EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

Safety and Efficacy of IRAK4 Degrader KT-474 (SAR444656) for Hidradenitis Suppurativa and Atopic Dermatitis

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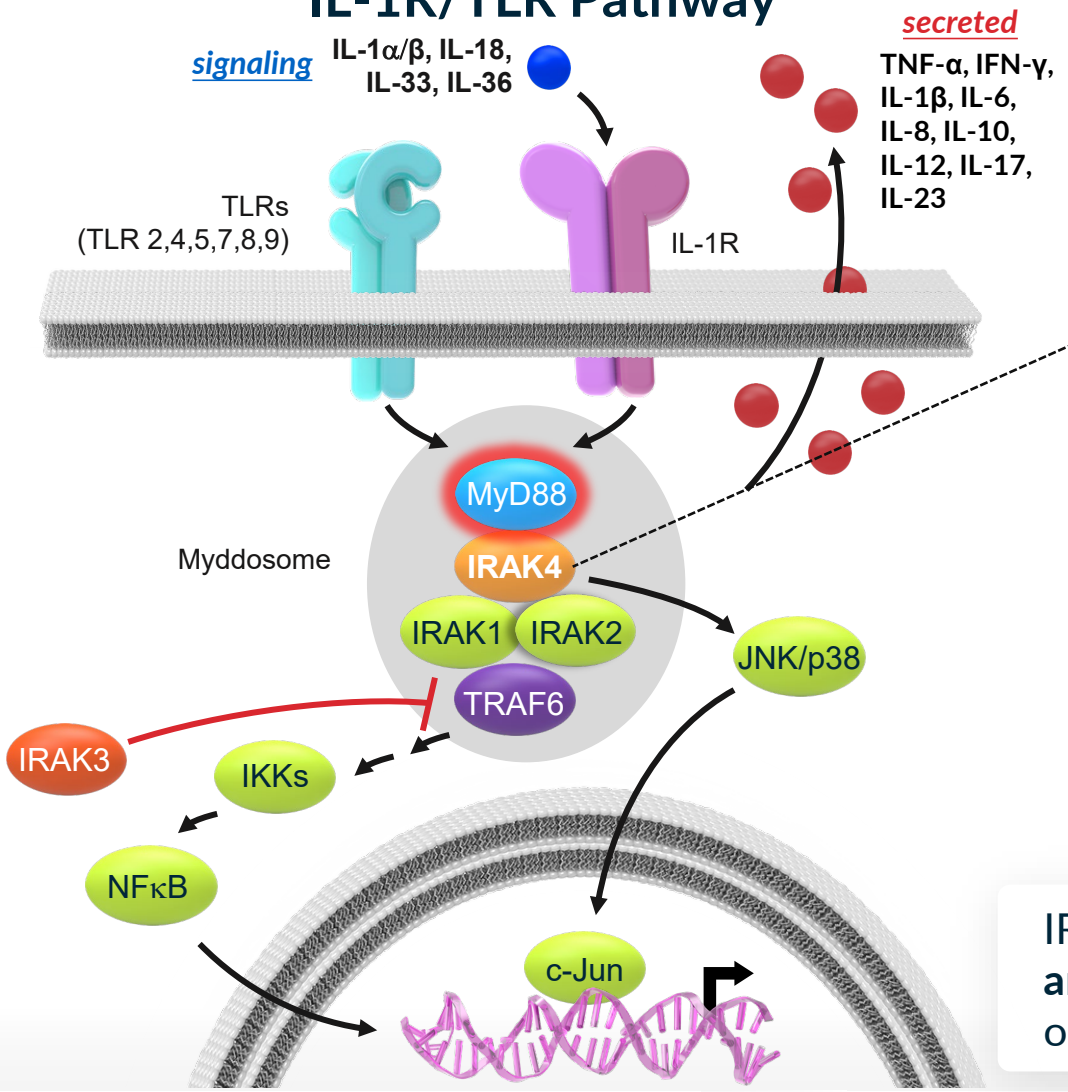
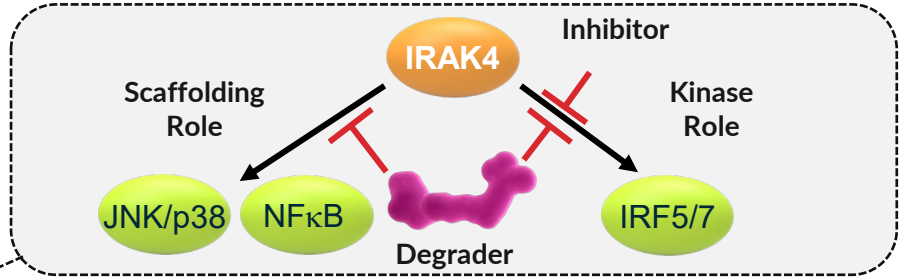
Degrading IRAK4: Best Approach to Block IL-1R/TLR driven Inflammation

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

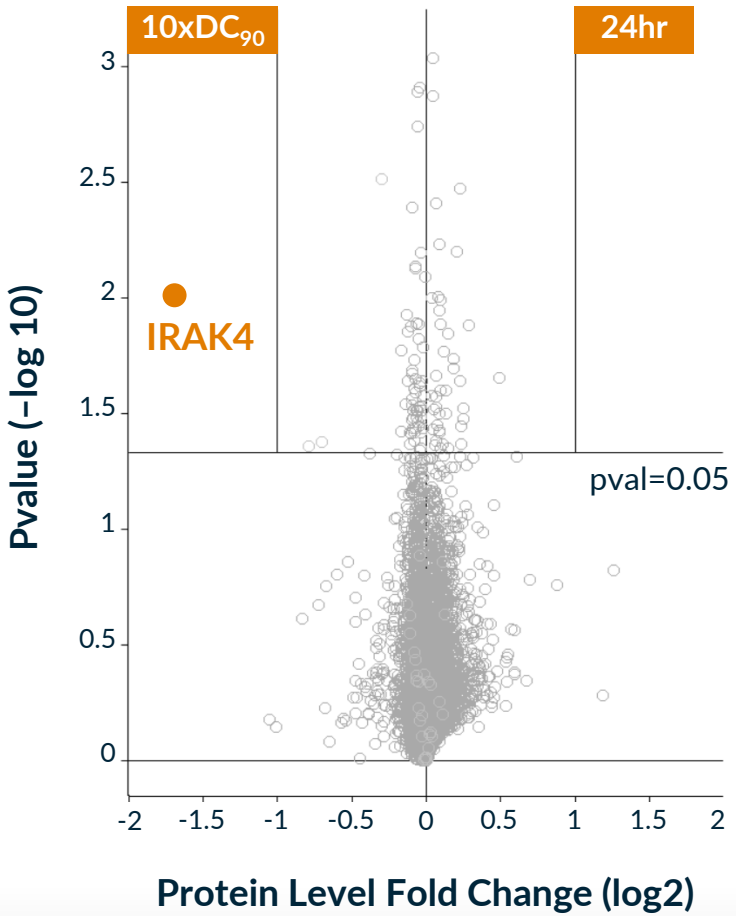
Human Genetics

Adult humans with **IRAK4 Null Mutation are healthy**

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

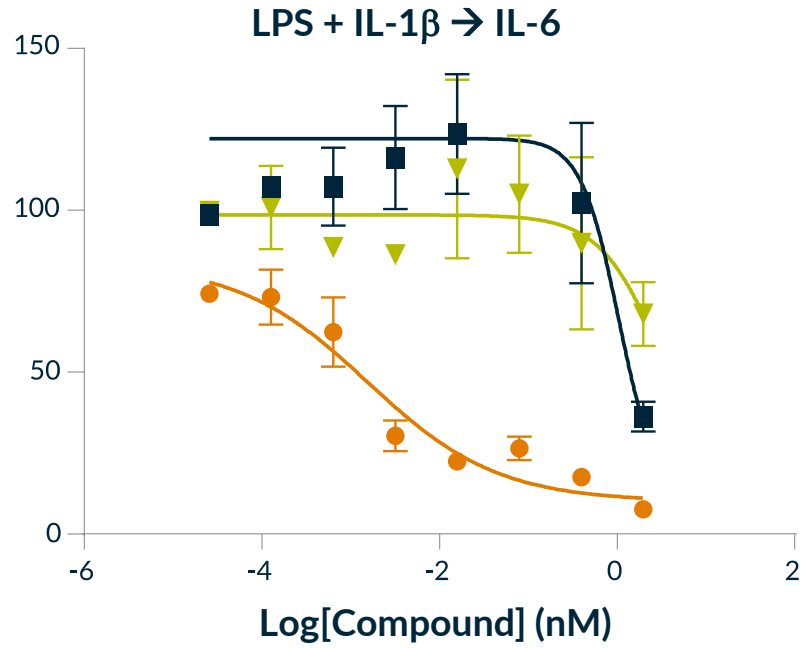
KT-474: Potent and Specific IRAK4 Degradation with Impact on Cytokines Superior to Kinase Inhibition

