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Soquelitinib, a Selective ITK Inhibitor, Demonstrates Activity in Atopic Dermatitis (AD) Phase 1 Clinical Trial by a Novel Mechanism of Action

Albert S. Chiou[1], James T. Rosenbaum[2], Lih-Yun Hsu[2], Dan Li[2], Gabriel Luciano[2], Suresh Mahabhashyam[2], Richard Miller[2]

[1]Stanford Medical Center, Palo Alto, CA, USA; [2]Corvus Pharmaceuticals Inc., South San Francisco, CA, USA

Stanford MEDICINE School of Medicine

ABSTRACT

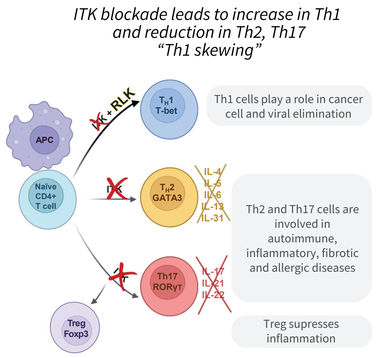
Interleukin-2-inducible T cell kinase (ITK) is required for the differentiation of naïve helper T cells (Th) into Th2 and Th17 subsets. Given the critical role of these cells in AD, we are evaluating soquelitinib (SQL), an oral, covalent selective ITK inhibitor shown to block Th2 and Th17 differentiation and the production of their associated cytokines such as IL-4, 5, 13, 31, 17, for the treatment of AD. We report interim results of a Phase 1 study evaluating SQL's safety and preliminary efficacy in patients (pts) with moderate to severe AD. The randomized, double blind study design is: 4 cohorts (sequentially enrolled) of 16 pts (12 active to 4 placebo [PBO]); 4 week treatment with additional 30 day follow-up; dosages from 100mg BID, 200mg QD, 200mg BID, to 400mg QD. The 100mg BID and 200mg QD cohorts are fully enrolled. SQL-treated pts demonstrated disease response vs PBO at either dose in terms of mean %EASI reduction at Day 28. EASI 75 or IGA 0/1 was achieved in 25% of pts at 100mg BID dose and in 57% at 200mg QD dose. No PBO pts achieved either measure of response. Serum cytokines including IL-5, 17F, 31, 33 and TSLP were reduced more from baseline to Day 28 in treated responders vs non-responders (p≤0.02 for each comparison) while PBO pts showed little change in these cytokines. Day 58 safety follow-up showed continued improvement in EASI in the "off period" for SQL-treated pts but not in PBO. Increased circulating FoxP3 +Tregs were found in the blood of SQL treated pts and a reduction in circulating (type 2 innate lymphoid cells) ILC2 cells were seen. In SQL-treated pts, AEs were limited to 1 Gr 1 nausea and 1 Covid 19; all pts received the full course of treatment. This is the first report of selective ITK inhibition for treatment of AD and indicates that this mechanism has the potential for more durable control of AD with an oral agent due to blockade of multiple Th2/Th17 cytokines, induction of Treg suppression and blockade of ILC2.

INTRODUCTION

SOQUELITINIB BLOCKS TH2 AND TH17 AND INDUCES TH1 SKEWING

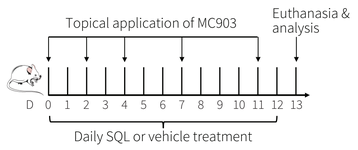
- ITK (interleukin-2-inducible T cell kinase) is expressed in T, NK and ILC-2 cells and plays a role in T cell activation, differentiation, migration and apoptosis
- Soquelitinib is an oral, selective covalent inhibitor of ITK
  - Nanomolar binding to ITK while sparing RLK
  - Inhibits Th2 and Th17 differentiation and inhibits the production of IL-4, 5, 17, 31, etc.
- Blocking ITK results in a switch from Th17 to Tregs
- Active in animal models of asthma, psoriasis, GVHD, AD and systemic sclerosis
- Safety shown in T cell lymphoma; a phase 3 registration trial is ongoing
- We report here the interim results of a phase 1 trial in patients with moderate to severe AD

