ATI-2138 Phase 2a Top-Line Results

July 29, 2025

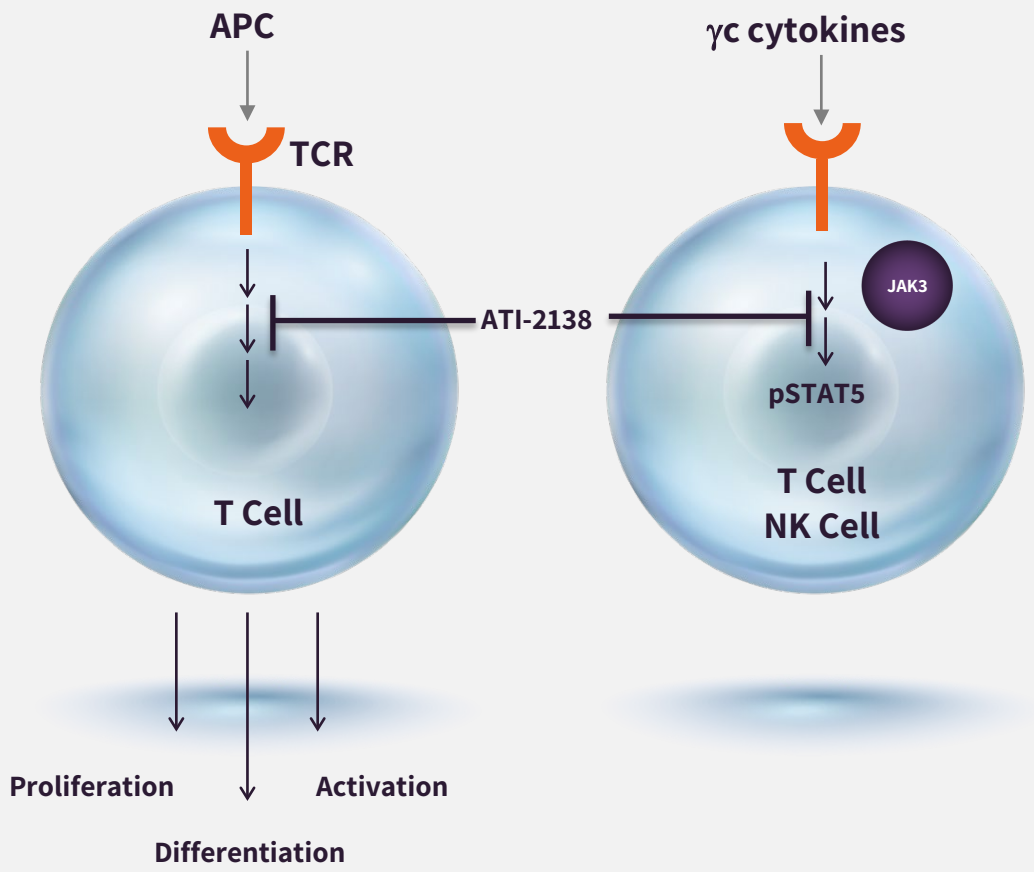
Disclaimer and Cautionary Note Regarding Forward -Looking Statements

Any statements contained in this press release that do not describe historical facts may constitute forward-looking statements as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as “anticipate,” “believe,” “expect,” “intend,” “may,” “plan,” “potential,” “will,” and similar expressions, and are based on Aclaris’ current beliefs and expectations. These forward-looking statements include expectations regarding its development plans for ATI-2138 and its next generation ITK inhibitors, including plans to development ATI-2138 in alopecia areata and potentially other indications, the therapeutic potential for ATI-2138 and next generation ITK inhibitors, as well as expectations related to the timing for the initiation, completion, and reporting results from, and submitting regulatory submissions for, its development programs, and its expected cash runway into the second half of 2028. These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements. Risks and uncertainties that may cause actual results to differ materially include uncertainties inherent in the conduct of clinical trials, Aclaris’ reliance on third parties over which it may not always have full control, Aclaris’ ability to enter into strategic partnerships on commercially reasonable terms, the uncertainty regarding the macroeconomic environment and other risks and uncertainties that are described in the Risk Factors section of Aclaris’ Annual Report on Form 10-K for the year ended December 31, 2024, and other filings Aclaris makes with the U.S. Securities and Exchange Commission from time to time. These documents are available under the “SEC Filings” page of the “Investors” section of Aclaris’ website at www.aclaristx.com. No head-to-head clinical studies have been conducted against JAK and IL-4/13 inhibitors. Differences exist between data and trial designs, and caution should be exercised when comparing data across studies. Any forward-looking statements speak only as of the date of this press release and are based on information available to Aclaris as of the date of this release, and Aclaris assumes no obligation to, and does not intend to, update any forward-looking statements, whether as a result of new information, future events or otherwise.

ATI-2138

Oral Small Molecule Covalent ITK & JAK3 Inhibitor for I&I Disease

- Investigational oral compound which interrupts T cell receptor (TCR) signaling by inhibiting ITK and JAK3 signaling of common γ chain cytokines in lymphocytes (including IL-2 & IL-15)
- Highly potent for both ITK and JAK3 (IC50: 0.2nM ITK; 0.5nM JAK3)
- Unique dual pharmacology; best-in-class potential

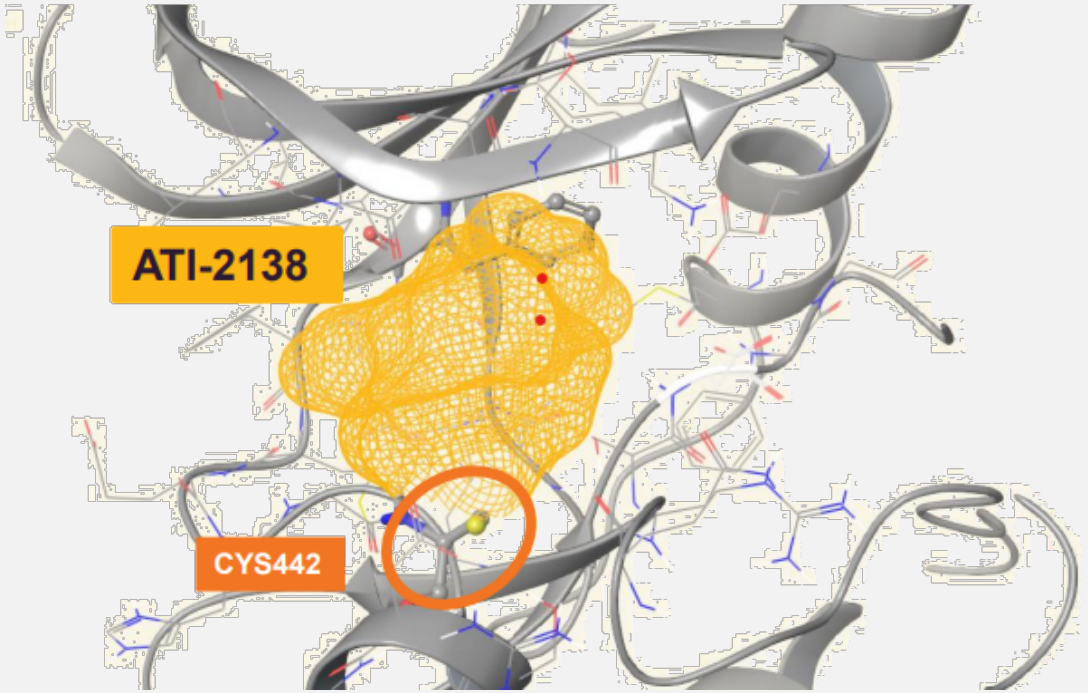


ITK = Interleukin-2-inducible T cell kinase; JAK=Janus Kinase 3

ATI-2138

Covalently Inhibits ITK and JAK3

- Design guided by modeling and proprietary crystal structures
- Designed to interact with the ATP site and covalently modifies CYS442 in ITK and CYS909 in JAK3
- Other oral drugs have successfully targeted this positional cysteine
  - Ritlecitinib (JAK3), Ibrutinib (BTK)
  - Afatinib, Neratinib (EGFR/Her2)



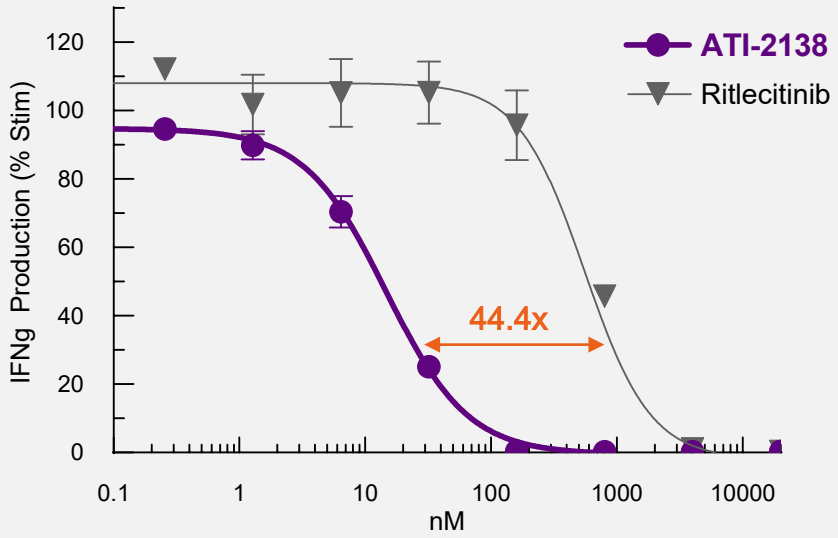
ATI-2138 differs from reversable JAK inhibitors in important ways:

- Unlike approved JAK inhibitors, **ATI-2138 is specific for JAK3; does not inhibit other JAKs**
- Although both are selective for JAK3, **ATI-2138's potency on ITK is ~44X greater than ritlecitinib**

