Upadacitinib Treatment Induces Significant Improvements in Th2 (Eosinophil Count, Serum CCL17/18/26) and Th22 (IL-22) Levels in Atopic Dermatitis That Are Associated With Improvements in Itch and Clinical Severity

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OBJECTIVE

- To evaluate the effect of upadacitinib on inflammatory measures in blood previously associated with atopic dermatitis (AD) including serum levels of interleukin (IL)-4/IL-13–related chemokines, T-helper (Th) type 2– and Th17/IL-23–related markers, absolute eosinophil count (AEC), and serum total and antigen-specific immunoglobulin E (IgE) levels
- We also aimed to investigate the relationship between these changes and clinical disease improvements (ie, severity, itch) in adult patients with moderate-to-severe AD

INTRODUCTION

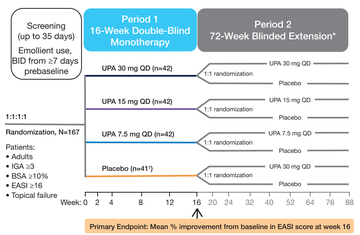
- AD is an inflammatory skin disease characterized by Th2–mediated inflammation and epidermal barrier defects[1]
- Patients with moderate-to-severe AD were shown to have high levels of circulating inflammatory mediators[2,3]
- Serum levels of Th2- and Th22-related biomarkers correlate with AD severity in patients with moderate-to-severe AD[2,3]
- Serum thymus and activation-regulated chemokine (TARC/CCL17) has been reported to be robustly correlated to disease severity in patients with AD across multiple longitudinal and cross-sectional studies[4]
- Activation of Janus kinase and signal transducer and activator of transcription (JAK-STAT) pathways has been proposed to have a role in AD[5]
- Upadacitinib, an oral selective JAK 1 inhibitor, is currently being investigated for the treatment of AD and other immune-mediated inflammatory diseases[6]

METHODS

STUDY DESIGN AND PATIENTS

- Results from the initial 16-week, randomized, placebo-controlled period of a phase 2 upadacitinib study (NCT02925117; **Figure 1**) are reported here
  - Patients were randomized 1:1:1:1 to receive daily oral placebo or upadacitinib 7.5, 15, or 30 mg
- Adults (18–75 years of age) with dermatologist-confirmed diagnosis of moderate-to-severe AD (see criteria in **Figure 1**) with symptom duration ≥1 year before baseline were eligible
  - Inadequate response or contraindication to topical corticosteroids or topical calcineurin inhibitors within 1 year before screening
- Patients were excluded if they had prior exposure to any JAK inhibitor or dupilumab

Figure 1. Study Design



BID, twice daily; BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; QD, once daily; UPA, upadacitinib. Moderate-to-severe atopic dermatitis defined as EASI ≥16, affected BSA ≥10%, and IGA score ≥3 at baseline.

*Double-blind, randomized withdrawal period is ongoing.

†40 patients received treatment.

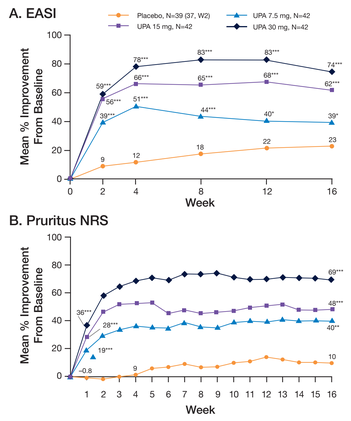
OUTCOMES

- Mean percentage improvements from baseline to week 16 in Eczema Area and Severity Index (EASI) and pruritus numeric rating scale (NRS; weekly average of daily patient assessments) were assessed
- AEC from complete blood count with differential (Covance), serum CCL17 (BioRad), CCL18 (R & D systems), CCL20 (Olink), CCL26 (BioRad), IL-17A (Singulex), IL-17F (Singulex), and IL-22 (Singulex) levels as well as serum total and antigen-specific IgE (ImmunoCAP) levels were analyzed at various time points up to week 16
- Spearman correlations between changes in circulating mediators and clinical improvements were considered significant if <0.05

RESULTS

- Of the 166 patients who were randomized and received treatment, 126 completed the 16-week period (placebo, n=20; upadacitinib 7.5/15/30 mg, n=31/37/38)
- Improvements in EASI and pruritus NRS were significantly greater with all doses of upadacitinib vs placebo **(Figure 2)**