Degradation and Selectivity



- KT-474 DC_{50} = 2.1 nM in human immune cells
- KT-474 was selective for IRAK4 in human immune cells at concentration 10-fold above the DC_{90}
- KT-474 better able to inhibit IL-6 under both LPS and LPS + IL-1β than clinically active IRAK4 SM kinase inhibitor PF-06550833

Superiority over SM kinase Inhibitor



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

KT-474 Phase 1 Design

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

Parts A & B

Healthy Volunteers SAD and MAD

7 SAD cohorts
- 8 subjects per cohort (6:2 randomization)
- 57 adult healthy subjects dosed

Single dose (25-1600 mg)

4 MAD cohorts
- 12 subjects per cohort (9:3 randomization)
- 48 adult healthy subjects dosed

14x daily doses (25-200 mg)

Primary
- Safety & tolerability

Secondary/ Exploratory
- Pharmacokinetic measures (half-life, bioavailability)
- IRAK4 knockdown in PBMC and skin (MAD only)
- *Ex vivo* response of whole blood to TLR agonists (SAD & MAD)

Part C

HS and AD Patients

1 cohort
21 HS and AD patients

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

Open-label

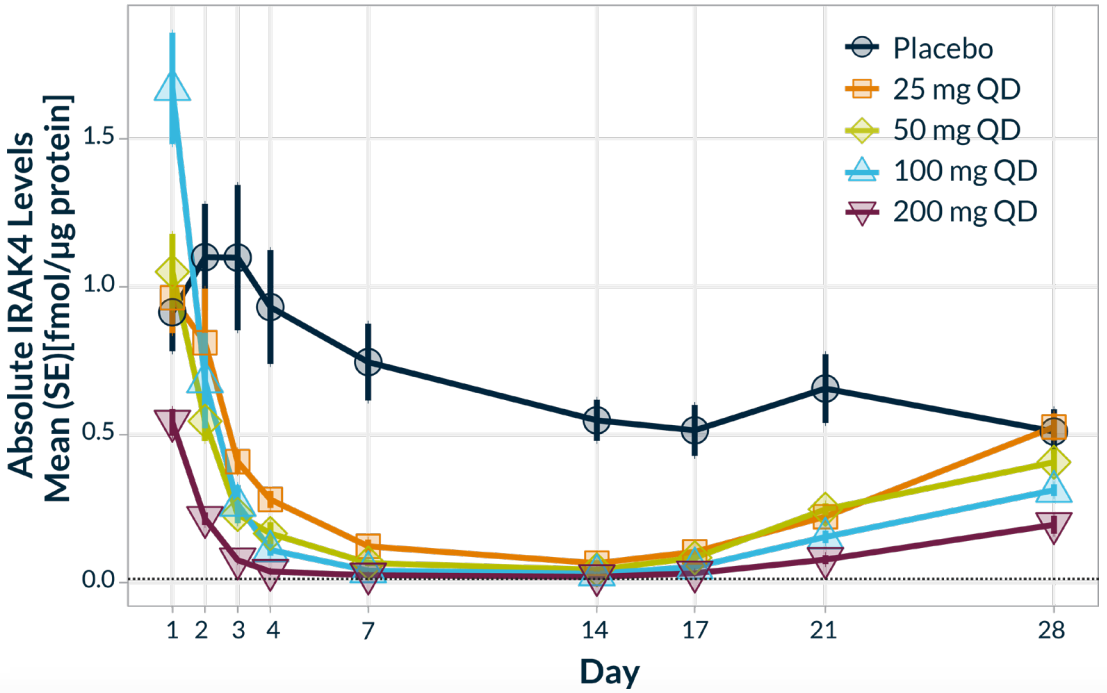
28x daily doses

Primary
- Safety & tolerability

Secondary/ Exploratory
- Pharmacokinetic measures (half-life, bioavailability)
- IRAK4 knockdown in PBMC and skin
- Change in circulating inflammatory biomarkers and proinflammatory gene transcripts in skin
- Clinical endpoints: EASI (AD), Total AN Count (HS), symptom scores and global assessments

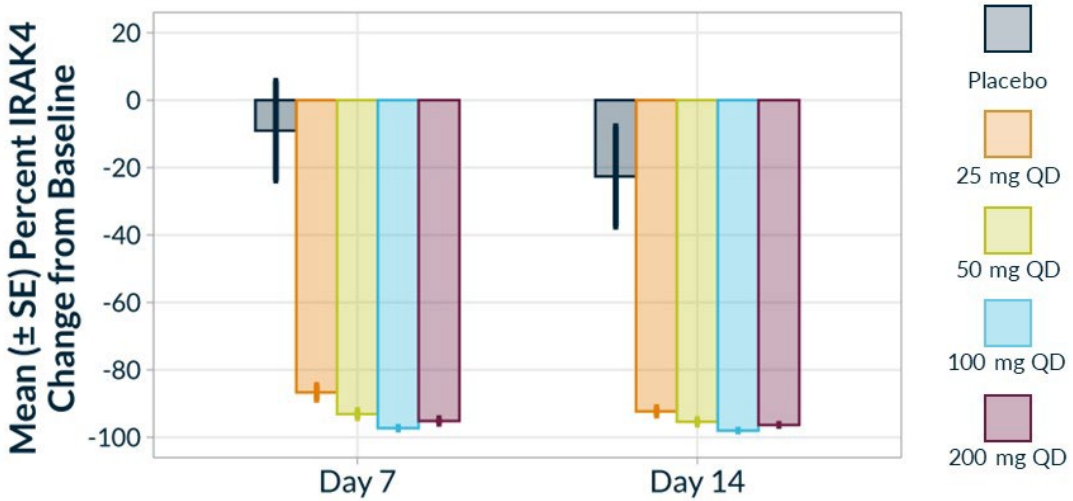
KT-474 Achieved Robust and Sustained IRAK4 Degradation with Multiple Daily Oral Doses (14 Days)

Absolute IRAK4 Levels



- 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)

Percent IRAK4 Reduction at Steady State

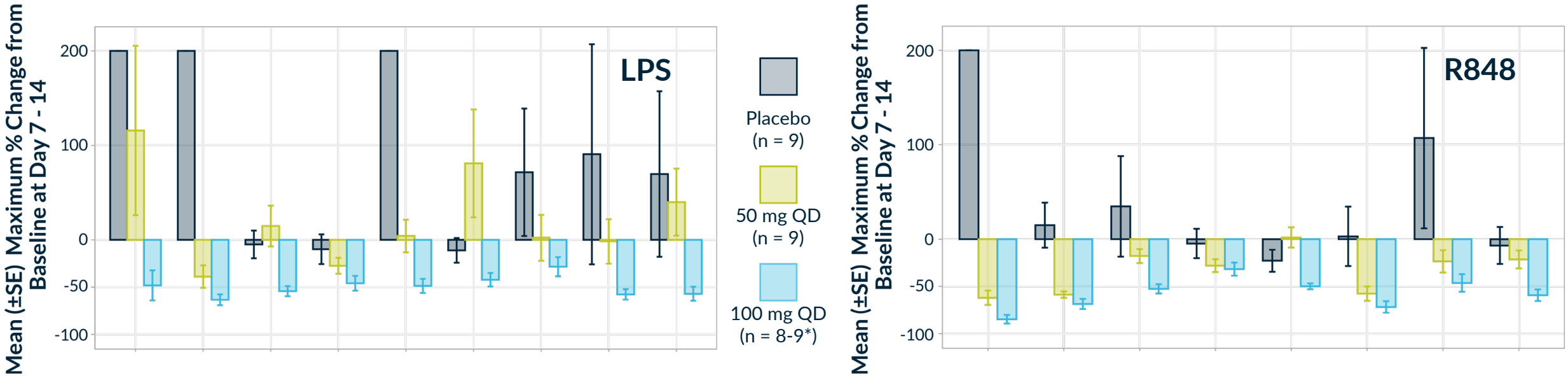


	Placebo (n=12)	25 mg QD (n=9)	50 mg QD (n=9)	100 mg QD (n=9)	200 mg QD (n=9)
Mean Day 7	-9%	-87%	-93%	-97%	-95%
Mean Day 14	-23%	-92%	-95%	-98%	-96%
*p value**		*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*

