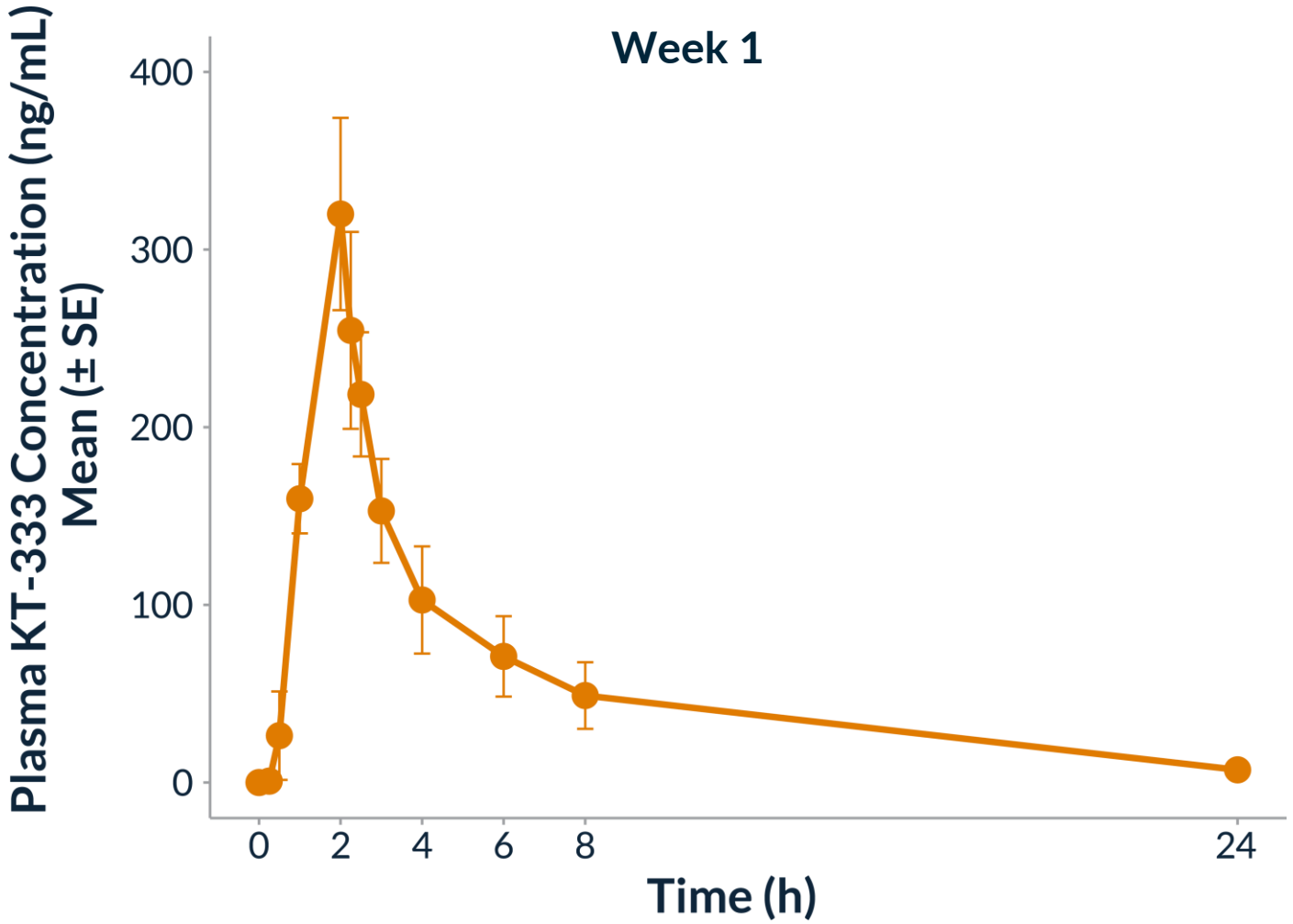
MTD: Maximum Tolerated Dose. RP2D: Recommended Phase 2 Dose. ORR: Overall Response Rate

Interim Safety Data Summary

Dose Level 1

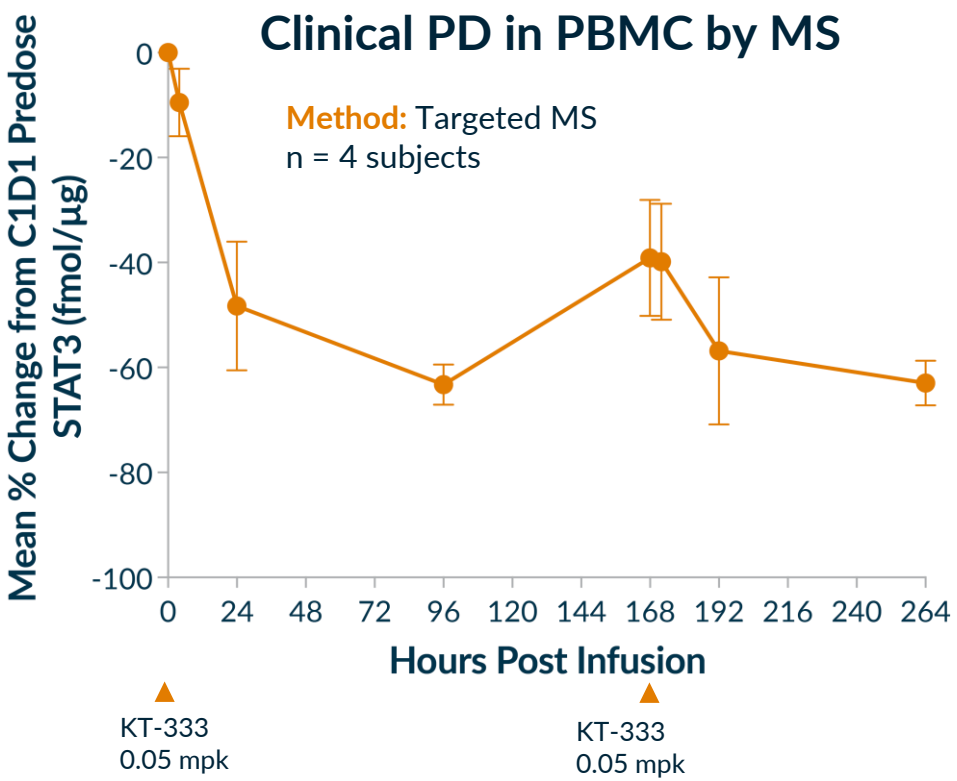
- 4 patients at Dose Level 1 (DL1, 0.05 mg/kg)
- All 4 patients heavily pretreated (≥3 prior lines)
  - 3 solid tumor
  - 1 CTCL
- No DLTs, no treatment-related SAEs, no AEs leading to discontinuation

Summary of PK Data From 4 Patients Enrolled in DL1



PK Parameter	DL1 → 0.05 mg/kg Week 1 (n = 4)
C_{max} (ng/mL)	306 (30.9%)
AUC (ng.h/mL)	1550 (66.4%)
Vd (L/kg)	0.278 (17.5%)
CL (L/h/kg)	0.0450 (62.5%)
$t_{1/2}$ (h)	6.25 (78.8%)

STAT3 Degradation in Blood at Dose Level 1 (DL1: 0.05 mpk) Consistent with Prediction from Preclinical Modeling



Subject ID	Mean Max Degradation* Post-doses 1&2 (Range)
DL1-1	**-79.8 %** (-75.6 % to **-84.1 %**)
DL1-2	**-67.8 %** (-73.5 % to **–62.0 %**)
DL1-3	**-50.0 %** (-47.4 % to **-52.6 %**)
DL1-4	**-66.7 %** (-47.7 % to **-85.8 %**)
Cohort Average	**-66.0 %**

*Max degradation as measured across timepoints sampled

- Observed STAT3 degradation of 50-80% in PBMCs at Dose Level 1 is consistent with the range predicted for tumor based on preclinical modeling of SUDHL1 xenograft PK-PD data
- Maximal degradation in DL1 patients is observed between 24-96 hours post infusion in Cycle 1 weeks 1 & 2, with recovery of STAT3 levels between doses, as seen in preclinical models

Demonstration of Initial Proof-of-Mechanism (POM) for KT-333

- Accrual to first dose level completed
- STAT3 degradation in blood at first dose level consistent with preclinical predictions, with mean maximum degradation following first 2 doses of Cycle 1 averaging 66%, with maximum knockdown of up to 86%
- At least 48h of target degradation observed that in preclinical species led to robust antitumor activity in STAT3 sensitive preclinical models
- DL1 level generally well-tolerated with no DLTs or treatment-related SAEs
- DL2 currently enrolling patients
- DL3-4 expected to be clinically active doses

IRAKIMiD (KT-413)

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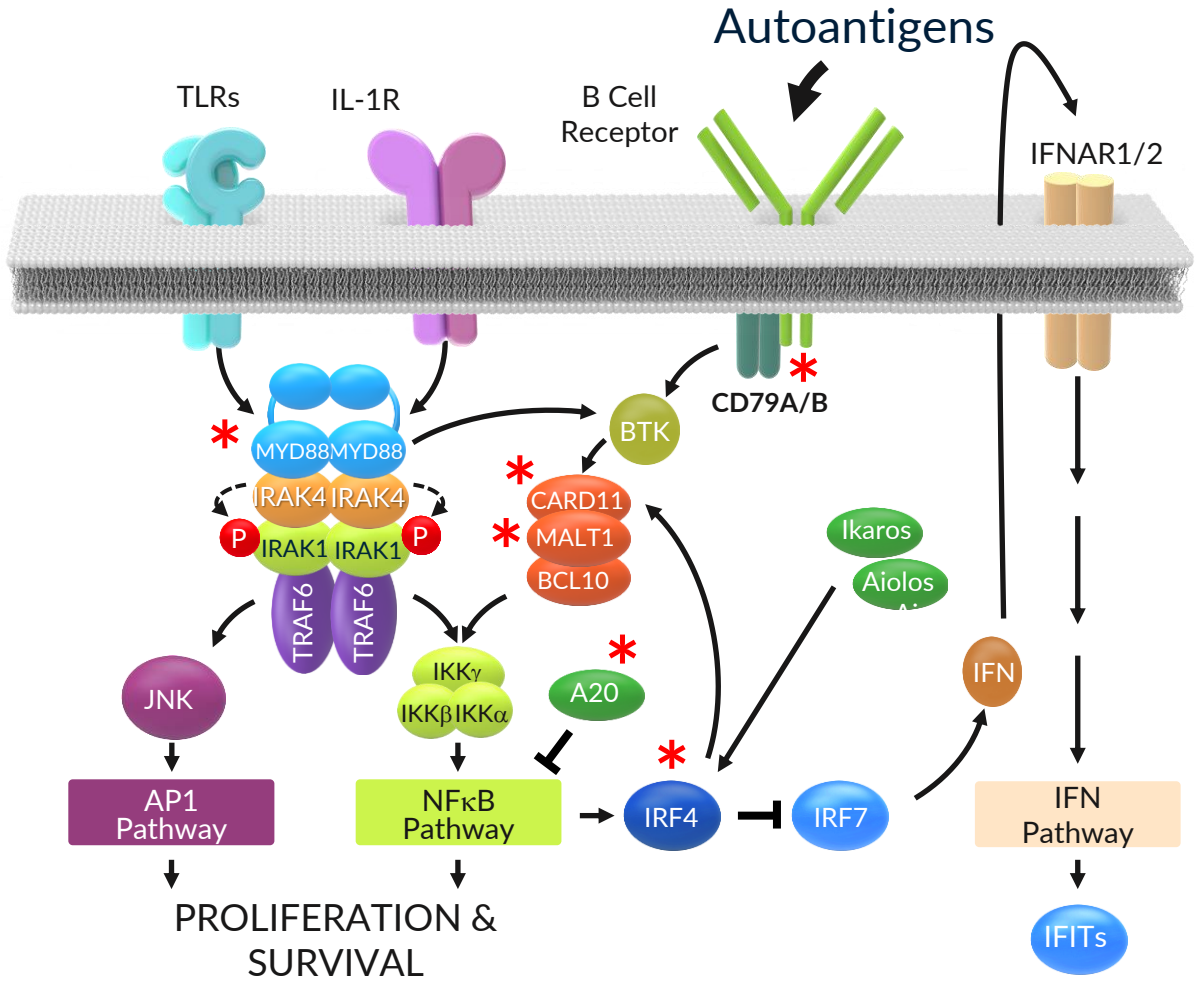
IRAKIMiDs are Potent Degraders of IRAK4 and IMiD Substrates Targeting Redundant Pro-survival Pathways in MYD88^{MT} DLBCL

- Single-agent therapies targeting activated NFκB signaling in DLBCL show limited activity
- Redundant NFκB pathway activation and downregulation of Type 1 IFN common in MYD88^{MT} lymphoma
- Simultaneous degradation of IRAK4 and IMiD substrates Ikaros and Aiolos shows synergistic activity in MYD88^{MT} models

	U.S.		R.O.W.	
	Prevalence	Incidence	Prevalence	Incidence
MYD88 MT DLBCL	~8k	2.8 / 100k	~10k	1.2 / 100k
MYD88 MT Waldenström's Macroglobulinemia	~9k	0.3 / 100k	~26k	0.7 / 100k
MYD88 MT PCNS Lymphoma	~2k	0.6 / 100k	~10k	0.6 / 100k

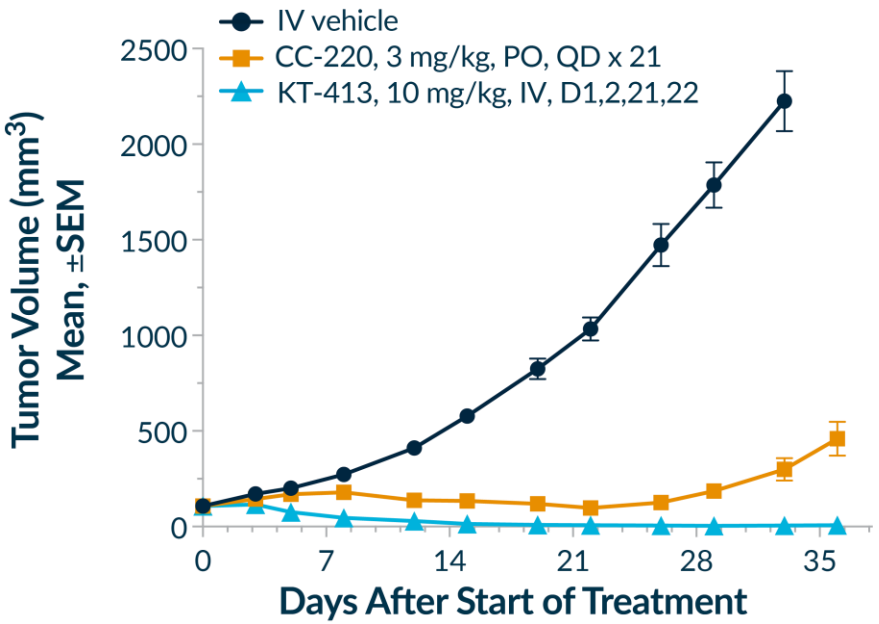
Source: Bionest and Global Data. ROW includes E.U., U.K. and Japan.