Figure 2. Mean Percentage Improvement From Baseline to Week 16 in (A) EASI and (B) Pruritus NRS



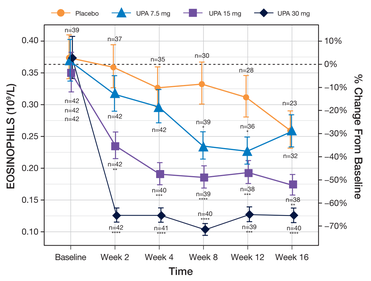
EASI, Eczema Area and Severity Index; NRS, numeric rating scale; UPA, upadacitinib. Missing data handled by last observation carried forward.

***P<0.001, **P<0.01, *P<0.05, UPA vs placebo.

EFFECT OF UPADACITINIB ON AEC

- Reductions in AEC over time were significantly greater with 15 and 30 mg upadacitinib vs placebo **(Figure 3)**
  - Significant differences vs placebo were observed as early as week 2 in the upadacitinib 15-mg (*P*=0.003) and 30-mg (*P*<0.0001) groups **(Figure 3)**

Figure 3. AEC Over Time



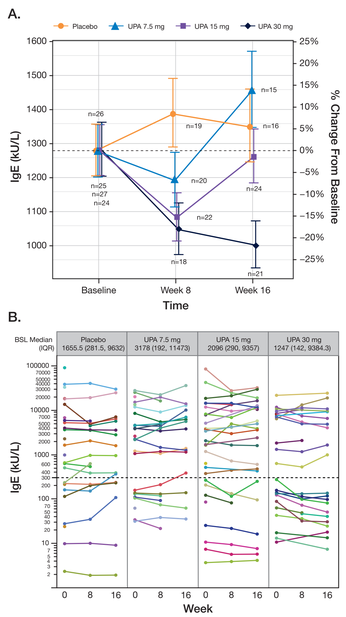
EASI, Eczema Area and Severity Index; NRS, numeric rating scale; UPA, upadacitinib. Missing data handled by last observation carried forward.

****P<0.0001, ***P<0.001, **P<0.01, *P<0.05, UPA vs placebo.

EFFECT OF UPADACITINIB ON SERUM IgE

- Total IgE levels over time and changes from baseline to week 16 were not significant with upadacitinib 7.5, 15, and 30 mg vs placebo **(Figure 4)**; however, the 30-mg dose showed non-significant reductions in IgE at both 8 and 16 weeks compared with baseline levels
- No trends in allergen-specific IgE levels were observed **(Table 1)**

Figure 4. (A) Mean Total IgE Levels Over Time and (B) Individual Patient Total IgE Levels Over Time



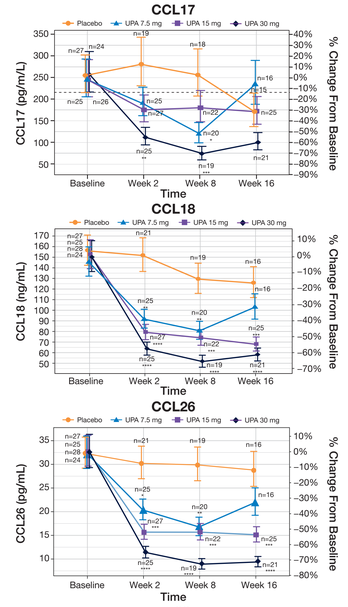
BSL, baseline; IgE, immunoglobulin E; IQR, interquartile range; QD, once daily; UPA, upadacitinib. Data are group means ± SE adjusted for baseline values.

****P<0.0001, ***P<0.001, **P<0.01, *P<0.05, UPA vs placebo.

EFFECT OF UPADACITINIB ON SOLUBLE SERUM PROTEINS

- Reductions in serum levels of Th2 cytokines CCL18 and CCL26 and Th22 cytokine, IL-22, over time were significantly greater with 15 and 30 mg upadacitinib vs placebo **(Figure 5)**
  - Significant differences vs placebo were observed as early as week 2 in the upadacitinib 15-mg and 30-mg groups
  - CCL17 showed similar trends (significant at weeks 2 and 8 vs baseline) with the upadacitinib 30-mg dose
- There were no clear trends of Th17 cytokines IL-17A, IL-17F, or CCL20 levels **(Figure 6)**