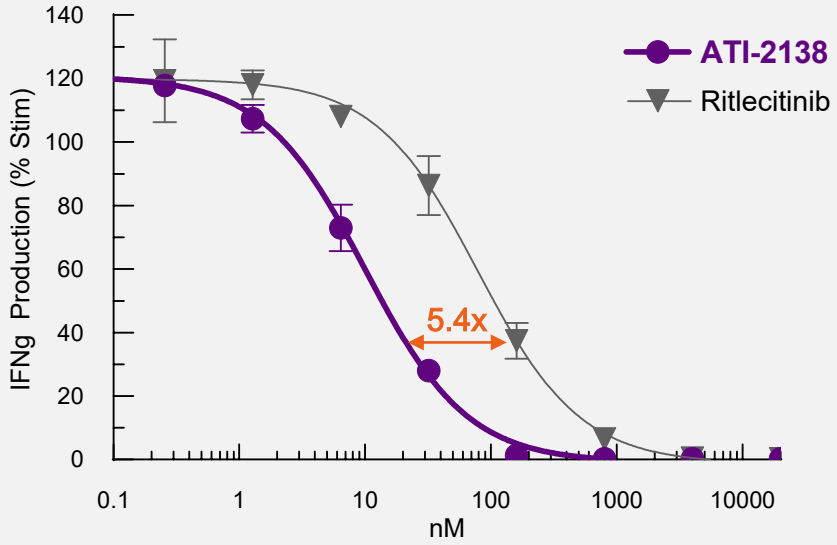
ATI-2138

Unique Dual Pharmacology and Best-in-Class JAK3 Inhibitor Potential

ITK: HWB αCD3 Stimulated IFNγ Release



JAK3: HWB IL2 Stimulated IFNγ Release



- ATI-2138 is 44.4x more potent than ritlecitinib for inhibiting anti-CD3 induced IFNγ production (ITK) and 5.4x more potent for inhibiting JAK3 dependent IL-2 induced IFNγ production in human whole blood
- At the FDA recommended 50 mg QD dose for alopecia areata, ritlecitinib plasma levels may not impact ITK (anti-CD3 /IFNγ) for any appreciable time

ATI-2138 and CPI-818 (Soquelitinib)

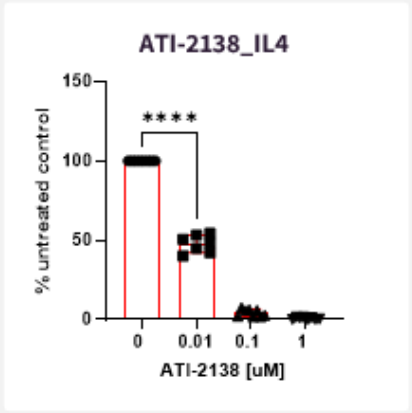
Potency Comparison

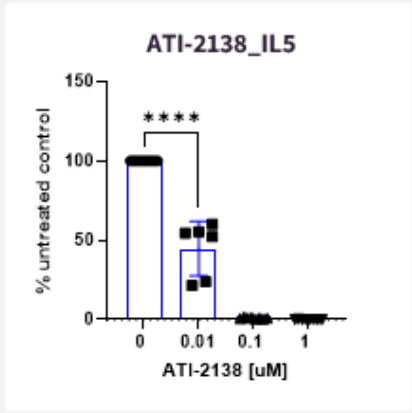
ITK Biochemical Enzyme Potency

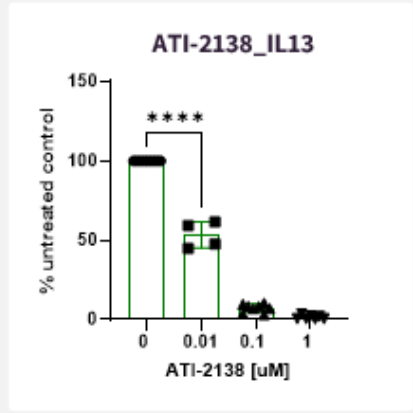
	ITK, IC50, nM	Kinact/Ki (uM-1s-1)
ATI-2138	0.25	0.34
CPI-818	9.5	0.022
Potency Ratio	**38x**	**15x**

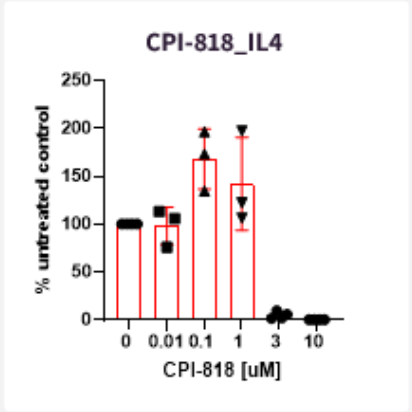
- ATI-2138 is 15-38x more potent than CPI-818 in inhibiting the ITK enzyme activity
- ATI-2138 is significantly more potent than CPI-818 in blocking the Th2 derived cytokines, IL4, IL-5 and IL-13 (~100x)

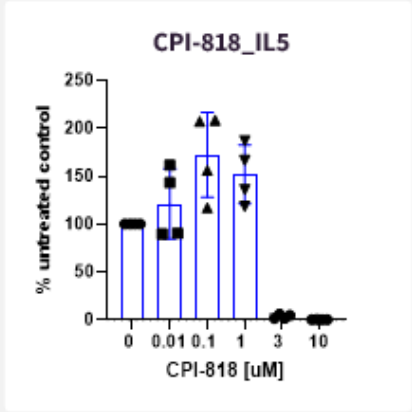
Anti-CD3/CD28-Induced Cytokines from Human Th2 Cells

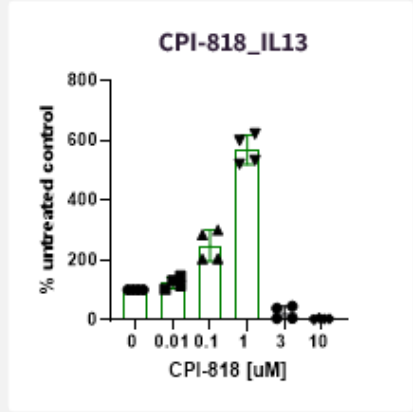






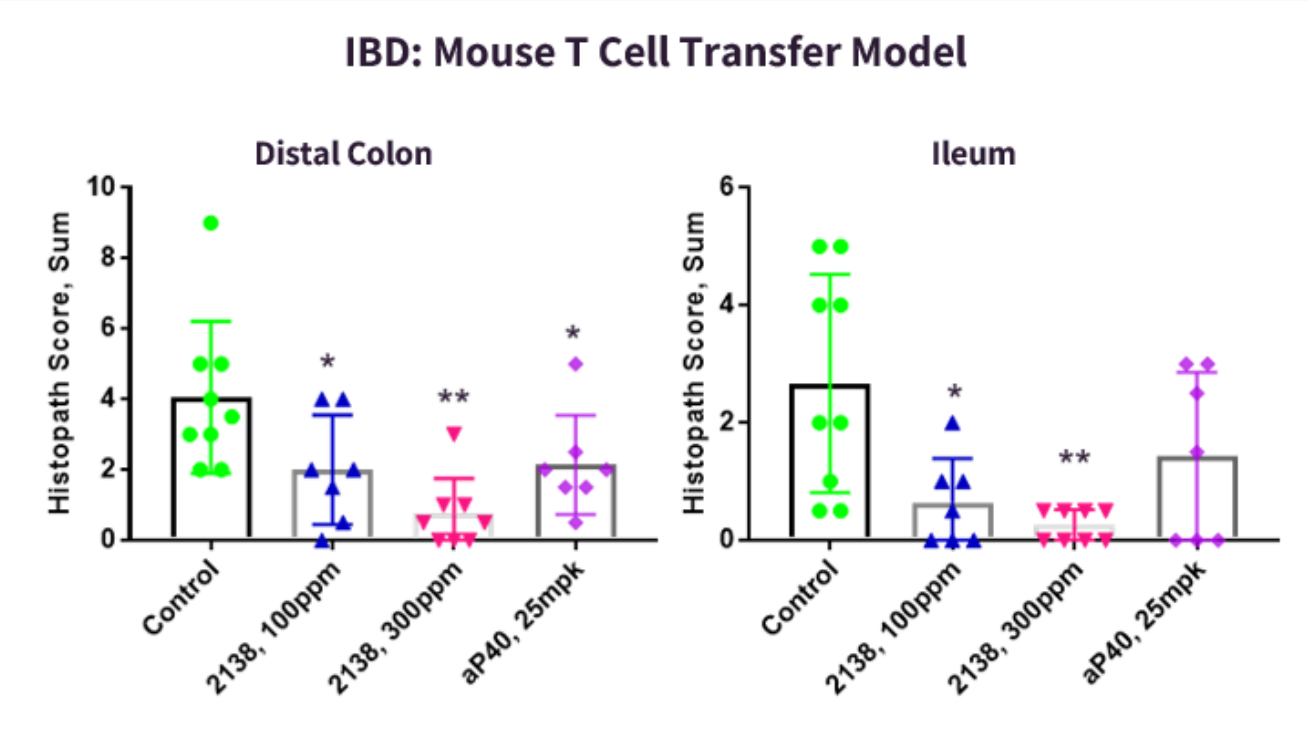


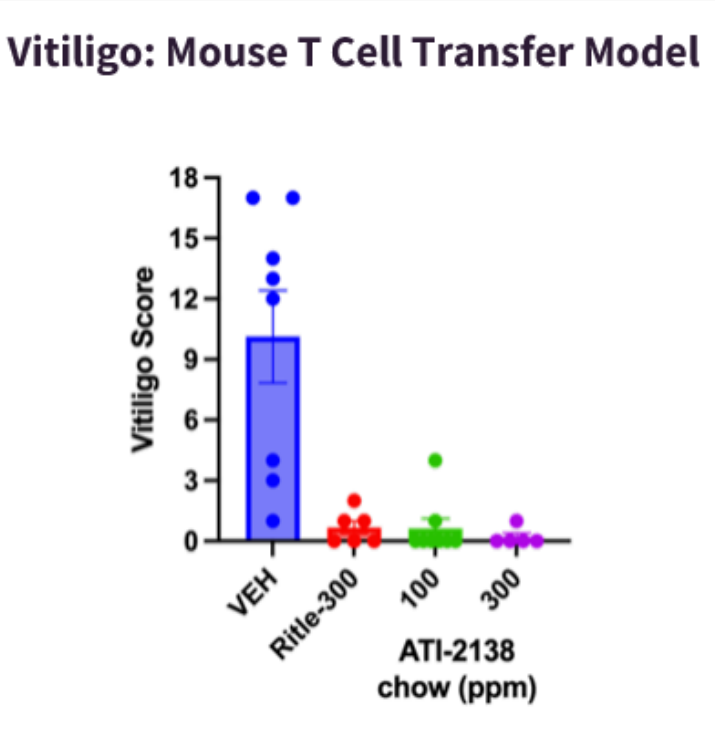




ATI-2138

Anti-inflammatory Activity in Mouse Models of IBD and Vitiligo





ATI-2138 has demonstrated robust anti-inflammatory activity in mouse models of disease

ATI-2138: SAD/MAD Study Summary

Safety

- ATI-2138 was generally well tolerated at all doses tested in the trial.
- No serious adverse events were reported.