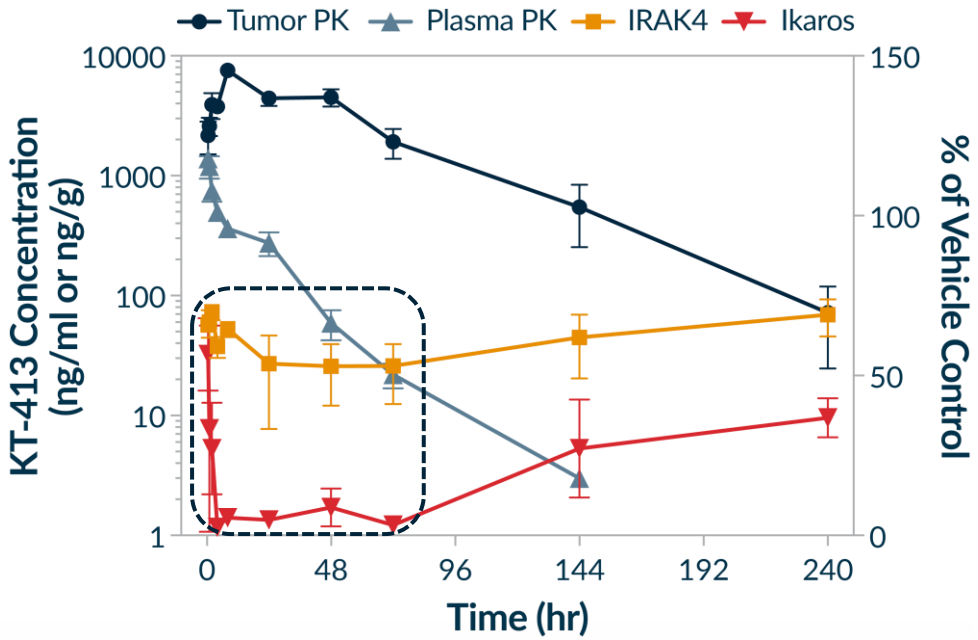


Adapted from Yang et al. (2012) *Cancer Cell* 21, 6, pp723-737

KT-413 Highly Active on Intermittent Dosing in Preclinical Models

Complete Tumor Regressions Associated with Robust IRAK4 and Ikaros/Aiolos Degradation for ~72h





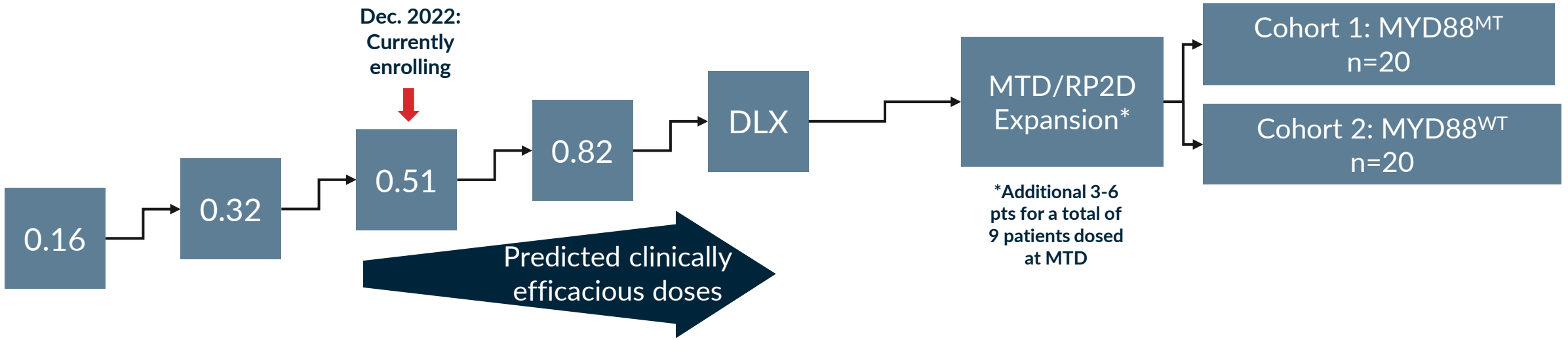
Drug (Day 33)	T/C% (REG%)	CR	PR	SD	PD
CC-220	9	0	0	0	7
KT-413 10 mg/kg	(94)	5	2	0	0

- In the OCI-LY10 MYD88^{MT} xenograft model, intermittent dosing of KT-413 induced strong antitumor activity, including complete regressions.
- **Superior activity compared to IMiD CC-220 alone**

- Single 10 mg/kg dose showed extended tumor exposure and strong degradation of both IRAK4 and IMiD substrates that was maintained for least 72hr in preclinical models
- **Target PD 80-90% Ikaros KD and 50-70% IRAK4 KD *in tumor* for ≥72 hrs to achieve robust anti-tumor activity**

KT-413: Phase 1, Multicenter, Dose-Escalation and Expansion Trials to Evaluate KT-413 in Patients with R/R DLBCL

Phase 1a (n up to 40)	Phase 1b (n=40)
R/R B-cell NHL	R/R DLBCL
Regimen: mg/kg IV Infusion q 3 weeks	



Key Objectives	Phase 1a	Phase 1b
Primary	• Safety/Tolerability and MTD and RP2D	• Safety/Tolerability at RP2D in Patients with DLBCL
Secondary	• PK Parameters of KT-413 • Preliminary Estimates of Activity	• Preliminary Clinical Activity (ORR, DoR, PFS, DCR, OS) • PK Parameters of KT-413
Exploratory	• PD Effects of KT-413	• PD Effects of KT-413

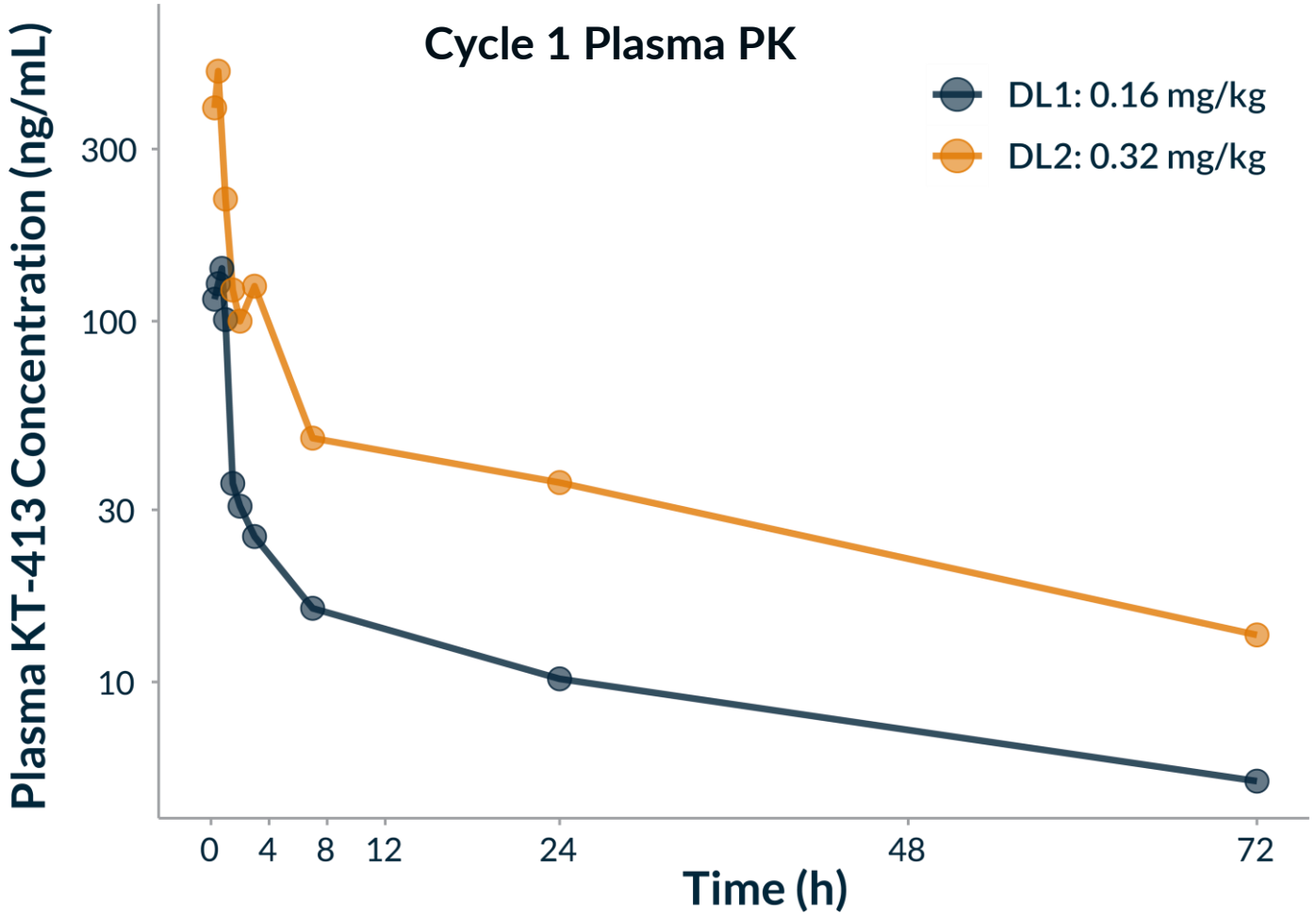
MTD: Maximum Tolerated Dose. RP2D: Recommended Phase 2 Dose. ORR: Overall Response Rate

Interim Safety Data Summary

Dose Levels 1-2

- All patients with heavily pretreated B-cell lymphoma (up to 3 prior lines of therapy)
- Follicular lymphoma, DLBCL (all wild-type MYD88)
- No DLTs, no treatment-related SAEs or AEs leading to discontinuation, no neutropenia in first two dose levels

Plasma PK Showing Dose-Proportional Increase in Exposure

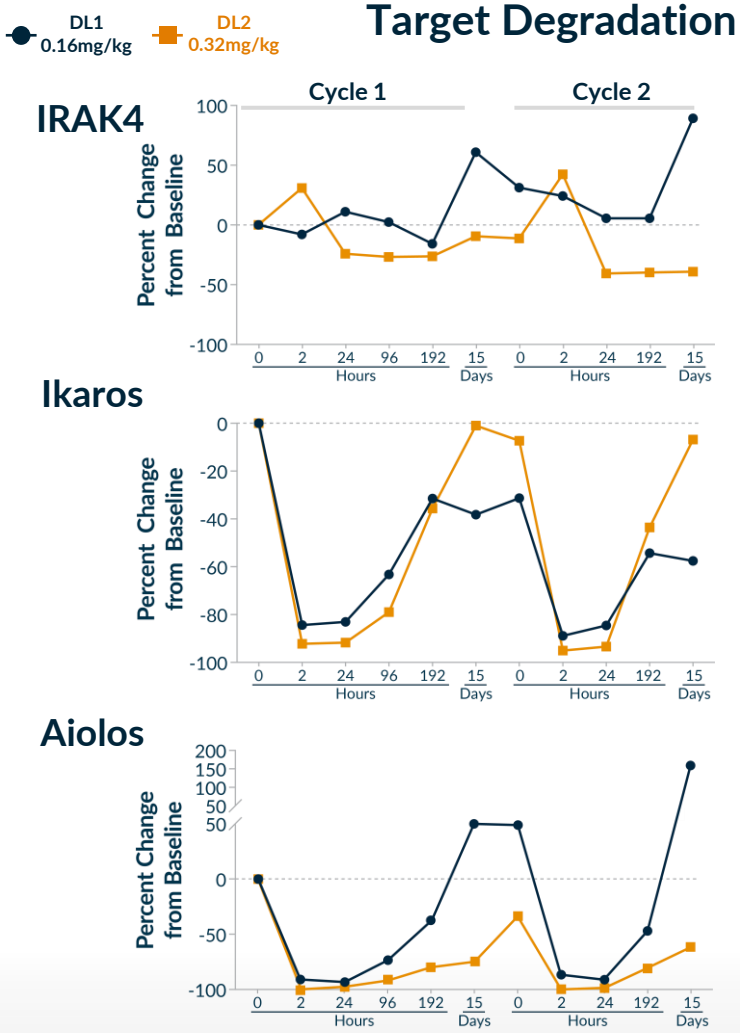


PK Parameter	0.16 mg/kg (DL1)	0.32 mg/kg (DL2)
	Cycle 1	Cycle 1
C_{max} (ng/mL)	140	493
AUC_{inf} (ng.h/mL)	1360	3490
Vd (L/kg)	10.1	3.99
CL (L/h/kg)	0.118	0.092
$t_{1/2}$ (h)	59.3	30.2

Degradation Profile of IRAK4, Ikaros and Aiolos in DL1/DL2 Consistent with Preclinical Models in Blood and Tumor

At least 72h of Target Degradation Observed with Once Every Three-week Dosing

Target Degradation in PBMC by FLOW



Dose Level	Cycle 1	Cycle 2
DL1	-16%	0
DL2	-27%	-40%

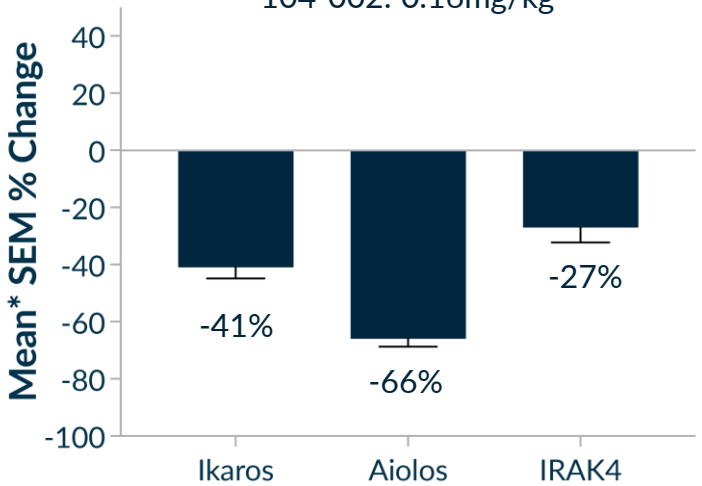
Dose Level	Cycle 1	Cycle 2
DL1	-84%	-88%
DL2	-92%	-95%

Dose Level	Cycle 1	Cycle 2
DL1	-93%	- 91%
DL2	-100%	-100%

- **Up to 40% KD of IRAK4 and 95/100% KD of Ikaros and Aiolos in PBMC at DL1-2**

Target Knockdown in Tumor by Targeted MS

Percent Change from Baseline at C3D4
104-002: 0.16mg/kg



*Mean is from 2-3 peptides measured for each analyte

Demonstration of Initial POM for KT-413

- First two dose levels completed
- PK and PD profiles in DL1 and DL2 consistent with preclinical data supporting once every three-week dosing regimen
  - Up to 95/100% KD of Ikaros/Aiolos and 40% KD of IRAK4 in blood
  - Consistent degradation in blood and tumor
  - At least 72h target degradation observed, a profile that in preclinical species led to robust antitumor activity in MYD88 mutant tumors
- First 2 dose levels generally well-tolerated with no DLTs, treatment-related SAEs or neutropenia observed
- DL3 currently enrolling patients
- DL3/4 expected to be clinically active doses

IRAK4 (KT-474)

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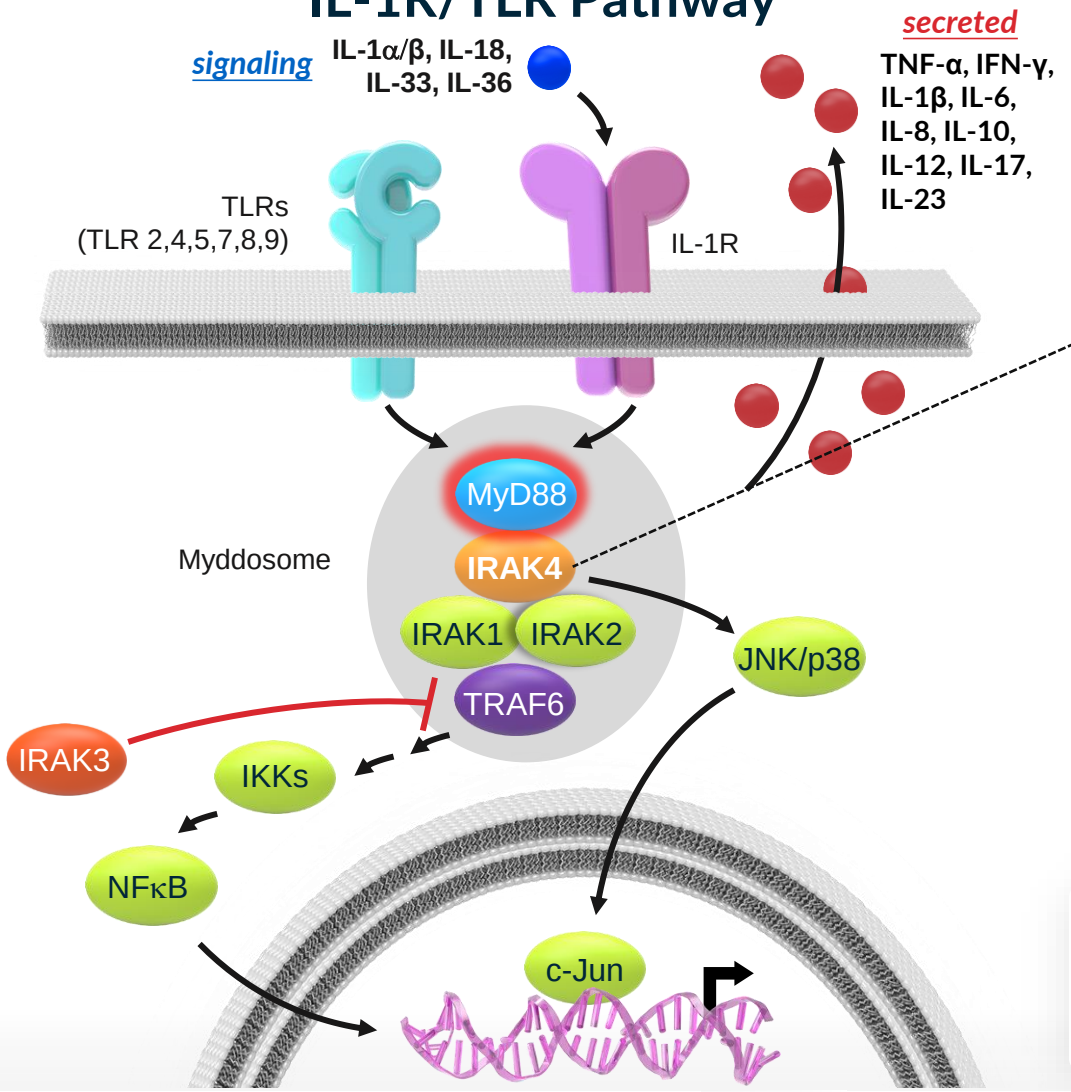
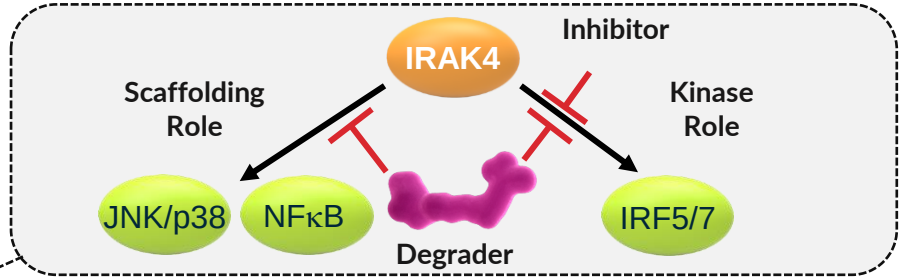
Degrading IRAK4