* p-values relative to placebo

Ex Vivo Inhibition of 9 Disease-Relevant Cytokines, Day 7-14

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



	IFNγ	IL1β	IL6	IL8	IL10	IL12	IL17	IL23	TNFα
Pbo	357%	292%	-5%	-10%	880%	-11%	72%	91%	70%
50 mg QD	116%	-39%	15%	-27%	4%	81%	2%	-2%	40%
100 mg QD	-48%	-63%	-54%	-46%	-49%	-42%	-28%	-58%	-57%

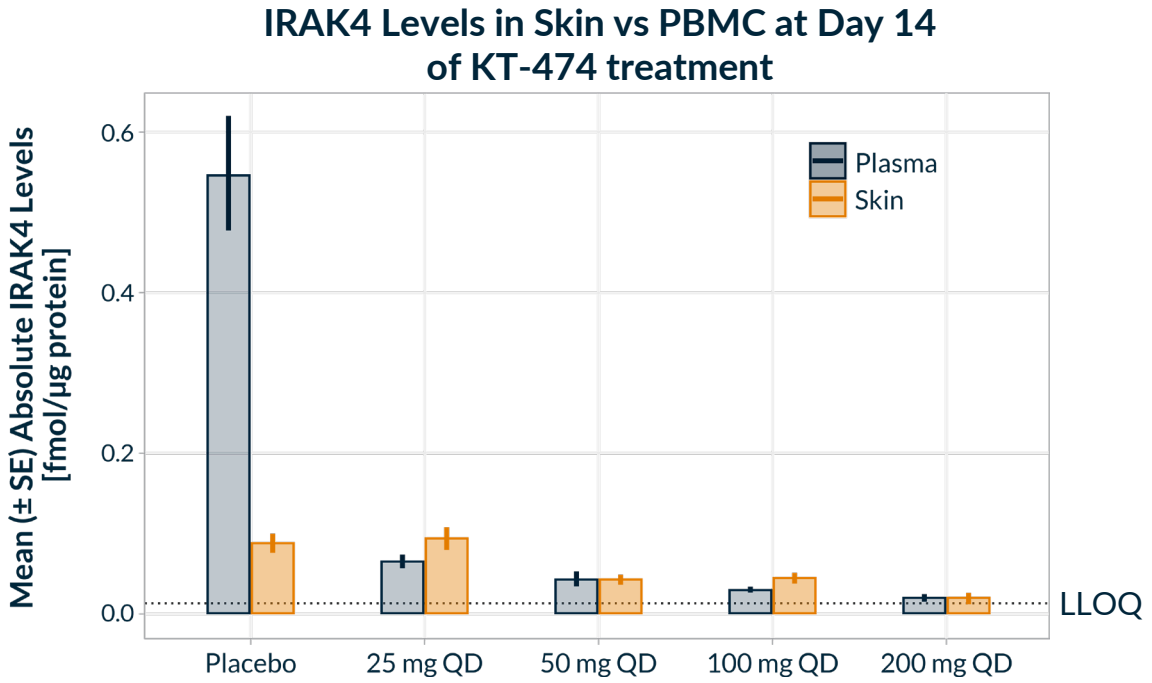
	IFNγ	IL1β	IL6	IL8	IL10	IL12	IL17	TNFα
Pbo	>500%	15%	35%	-5%	-23%	3%	107%	-7%
50 mg QD	-62%	-59%	-18%	-28%	2%	-58%	-24%	-21%
100 mg QD	-85%	-68%	-53%	-32%	-50%	-72%	-46%	-59%

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

KT-474 Reduced IRAK4 to Near LLOQ in the Skin (MS)



- Baseline IRAK4 levels in skin substantially lower compared to PBMC
- Dose-dependent IRAK4 degradation in skin by mass spectrometry
- Mean IRAK4 levels at 200 mg dose nearing LLOQ, with knockdown up to 90% at 200 mg
- Comparable degradation in PBMC shows that effect of KT-474 is independent of baseline expression level

Patient Cohort: 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**

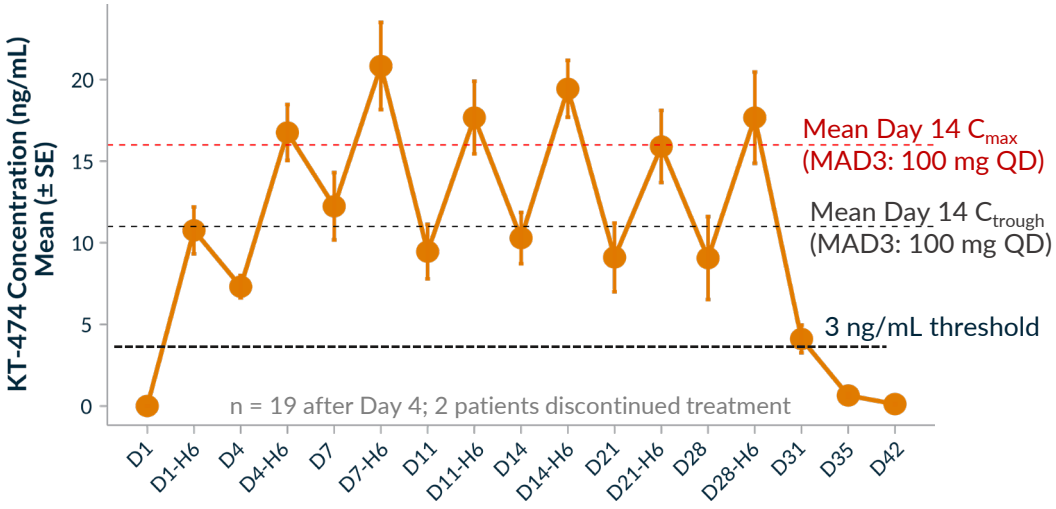
*worst score over past week **includes clindamycin and chlorhexidine

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

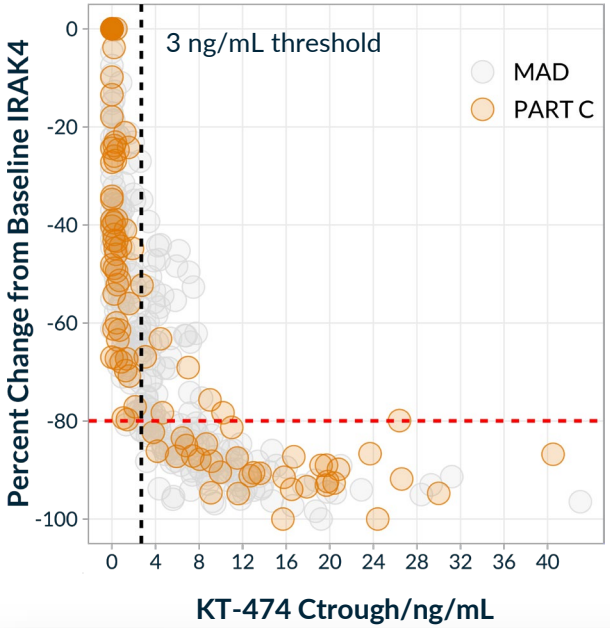
AD=Atopic Dermatitis; AN=Abscess and Inflammatory Nodule Count; EASI=Eczema Area and Severity Index; HS=hidradenitis suppurativa; Min=minimum; Max=maximum; Pain-NRS=Skin Pain Numerical Rating Score; Pruritus-NRS=Peak Pruritus Numerical Rating Score; PGA-Physicians Global Assessment; IGA=Investigator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

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

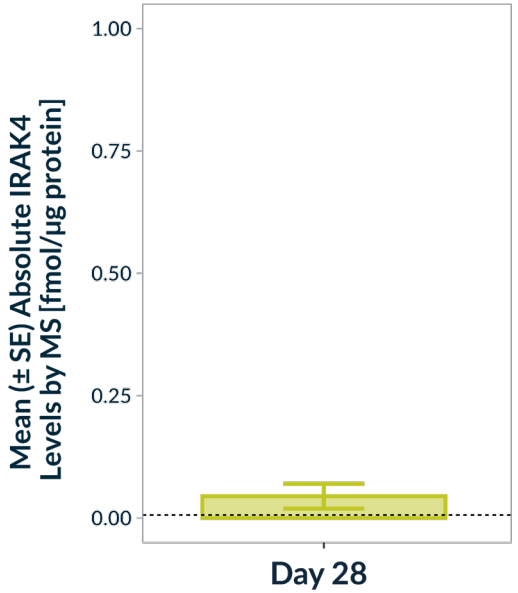
Part C KT-474 Plasma PK



PK/PD Correlation in Plasma/Monocytes (FLOW)