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

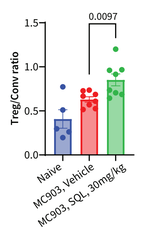


INCREASED TREGS IN SKIN FROM MURINE MODELS OF AD AND PSORIASIS

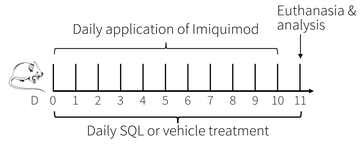
MC903-induced murine AD model



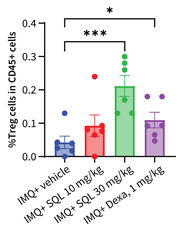
Increased Treg/Conv ratio in skin



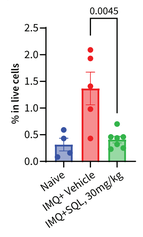
Imiquimod-induced murine psoriasis model



Increased Tregs in skin

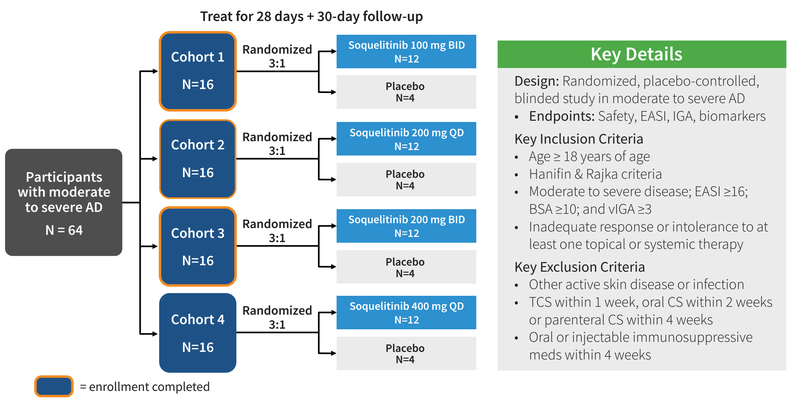


Inhibits IL-17A production in skin



Murine models of AD and psoriasis. Involved skin removed during treatment and infiltrating lymphoid cells are isolated and evaluated by flow cytometry. Treg cells identified based on FoxP3, CD25 markers.

PHASE 1 STUDY DESIGN



Key Details

Design: Randomized, placebo-controlled, blinded study in moderate to severe AD

- **Endpoints:** Safety, EASI, IGA, biomarkers

Key Inclusion Criteria

- Age ≥ 18 years of age
- Hanifin & Rajka criteria
- Moderate to severe disease; EASI ≥16; BSA ≥10; and vIGA ≥3
- Inadequate response or intolerance to at least one topical or systemic therapy

Key Exclusion Criteria

- Other active skin disease or infection
- TCS within 1 week, oral CS within 2 weeks or parenteral CS within 4 weeks
- Oral or injectable immunosuppressive meds within 4 weeks

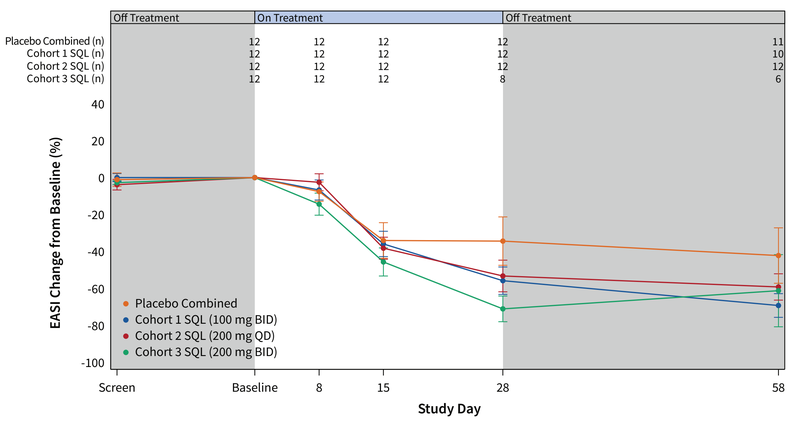
Studies in pts with T cell lymphoma have demonstrated complete target occupancy at doses of 200 mg BID.