Pharmacokinetics (PK)

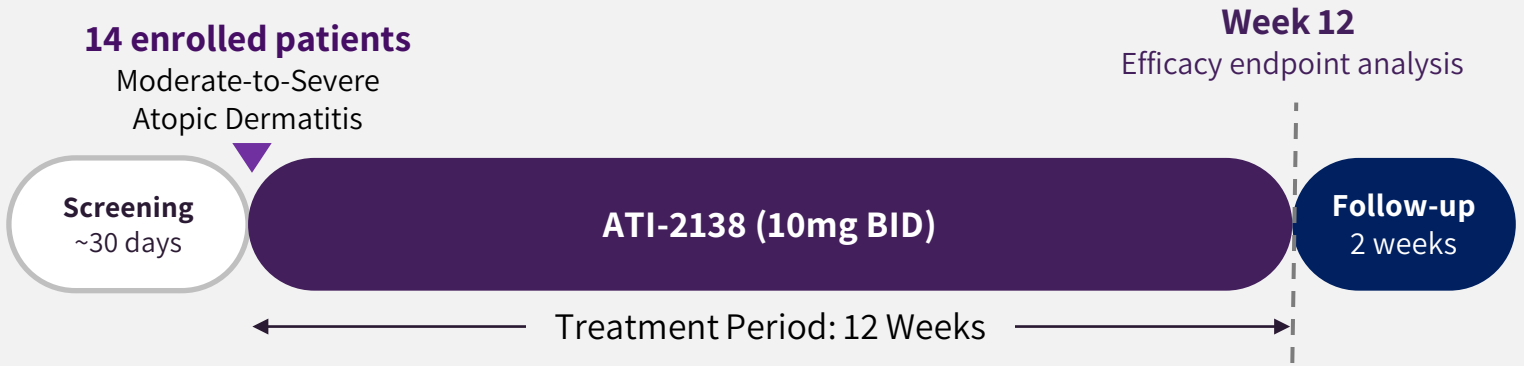
- ATI-2138 was rapidly absorbed.
- Multiple doses ranging from 10 to 80 mg daily over two weeks in healthy volunteers showed linear PK and dose dependent increases in exposure.
- At 10-30 mg daily, ATI-2138 plasma concentration reached the targeted level established using preclinical data.

Pharmacodynamics (PD)

- Dose-dependent inhibition of both ITK and JAK3 exploratory PD biomarkers was observed.
- 50% to 90% inhibition of the ITK and JAK3 functional markers observed.

ATI-2138 Phase 2a Trial Design in Atopic Dermatitis

Single-Arm, Open-Label Trial



Single-arm Phase 2a trial conducted to assess tolerability, ITK contribution (PD), and identify efficacy signals to be explored in future clinical trials

PRIMARY OBJECTIVE

- Safety

SECONDARY/EXPLORATORY OBJECTIVES

- Pharmacokinetics, pharmacodynamics (RNA analysis, proteomics, IHC to analyze specific pathway inhibition)
- Efficacy measurements at week 12

Phase 2a: Patient Demographics

Age	Sex M0,F1	Race	Baseline EASI
56	F	White	16.5
34	M	Mixed-multiple	**33.5**
50	M	Black or African American	17.6
28	F	Black or African American,White	16.8
20	M	Not Reported	19.2
19	F	White	**28.1**
22	F	Asian	**23.7**
56	M	Black or African American	16.8
44	F	Black or African American	**31.1**
28	M	Black or African American	**21.3**
39	F	Not Reported	19.6
30	M	White	**31.5**
21	F	Asian	17.1
55	M	Black or African American	**24.6**
Average 36	**50/50 M/F**	**7 Black/African American**	**22.7 (7 severe)**

Phase 2a Results: Primary Endpoint (Safety)

Primary Endpoint Analysis Confirms Strong Tolerability Profile of ATI -2138

- ATI-2138 was very well tolerated in the 12 patients in the safety population
  - No severe adverse events (SAEs) or treatment-emergent adverse events (TEAEs)
  - No discontinuations due to adverse events
  - Most adverse events were mild and resolved spontaneously during treatment
  - Three patients experienced a combined total of four study drug-related adverse events (TRAE)
    - All but one (single case of moderate myalgia; starting on day 24 with no elevation in CPK) were mild, transient, and resolved during treatment
  - No safety signal observed in chemistry, hematology (e.g., leukocytes, lymphocytes, neutrophils), lipids, electrocardiogram (ECG), ECG with corrected QT (ECG-QTcF), or vital signs

Phase 2a Results: Secondary Endpoints (EASI)

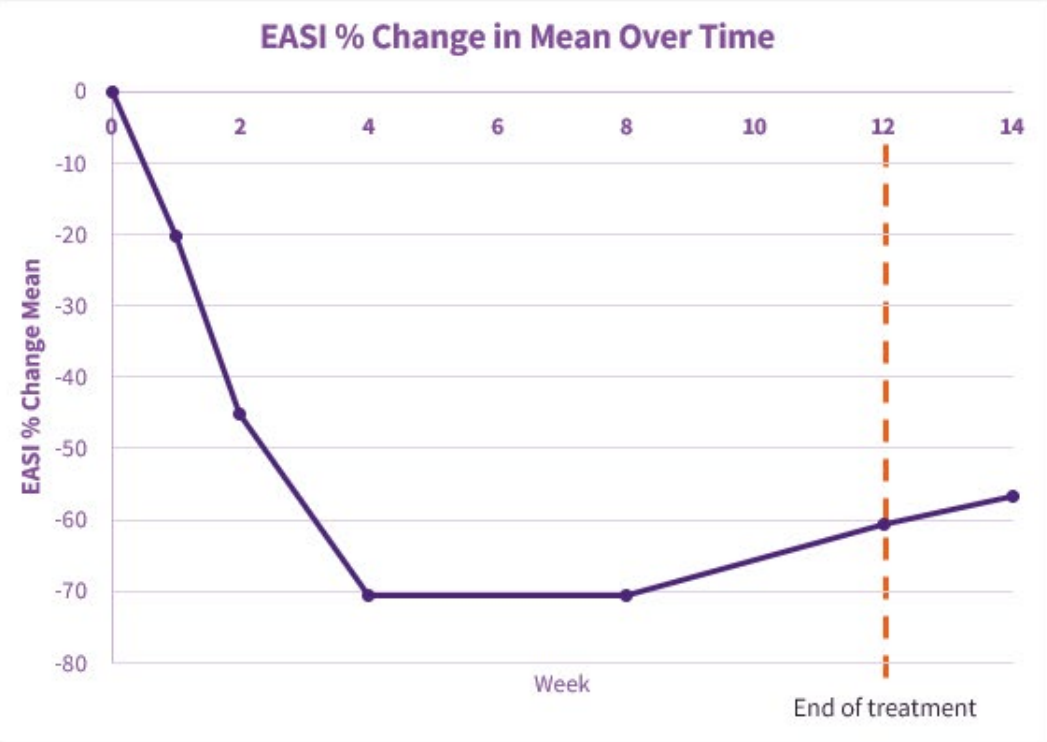
% Reduction from Baseline in Eczema Area and Severity Score (EASI) Over Time, Per Protocol (N=10)

