Immunologic and Clinical Activity of Soquelitinib, a Selective ITK Inhibitor, in Atopic Dermatitis

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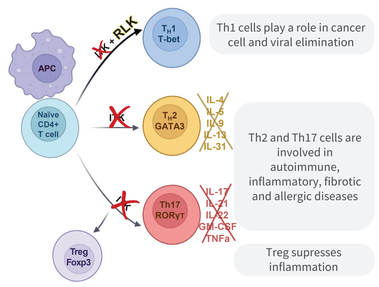
INTRODUCTION

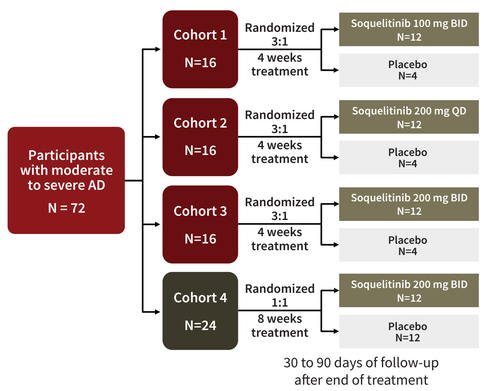
SOQUELITINIB BLOCKS TH2 AND TH17 AND INDUCES TH1 SKEWING

- ITK (interleukin-2-inducible T cell kinase) is expressed in T, NK and ILC-2 cells
- Soquelitinib is an oral, selective covalent inhibitor of ITK
  - Nanomolar binding to ITK while sparing RLK
  - Inhibits Th2 and Th17 differentiation and inhibits the production of IL-4, IL-5, IL-13, IL-17, IL-31, etc.
- Blocking ITK results in a switch from Th17 to Tregs [1,2]
  - Soquelitinib increases Tregs
- Active in animal models of atopic dermatitis, asthma, psoriasis, GVHD, and systemic sclerosis
- A phase 2 trial in AD and a phase 3 trial in T cell lymphoma are ongoing

ITK blockade leads to reduction in Th2, Th17 "Th1 skewing"



PHASE 1 STUDY DESIGN



Study Design

- Endpoints
  - Primary: safety
  - Secondary: % change in EASI, EASI75, EASI90, IGA 0 or 1
- Design
  - Blinded with placebo
  - No comcomitant topical steroids
  - 28 day treatment for cohorts 1-3 (3:1 randomization)
  - 56 day treatment for cohort 4 (1:1 randomizatoin)
  - Off treatment follow-up
- Prior systemic therapy allowed
- 14 sites all U.S.

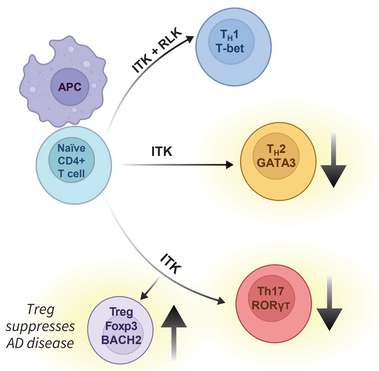
PATIENT BASELINE CHARACTERISTICS

	4-week			8-week	
	Cohorts 1 & 2*	Cohort 3	Cohorts 1–3	Cohort 4	
	SQL 100 mg BID or 200 mg QD (n=24)	SQL 200 mg BID (n=12)	Placebo (n=12)	SQL 200 mg BID (n=12)	Placebo (n=12)
Age, mean (range), yrs	44.4 (21–66)	46.4 (25–71)	38.8 (20–62)	40.5 (18–69)	42.3 (21–67)
Gender, male n (%)	14 (58.3)	4 (33.3)	7 (58.3)	6 (50)	7 (58.3)
Race/ethnicity, n (%)					
Asian	2 (8.3)	0 (0)	1 (8.3)	3 (25)	2 (16.7)
Black or African American	13 (54.2)	5 (41.7)	5 (41.7)	5 (41.7)	5 (41.7)
White	4 (16.7)	4 (33.3)	2 (16.7)	3 (25)	2 (16.7)
Hispanic or Latino	5 (20.8)	2 (16.7)	4 (33.3)	1 (8.3)	3 (25)
Not Reported	0 (0)	1 (8.3)	0 (0)	0 (0)	0 (0)
Baseline EASI, mean (range)	19.9 (14.7–46.6)	27.2 (18.0–41.5)	21.2 (14.4–46.6)	25.7 (16.6–64.7)	21.9 (16.4–32.9)
Baseline IGA 4, n (%)	2 (8.3)	1 (8.3)	2 (16.7)	2 (16.7)	1 (8.3)
Prior AD therapies, n (%)					
Topical corticosteroids	24 (100)	12 (100)	12 (100)	12 (100)	12 (100)
Systemic therapies	6 (25)	4 (33.3)	3 (25)	5 (41.7)	7 (58.3)
Dupilumab	2 (8.3)	2 (16.7)	2 (16.7)	2 (16.7)	3 (25)
JAK inhibitor	0 (0)	1 (8.3)	0 (0)	1 (8.3)	2 (16.7)
Other	4 (16.7)	4 (33.3)	2 (16.7)	5 (41.7)	6 (50)