INTERIM PHASE 1 RESULTS

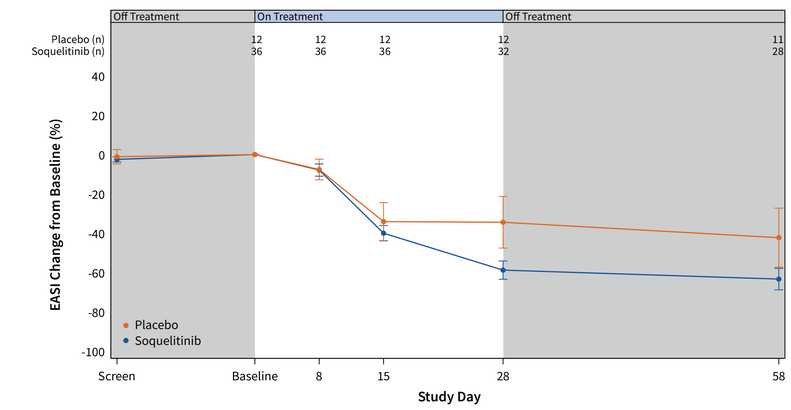
PATIENT CHARACTERISTICS

	Cohort 1 100 mg BID		Cohort 2 200 mg QD		Cohort 3 200 mg BID		All Cohorts	
	SQL (n=12)	PBO (n=4)	SQL (n=12)	PBO (n=4)	SQL (n=12)	PBO (n=4)	SQL (n=36)	PBO (n=12)
Age, mean (range), yrs	46.3 (30–66)	50.5 (32–62)	42.5 (21–63)	43.0 (27–52)	46.4 (25–71)	23.0 (20–29)	45.1 (21–71)	38.8 (20–62)
Gender, male n (%)	7 (58.3)	4 (100)	7 (58.3)	1 (25)	4 (33.3)	2 (50)	18 (50)	7 (58.3)
Race/ethnicity, n (%)								
Asian	2 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)	2 (5.6)	1 (8.3)
Black or African American	6 (50)	4 (100)	7 (58.3)	1 (25)	5 (41.7)	0 (0)	18 (50)	5 (41.7)
White	3 (25)	0 (0)	1 (8.3)	1 (25)	4 (33.3)	1 (25)	8 (22.2)	2 (16.7)
Hispanic or Latino	1 (8.3)	0 (0)	4 (33.3)	2 (50)	2 (16.7)	2 (50)	7 (19.4)	4 (33.3)
Not Reported	0 (0)	0 (0)	0 (0)	0 (0)	1 (8.3)	0 (0)	1 (2.8)	0 (0)
Baseline EASI, mean (range)	20.4 (15.0–46.6)	18.5 (14.9–24.8)	19.4 (14.7–29.2)	17.1 (14.4–19.1)	27.2 (18.0–41.5)	28.1 (16.3–46.6)	22.3 (14.7–46.6)	21.2 (14.4–46.6)
Baseline IGA, mean (range)	3.0 (2–4)	3.3 (3–4)	3.1 (3–4)	3.0 (3–3)	3.1 (3–4)	3.3 (3–4)	3.1 (2–4)	3.2 (3–4)
Prior AD therapies, n (%)								
Topical corticosteroids	12 (100)	4 (100)	12 (100)	4 (100)	12 (100)	4 (100)	36 (100)	12 (100)
Systemic therapies	4 (33.3)	2 (50)	2 (16.7)	0 (0)	5 (41.7)	1 (25)	11 (30.6)	3 (25)
Concomitant TS	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8.3)

MEAN % EASI CHANGE BY COHORT



MEAN % EASI CHANGE: SOQUELITINIB VS PLACEBO

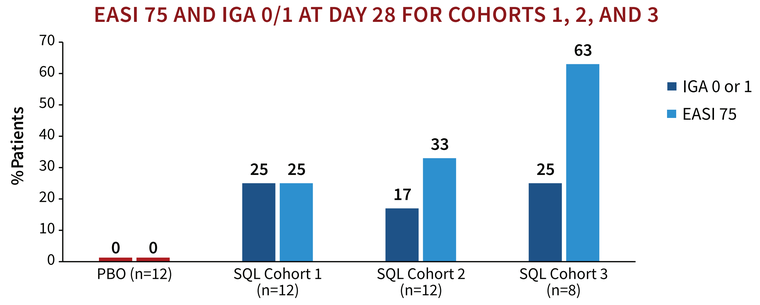


EFFICACY RESULTS AT DAY 28 FOR COHORTS 1, 2, AND 3

	Cohorts 1 and 2*		Cohort 3	
	4 week			
	SQL (n=24)	PBO (n=8)	SQL (n=8)	PBO (n=4)
Change EASI Mean % Reduction	54.6	30.6	71.1	42.1
EASI 50 (%pts)	75	50	88	75
EASI 75 (%pts)	29	0	63	0
EASI 90 (%pts)	4	0	13	0
IGA 0 or 1 (%pts)	21	0	25	0

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

EASI 75 AND IGA 0/1 AT DAY 28 FOR COHORTS 1, 2, AND 3



28-day follow-up available on 32 active patients and 12 placebo patients. No placebo patients achieved IGA 0/1 or EASI 75.