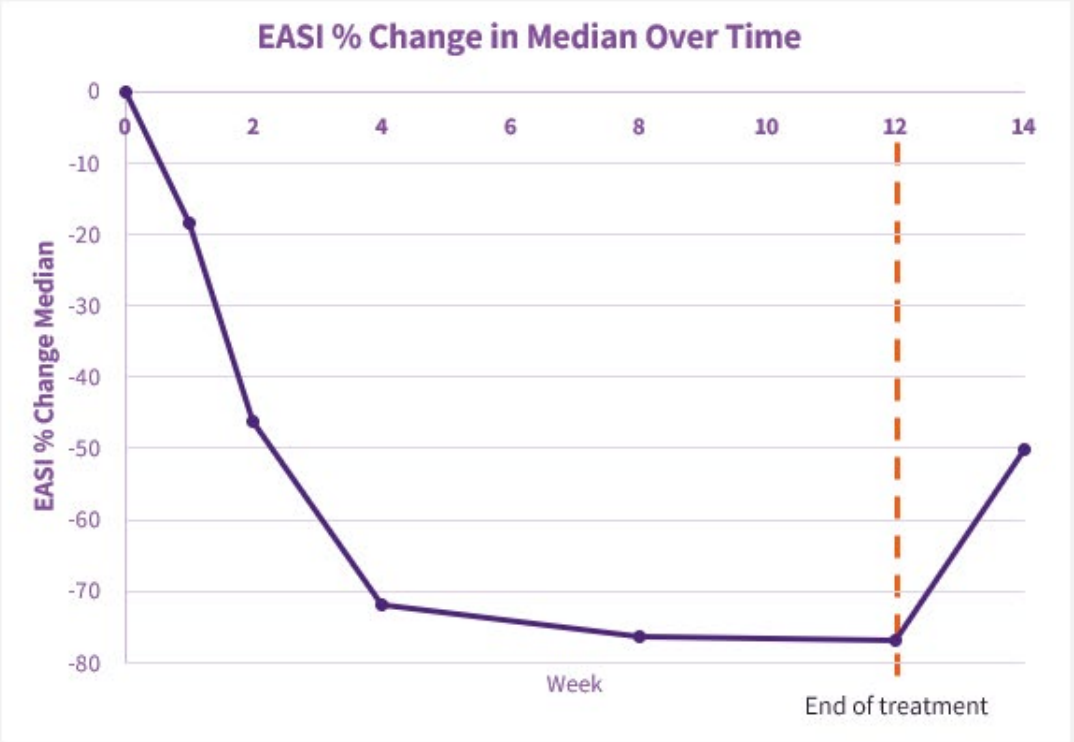
Mean improvement in EASI score
12 weeks

61%

Median improvement in EASI score
12 weeks

77%

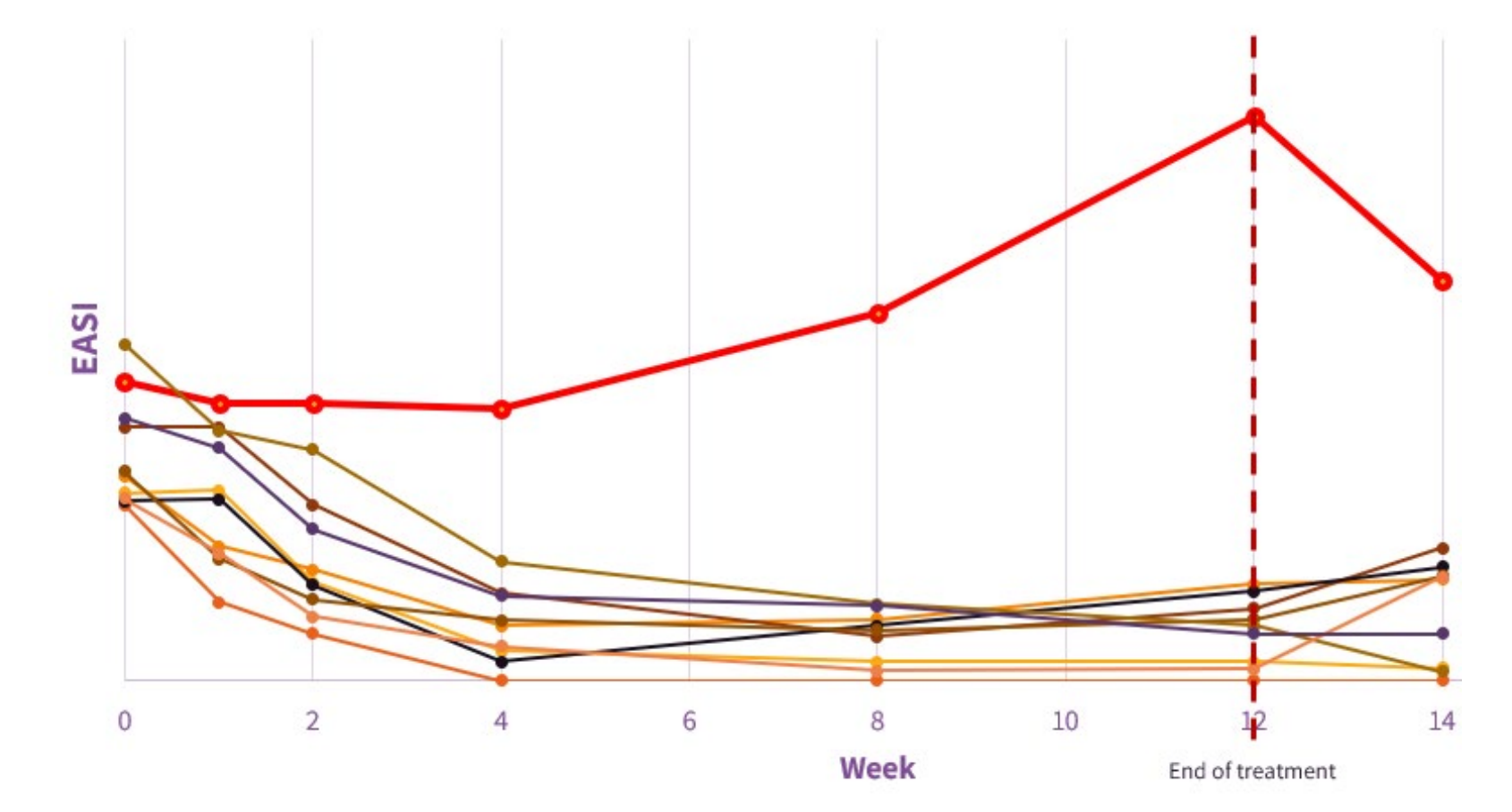




EASI = Eczema Area and Severity Score: Measures the extent and severity of lesional skin associated with atopic dermatitis across different body regions

Phase 2a Results: Secondary Endpoints (EASI)

Absolute Mean Reduction Over Time by Patient, Per Protocol



Outlier (in red)

- Statistical molecular outlier by >4 SD
- Systemic symptoms inconsistent with AD alone including significant non-lesional inflammation
- Not fully compliant with study drug administration

EASI = Eczema Area and Severity Score: Measures the extent and severity of lesional skin associated with atopic dermatitis across different body regions

Phase 2a Results: EASI Score Excluding Outlier

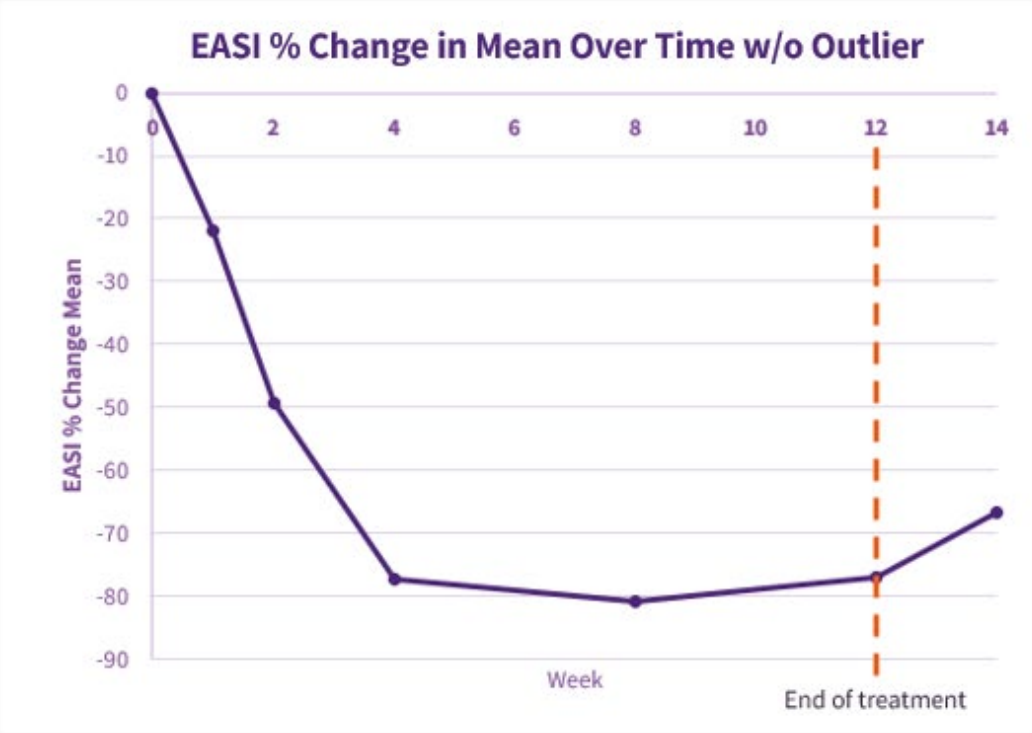
% Reduction from Baseline in Eczema Area and Severity Score (EASI) Over Time