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



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

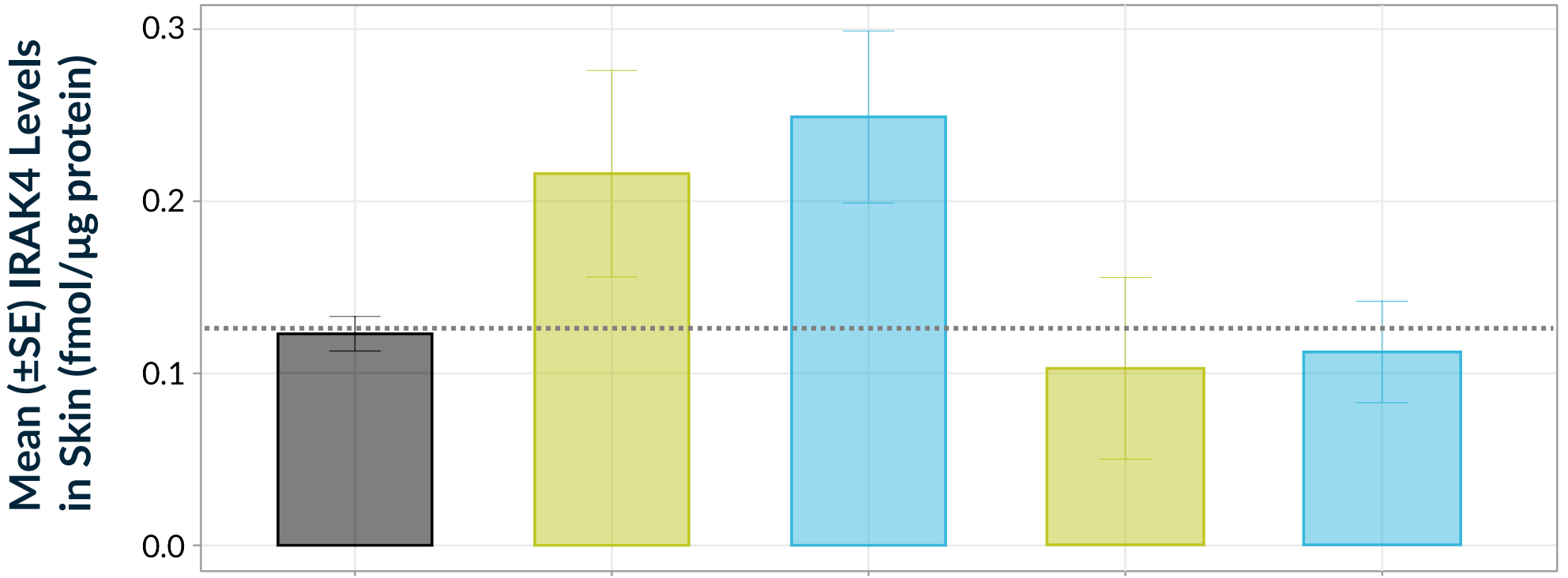
- Mean C_{max} and C_{trough} levels at steady state in Part C are in line with MAD3 levels at Day 14
- Mean half-life of 44 hours is within the range observed in MAD (34-59 hours)

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

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

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

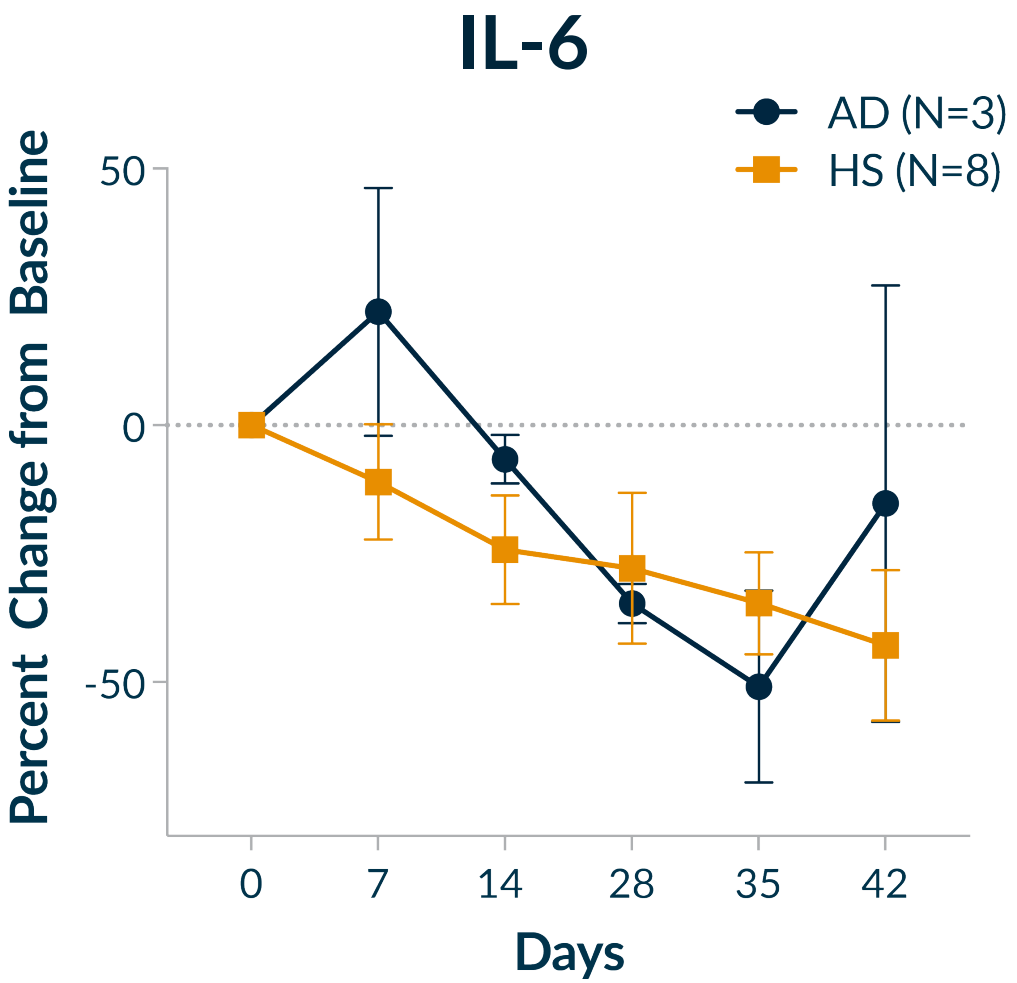


	MAD Healthy Subjects (Baseline)	AD Patients (Baseline)	HS Patients (Baseline)	AD Patients (Day 28)	HS Patients (Day 28)
N	46	7	11	6	9
Mean (± SE)	0.123 (± 0.01)	0.216 (± 0.06)	0.236 (± 0.05)	0.103 (± 0.05)	0.112 (± 0.03)

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)

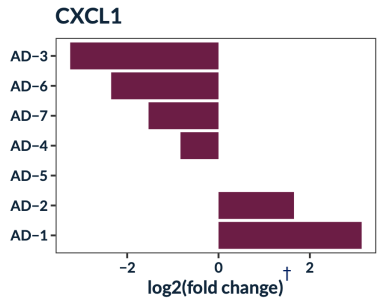
*Max % reduction through Day 42
†Analysis performed only on patients with values >ULN at baseline
IL-6, IL-1β and CRP are high sensitivity assays
NA: not applicable

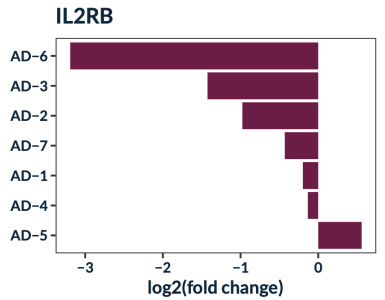


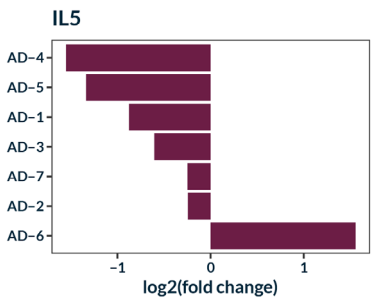
Disease-Relevant Genes Downregulated in Skin Lesions in ≥ 50% of Evaluable* AD (N=7) and HS (N=10) Patients at Day 28 (RNAseq)