Superior Approach to Block IL-1R/TLR-driven Inflammation

IL-1R/TLR Pathway



Degrader Advantage



Clinical Pathway Validation

IL-1α/IL-1β : Rheumatoid Arthritis, CAPS, Hidradenitis Suppurativa

IL-1α: Atopic Dermatitis

IL-1β: Gout; CANTOS Outcomes Data in Atherosclerosis and Lung Cancer

IL-18: Macrophage Activation Syndrome

IL-36: Generalized Pustular Psoriasis, Atopic Dermatitis

IRAK4 SMI: Rheumatoid Arthritis

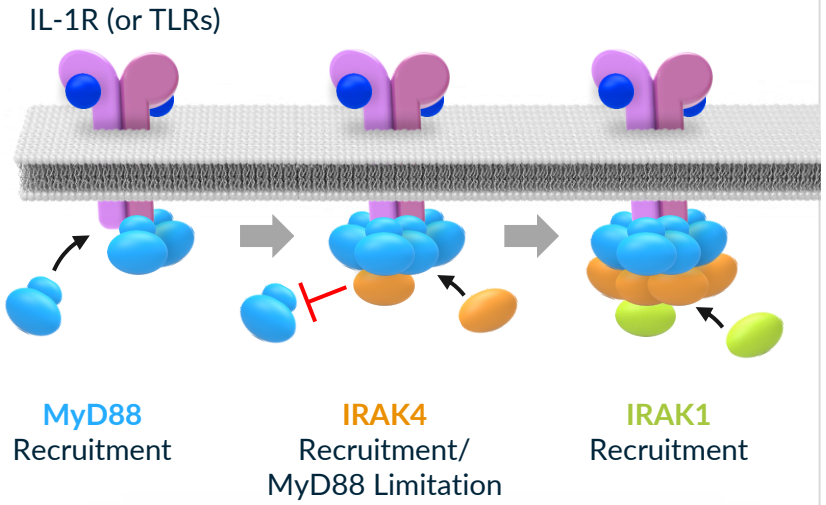
Human Genetics

Adult humans with **IRAK4 Null Mutation have no clinical phenotype**

IRAK4 degrader has potential to achieve a **broad, well-tolerated anti-inflammatory effect,** providing multiple development opportunities in autoimmune inflammatory diseases

IRAK4 Degradation but Not Inhibition is Required to block IL1R/TLR Pathway

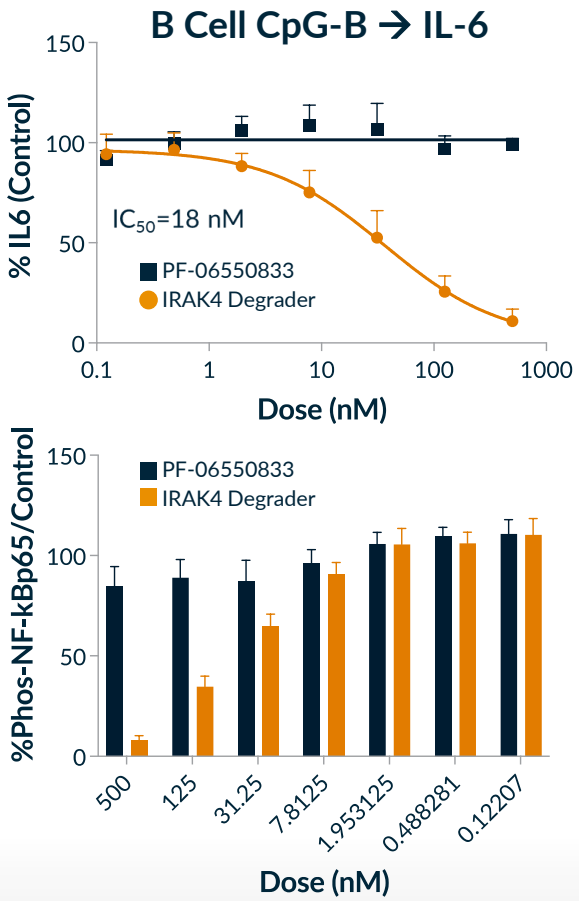
IRAK4 Scaffolding Function is Critical in Myddosome Formation and Pathway Signaling



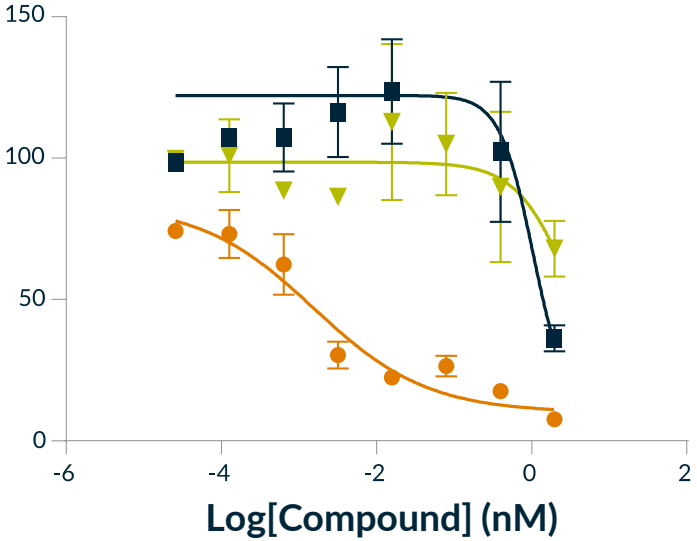
- IRAK4 scaffolding role functions to limit MYD88 oligomer size and trigger myddosome formation

Source: Deliz-Aguirre, et al. *J. Cell Biol.*, 2021

IRAK4 Degradation, but not Kinase Inhibition, can Block TLR-induced NF-κB Translocation



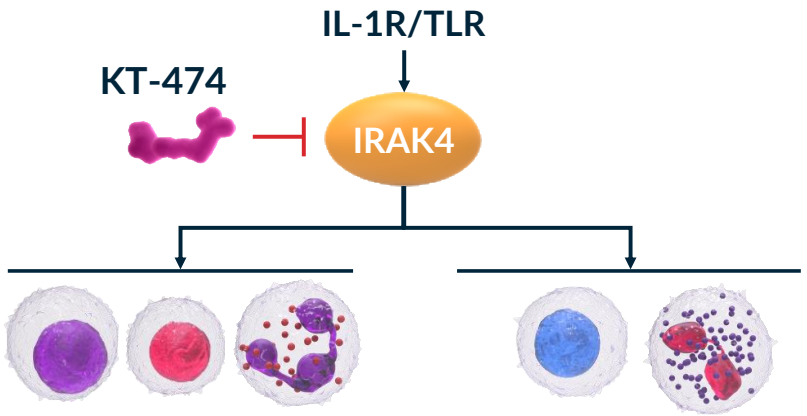
IRAK4 Degradation, but not Kinase Inhibition, can block IL1R+TLR activation



Compound	IL-6 IC_{50} (nM)
IRAK4 Degrader	0.8
Negative Control	450
IRAK4 SMI (PF-06550833)	N/A

IRAK4 Degrader Best-in-class Potential in Immune-inflammation

Potential for Broad Activity Across Th1-Th17 and Th2 Diseases



Th1-Th17/Neutrophils

- **Hidradenitis Suppurativa**
- **Rheumatoid Arthritis**
- Lupus
- IBD
- Gout
- Psoriasis

Th2/Eosinophils

- **Atopic Dermatitis**
- Asthma
- COPD
- CRSwNP

$ 150B Combined global drug sales

Indication	2021 Prevalence US/EU5/JP	2021 Global Sales
AD	~82.5 M	$5,760 M
HS	~785 K	$1,106 M
RA	~4.6 M	$27,634 M
SLE	~580 K	$1,333 M
IBD	~3.2 M	$21,710 M
Gout	~18.2 M	$1,319 M
Psoriasis	~15.8 M	$23,268 M
Asthma	~87.3 M	$15,664 M
COPD	~61.7 M	$9,960 M
CRSwNP	~20.4 M	$2,622 M

Limitations of Current Therapies

- **Anti-Cytokine/Cytokine Receptor Antibodies**
  - Target only 1-2 cytokines
  - Require injection
- **Small Molecule Inhibitors**
  - Limited pathway blockade (IRAK4 SMI)
  - Safety issues (JAK family)

Source: EvaluatePharma; GlobalData; Dash. Allied Market Research. 2021; Koto. Modern Rheumatology. 2021; Ahn. JAMA Otolaryngol Head Neck Surg. 2016; UC: Ulcerative Colitis; CD: Crohn's Disease.

KT-474 Phase 1 Trial Design

Double-blind, Placebo-controlled SAD and MAD in Adult HV; Open Label Patient Cohort in HS & AD Patients

Parts A & B

Healthy Volunteers (HV) SAD and MAD

9 SAD cohorts
- 8 subjects per cohort (6:2 randomization) including 2 food-effect cohorts
- 72 adult healthy subjects dosed
  Single dose (25-1600 mg)

5 MAD cohorts
- 12 subjects per cohort (9:3 randomization)
- 60 adult healthy subjects dosed
  14x daily doses (25-200 mg, MAD 1-4);
  5x twice-weekly doses (200 mg, MAD5)

Summary of Key Findings in MAD

- IRAK4 degradation of 80-90% in PBMC using Flow Cytometry; reduction to near lower limit of quantification with Mass Spectrometry
  - Associated with up to 85% inhibition of multiple disease-relevant cytokines and chemokines in *ex vivo* TLR stimulation assay at 100 mg dose
- Dose-dependent IRAK4 degradation in skin of >50%
- Generally well tolerated at doses up to 200 mg with no SAEs
- Non-adverse, self-limiting QTcF prolongation in 10-20 msec range was neither dose- nor exposure-dependent

Todays' Focus

Part C

HS and AD Patients

1 cohort
21 HS and AD patients

75 mg (fed state)
(~equivalent exposure to 100mg fasted MAD cohort dose level)

Open-label

28x daily doses

Primary
- Safety & tolerability

Secondary/ Exploratory
- Pharmacokinetic measures (half-life, bioavailability)
- IRAK4 knockdown in PBMC and skin
- Change in systemic inflammatory biomarkers and proinflammatory gene transcripts in skin
- *Ex vivo* response of whole blood to TLR agonists
- Clinical endpoints: EASI (AD), Total AN Count (HS), symptom scores and global assessments

KT-474 Part C: Demographics/Disposition

KYMERA

Patient Demographics

	HS (n=13)	AD (n=8)
Gender, n		
Female	10	3
Male	3	5
Median age, years (range)	40 (21-53)	31 (23-55)
Race/Ethnicity		
White / Hispanic, Latino	7	6
White / Non-Hispanic, Latino	1	0
Black / Hispanic, Latin	0	1
Black / Non-Hispanic, Latino	5	0
Other*	0	1

*Native American or Alaskan Native/ Hispanic, Latino

Baseline Disease Characteristics

	HS (n=13)	AD (n=8)
Disease Severity	**(HS-PGA)**	**(vIGA-AD)**
Mild	--	**1**
Moderate	**10**	**5**
Severe	**1**	**2**
Very Severe	**2**	--
Extent of Disease	**Mean (min, max)**	**Mean (min, max)**
AN Count	**8** (5, 18)	--
Fistula Count	**4** (0, 15)	--
Pain-NRS*	**7** (3, 10)	--
Pruritus-NRS*	**5** (0, 10)	**8** (4, 10)
EASI Score	--	**17.6** (4.4, 52.3)
Patients with any prior Therapy, n (%)	**8 (62)**	**7 (88)**
Antibiotics/Antibacterials**	**6** (46)	**1** (13)
Corticosteroids	**0**	**7** (88)
Adalimumab	**3** (23)[₴]	**0**
Other Biologics	**1** (8)[₹]	**0**

*worst score over past week **includes clindamycin and chlorhexidine

[₴]includes 2 pts with very severe disease;
[₹]1 patient with very severe disease received infliximab and bimekizumab (and adalimumab)

AD=Atopic Dermatitis; AN=Abscess and Inflammatory Nodule Count; EASI=Eczema Area and Severity Index; HS=hidradenitis suppurativa; Min=minimum; Max=maximum; Pain-NRS=Skin Pain Numerical Rating Score; Pruritus-NRS=Peak Pruritus Numerical Rating Score; PGA-Physicians Global Assessment; IGA=Investigator Global Assessment

Patient Disposition

	HS	AD	Total
Enrolled patients	13	8	21
Primary reason for Treatment Completion			
Completed	12 • 9 Moderate • 1 Severe • 2 Very Severe	7 • 1 Mild • 4 Moderate • 2 Severe	19
Withdrawal by patient	1*	1**	2

* Withdrew treatment after 4 doses for personal reasons
** Withdrew treatment after 5 doses for personal reasons

KT-474 PK and Degradation

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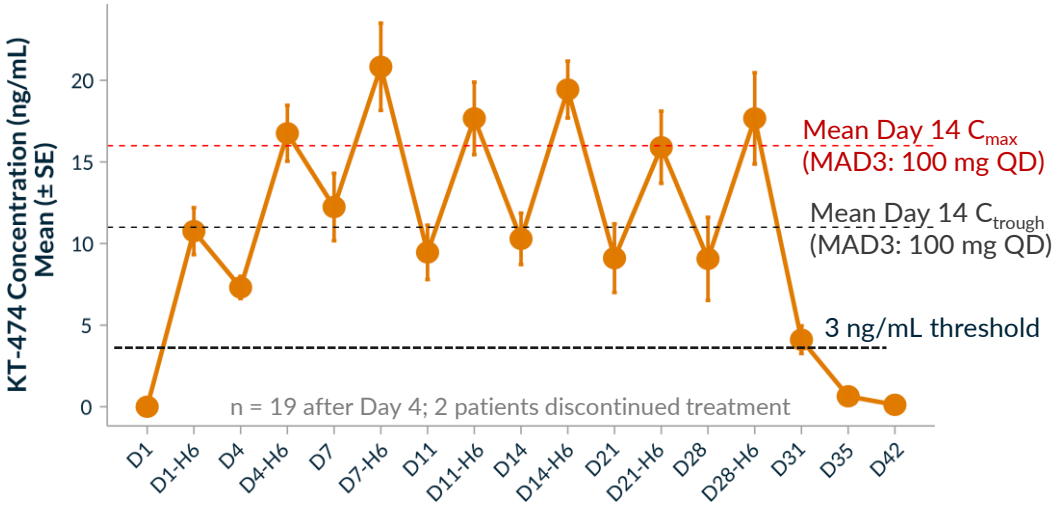
KT-474 Plasma PK and IRAK4 Degradation in Patients Dosed for 28 Days is Comparable to HV

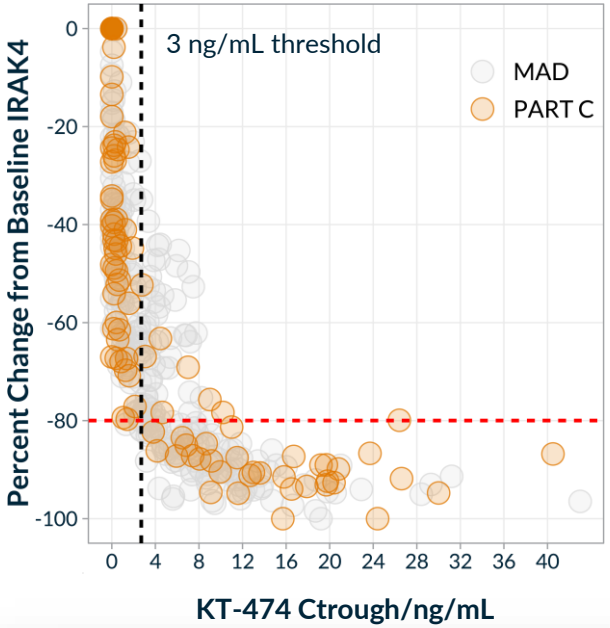
Part C KT-474 Plasma PK



KT-474 PK at the **75 mg QD dose (fed state) in patients is comparable to 100 mg QD (fasted state) in HV**

