Soquelitinib, an ITK inhibitor, Produces Prolonged Drug-Free Remissions in Atopic Dermatitis

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ABSTRACT

Interleukin-2-Inducible T cell Kinase (ITK) is critical for differentiation of naïve T cells into Th1, Th2 and Th17 cells. ITK inhibition leads to a switch from Th17 to Treg cells that have suppressive function. Soquelitinib (SQL) is an oral, selective ITK inhibitor that suppresses Th2/Th17 cytokines while enhancing Tregs. In animal models of atopic dermatitis (AD) and inflammation, SQL results in accumulation of Tregs in lesions. We evaluated SQL in a Phase 1 trial for moderate-to-severe AD.

72 patients were enrolled. Dose-escalation cohorts 1–3 (N=16 each) were randomized, blinded 3:1 to receive SQL:placebo for 4 weeks; doses were 100 mg BID, 200 mg QD, 200 mg BID or placebo. 200 mg BID was selected for 8-week treatment in Cohort 4 (N=24, randomized 1:1).

At week 4, Cohort 1-3 achieved EASI75 rates of 25%, 33%, and 50% in SQL arms, respectively vs 0% placebo; vIGA0/1 achieved by 25%, 17%, and 25% vs 0% placebo. Cohort 3 mean EASI reduction at week 4 (64.8%) continued to improve during a 90-day off-drug period (71.1%), correlating with a concomitant increase in circulating FOXP3+ Tregs. In the 8-week Cohort 4, mean EASI reduction was 72% for SQL vs 40% for placebo. EASI75, EASI90 and IGA0/1 were achieved in 75%, 25% and 33% of the SQL arm vs. 20%, 0% and 0% for placebo. EASI was maintained after 30 days off drug. 35% of all patients had received prior systemic AD therapy; efficacy was consistent regardless of prior treatment, including in non-responders to dupilumab or JAK inhibitors. Adverse events were similar to placebo.

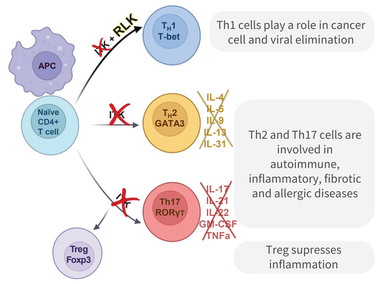
SQL is well tolerated and produces prolonged drug-free remissions following short treatment periods of 4 or 8 weeks. ITK blockade is a novel therapeutic approach for AD and inflammatory diseases that appears to be based on induction of Tregs.

INTRODUCTION

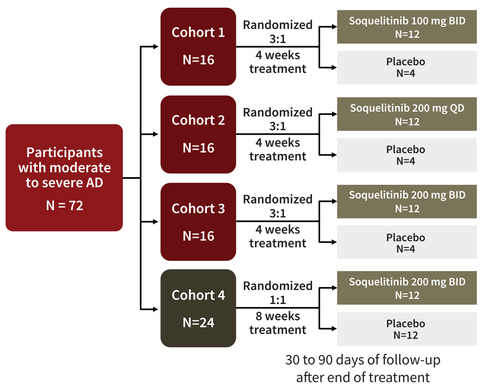
SOQUELITINIB BLOCKS TH2 AND TH17 AND INDUCES TH1 SKEWING

- 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.*

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

RESULTS

EFFICACY RESULTS OF COHORTS 1–3 WITH 4-WEEK TREATMENT

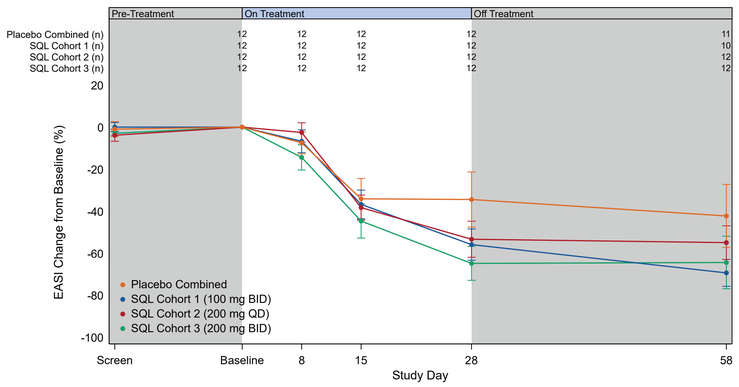


Figure 1. Mean % EASI reduction in Cohorts 1–3. Placebo is combined from Cohorts 1–3. No disease rebound seen during drug-free follow-up in soquelitinib treated patients.