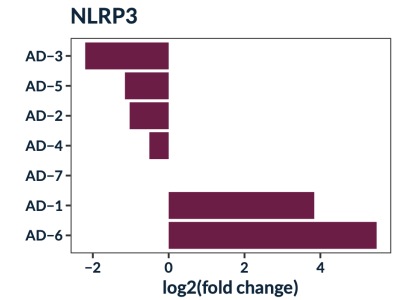
- Substantial **downregulation of many disease relevant genes** in both HS and AD patients
- **Downregulation exceeded 90%** for many genes
- Broad **anti-inflammatory signature** with downregulation of genes responsible for:
  - ✓ IL1 family cytokines
  - ✓ Th1
  - ✓ Th17
  - ✓ Th2
  - ✓ Innate immunity

AD

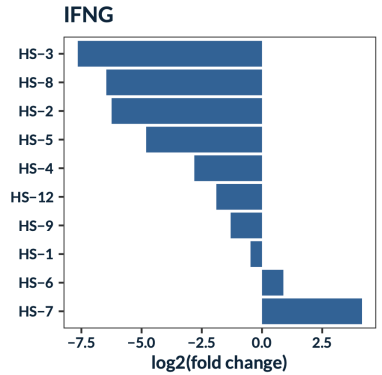


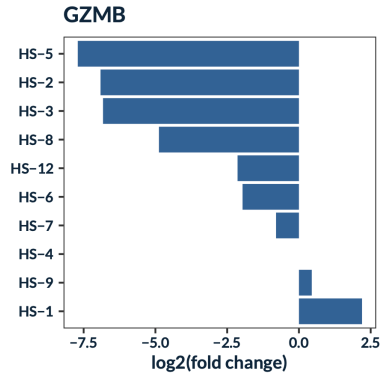


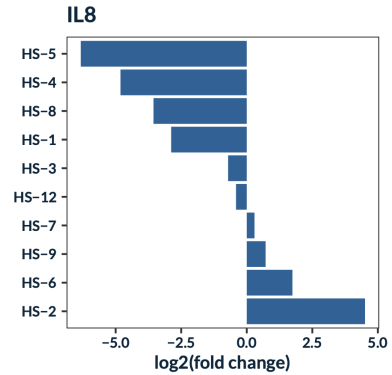


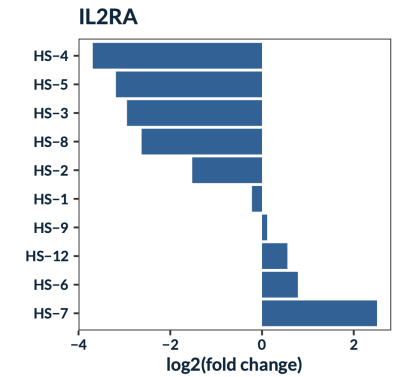


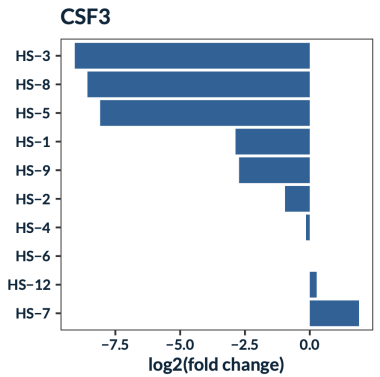
HS

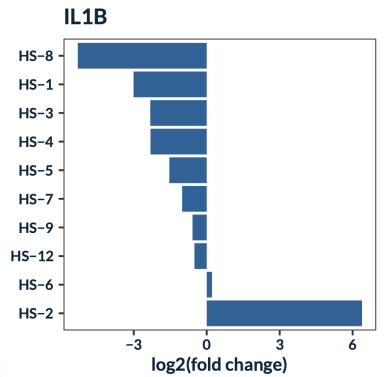


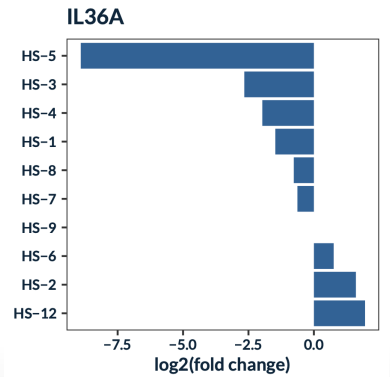


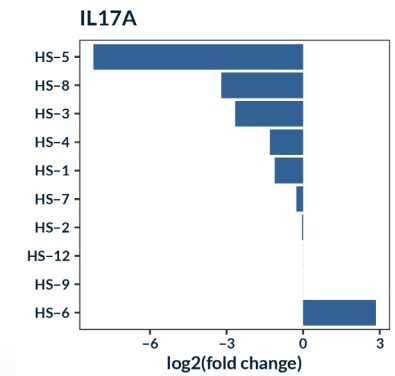










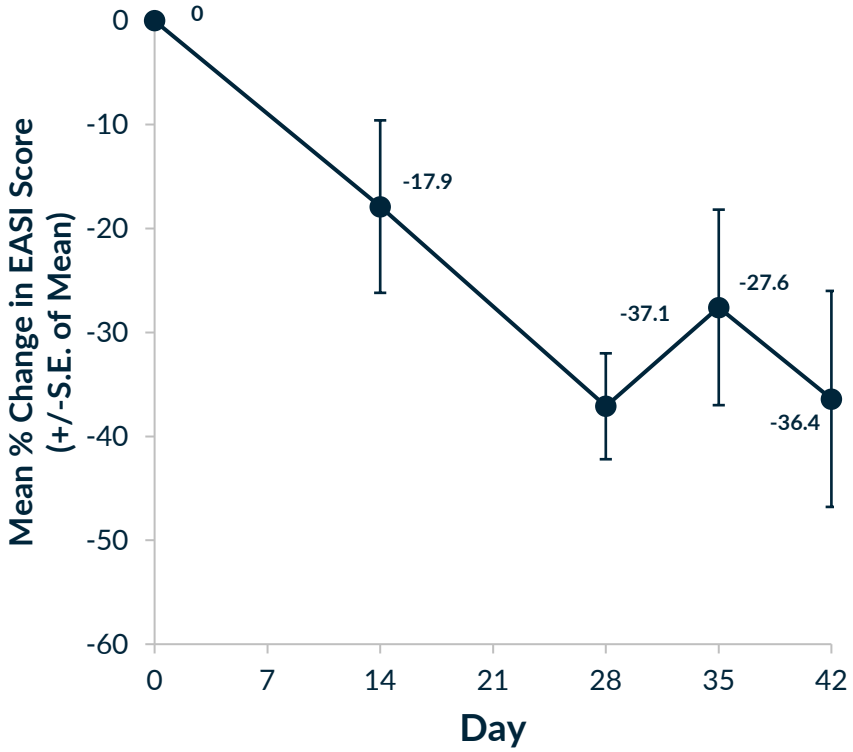


†log2(fold change relative to baseline): -1 = 50% decrease, -2 = 75% decrease, -3 = 87.5% decrease

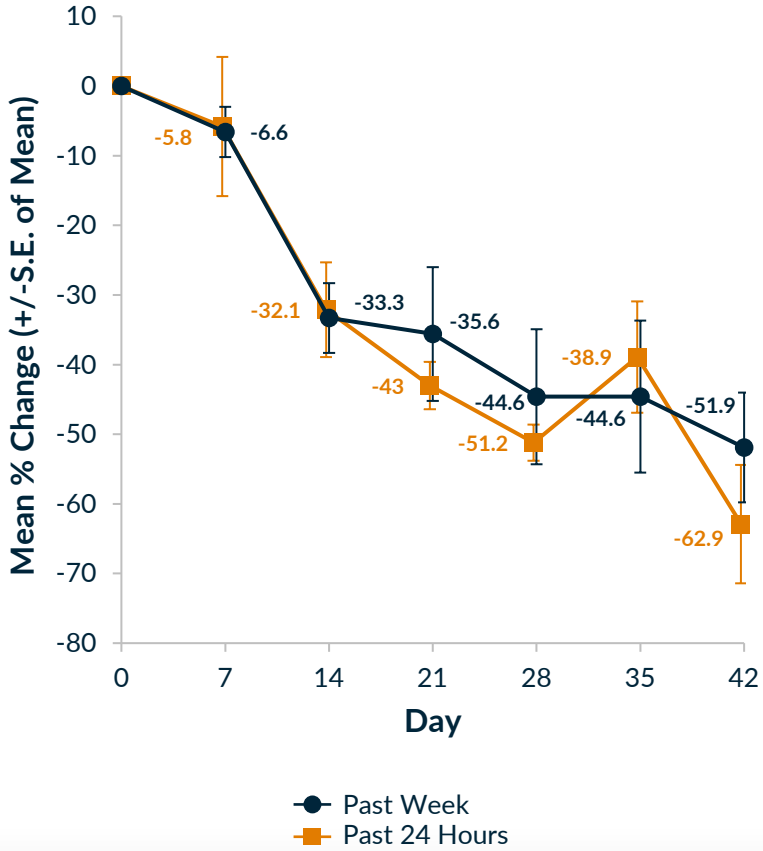
*Evaluable patients for whom the samples were of sufficient quality for analysis.