- Mean C_{max} and C_{trough} levels at steady state in Part C are in line with MAD3 levels at Day 14
- Mean half-life of 44 hours is within the range observed in MAD (34-59 hours)

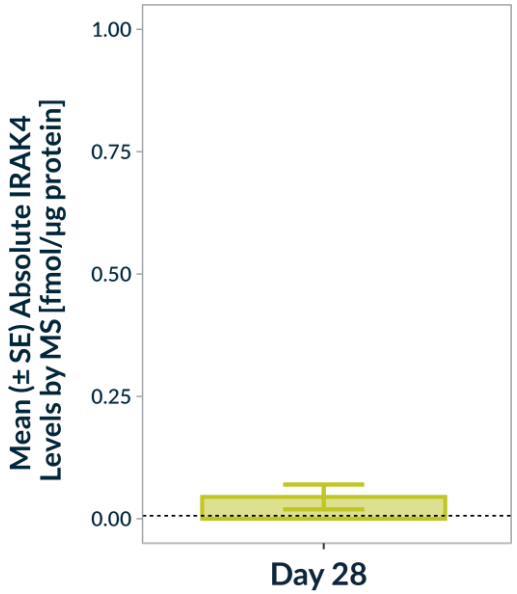
PK/PD Correlation in Plasma/Monocytes (FLOW)



KT-474 concentrations in plasma lead to **same level of IRAK4 degradation** in HV (n=48) and HS/AD (n=20) patients

- Concentrations above 3 ng/mL lead to same level of degradation (>80%) in HV and Patients

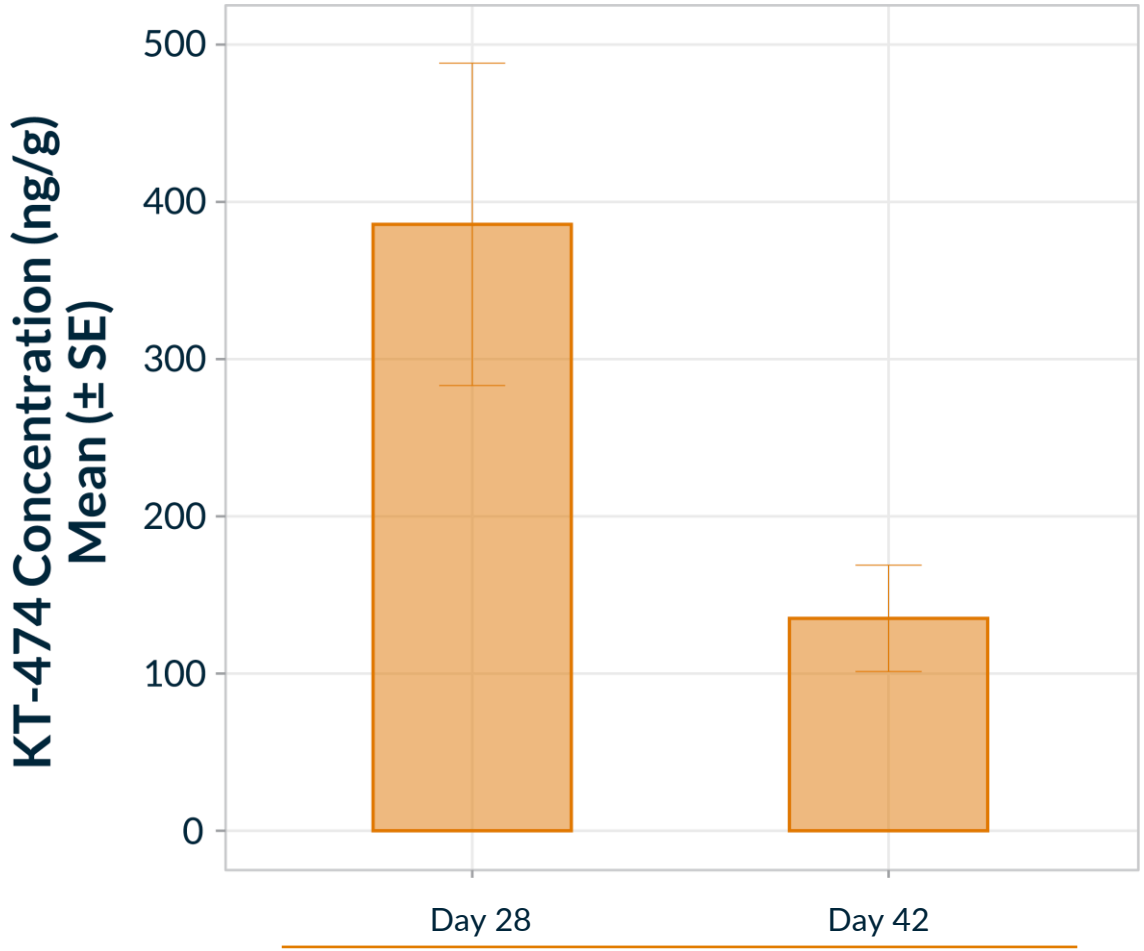
IRAK4 Levels in PBMC in Patients at Day 28 (MS)



HS and AD Patients **IRAK4 Levels at Day 28 (n=4) near LLOQ**

Skin PK: KT-474 Has High Skin Concentration In Patients at Day 28

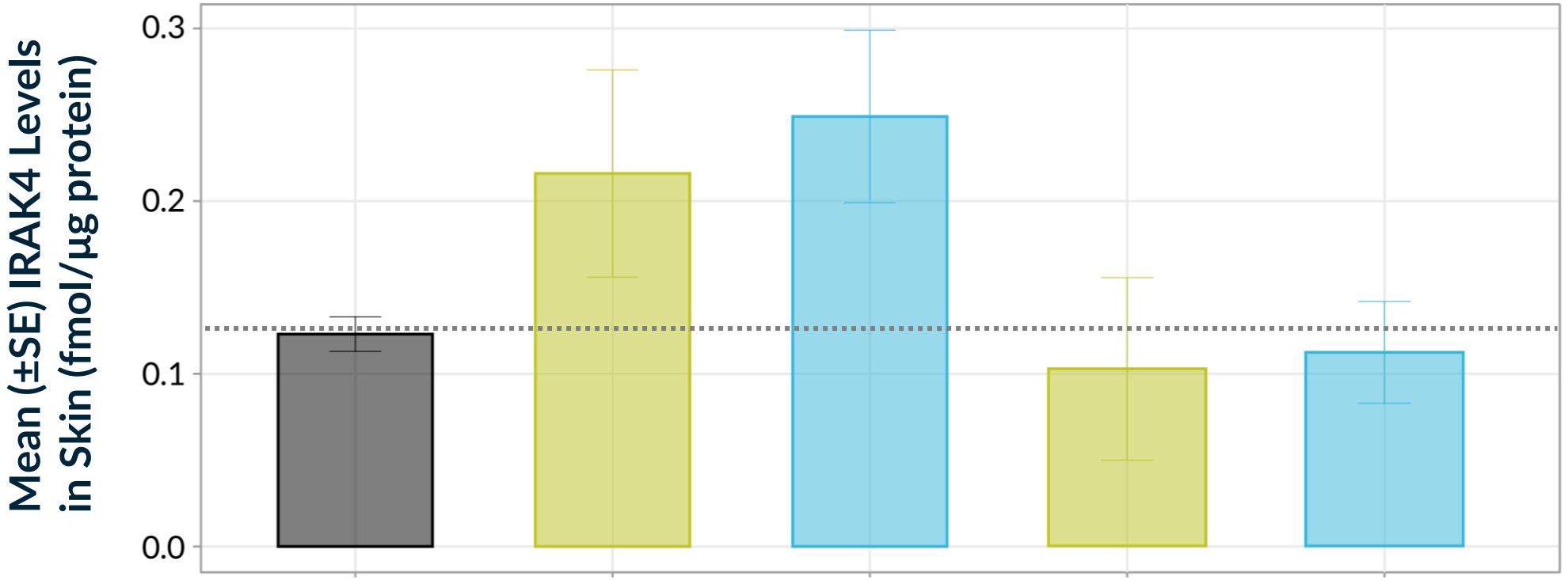
Higher than MAD3 HV



	Day 28	Day 42
Part C: 75 mg QD (fed)*	386 (± 103)	135 (± 33.8)

* n=11 for Day 28 and n=10 for Day 42

KT-474 Reduced IRAK4 in Skin Lesions of AD and HS Patients on Day 28 to at Least Same Level as Healthy Subjects



	MAD Healthy Subjects (**Baseline**)	AD Patients (**Baseline**)	HS Patients (**Baseline**)	AD Patients (**Day 28**)	HS Patients (**Day 28**)
N	**46**	**7**	**11**	**6**	**9**
Mean (± SE)	**0.123 (± 0.01)**	**0.216 (± 0.06)**	**0.236 (± 0.05)**	**0.103 (± 0.05)**	**0.112 (± 0.03)**

KT-474 Safety

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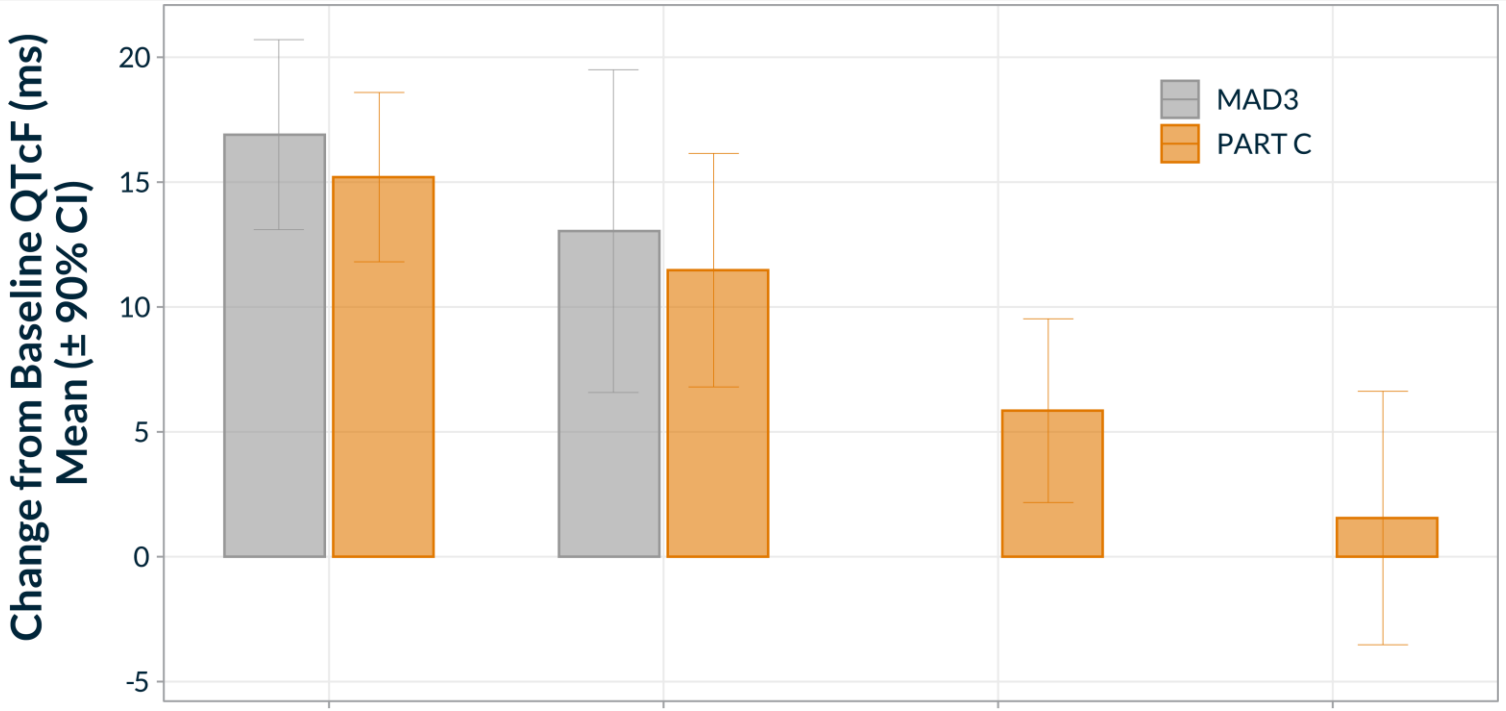
Adverse Events Related to Study Drug (Occurring in > 1 Patient)

Adverse Event (Preferred Term)	# of Patients	Severity (# of Pts)	Outcome (# of Pts)
Headache	6	Mild (5) Severe (1)	Recovered (6)
Fatigue	4	Mild (4)	Recovered (4)
Diarrhea	2	Mild (2)	Recovered (2)

No SAEs, no drug-related infections, and no AEs observed leading to dose interruption or discontinuation

QTc Prolongation Spontaneously Resolves to Baseline by Day 28

- ΔQTcF in Part C is in the range observed in MAD3 (100 mg QD) up to Day 14
- Declines to baseline with continued dosing and sustained plasma exposure through Day 28
- Profile is maintained through day 42 upon cessation of dosing after Day 28
- No QTc-related AEs observed



	Mean	Baseline	Day 7	Day 14	Day 21	Day 28
ΔQTcF	MAD3	-	17	13	--	--
	Part C	-	15	12	5.9	1.6
QTcF	MAD3	395	411	408	--	--
	Part C	403	419	416	410	405

* n=9 for MAD3 and n=20 for Part C, except day 14 (n=19)

KT-474 Pharmacodynamics

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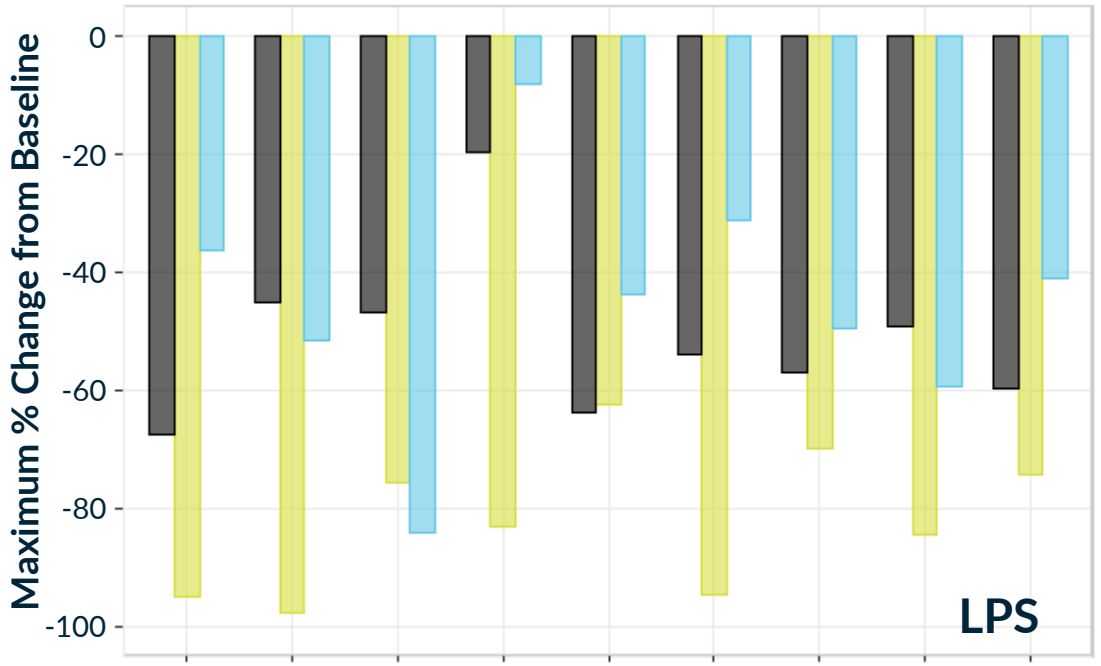
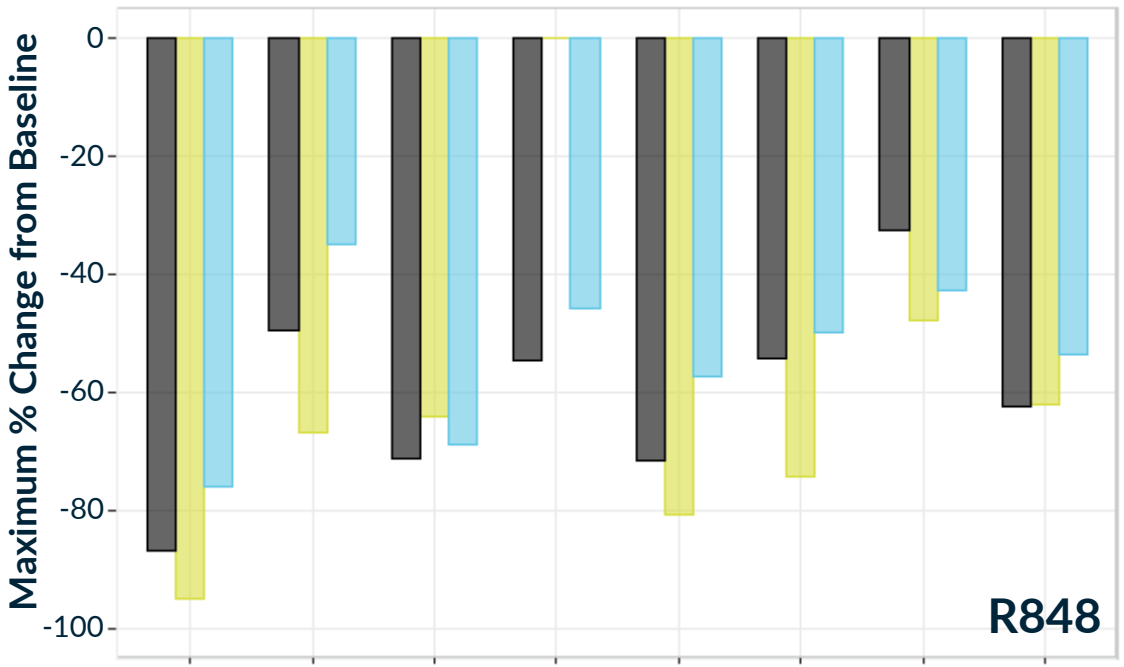
Up to 98% Inhibition of 9 Disease-Relevant Cytokines *Ex Vivo* in both HS and AD Patients