EFFICACY RESULTS OF COHORT 4 WITH 8-WEEK TREATMENT

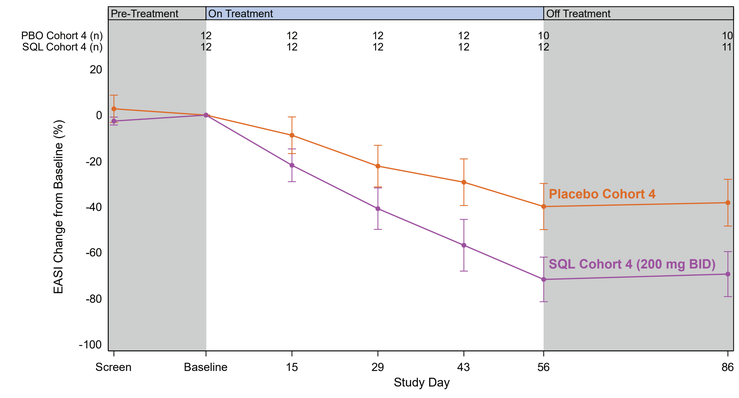


Figure 2. Mean % EASI reduction in Cohort 4. No disease rebound seen during drug-free follow-up in soquelitinib treated patients.

EFFICACY IN PATIENTS WITH PRIOR SYSTEMIC THERAPY

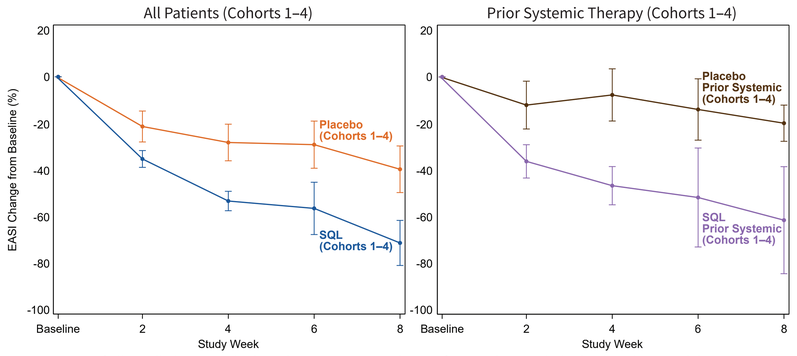
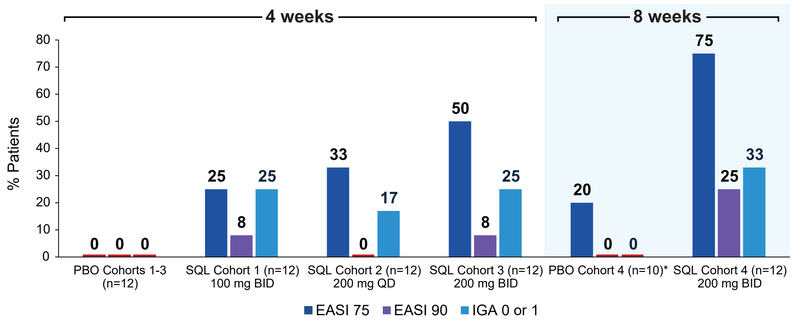


Figure 3. 35% of all enrolled patients had used a prior systemic therapy for AD. These include dupilumab, JAK inhibitors, systemic corticosteroids, and investigational drugs. Soquelitinib showed comparable efficacy in patients with prior systemic therapy.

RESPONSE IN SYSTEMIC TREATMENT RESISTANT PATIENTS (COHORTS 3&4)

Study Treatment	Age/Gender	Prior Treatment Resistant	Baseline EASI	% EASI change
Soquelitinib	60/F	Dupilumab	24.6	–91%
Soquelitinib	18/M	Dupilumab, anti-OX40L	23.8	–96%
Soquelitinib	52/M	Dupilumab, methotrexate, upadacitinib	41.5	–27%
Soquelitinib	34/M	Dupilumab, anti-OX40, abrocitinib	23.9	29%
Placebo	37/M	Dupilumab, upadacitinib	17.2	Flare (Rescue Meds)
Placebo	26/F	Dupilumab, upadacitinib	32.9	Flare (Rescue Meds)

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 4. 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 REMISSION IN COHORT 3 WITH INCREASED TREGS

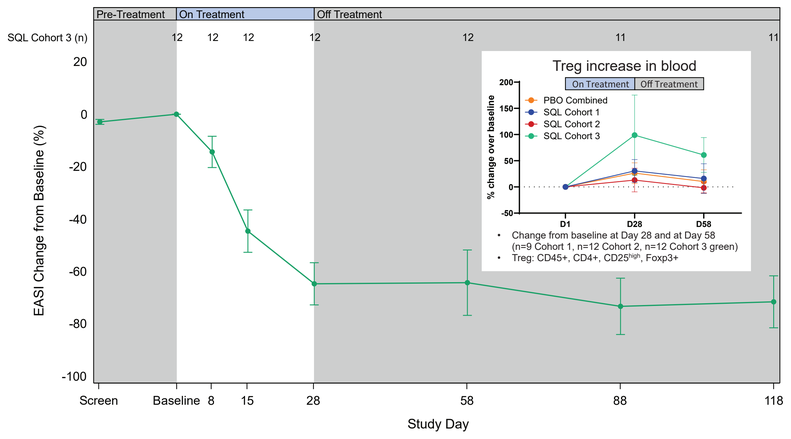


Figure 5. Cohort 3 (200 mg BID for 4 weeks) maintained treatment response during a 90-day off-drug follow up. This durable response correlated with increased FoxP3+ Tregs in the blood.