ADVERSE EVENT SUMMARY

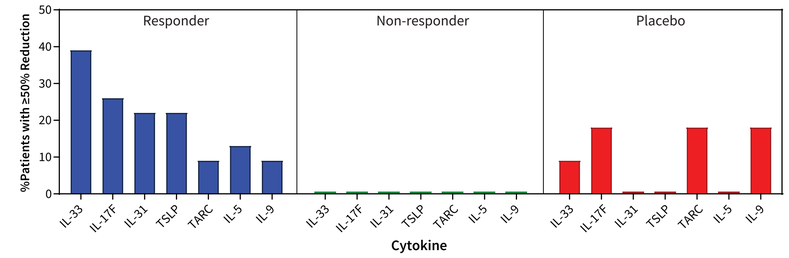
	Soquelitinib (n=36)	Placebo (n=12)
Subjects with AEs	12 (33.3%)	3 (25%)
Severe AEs	0	0
Serious AEs	0	0
AEs leading to study drug discontinuation	0	0
Treatment-related AEs		
Nausea (Grade 1)	1 (2.8%)	0

- No clinically significant laboratory abnormalities
- Safety observed in over 100 patients with lymphoma and AD
- Experience in ~9,000 patient-treatment days

Reported AEs – SQL Arm: Nausea (n=1), Covid-19 (n=1), headache (n=4), neck pain (n=1), drowsiness (n=1), increased eosinophil count (n=1); upper abdominal pain (n=1), nasopharyngitis (n=1), lower respiratory tract congestion (n=1), and menstrual spotting (n=1); all resolved without any dose modification. Reported AEs – Placebo Arm: Upper respiratory tract infection (n=1), nausea (n=1), headache (n=1), and insomnia (n=1).

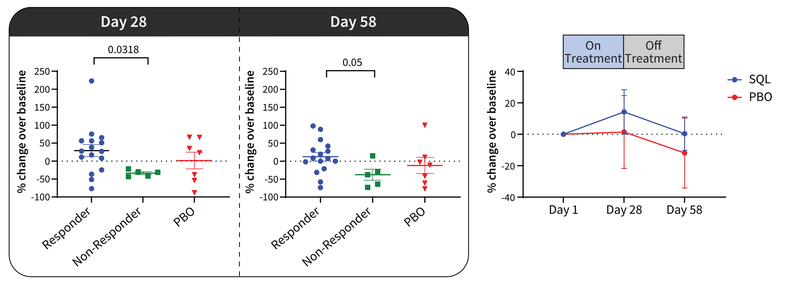
TREATMENT RELATED REDUCTION (≥50%) AT DAY 28 IN SERUM CYTOKINES

Cytokine	Responder (n=23)	Non-responder (n=7)	Placebo (n=11)
IL-33	9	0	1
IL-17F	6	0	2
IL-31	5	0	0
TSLP	5	0	0
TARC	2	0	2
IL-5	3	0	0
IL-9	2	0	2



Numbers of patients (top) and percentage of patients (bottom) with ≥50% reduction from baseline in serum cytokines. Treatment related differences in cytokines are more frequently seen for responders (EASI 50) vs non-responders and placebos.

SOQUELITINIB INCREASES TREG CELLS IN BLOOD OF RESPONDERS



Change from baseline at Day 28 and at Day 58 (n=21 soquelitinib [SQL], n=7 placebo [PBO]). Treg: CD45+, CD4+, $CD25^{high}$, Foxp3+

CONCLUSIONS

- Soquelitinib is a selective oral ITK inhibitor that suppresses Th2 and Th17 inflammatory responses and may increase Tregs
- Soquelitinib demonstrates acceptable safety and tolerability with no dose-limiting toxicities
- A significant reduction in EASI score is observed within 28 days of treatment, with sustained benefit for an additional 30 days without therapy
- Trends in dose response effect are observed with 200 mg BID demonstrating earlier and deeper responses; future studies will evaluate longer treatment durations
- Selective inhibition of ITK may represent a new approach for the treatment of autoimmune/inflammatory diseases

ACKNOWLEDGMENTS

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