MAD 3
Healthy Subjects
100 mg QD (n = 9)

Part C
AD Patients (n=7)

Part C
HS Patients (n=9)



	IFNγ	IL10	IL12	IL17	IL1b	IL23	IL6	IL8	TNFα
HV (MAD3)	-67%	-45%	-47%	-20%	-64%	-54%	-57%	-49%	-60%
AD	-95%	-98%	-76%	-83%	-63%	-95%	-70%	-85%	-74%
HS	-36%	-52%	-84%	-8%	-44%	-31%	-50%	-59%	-41%

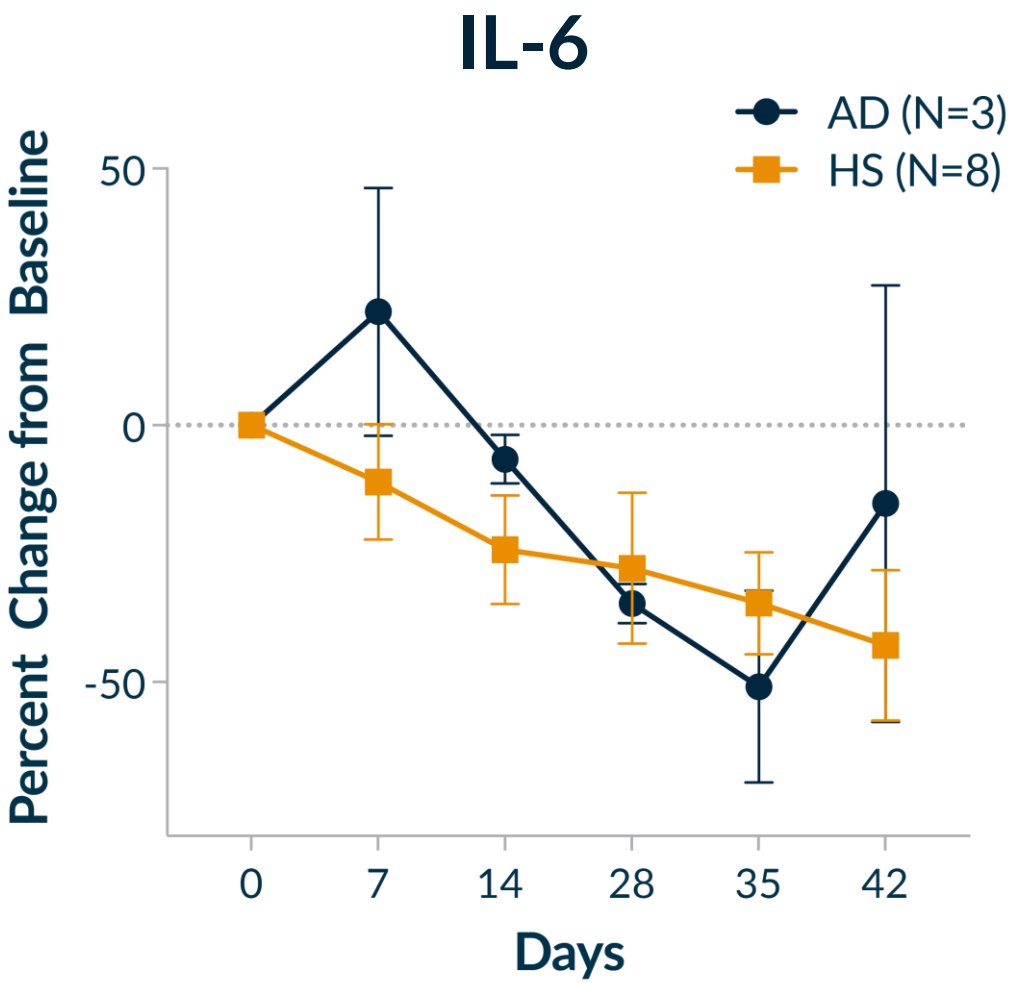
	IFNγ	IL10	IL12	IL17	IL1b	IL6	IL8	TNFα
HV (MAD3)	-87%	-50%	-71%	-55%	-72%	-54%	-33%	-62%
AD	-95%	-67%	-64%	0%	-81%	-74%	-48%	-62%
HS	-76%	-35%	-69%	-46%	-57%	-50%	-43%	-54%

* Plots show median of the maximum change from baseline between Days 7-14 in MAD3, and Days 14-28 in Part C

In Vivo Inhibition of Disease-Relevant Plasma Cytokines and Acute Phase Reactants by KT-474 in HS/AD Patients

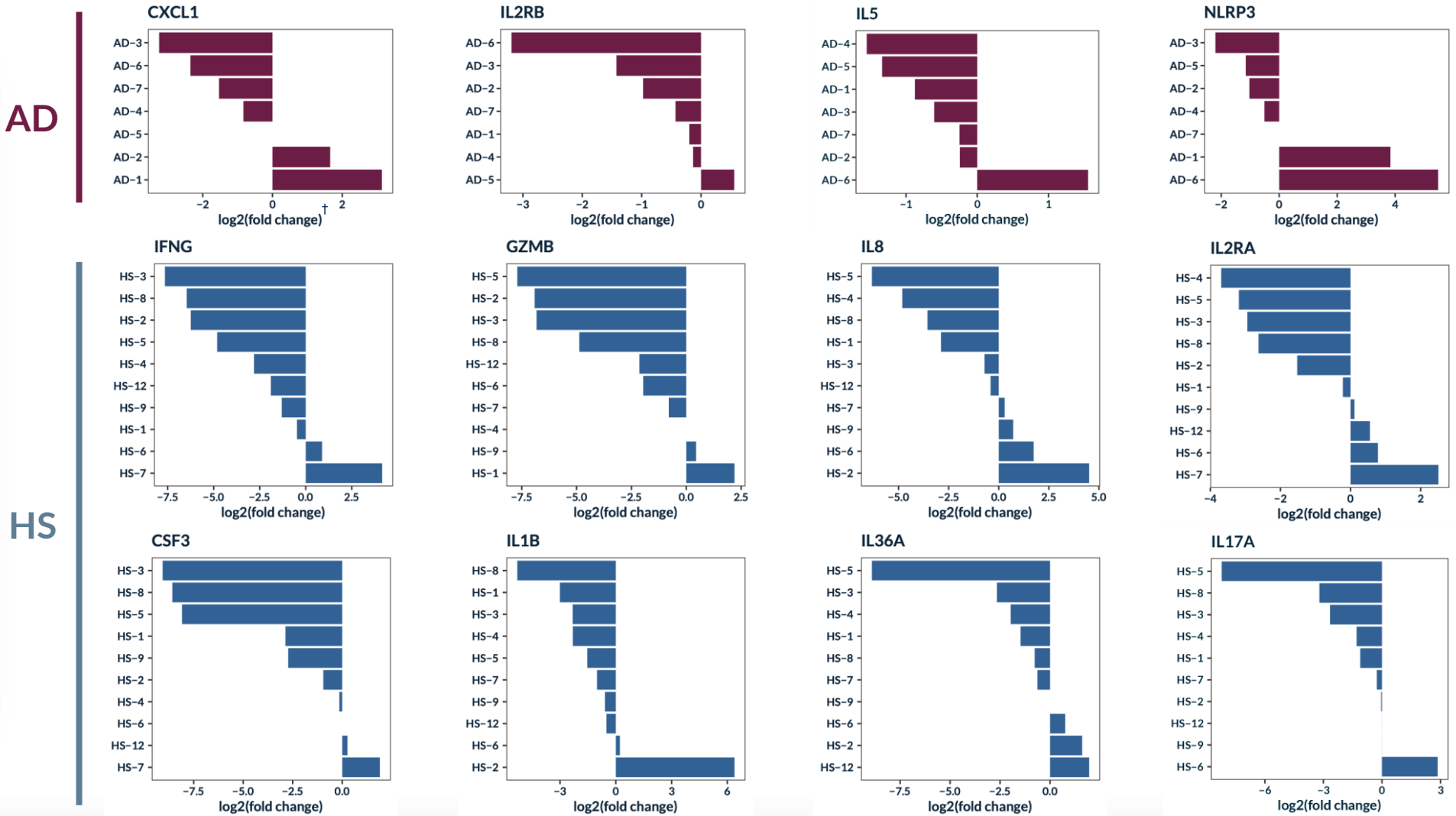
Analyte	Mean Max* AD (n)	Mean Max* HS (n)
IL-6†	-56% (3)	-63% (8)
CRP†	NA	-58% (5)
IL-1β	-36% (7)	-48% (8)
SAA†	-51% (4)	-41% (10)

*Max % reduction through Day 42
†Analysis performed only on patients with values >ULN at baseline
IL-6, IL-1β and CRP are high sensitivity assays



Disease-Relevant Genes Downregulated in Skin Lesions in ≥ 50% of Evaluable* AD (N=7) and HS (N=10) Patients at Day 28 (RNAseq)

- Substantial **downregulation of many disease relevant genes** in both HS and AD patients
- **Downregulation exceeded 90%** for many genes
- Broad **anti-inflammatory signature** with downregulation of genes responsible for:
  - ✓ IL1 family cytokines
  - ✓ Th1
  - ✓ Th17
  - ✓ Th2
  - ✓ Innate immunity



†log2(fold change): -1 = 50% decrease, -2 = 75% decrease, -3 = 87.5% decrease

*Evaluable patients for whom the samples were of sufficient quality for analysis.

KT-474 Part C: Clinical Endpoints

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Clinical Endpoints

Included as Exploratory Endpoints

- Skin lesions and global assessments performed on Days 1, 14, 28, 35 and 42
- Symptom scores performed at additional time points

AD

- Change from baseline in Eczema Area and Severity Index (EASI)
- Peak pruritus NRS
- Investigator Global Assessment (vIGA-AD)
- Additional ad hoc analysis included: Peak Pruritus NRS Response (≥4-point improvement from baseline)

HS

- Change from baseline in Total Abscess and Inflammatory Nodule (AN) count
- Skin pain Numerical Rating Scale (NRS)
- Peak pruritus NRS
- HS-Physician's Global Assessment (HS-PGA)
- Additional ad hoc analyses included: AN0/1/2 Response, HiSCR50, HiSCR75, and Pain NRS30

AD Clinical Endpoints

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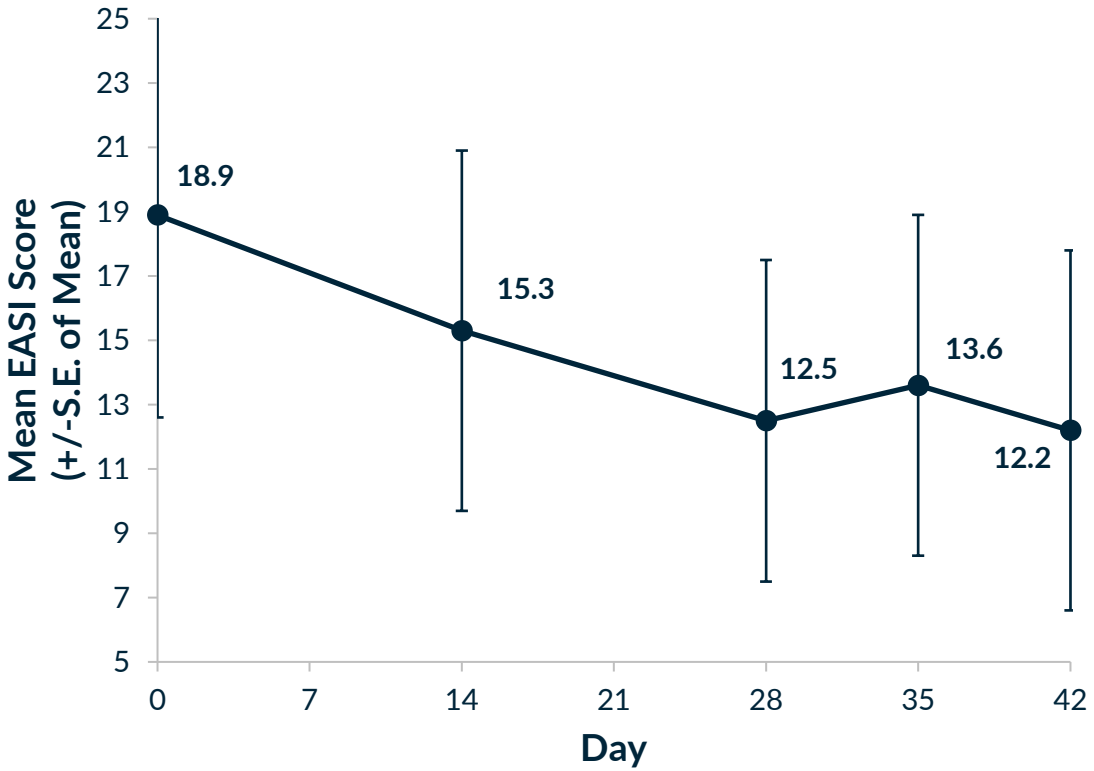
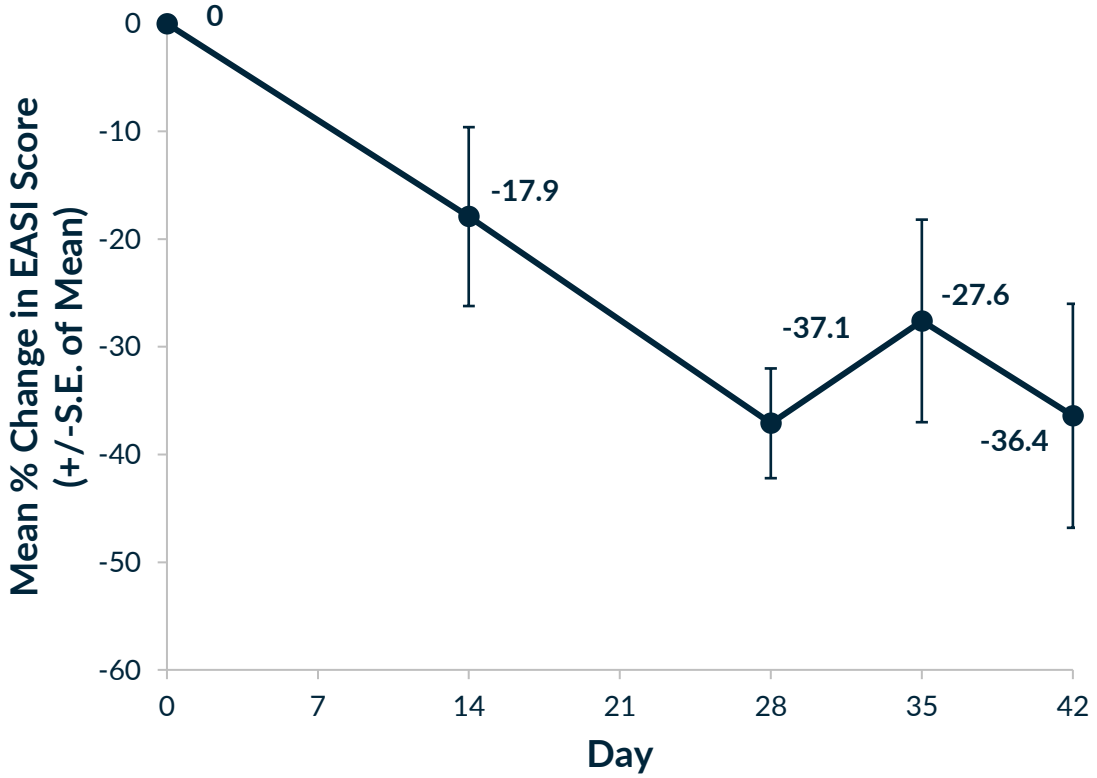
EASI Score: Mean 37% and Max 76% Reduction