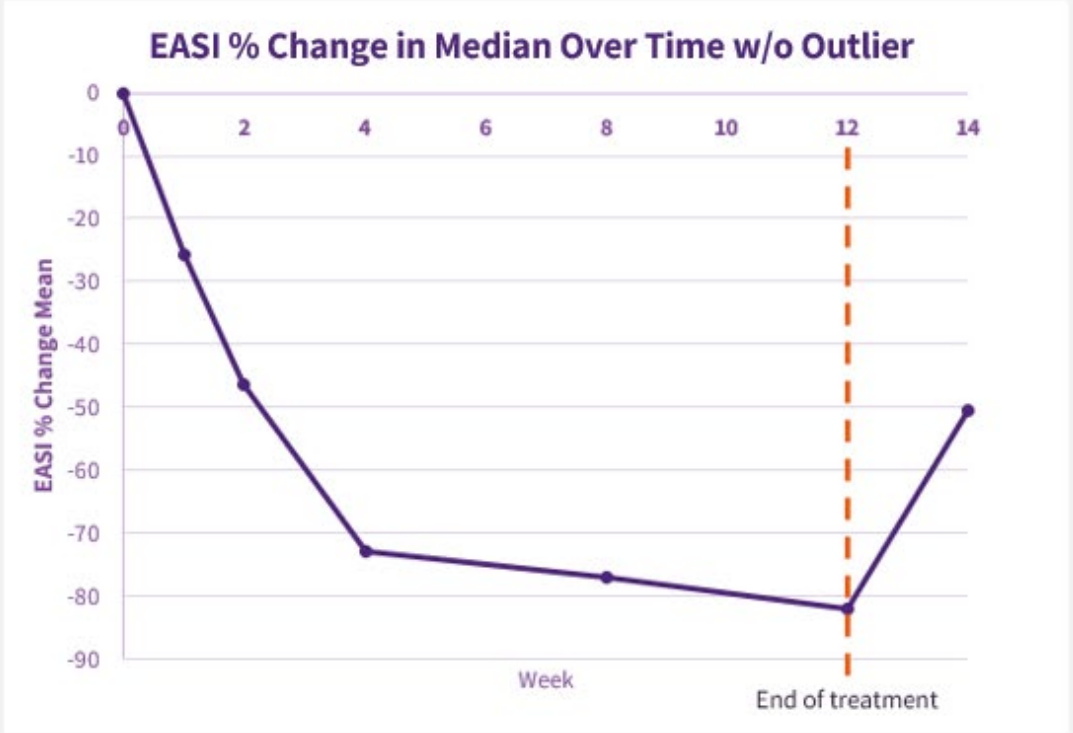
Mean improvement in EASI score
12 weeks

77%

Median improvement in EASI score
12 weeks

82%

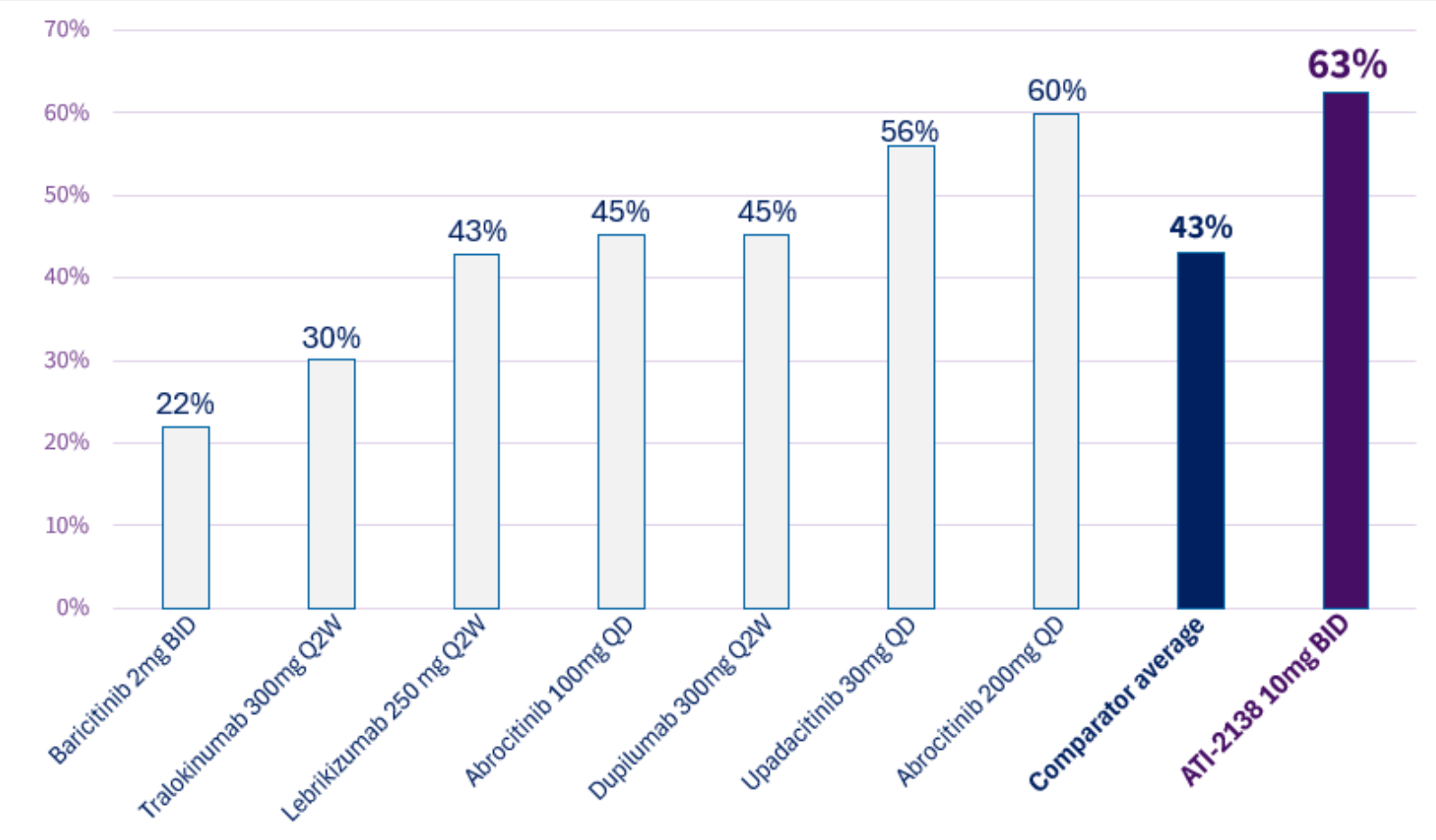




EASI = Eczema Area and Severity Score: Measures the extent and severity of lesional skin associated with atopic dermatitis across different body regions

Phase 2a Results: Secondary Endpoints (PP -NRS)

% of Patients with ⩾4 Point Improvement in Worst Itch over Prior 24 Hours



- At week 12, **63%** of patients receiving a low dose of ATI-2138 experienced a ≥4-point improvement worst itch in the past 24 hours
- A ≥4-point improvement in PP-NRS score is considered a clinically meaningful result
- Though a small open-label study, results are comparable to that seen with approved JAK and IL-4 and -13 inhibitor products

PP-NRS = Peak Pruritus Numerical Rating Scale: Assesses the severity of itch at the worst moment during the previous 24 hours on a scale of 0 (“no itch”) to 10 (“worst itch imaginable”).

Note: Each other compound efficacy is the average percent improvement from multiple studies, at week 12 or 16 data from Phase 2 and Phase 3 published sources; head-to-head clinical studies have not been conducted. Differences exist between trial designs and subject characteristics, and caution should be exercised when comparing data across studies. Data collected on 8 of 10 PP patients.

Phase 2a Results: Secondary Endpoint

Pharmacodynamic Assessments

Goal: Confirm that ATI-2138 is mechanistically unique, provide support for Phase 2a clinical results, and validate ITK as a target

Assess Target, Pathway & Disease biomarkers to support mechanism of action

In-House PD Efforts

ITK Assay
- αCD3/αCD28 *ex vivo* stim mRNA (IL2 and IFNγ) production

ITK Target Occupancy

JAK3 Assay
- IL15 *ex vivo* stim IFNγ protein production

Immunophenotyping

PD Efforts at EG Mt Sinai Lab

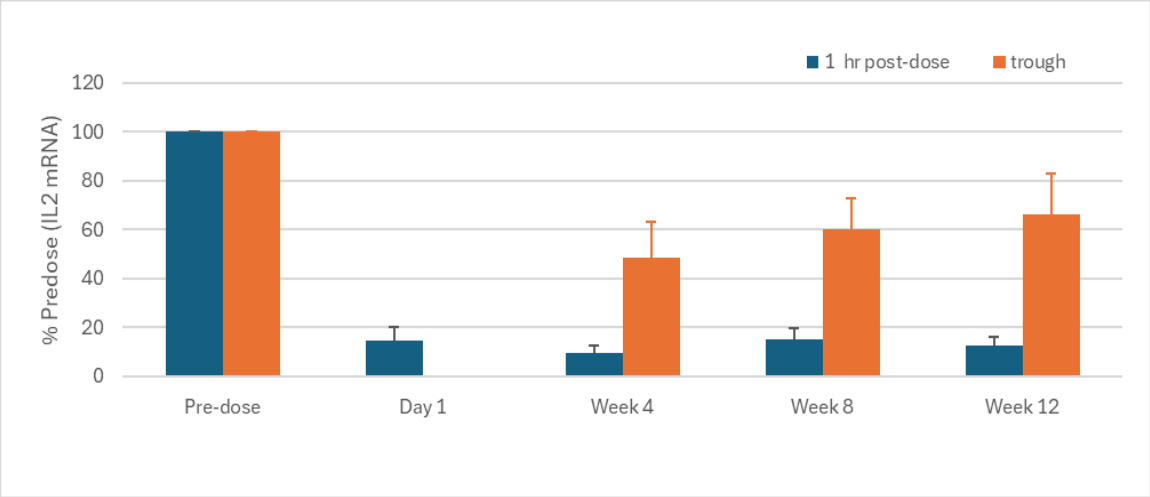
Punch Biopsy Analysis
- Immunohistochemistry
- RNAseq Analysis (>16,000 genes)

Tape Strip Analysis
- RNAseq Analysis (>16,000 genes)
- O-link Proteomics (300+ analytes)

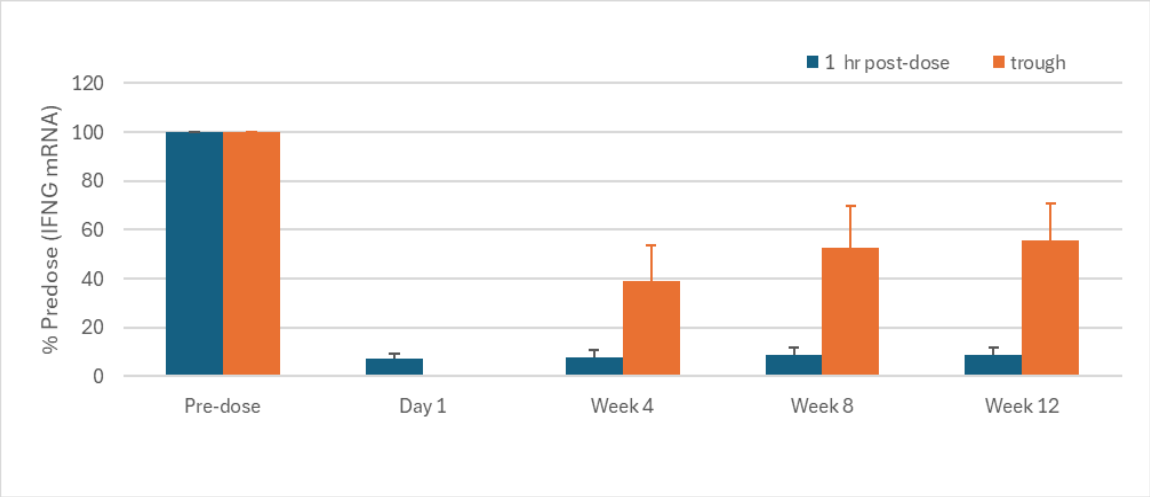
Endogenous Biomarkers in Plasma
- O-Link Proteomics (300+ analytes)