AD: Significant Reduction in EASI Score and Pruritus

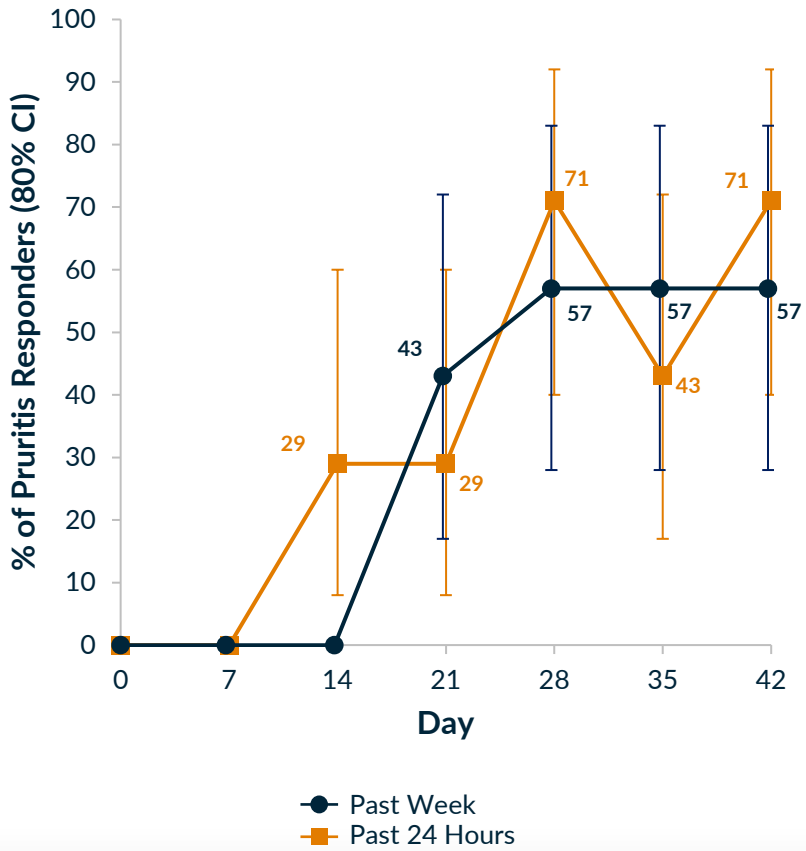
Mean % Change in EASI Score Over Time (N=7)



Mean % Change of Worst Pruritus Over Time (N=7)



Patients with ≥4 Unit Reduction from Baseline in Worst Pruritus (N=7)

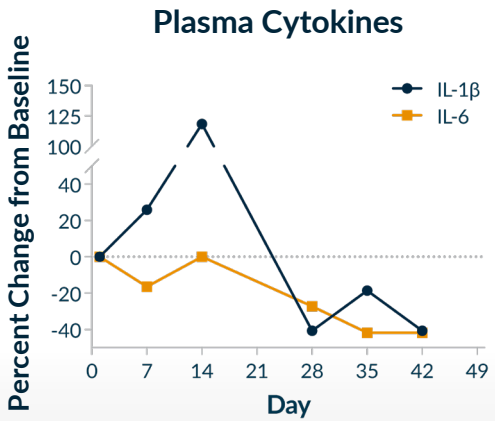


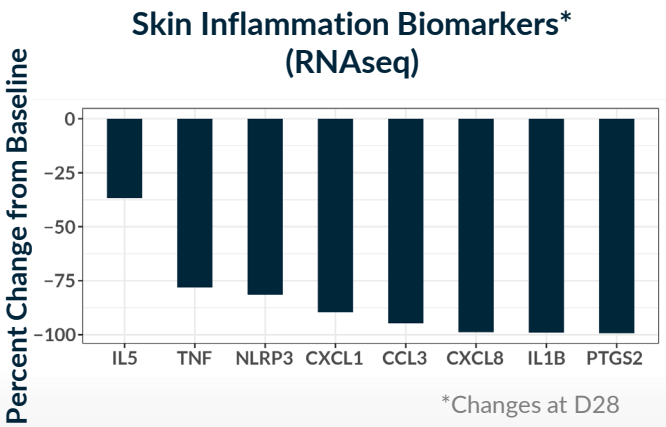
AD Case Study: Patient AD-3

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

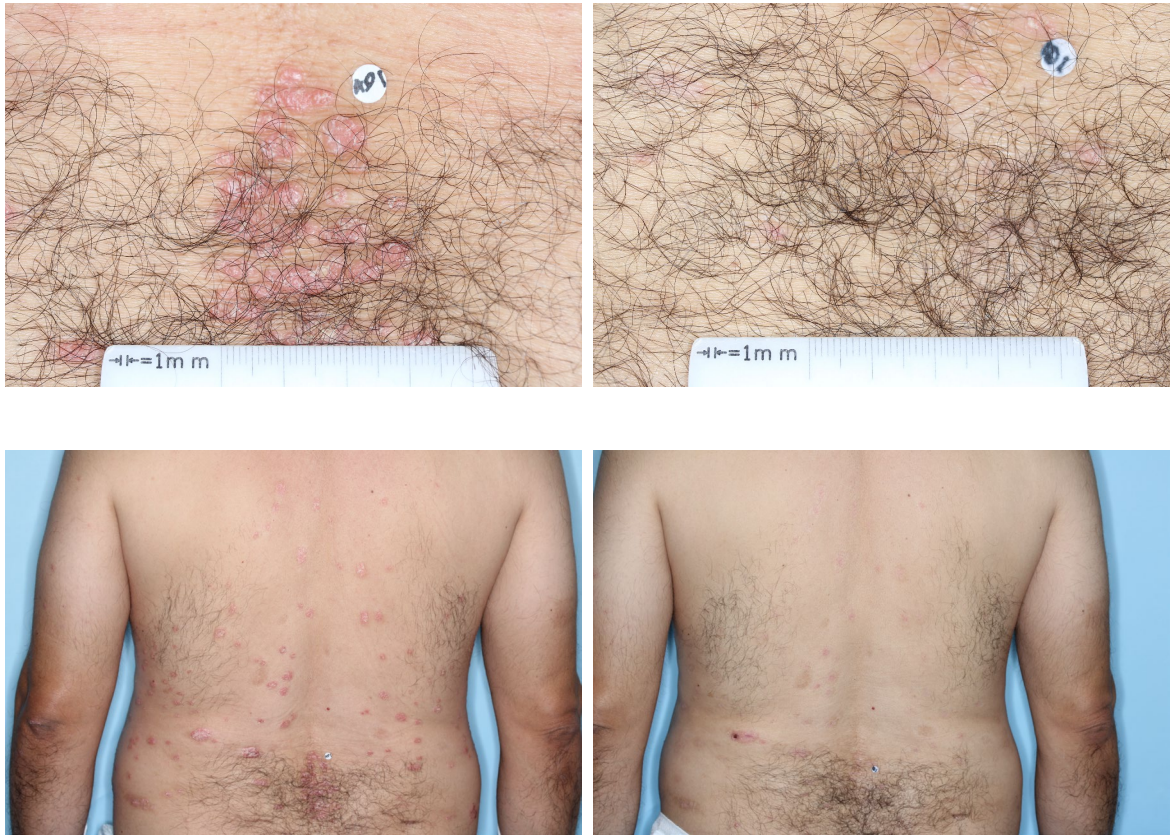
Efficacy Endpoints	BL	Day 28	Day 35	Day 42
IGA-AD Score	Severe	Moderate	Moderate	Mild
EASI Score (% Change)	28.2	14 (-50)	16.45 (-42)	9.2 (**-67**)
Peak Pruritis NRS - past week (% Change)	4	1 (-75)	1 (-75)	1 (**-75**)