Mean EASI Score Over Time (N=7)

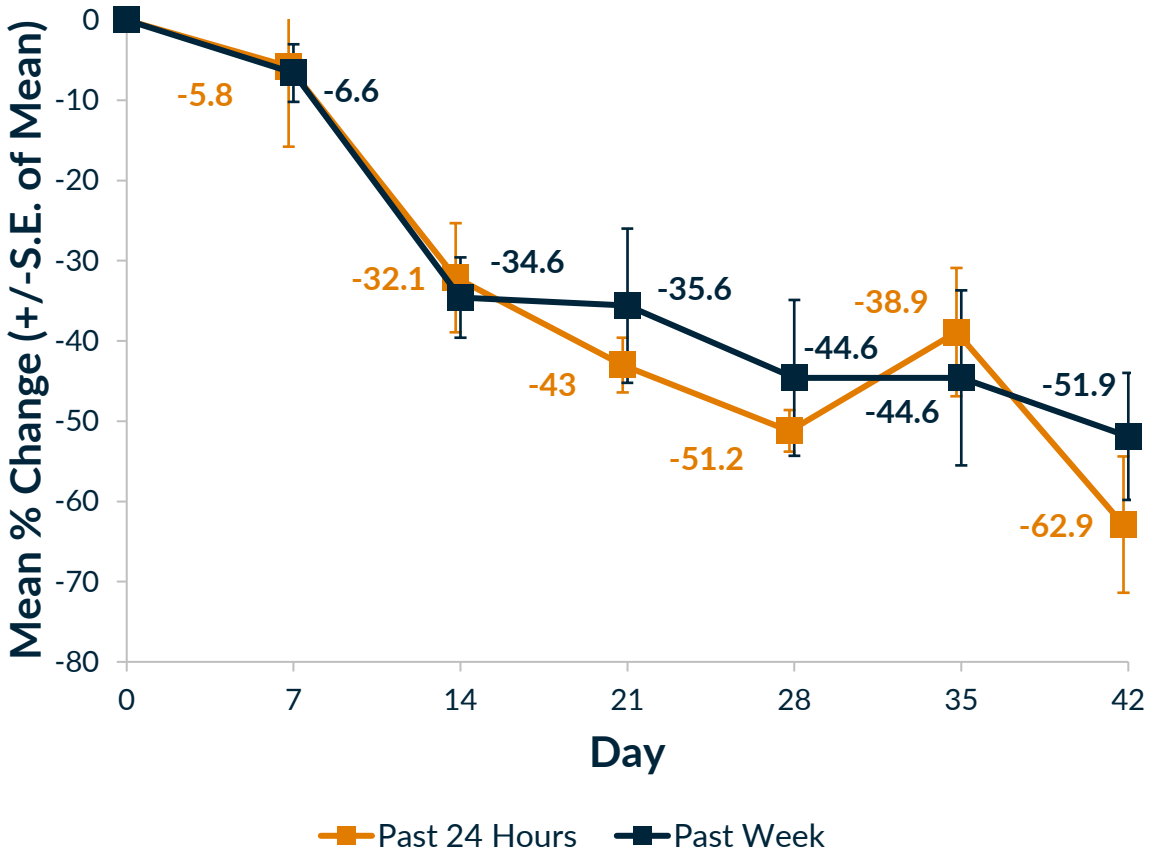


Mean % Change in EASI Score Over Time (N=7)

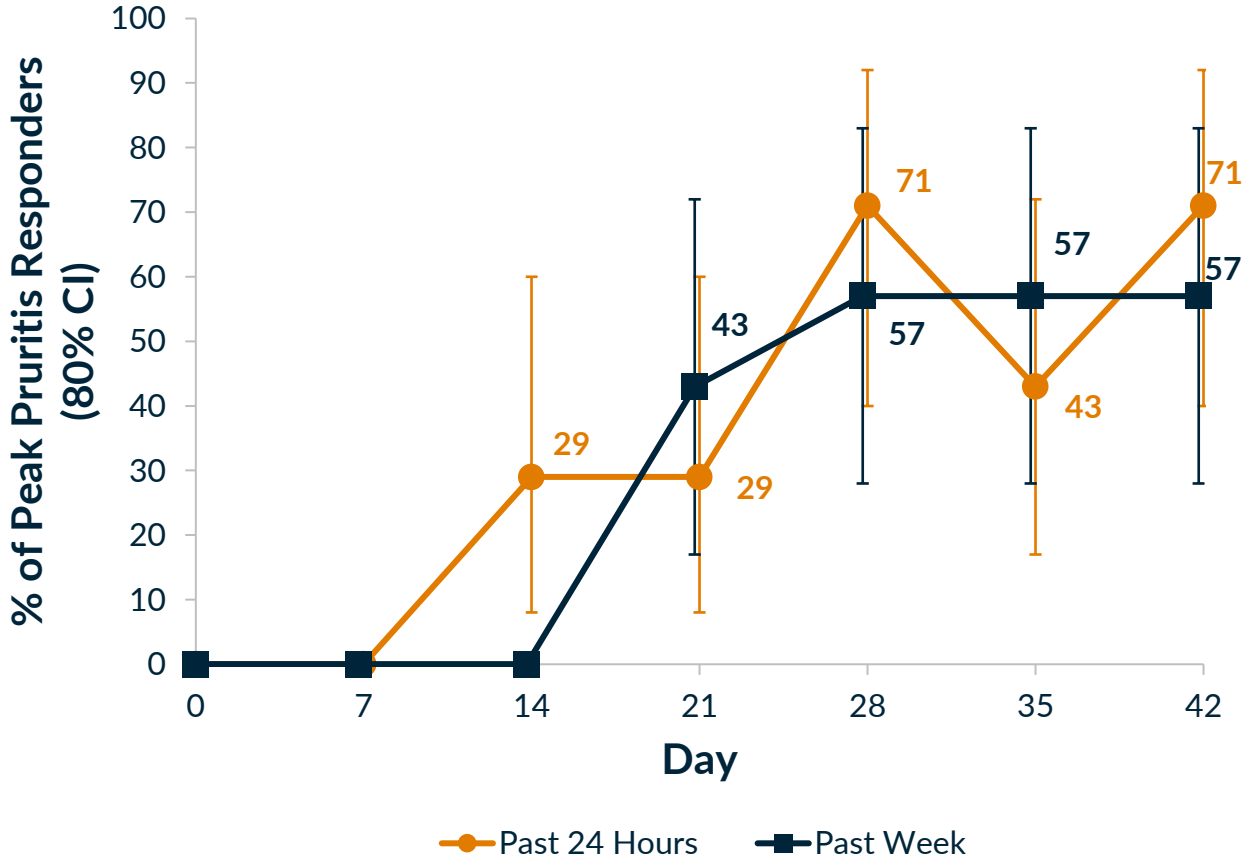


Peak Pruritus NRS: Mean 52 to 63% Reduction
Peak Pruritus NRS Responders: 57 to 71%

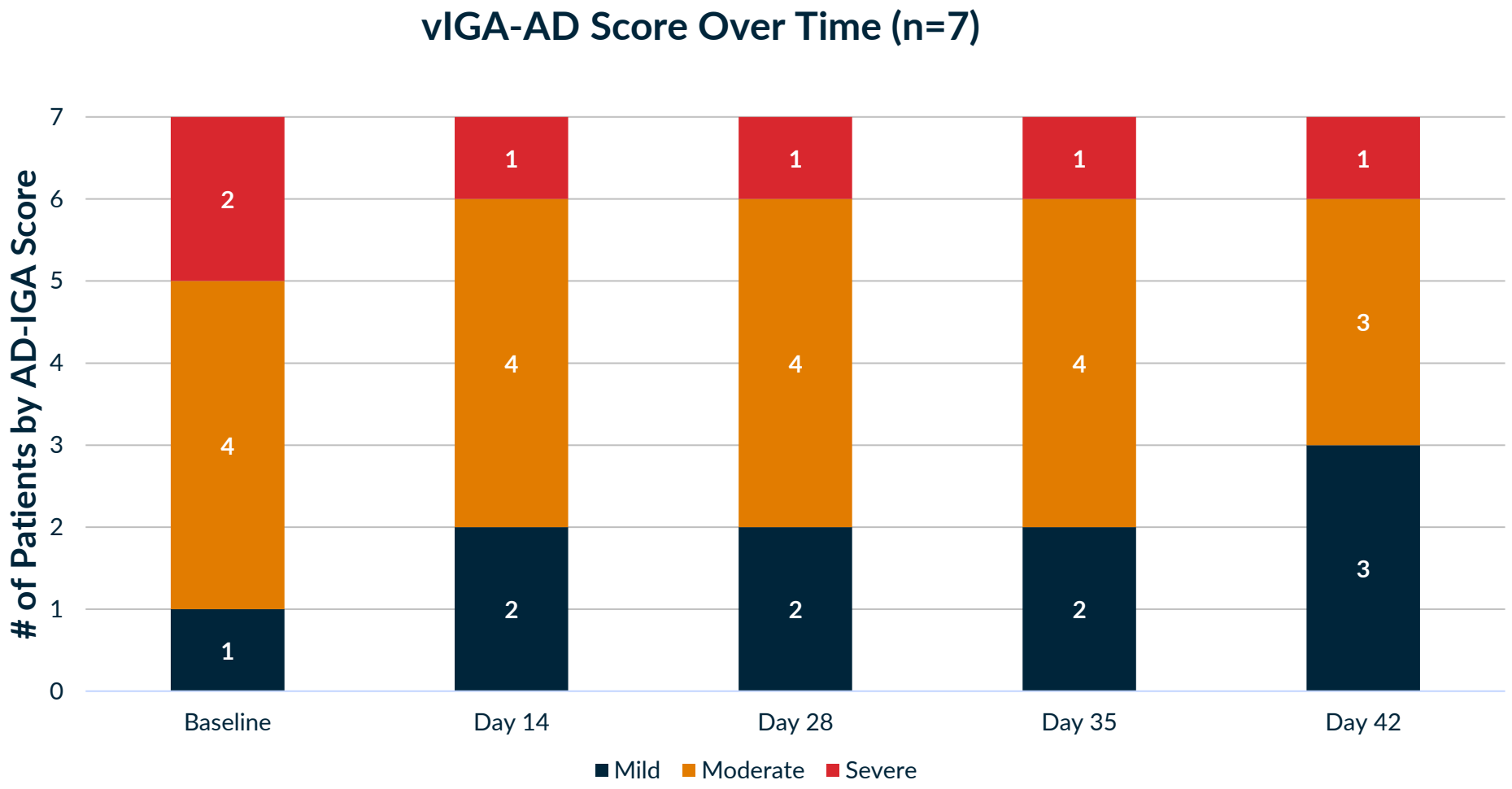
Mean % Change in Peak Pruritus Over Time (N=7)



% of Patients with ≥4 Unit Reduction from Baseline in Peak Pruritus (N=7)



Investigator's Global Assessment (vIGA-AD)



- IGA scores remained stable or improved in all patients

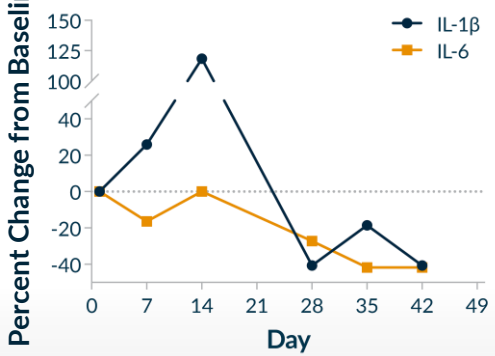
AD Case Study: Patient AD-3

Improvement in Disease Severity from Severe to Mild

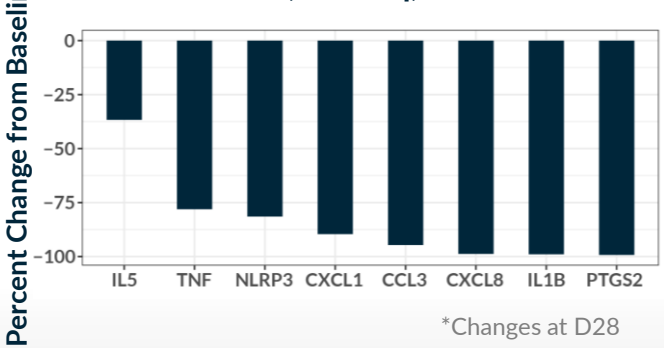
- 51-year-old Hispanic/Latino male with severe AD (vIGA-AD) and EASI score of 28.2 at baseline
- Previously treated with topical betamethasone 2018-2020

Efficacy Endpoints	BL	Day 28	Day 35	Day 42
IGA-AD Score	Severe	Moderate	Moderate	Mild
EASI Score (% Change)	28.2	14 (-50)	16.45 (-42)	9.2 (**-67**)
Peak Pruritis NRS - past week (% Change)	4	1 (-75)	1 (-75)	1 (**-75**)

Plasma Cytokines

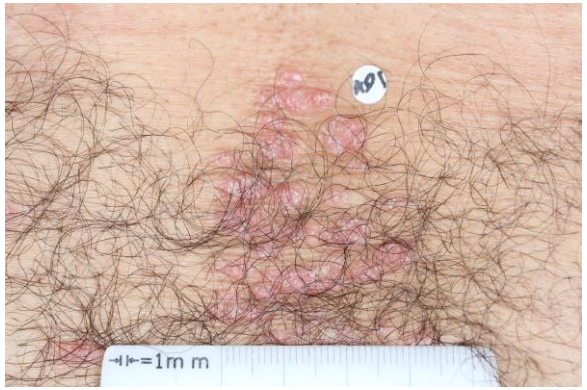


Skin Inflammation Biomarkers* (RNAseq)