*Cohorts 1 and 2 combined because they have similar characteristics and outcomes.

METHODS

MECHANISM-DRIVEN BIOMARKER STRATEGY



Based on MOA, we evaluated effects on **Th1, Th2, Th17, and Tregs**:

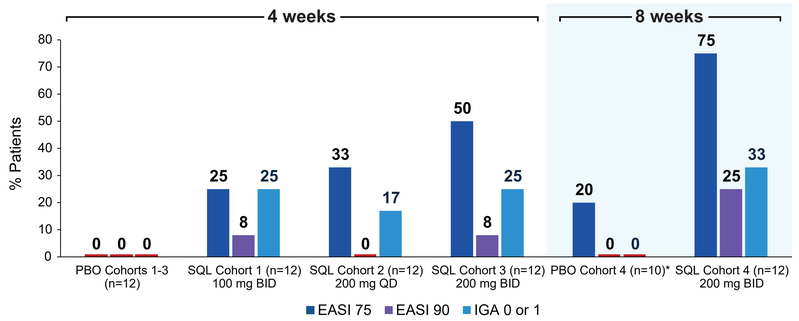
- Serum cytokines (MSD)
- Blood flow cytometry (Foxp3)
- PBMC single cell RNAseq

REFERENCES

1. Sci Signal 17:1, 2024. DOI: 10.1126/scisignal.adh2381
2. PLOS ONE 14 (4): 1, 2019. DOI: 10.1371/journal.pone.0215963
3. Cells 13(11):891, 2024. DOI: 10.3390/cells13110891
4. Nat Commun 11(1):252, 2020. DOI: 10.1038/s41467-019-14112-2

RESULTS

EASI75, EASI90 AND IGA 0/1 RATES IN ALL COHORTS



**2 placebo (PBO) patients missed the Day 56 visit and are not included. They did return for later visits and did not achieve EASI75 at any time point. If included in the placebo analysis the 8-week EASI75 is 17%.*

Figure 1. Efficacy results for Cohorts 1 through 4 evaluating EASI75, EASI90 and IGA 0/1. Cohort 3 and 4 results appear similar, with Cohort 4 exhibiting higher frequency of EASI75, EASI90 and IGA 0/1. EASI75, EASI90 and IGA 0/1 for Cohort 4 was achieved in 75%, 25% and 33% of patients receiving soquelitinib, respectively, compared to 20%, 0% and 0%, respectively, for the placebo group.

DURABLE RESPONSES AFTER DRUG WITHDRAWAL

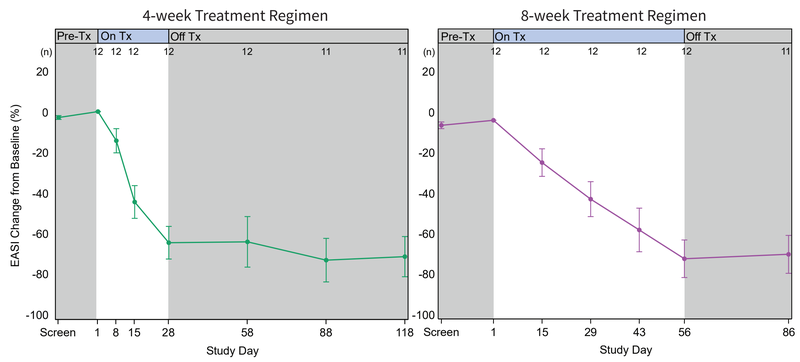
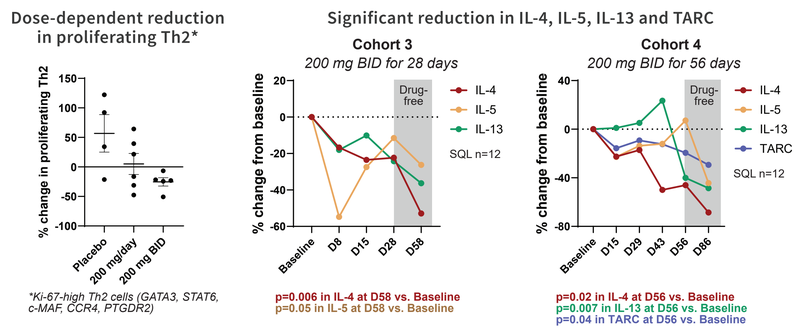