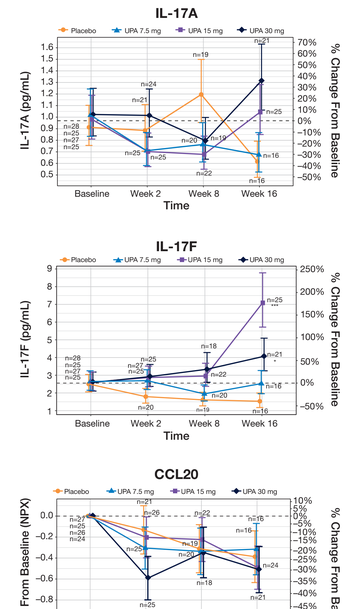
Figure 5. Serum CCL17, CCL18, CCL26, and IL-22 Levels Over Time



CCL, chemokine ligand; IL, interleukin 22; UPA, upadacitinib. Data are group means ± SE adjusted for baseline values.

****P<0.0001, ***P<0.001, **P<0.01, *P<0.05, UPA vs placebo.

Figure 6. Serum IL-17A and IL-17F levels, and CCL20 Change from Baseline



CCL, chemokine ligand; IL, interleukin; UPA, upadacitinib.

****P<0.0001, ***P<0.001, **P<0.01, *P<0.05, UPA vs placebo.

CORRELATIONS BETWEEN CHANGES IN SERUM MARKERS AND CLINICAL IMPROVEMENTS

- Significant correlations were observed for changes in AEC, total serum IgE, and Th2/Th22-associated serum proteins with baseline disease severity and clinical improvements **(Table 2)**

Table 1. Antigen-Specific IgE at Baseline and Percentage Change at Week 16

	Placebo				UPA 7.5 mg				UPA 15 mg				UPA 30 mg			
	Baseline, kU/L		Wk 16 % Chg		Baseline, kU/L		Wk 16 % Chg		Baseline, kU/L		Wk 16 % Chg		Baseline, kU/L		Wk 16 % Chg	
Antigen-specific IgE	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Cat dander	26	3.3 (0.1, 42.4)	15	0 (−10.4, 32.3)	24	6.7 (0.6, 19.7)	15	2.6 (−18.6, 78.8)	26	0.4 (0.1, 13.5)	23	0 (−23.1, 4.3)	24	4.8 (0.1, 29.0)	20	5.3 (0, 23.4)
Dermatophagoides farinae	27	8.1 (0.1, 95.9)	16	0 (−15.7, 24.8)	25	48.8 (1.9, 200)	15	−4.5 (−29, 0)	26	25.5 (0.3, 122)	23	0 (−28.1, 24)	24	4.8 (0.1, 200)	20	0 (0, 0)
Dermatophagoides pteronyssinus	26	15.7 (0.2, 200)	15	0 (−26.3, 14.3)	24	44.0 (2.7, 200)	16	−4.7 (−14.1, 0.8)	26	29.5 (0.4, 200)	23	0 (−25.9, 28)	24	3.5 (0.1, 200)	20	0 (0, 0)
Dog dander	26	1.5 (0.2, 46.3)	14	0 (−7.5, 60.5)	24	4.1 (0.7, 28.0)	15	10.3 (−16.2, 67)	26	1.1 (0.1, 17.9)	23	0 (−19.4, 0)	24	1.5 (0.1, 56.5)	20	0 (0, 29.3)
German cockroach	25	0.4 (0.1, 1.9)	14	−1.6 (−20.8, 10.1)	24	0.9 (0.2, 8.7)	15	−7.8 (−25.2, 10)	26	0.7 (0.1, 4.9)	23	0 (0, 41.3)	23	0.2 (0.1, 1.4)	20	0 (−19.1, 6.3)
Pityrosporum orbiculare	26	0.7 (0.1, 12.9)	15	0 (−16.2, 0)	23	8.5 (0.3, 21.8)	15	11.3 (−6.9, 78.1)	26	3.2 (0.1, 25.8)	23	0 (−0.5, 45.3)	24	1.8 (0.1, 6.7)	20	0 (−17.1, 17.1)
Silver birch	24	5.4 (0.14, 22.9)	14	27.6 (−7, 225.4)	24	1.5 (0.1, 13.6)	15	21.1 (0, 164.2)	26	0.6 (0.1, 6.2)	23	2.2 (0, 109.1)	24	0.3 (0.1, 14.0)	20	3.8 (0, 130.1)
Staph enterotoxin A	26	0.5 (0.1, 4.0)	15	0 (−15.5, 23.6)	23	0.2 (0.1, 0.9)	15	13.7 (0, 78.1)	26	0.4 (0.1, 1.4)	23	0 (−11.1, 13.5)	24	0.4 (0.1, 1.0)	20	0 (−9.8, 0)
Staph enterotoxin TSST	27	0.3 (0.1, 0.7)	16	0 (−10.8, 22.6)	23	0.2 (0.1, 0.7)	15	0 (−9.8, 28)	26	0.3 (0.1, 1.4)	23	0 (−4%, 34.2)	24	0.2 (0.1, 1.0)	20	0 (−5, 23.7)
Staph enterotoxin B	25	0.4 (0.1, 1.9)	15	0 (−33.3, 0)	22	0.4 (0.1, 1.2)	14	−3 (−13.9, 39.4)	26	0.3 (0.1, 1.1)	23	0.5 (0, 35.7)	24	0.2 (0.1, 1.0)	20	0 (−19.7, 13.3)
Timothy grass	26	4.5 (1.3, 16.0)	14	0 (−18.1, 37)	24	3.5 (0.5, 16.0)	15	14.8 (−5.9, 71.6)	26	1.5 (0.2, 8.6)	23	0 (−12.4, 26.6)	24	2.5 (0.1, 30.5)	20	0 (−3.8, 2.2)
Total IgE	26	1655 (281, 9632)	15	−2.8 (−21.2, 41.9)	25	3178 (192, 11473)	15	7.8 (−7.9, 49.5)	27	2096 (290, 9357)	23	−5.7 (−27.1, 43)	24	1247 (142, 9384)	20	−18.4 (−42.1, 18.7)