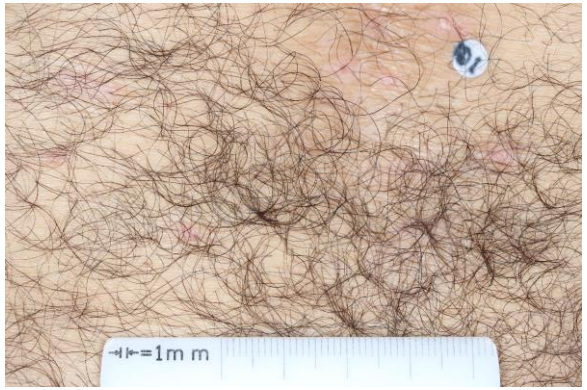


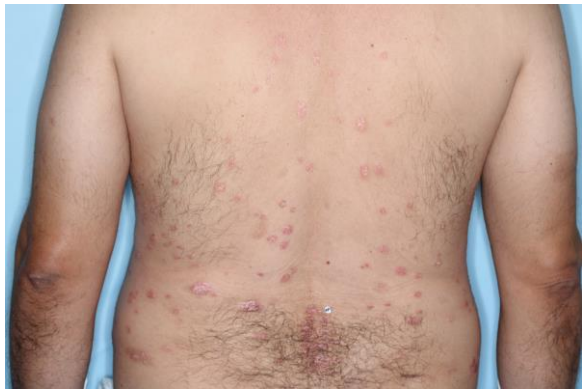
*Changes at D28

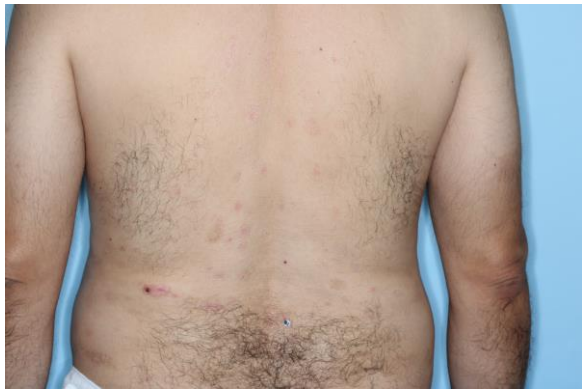
Day 1 - BL



Day 42







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

HS Clinical Endpoints

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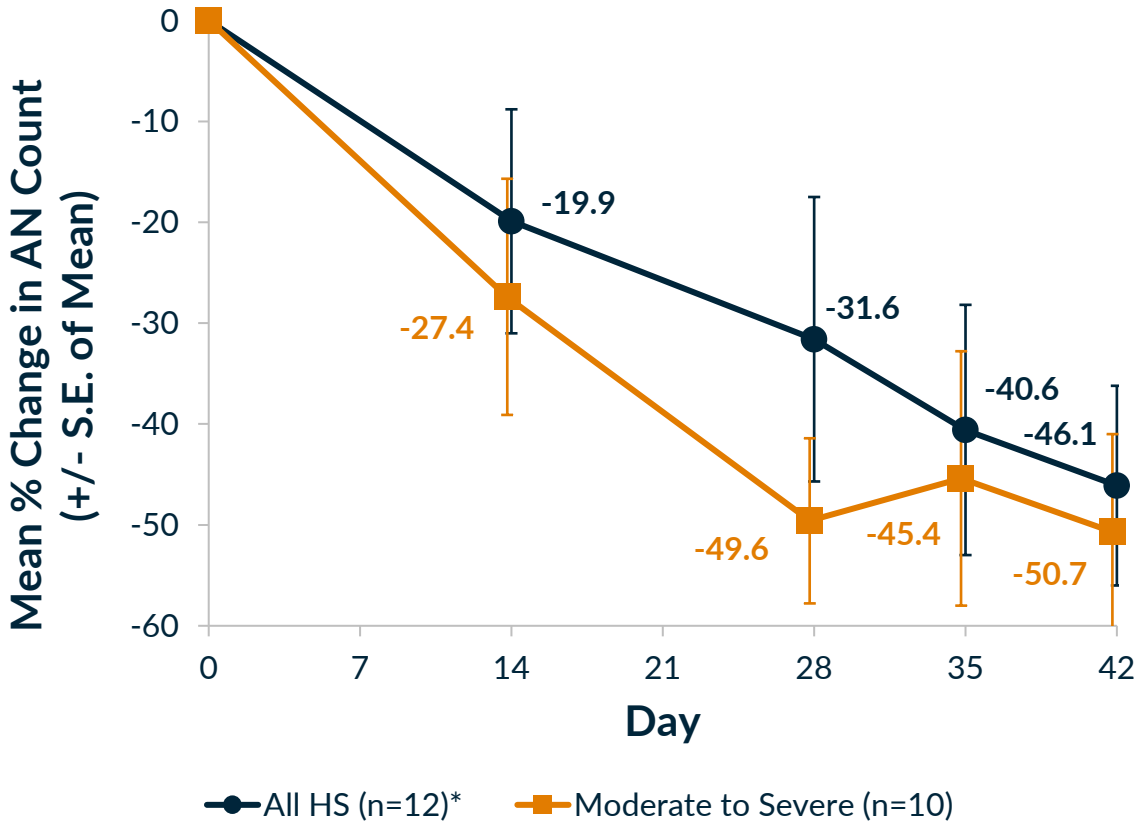
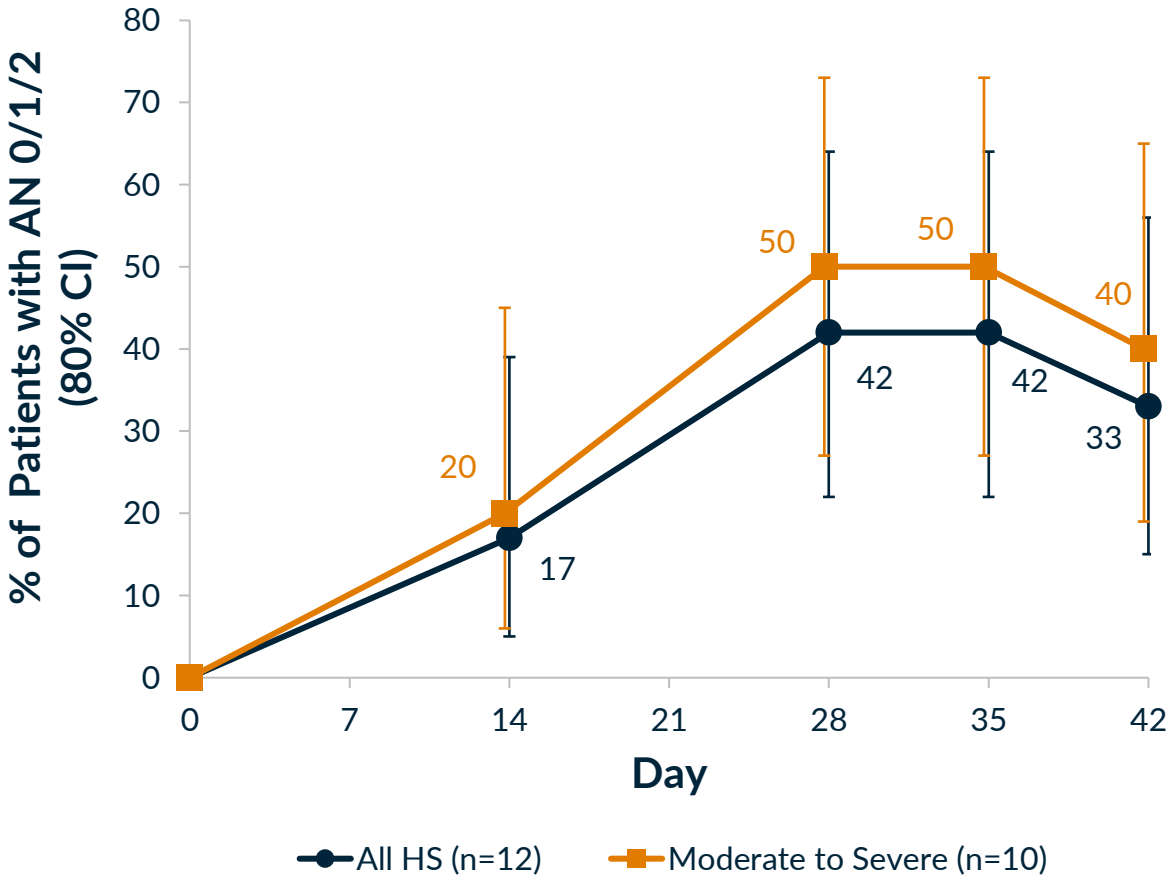
AN Count: Mean 46 to 51% and Max 100% Reduction
AN 0/1/2 Responders: 42 to 50% Response Rate

Mean % Change in Total AN Count Over Time

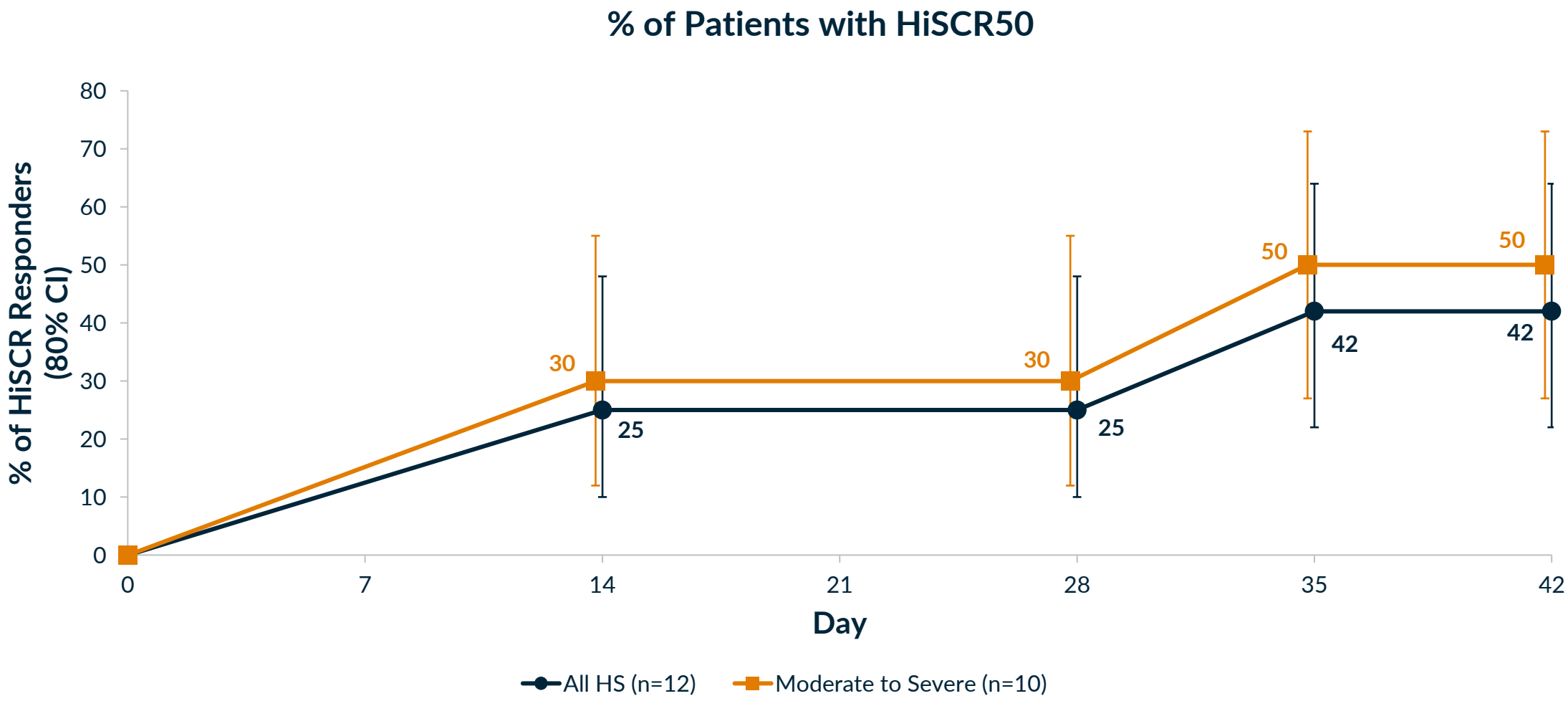


% of Patients with AN Count 0/1/2



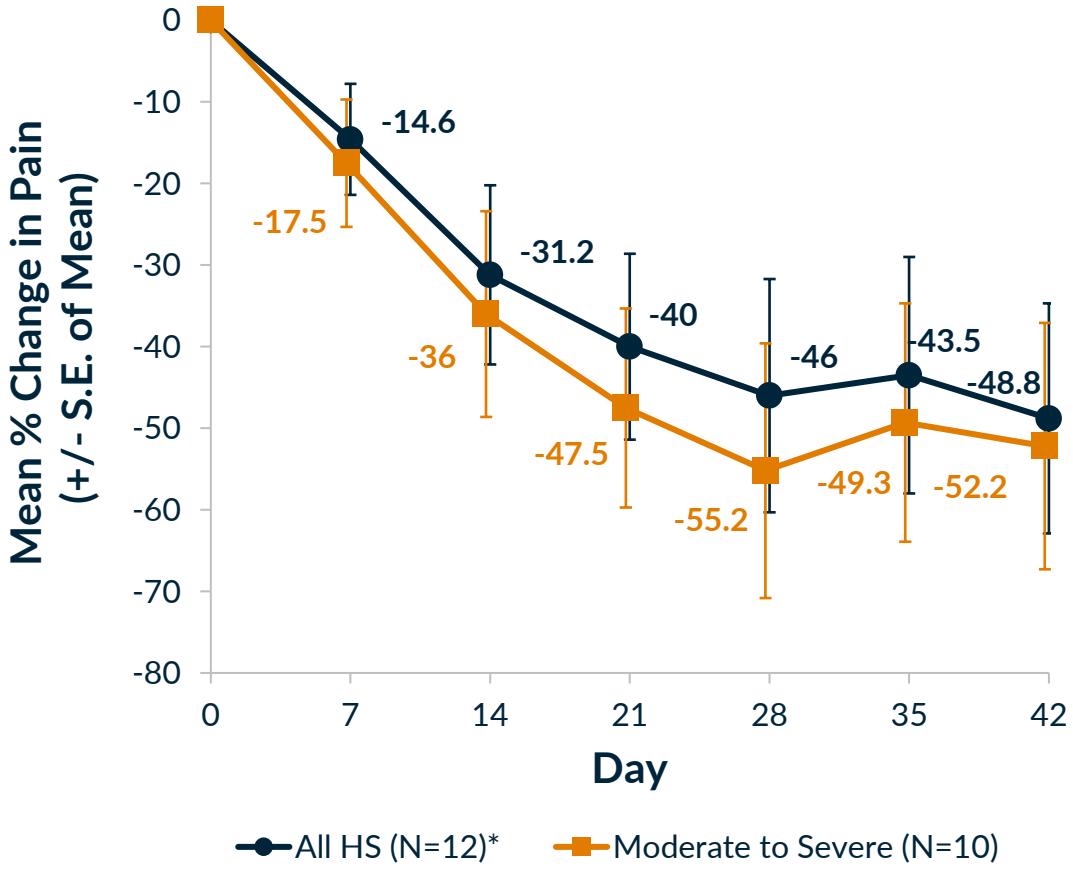
*One patient is censored for Day 35 and Day 42 since the patient started on ustekinumab, steroids and abx on Day 34.