Phase 2a Results: Ex vivo Stimulated ITK HWB Assays

ITK-TCR Assay – IL2 mRNA



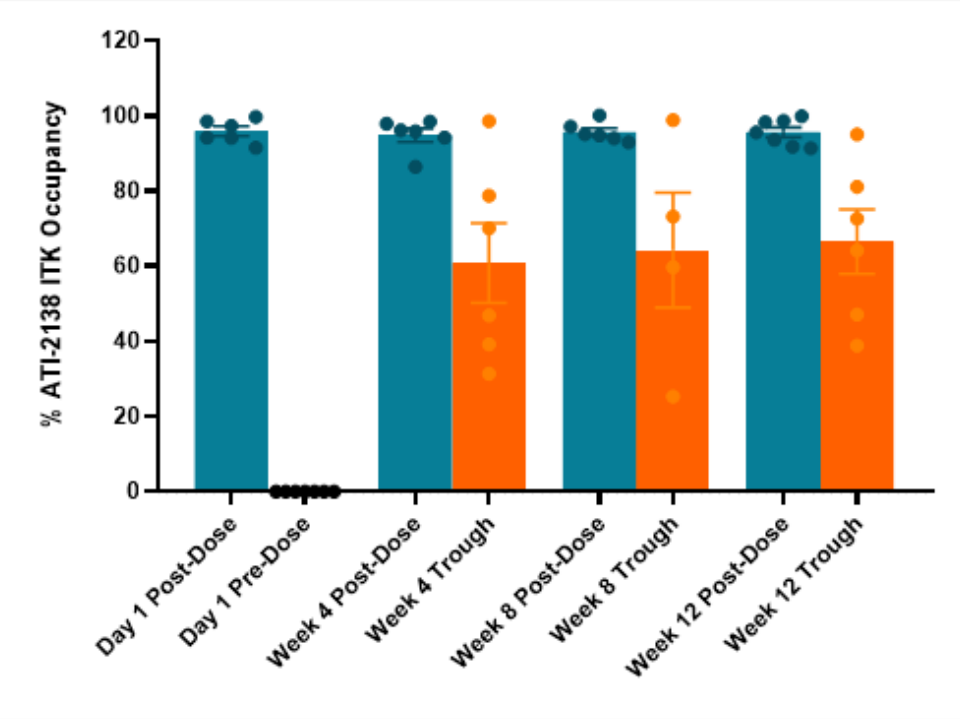
ITK-TCR Assay – IFNγ mRNA



- ~90% inhibition of both IL2 and IFNγ mRNA observed 1 hr post dose (~peak) across the 12 weeks of dosing
- 40-60% inhibition of both IL2 and IFNγ mRNA observed at trough across the 12 weeks of dosing

Data collected on 8 of the 10 per protocol (PP) patients

Phase 2a Results: ITK Target Occupancy with ATI -2138

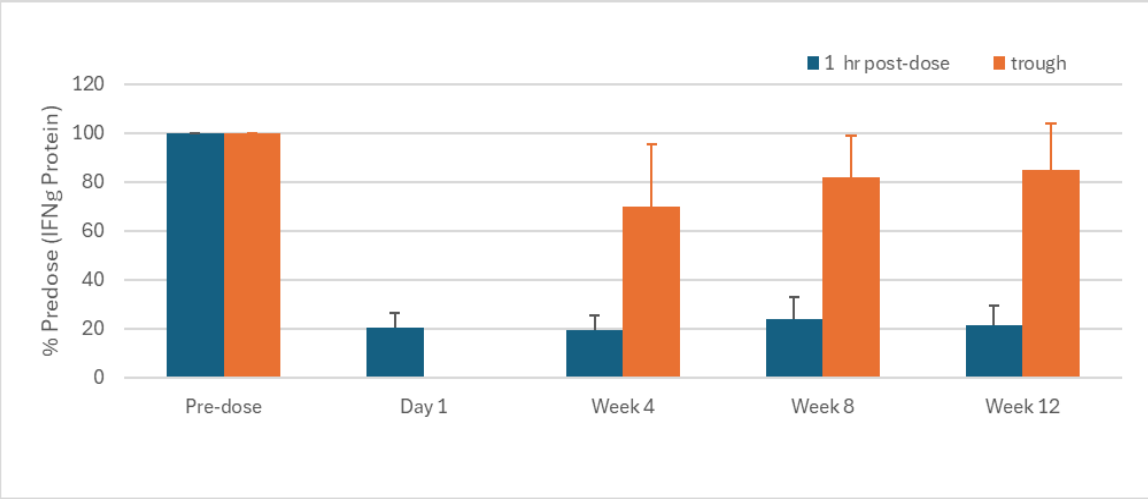


- Utilized biotinylated ITK probe with MSD readout using patient PBMCs
- Data collected on 7 of the 10 per protocol patients

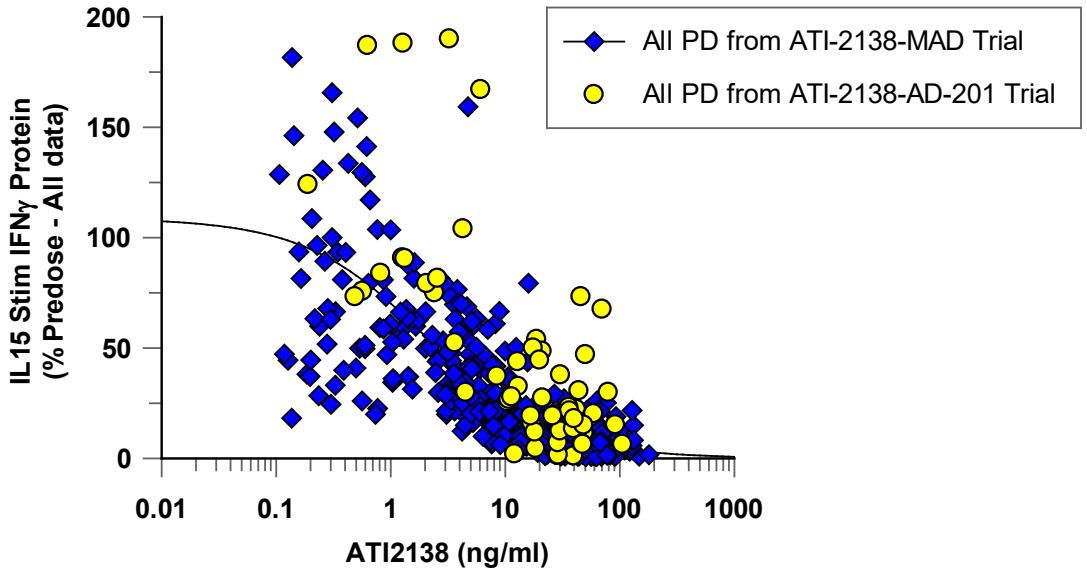
- Near complete ATI-2138 ITK target occupancy observed one hour post-dose (~peak) across the 12 weeks of dosing
- Approximately 60-70% ATI-2138 occupancy observed at trough across the 12 weeks of dosing