Figure 2. Mean percent reduction in EASI for Cohort 3 (left) and Cohort 4 (right). No disease rebound was observed and no rescue medications were required.

EFFECTS ON TH2 RELATED IMMUNOLOGY



**Ki-67-high Th2 cells (GATA3, STAT6, c-MAF, CCR4, PTGDR2)*

p=0.006 in IL-4 at D58 vs. Baseline
p=0.05 in IL-5 at D58 vs. Baseline

p=0.02 in IL-4 at D56 vs. Baseline
p=0.007 in IL-13 at D56 vs. Baseline
p=0.04 in TARC at D56 vs. Baseline

Figure 3. The left panel shows a dose-dependent reduction in proliferating circulating Th2 cells measured by scRNAseq in blood from patients evaluated in Cohorts 1–3 receiving placebo, soquelitinib 200 mg once a day or 200 mg twice per day. Each dot represents a patient with changes compared to baseline (Ki-67, proliferation marker; GATA3, c-MAF, CCR4 and PTGDR2 are Th2 markers; STAT6 is involved in inflammatory signaling). The right panel shows median values of serum cytokines measured over time from Cohorts 3 and 4. The decrease in levels of Th2 cytokines and TARC continue after the treatment is discontinued (drug-free period).

SOQUELITINIB TREATMENT LEADS TO INCREASE IN PERSISTENT TREGS

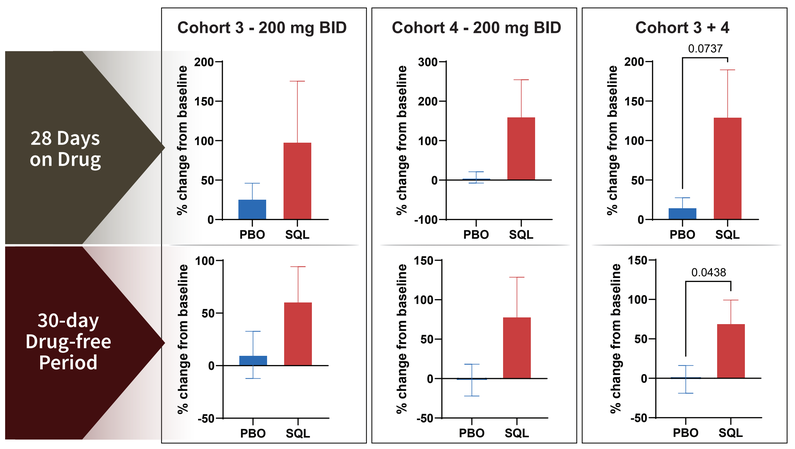


Figure 4. Percent change from baseline in circulating Treg cells for placebo (N=23 for Cohort 1–4 combined) and treated patients (N=24) from Cohort 3, Cohort 4 and combined. The top row shows values after 28 days of therapy and the bottom row shows values 30 days after stopping therapy (drug-free period).