HiSCR50: 42 to 50% Response Rate

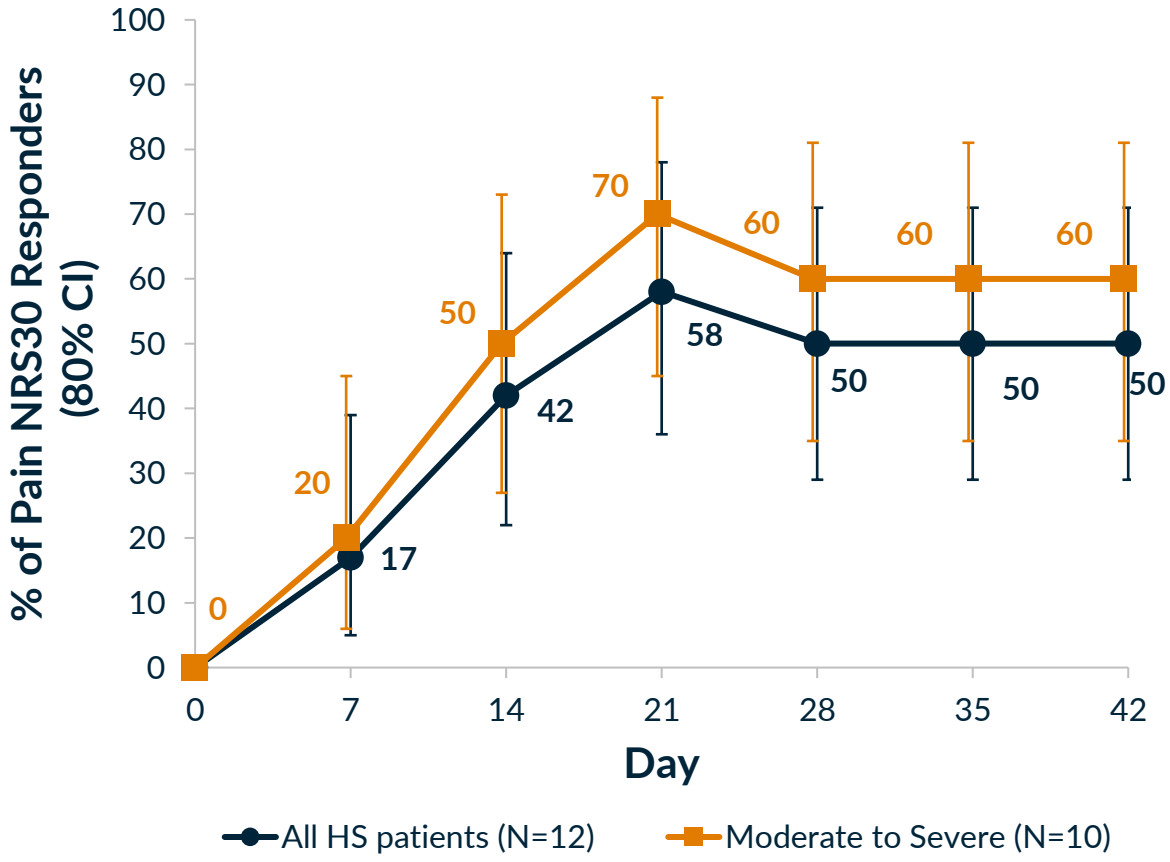


Pain NRS: Mean 49 to 55% Reduction
Pain NRS30: 50 to 60% Response Rate

Mean % Change in Worst Pain Over Past Week

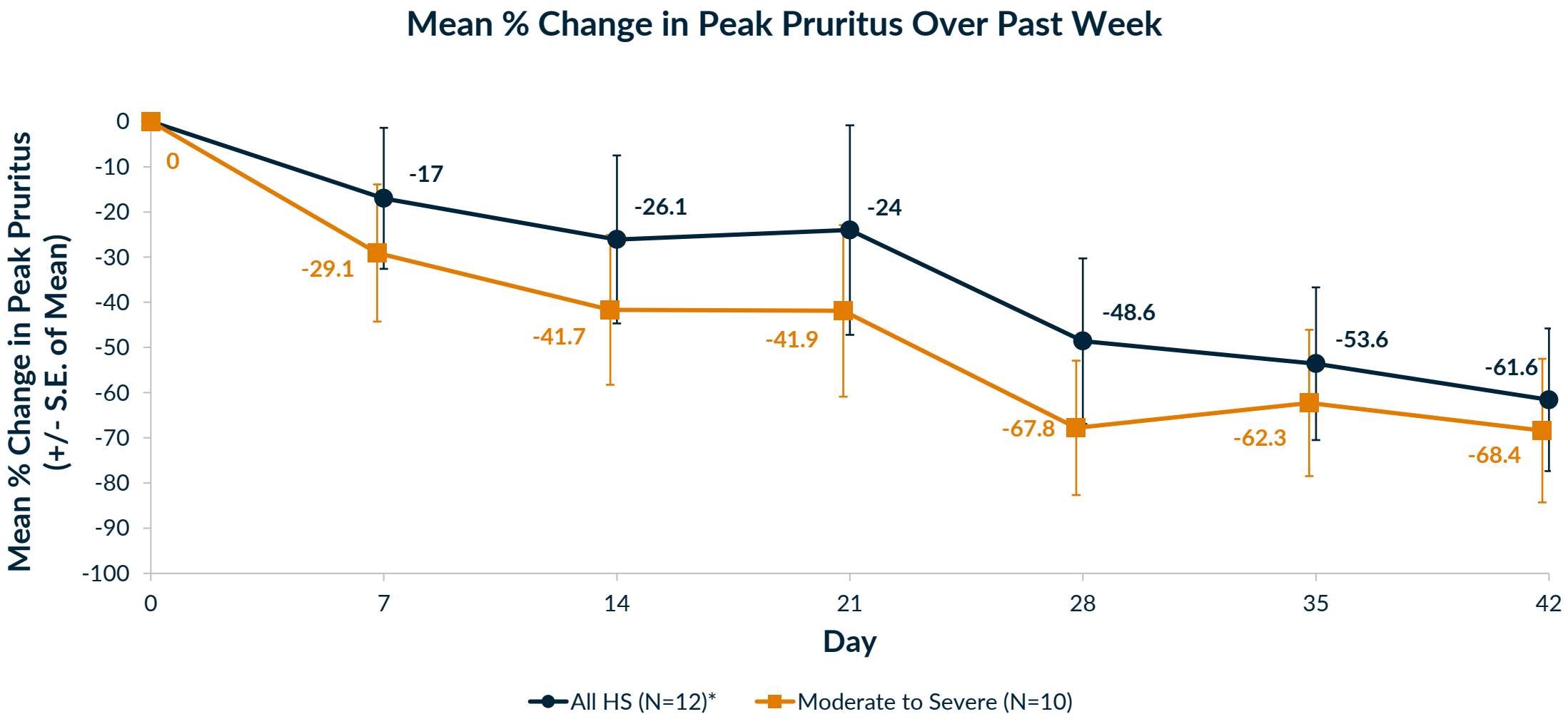


% of Patients with ≥30% and ≥1 Unit Reduction in Worst Skin Pain Over the Past Week



*One patient is censored for Day 35 and Day 42 since the patient started on ustekinumab, steroids and abx on Day 34.

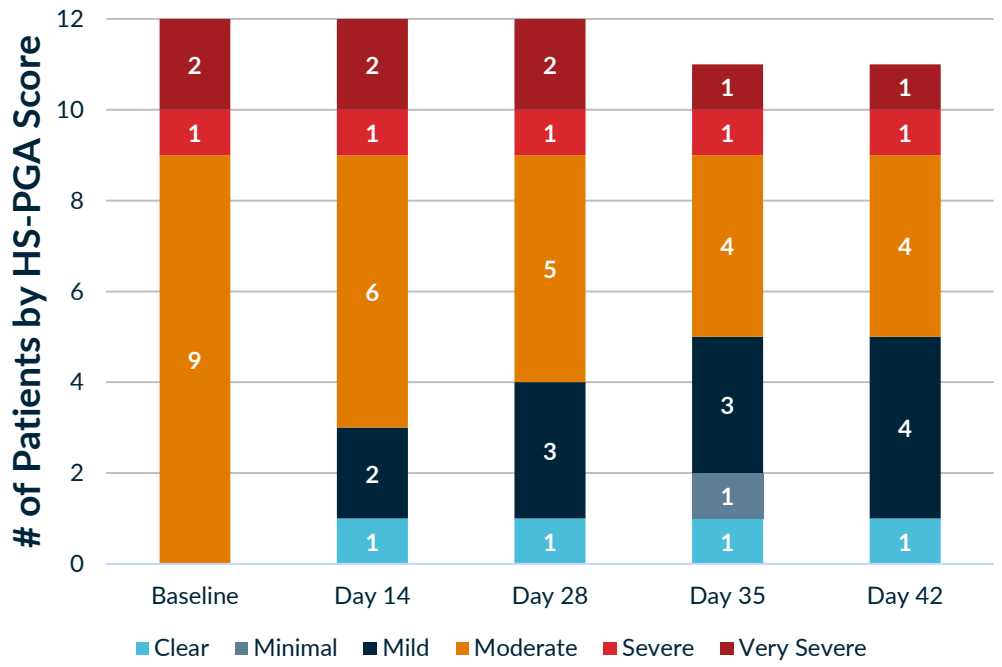
Peak Pruritus NRS: Mean 62 to 68% Reduction



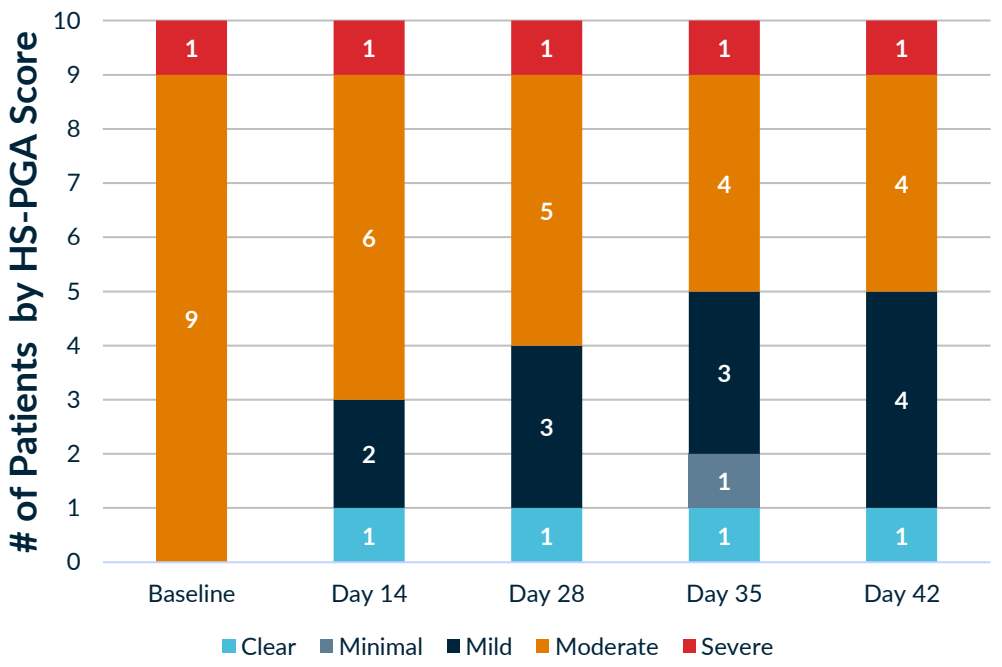
*One patient is censored for Day 35 and Day 42 since the patient started on ustekinumab, steroids and abx on Day 34.

Physician's Global Assessment (HS-PGA)

HS-PGA Score Over Time (N=12*)



HS-PGA Score Over Time Moderate to Severe Patients (N=10)



- HS-PGA scores remained stable or improved in all patients
  - Disease cleared in 1 patient with moderate disease at baseline

*One patient is censored for Day 35 and Day 42 since the patient started on ustekinumab, steroids and abx on Day 34.

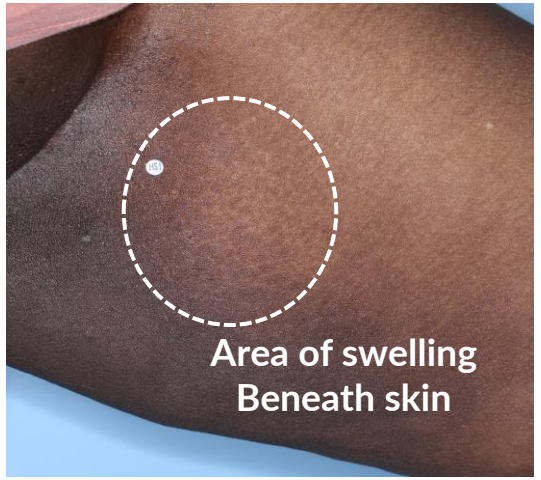
HS Case Study: Patient HS-3

Complete Clearing of Lesions and Symptoms in Patient with Moderate Disease at Baseline

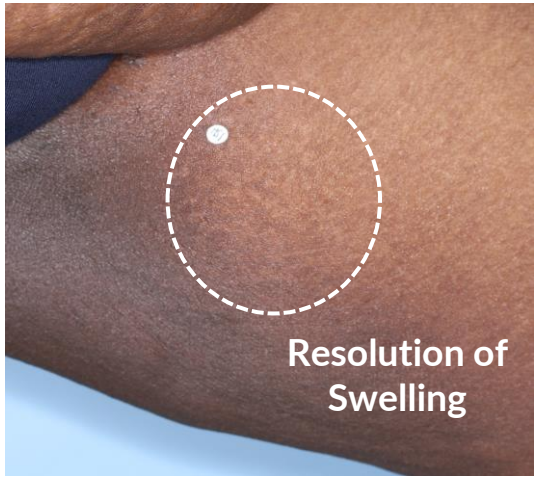
- 45 year old Black Female with Moderate HS (HS-PGA); Baseline AN count = 7
- Prior treatments: clindamycin (topical) and doxycycline

Efficacy Endpoints	BL	Day 28	Day 35	Day 42
HS-PGA Score	Moderate	Clear	Clear	Clear
AN Count (% Reduction)	7	0 (-100)	0 (-100)	0 (**-100**)
Skin Pain NRS – Worst, past week (% Change)	7	0 (-100)	0 (-100)	0 (**-100**)
Peak Pruritis NRS – past week (% Change)	6	0 (-100)	0 (-100)	0 (**-100**)

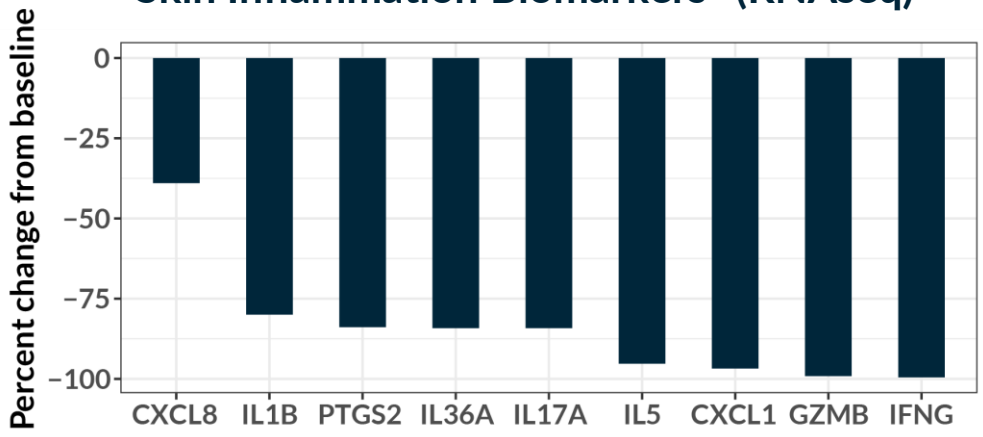
Day 1 - BL



Day 42



Skin Inflammation Biomarkers* (RNAseq)



*Changes at D28

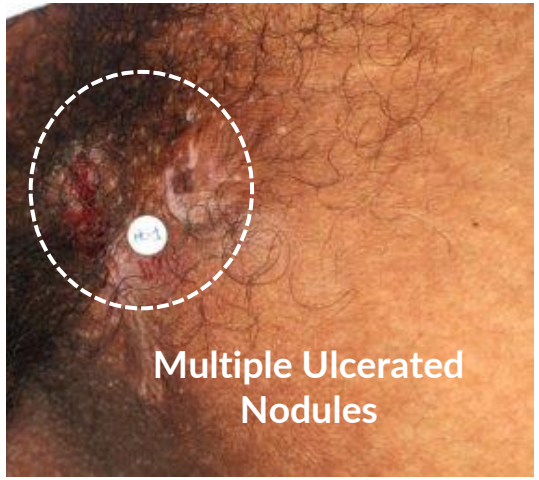
HS Case Study: Patient HS-10

Improvement in Disease Severity from Moderate to Mild

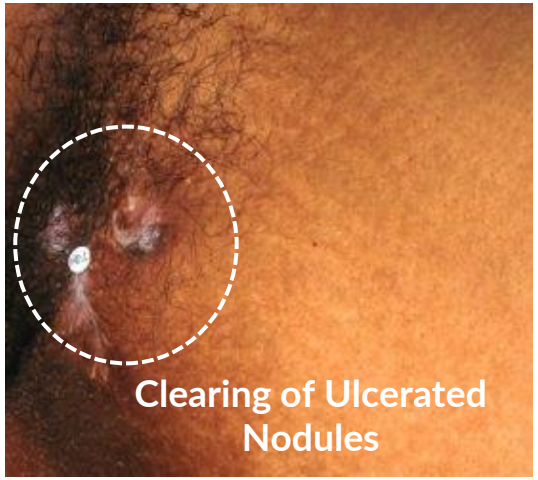
- 39 year old Black Female with Moderate HS (HS-PGA); Baseline AN count = 5
- Prior treatments: benzocaine ointment

Efficacy Endpoints	BL	Day 28	Day 35	Day 42
HS-PGA Score	Moderate	Mild	Mild	Mild
AN Count (% Reduction)	5	2 (-60)	2 (-60)	1 (**-80**)
Skin Pain NRS – Worst, past week (% Change)	8	3 (-63)	3 (-63)	1 (**-88**)
Peak Pruritis NRS – past week (% Change)	10	2 (-80)	0 (-100)	0 (**-100**)

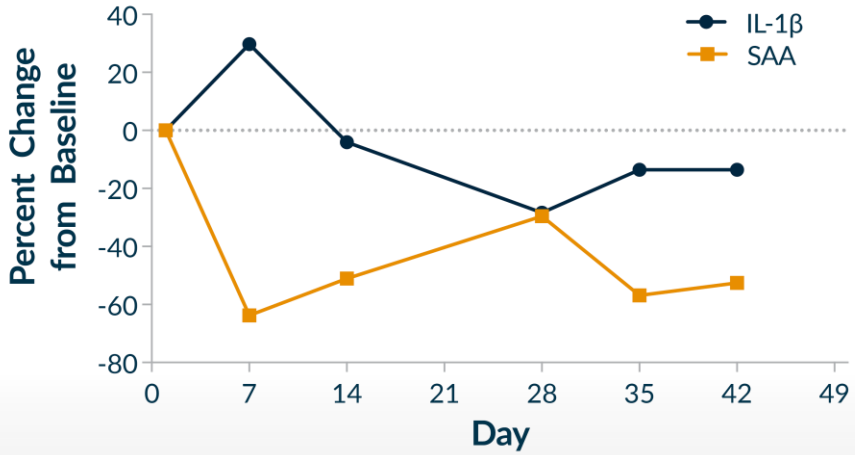
Day 1 - BL



Day 42



Plasma Cytokines/Acute Phase Reactants



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

Conclusions / Summary

KYMERA

Part C Summary

- KT-474 administered to HS and AD patients at 75 mg QD for 28 days shown to have safety, PK and PD **comparable to healthy volunteers**
- Modest, non-adverse QTcF prolongation observed **to spontaneously resolve back to baseline** during final 2 weeks of dosing in HS and AD patients
- Robust degradation of IRAK4 in blood and skin was associated with **systemic anti-inflammatory effect in HS and AD patients**
- Promising clinical activity observed in HS and AD **exceeding benchmark placebo rates** and **comparing favorably to SOC biologics**
- Data presented here **validate IRAK4 degradation as a potential best in class mechanism in inflammatory diseases and its superior clinical potential over SMI**
- Results support **advancing KT-474 into Phase 2 placebo-controlled trials, Sanofi has committed to start Ph2 clinical trials** initially in HS and AD

Meeting Summary

- Kymera **platform and discovery engine have been validated** across several programs in patients with cancer and inflammatory diseases, with fidelity of translation of PK, PD and safety
- Kymera's unique **target selection strategy**, using TPD to drug undrugged targets, **has been validated**, with initial demonstration of **IRAK4 degradation** providing a biologically and clinically differentiated/**superior profile than SMI**
- **KT-474 data positions this mechanism and drug as a potential best in class oral drug** in HS, AD and a broader variety of immune-inflammatory diseases with large market opportunity potential
- The successful target selection strategy, molecular design, discovery and clinical execution and insights **will allow acceleration and expansion of our pipeline in areas of high unmet need and large commercial opportunities**
- In 2023 Kymera expects to share **an expanded strategy to accelerate the path towards a disease agnostic global biotech**


Q&A
KYMERA