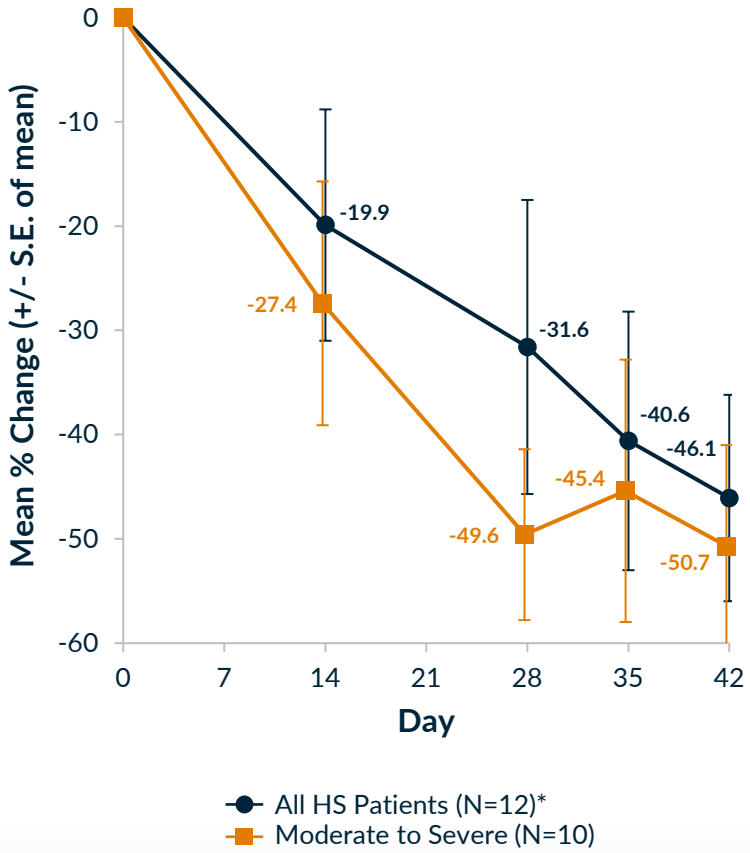
*Changes at D28

Day 1 - BL | **Day 42**

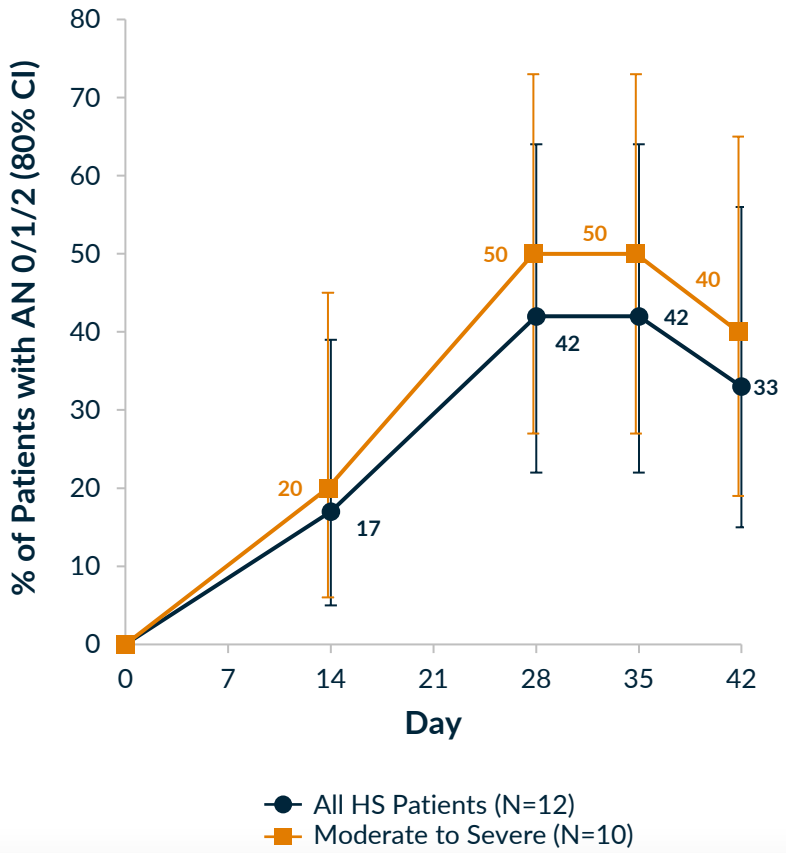


HS: Significant Reduction in AN Count Leading to HiSCR Responses

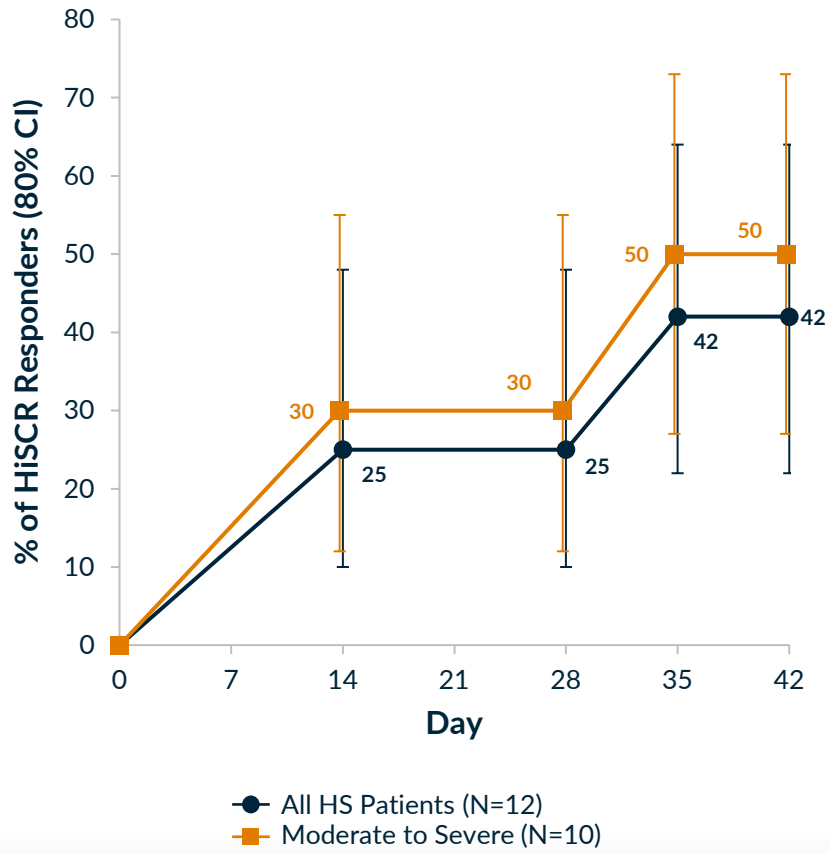
Mean % Change in Total AN Counts Over time