IgE, immunoglobulin E; IQR, interquartile range; toxic shock syndrome toxin; UPA, upadacitinib.

Table 2. Correlations Between Changes in Serum Markers and Clinical Improvements

	BSL Biomarker/ BSL Disease Severity	% Change Biomarker/ % Change Disease Severity	
		Week 2	Week 16
AEC vs EASI	0.39****	0.47****	0.62****
AEC vs NRS	0.23*	0.55****	0.66****
Total serum IgE vs EASI	0.35***	ND	0.38***
Total serum IgE vs NRS	0.14	ND	0.33**
CCL17 vs EASI	0.44****	0.35**	0.29*
CCL17 vs NRS	0.28**	0.43****	0.29*
CCL18 vs EASI	0.43****	0.58****	0.58****
CCL18 vs NRS	0.23*	0.48****	0.37**
CCL26 vs EASI	0.41****	0.51****	0.57****
CCL26 vs NRS	0.11	0.53****	0.43***
IL-22 vs EASI	0.43****	0.49****	0.48****
IL-22 vs NRS	0.28**	0.51****	0.38***

AEC, absolute eosinophil count; BSL, baseline; CCL, chemokine ligand; EASI, Eczema Area and Severity Index; IgE, immunoglobulin E; IL, interleukin; ND, not determined; NRS, pruritus numeric rating scale.

****P<0.0001, ***P<0.001, **P<0.01, *P<0.05.

CONCLUSIONS

- Upadacitinib induced significant improvements in EASI at week 16 in 7.5/15/30 mg groups compared with placebo (39.4%/61.7%/74.4% vs 23%, *P*<0.05/<0.001/<0.001)
- Serum levels of Th2 (AEC, CCL17/18/26) and Th22 (IL-22)-associated markers were significantly reduced with upadacitinib treatment (15 and 30 mg) as early as week 2, suggesting that upadacitinib may have early and robust effects on the Th2 and Th22 axes
- Significant correlations with baseline disease severity and clinical improvements were observed for CCL18, CCL26, and IL-22
- While no significant changes in total or specific IgE levels were observed, there was a significant correlation between changes in IgE and clinical disease improvement measures (EASI and NRS)
- In conclusion, upadacitinib induced significant improvements in Th2 and Th22 pathway activation characteristic of AD, and molecular improvements correlated with clinical improvements

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