RESPONSES MAINTAINED IN DRUG-FREE FOLLOW UP

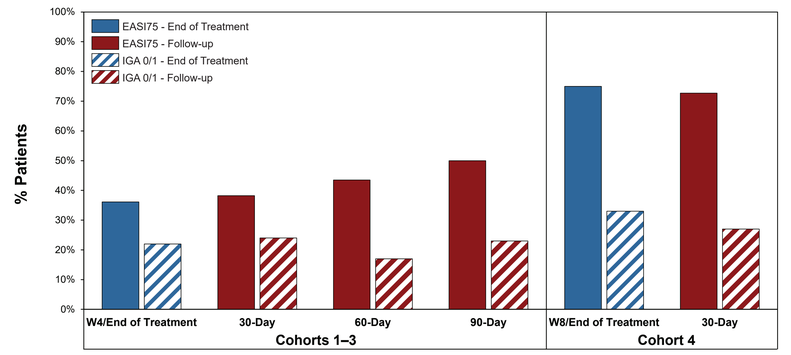


Figure 6. Proportion of patients achieving EASI75 and IGA 0/1 is maintained during the drug-free period.

ALL REPORTED ADVERSE EVENTS

	Cohorts 1–3		Cohort 4	
	SQL (n=36), n(%)	PBO (n=12), n(%)	SQL (n=12), n(%)	PBO (n=12), n(%)
Subjects with any TEAE	15 (41.7)	4 (33.3)	5 (41.7)	6 (50)
Headache	4 (11.1)	1 (8.3)	4 (33.3)	0 (0)
Abdominal pain upper	1 (2.8)	0 (0)	0 (0)	1 (8.3)
Nausea	1 (2.8)	1 (8.3)	0 (0)	0 (0)
Upper respiratory tract infection	1 (2.8)	1 (8.3)	0 (0)	0 (0)
Worsening of AD	0 (0)	0 (0)	0 (0)	2 (16.7)
Anemia	1 (2.8)	0 (0)	0 (0)	0 (0)
Eosinophilia	1 (2.8)	0 (0)	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)	1 (8.3)	0 (0)
Food poisoning	0 (0)	0 (0)	1 (8.3)	0 (0)
COVID-19	1 (2.8)	0 (0)	0 (0)	0 (0)
Cellulitis	0 (0)	1 (8.3)	0 (0)	0 (0)
Nasopharyngitis	1 (2.8)	0 (0)	0 (0)	0 (0)
Skin bacterial infection	0 (0)	0 (0)	0 (0)	1 (8.3)
Staphylococcal infection	0 (0)	0 (0)	1 (8.3)	0 (0)
Increased appetite	0 (0)	0 (0)	0 (0)	1 (8.3)
Arthralgia	0 (0)	0 (0)	0 (0)	1 (8.3)
Muscle spasms	0 (0)	0 (0)	0 (0)	1 (8.3)
Basal cell carcinoma	0 (0)	0 (0)	0 (0)	1 (8.3)
Neck pain	1 (2.8)	0 (0)	0 (0)	0 (0)
Somnolence	1 (2.8)	0 (0)	0 (0)	0 (0)
Insomnia	0 (0)	1 (8.3)	0 (0)	0 (0)
Menstruation irregular	1 (2.8)	0 (0)	0 (0)	0 (0)
Lower respiratory tract congestion	1 (2.8)	0 (0)	0 (0)	0 (0)
Skin neoplasm excision	0 (0)	0 (0)	0 (0)	1 (8.3)

Includes the AEs reported through 30-day follow-up. No severe or serious AEs and no AEs requiring dose modification. All AEs were Grade 1–2.

CONCLUSIONS

- Soquelitinib is a first-in-class selective oral ITK inhibitor that suppresses Th2 and Th17 inflammatory responses and increases Tregs
- Well-tolerated with no infection signal and no lab abnormalities
- Early and deep response with short dosing period
- Durable treatment effects with no evidence of rebound flare with cessation
- Activity seen in prior systemic therapy resistant patients
- Treatment of autoimmune/inflammatory diseases based on rebalancing of immunity could reduce need for chronic therapy

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