INHIBITING ITK REGULATES SWITCH TO TREG FROM TH17

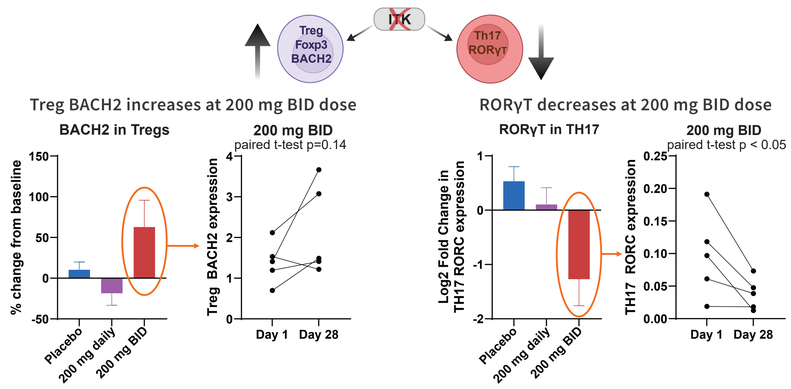
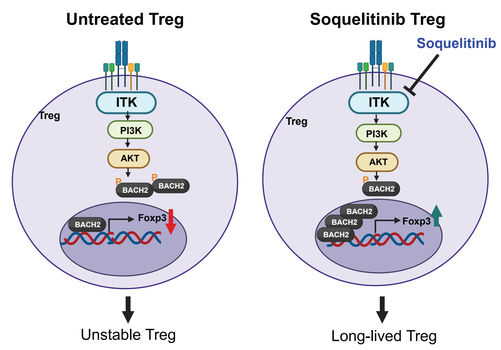


Figure 5. Changes from baseline for markers of Tregs and Th17 cells. BACH2 is a transcription factor that promotes Treg function and stability. RORγT is the master transcription factor for Th17 cell function. The data demonstrates an increase in Tregs and a decrease in Th17, consistent with soquelitinib induced "switch."

POTENTIAL MECHANISM OF TREG STABILIZATION



- Increased BACH2 expression promotes Treg survival [3,4]
- ITK signaling prevents nuclear localization of BACH2
- ITK inhibition promotes BACH2 nuclear localization and activation of Foxp3 gene

SOQUELITINIB UPREGULATES SOCS3 AND REDUCES JAK1 IN T HELPER CELLS

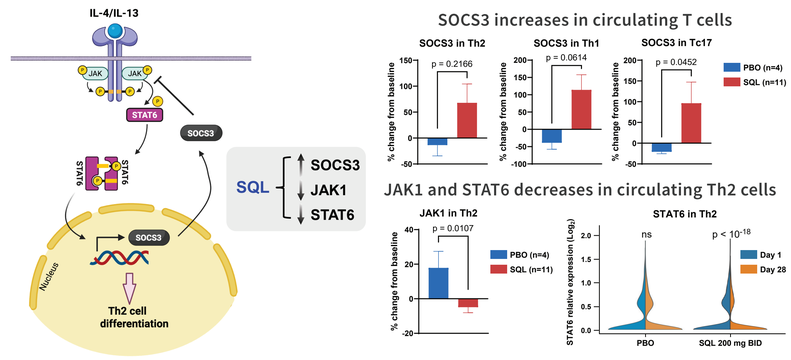


Figure 6. Top panel shows percent change from baseline of SOCS3 (suppressor of cytokine signaling-3) in Th2, Th1 and Tc17 cells for placebo and treated patients from Cohorts 1–3. SOCS3 regulates cytokine signaling in the JAK/STAT pathway, with increased levels of SOCS3 inhibiting T cell responses to cytokines. Tc17 cells produce IL-17, demonstrate high plasticity, are driven by transcription factor RORγT and are important in autoimmune diseases. These findings indicate that soquelitinib will reduce IL-17 production. The bottom panel shows change from baseline (Cohorts 1–3) in JAK1 and STAT6 resulting from treatment with soquelitinib compared to placebo. The violin plots on the right show a reduction in STAT6 expression at day 28 (gold) compared to baseline (blue) for the 200 mg twice daily (N=5) patients; no significant change was seen in placebo (N=4) patients.

CONCLUSIONS

Targeted Mechanism	Immune Reprogramming	Pathway Modulation	Clinical Impact
Soquelitinib is a **selective**, covalent **ITK inhibitor** Blocks Th2/Th17	Treg rebalancing: • Th2/Th17 reduced inflammatory signaling • Increased Tregs Shifts from inflammatory Th2/Th17 responses toward regulatory Treg responses	Soquelitinib modulates the JAK-STAT pathway in T cells ↑ SOCS3 and ↓ JAK1 reduce STAT signaling and inflammatory cytokine production	**Durable Remissions** Continued improvement after treatment discontinuation **Favorable Safety Profile** Well tolerated in Phase 1 **Potential for Broad Utility** In AD and other immune-mediated diseases

A new paradigm: Target upstream. Reprogram immunity. Achieve *durable* control.

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