Phase 2a Results: *Ex vivo* Stimulated JAK3 HWB Assays

ATI-2138-AD-201 JAK3 PD Data



Exposure Response Overlay of Phase 2a (ATI-2138-AD-201) and MAD Studies

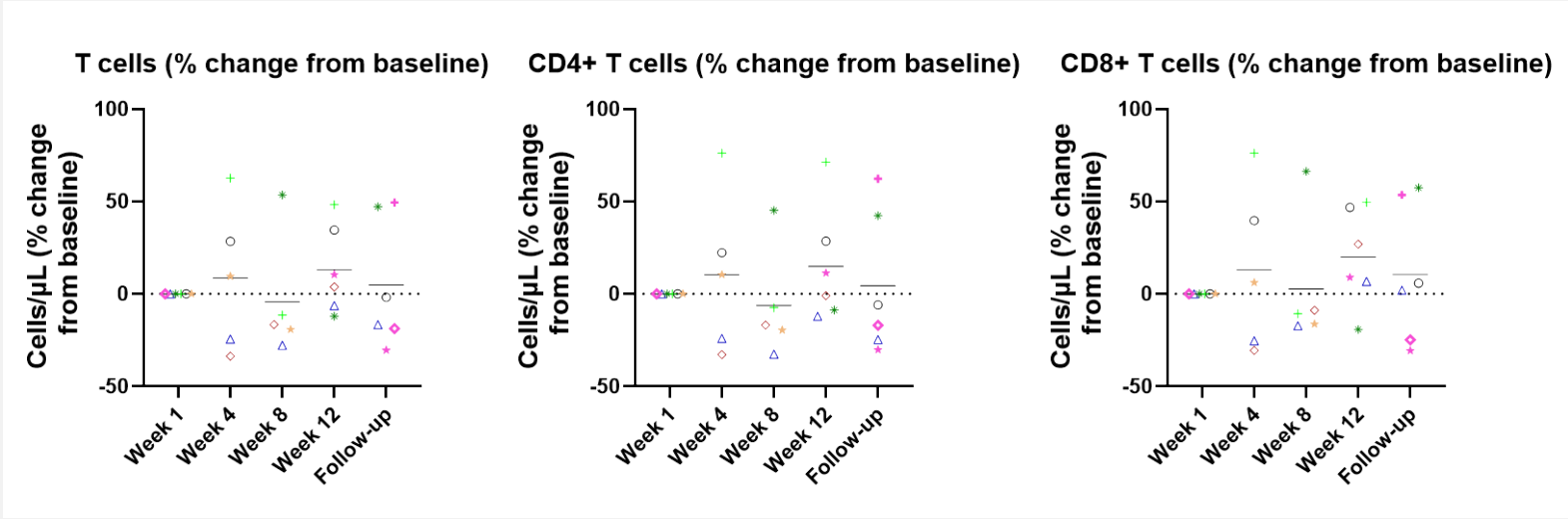


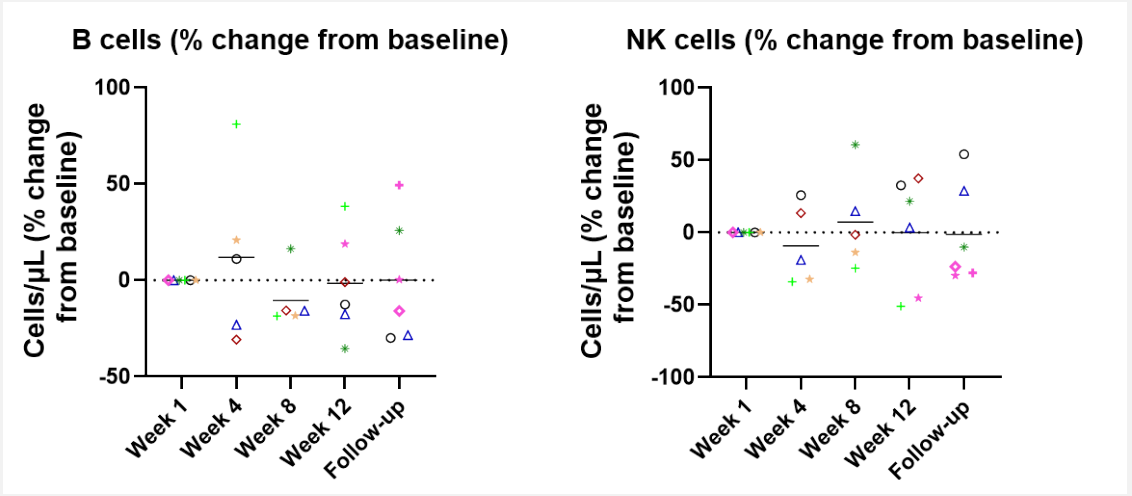
- ~80% inhibition of JAK3-induced IFNγ observed 1 hr post dose (~peak)
- ~20% inhibition of JAK3-induced IFNγ observed at trough across across the 12 weeks of dosing
- MAD study was predictive of PD response based on exposure response overlay

Data collected on 8 of the 10 per protocol (PP) patients

Phase 2a Results: Immunophenotyping Data

- No significant perturbations in T cells/T cell subsets, B cells or NK cells were observed
- No evidence of global immune suppression





Data collected on 6 of the 10 per protocol (PP) patients

Phase 2a Results: Plasma O-Link Analysis

Immune Subset Week 12 vs Baseline

- Evaluations at baseline, week 4, week 8 and week 12

Key Modulated Markers*:

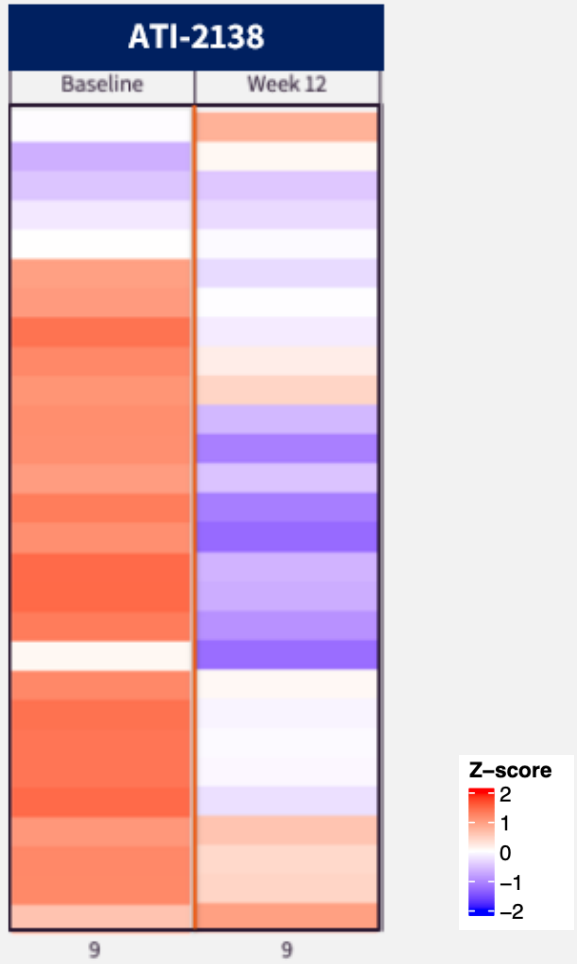
Th1:
IL8, IL2RA, IL2

Th2:
CCL13, CCL17, CCL24, IL4, IL33, IL7

Th17:
CXCL1, PI3, TGB1

T cell activation:
XCL1, IL1RL2

*significance observed at any timepoint



Strong downregulation of key ITK-dependent markers (Th2, TH17, and T cell activation pathways) observed

PP patient responders analyzed (9 patients)

Phase 2a Results: Skin Tape Strip O-Link Analysis

Immune Protein Subset

- Evaluations at baseline, week 4, week 8 and week 12
- Similar directionality observed with RNAseq data

Key Modulated Pathway Markers*:

Th1
CCL3, CXCL9, CXCL11, TNF, IL2RA

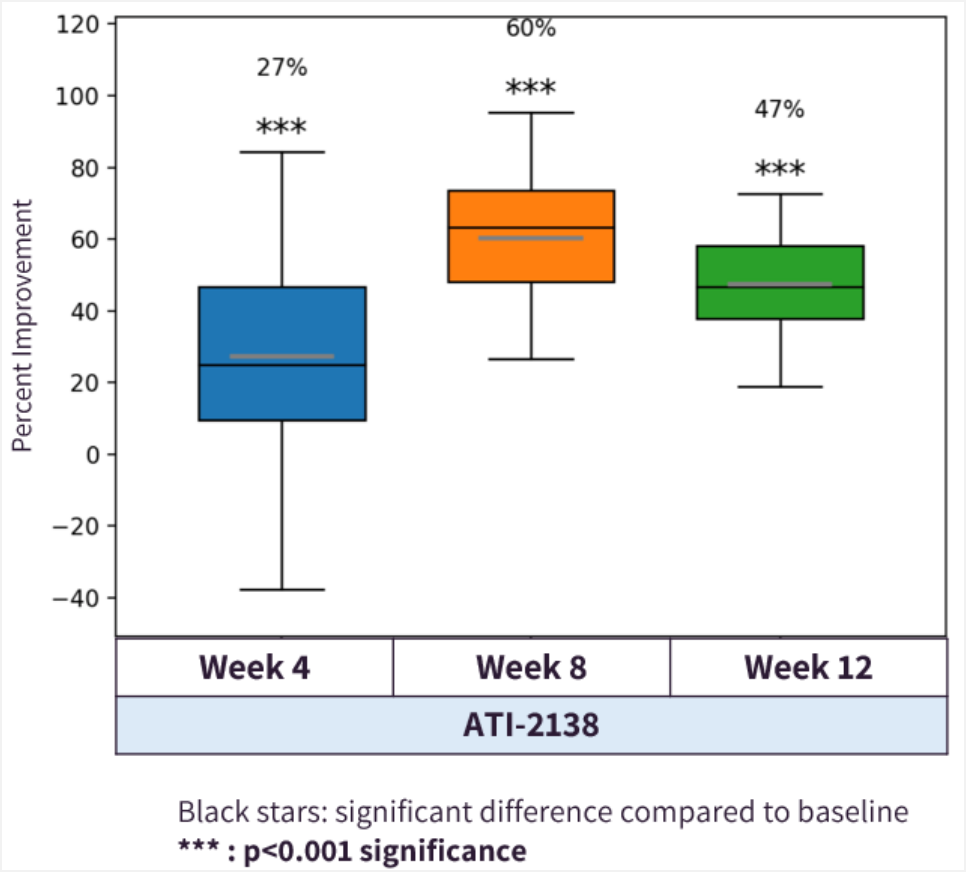
Th2
IL13, TSLP

Th17
IL17A, CXCL1, S100A12, TGFB1, IL6R

T cell activation /Immune Signaling
CCL19, IL17C, CCL8, CCL16, , CCL15, CCL23, TNFSF10

Fibrosis
TNFRSF9

*significant in any comparison



Black stars: significant difference compared to baseline
*** : p<0.001 significance