% of Patients with AN Count 0/1/2



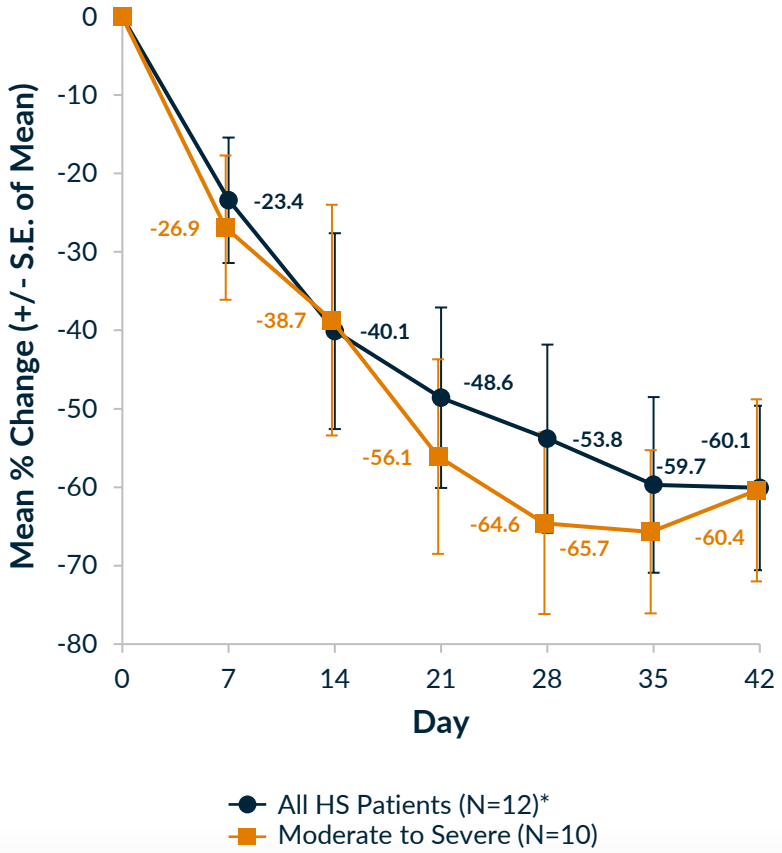
HiSCR50 Responders



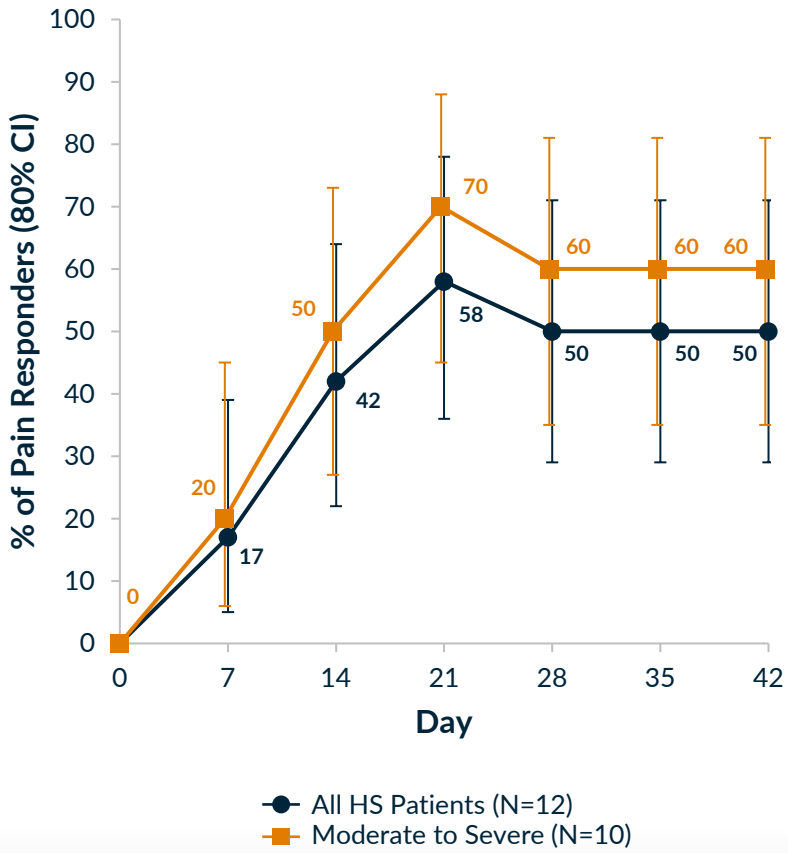
*One patient is censored for Day 35 and Day 42 since the patient started on ustekinumab, steroids and abx on Day 34.

HS: Significant Reduction in Pain/Pruritus

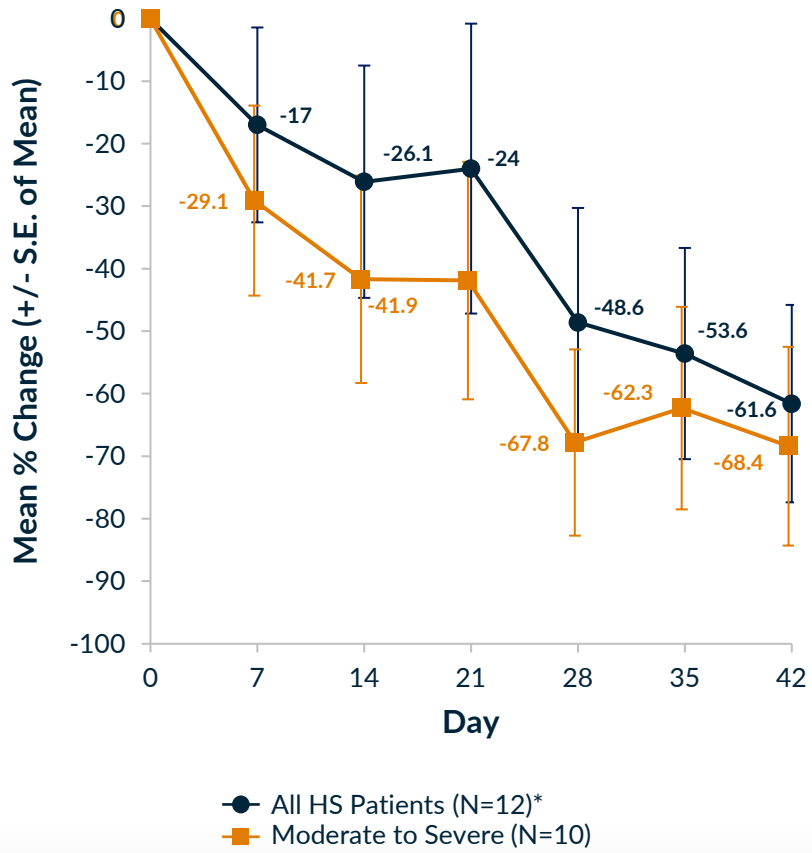
Mean % Change in Average Pain Over Past Week



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



Mean % Change in Worst Pruritus Over Past Week



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

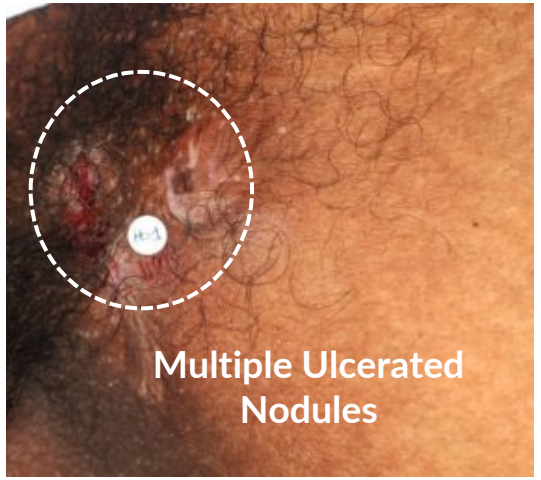
HS Case Study: Patient HS-10

Improvement in Disease Severity from Moderate to Mild

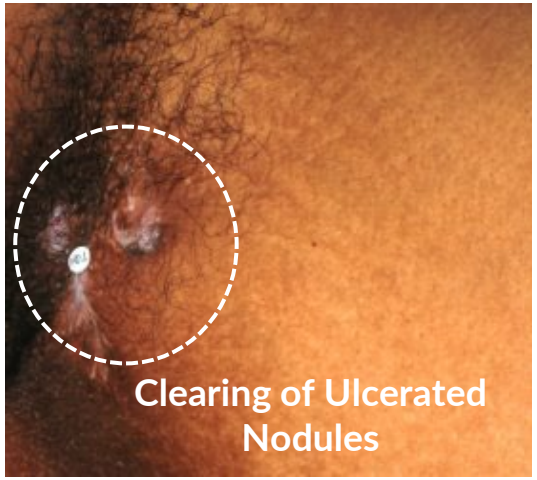
- 39 year old Black Female with Moderate HS (HS-PGA); Baseline AN count = 5
- Prior treatments: benzocaine ointment

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**)

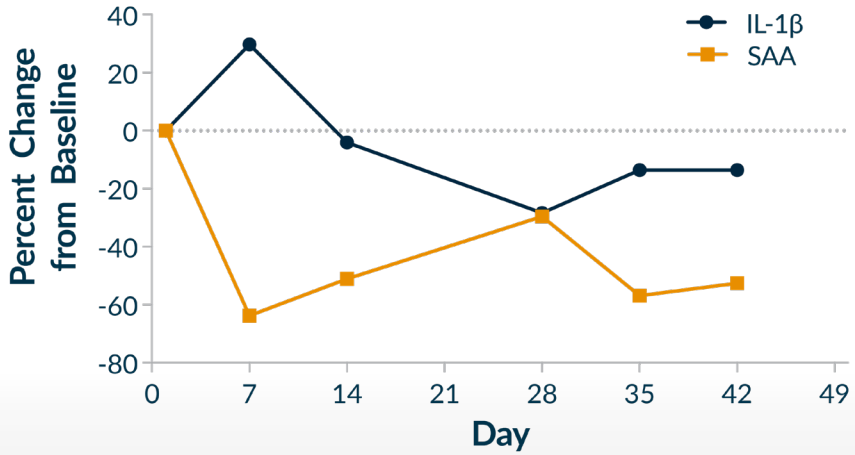
Day 1 - BL



Day 42



Plasma Cytokines/Acute Phase Reactants



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**

Summary

- Single and multiple doses of KT-474 were well-tolerated in healthy volunteers and resulted in **strong degradation of IRAK4 in blood and skin associated with inhibition of *ex vivo* whole blood cytokine induction**
- 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**
- 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 **support 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 plans to start Ph2 clinical trials** in HS and AD

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