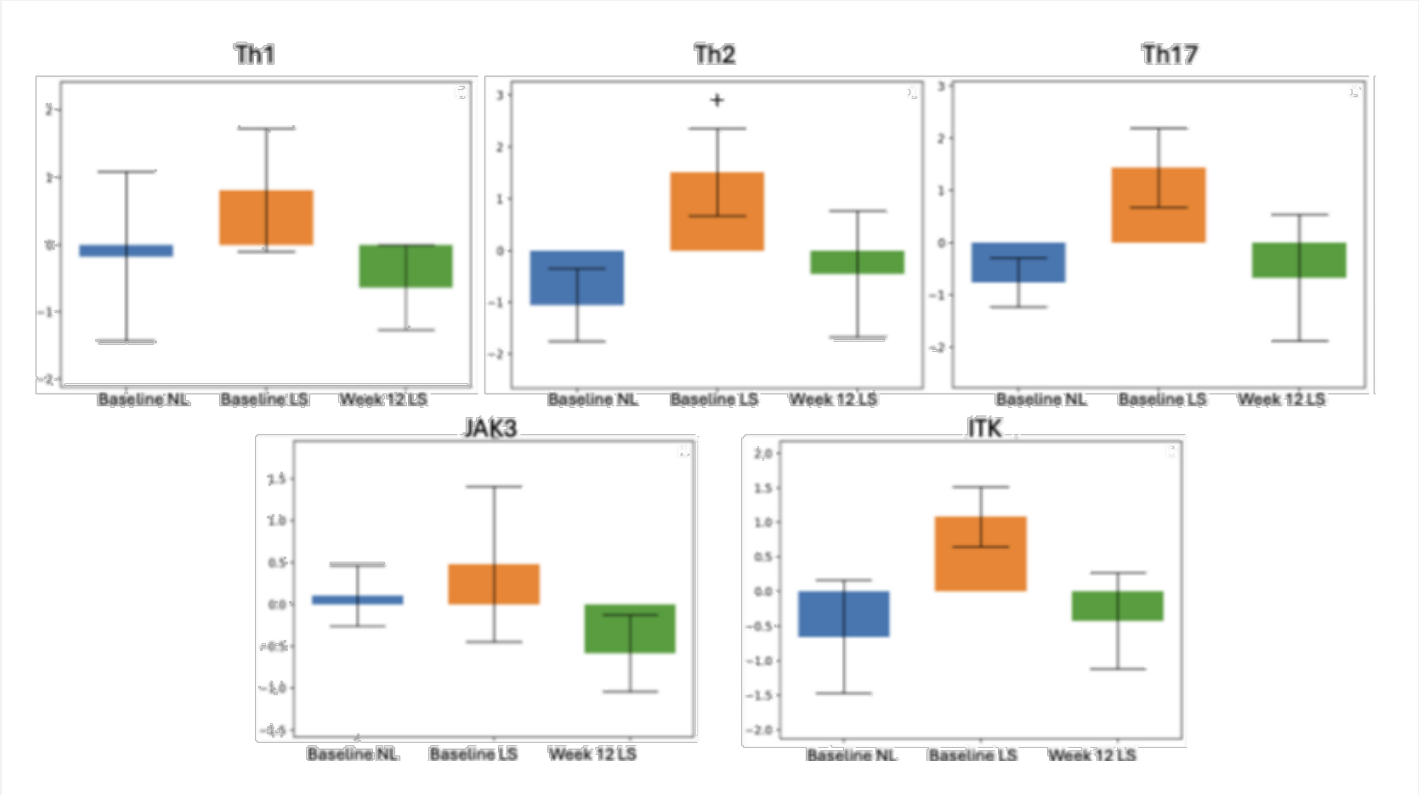
Significant reduction observed in multiple inflammatory pathways associated with ITK relative to baseline

PP patient responders analyzed (9 patients)

Phase 2a Results: Skin Biopsy RNAseq Immune Pathway Modulation

Week 12 vs Baseline

- Downward directional trends observed with key pathways
- Biopsy pathway modulation consistent with tape strip data



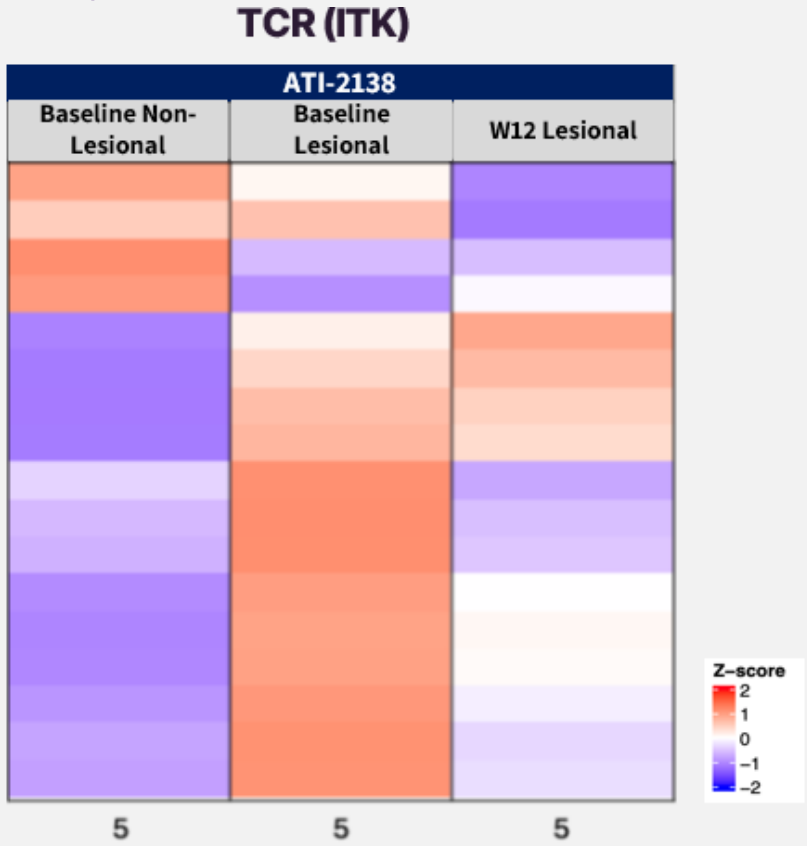
Downward trends observed in mRNA markers associated with key immunologic pathways at week 12; downregulation of ITK and JAK3 pathway markers

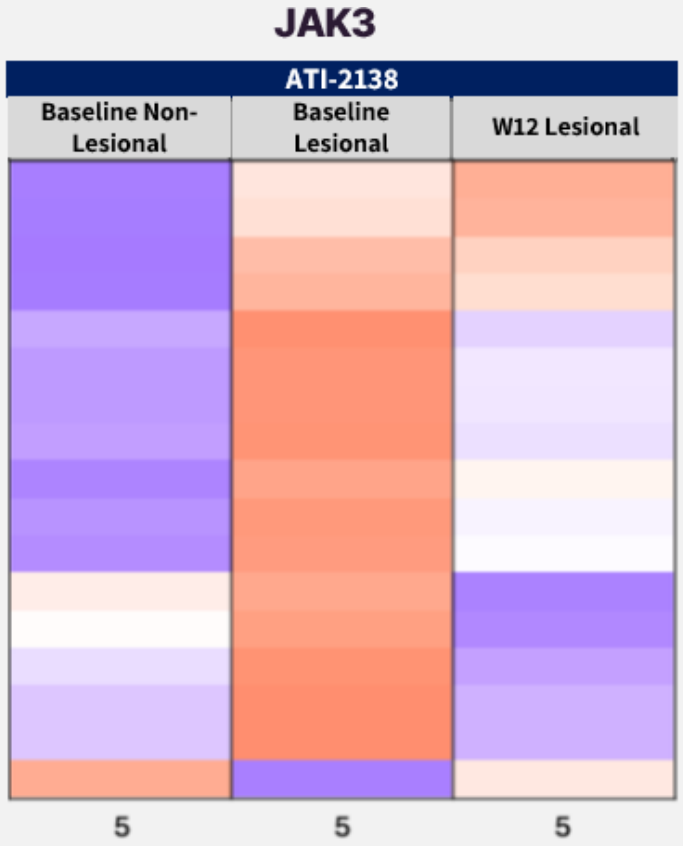
Biopsies from 5 PP patients

Phase 2a Results: Skin Biopsy RNAseq Analysis

TCR (ITK) and JAK3 Pathways

- Heat map describes impact on both (TCR) ITK and JAK3 pathways at week 12
- Similar to tape strip RNAseq data





Reduction observed in mRNA markers consistent with the expected ITK and JAK3 dual pharmacology

Biopsies from 5 PP patients

Phase 2a Conclusions: Secondary Endpoint (PD Assessments)

Results Support Conviction in Therapeutic Potential of ITK Inhibition

- PD analyses clearly demonstrate modulation of the ITK and JAK3 pathways as evidenced by inhibition of ex vivo pathway specific stimulation of patient whole blood
- Near complete and sustained inhibition and occupancy of ITK (measure of blockade of ITK enzyme) and a high level of inhibition of JAK3 observed
- Proteome and transcriptome lesional skin tape strip analyses measured at trough levels to better represent steady state showed significant ATI-2138-dependent reduction of multiple inflammatory pathways associated with ITK
  - Data consistent across analyses with both skin biopsies and tape strips and patient plasma
- Strong downregulation observed at week 8 and week 12 of key ITK-dependent markers including:
  - Th1 (e.g., CXCL11, CXCL9, IL2RA, TNF)
  - Th2 (e.g., CCL17, CCL24, IL13, TSLP)
  - Th17 (e.g., CXCL1, IL17A, IL6R)
  - TCR (ITK) pathway (e.g., ITK, IL-13, CD3, ZAP70, LCK, PLCg1)
- Fibrosis-related markers (e.g. MMP9, TNFRSF9) were also shown to be strongly downregulated by ATI-2138

Next Steps with ITK Franchise

- Positive results from single-arm Phase 2a open-label trial of ATI-2138 in AD validate ITK franchise; provide conviction on two programs:
  - ATI-2138
    - Aclaris intends to further develop ATI-2138 in alopecia areata
    - Also exploring other indications relevant to the mechanism of action
  - ITK selective program
    - Preclinical work ongoing for next-generation ITK inhibitors, which Aclaris expects to provide the basis for new INDs starting in 2026

Executing on Rich Clinical Catalyst Calendar

2025

- ✓ **ATI-052**
  IND Clearance by FDA
- ✓ **Bosakitug (ATI-045)**
  Initiation of Phase 2 Trial in Atopic Dermatitis
- ✓ **ATI-052**
  Initiation of Phase 1a/1b Program
- ✓ **ATI-2138**
  Atopic Dermatitis Phase 2a Top Line Data
  July 2025
- ☐ **ATI-052**
  Completion of dosing in Phase 1a SAD/MAD HV Portion
  Year-end 2025

2026

- ☐ **ATI-052**
  Phase 1a/1b Top Line Data
  Phase 1a SAD/MAD: Early 2026
  Phase 1b POC: 2H 2026
- ☐ **Bosakitug (ATI-045)**
  Atopic Dermatitis Phase 2 Top Line Data
  2H 2026
- ☐ **ATI-2138**
  Initiation of Phase 2 in Second Indication
  2026
- ☐ **ITK Selective Program**
  IND Submission and Start of Phase 1 Program
  2026

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All timelines are expectations, are based on current beliefs and assumptions, and are subject to change based on a variety of factors.

ATI-2138 Phase 2a Top-Line Results

July 29, 2025