

Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial



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Background: Atopic dermatitis is a chronic inflammatory skin disease characterized by pruritic skin lesions.

Objective: We sought to evaluate the safety and efficacy of multiple doses of the selective Janus kinase 1 inhibitor upadacitinib in patients with moderate to severe atopic dermatitis.

Methods: In the 16-week, double-blind, placebo-controlled, parallel-group, dose-ranging portion of this 88-week trial in 8 countries ([ClinicalTrials.gov](https://clinicaltrials.gov), NCT02925117; ongoing, not recruiting), adults with moderate to severe disease and inadequate control by topical treatment were randomized 1:1:1:1, using an interactive response system and stratified geographically, to once-daily upadacitinib oral monotherapy 7.5, 15, or 30 mg or placebo. The primary end point was percentage improvement in Eczema Area and Severity Index from baseline at week 16. Efficacy was analyzed by intention-to-treat in all randomized patients. Safety was analyzed in all randomized patients who received study medication, based on actual treatment.

Results: Patients (N = 167) enrolled from November 21, 2016, to April 20, 2017. All were randomized and analyzed for efficacy (each upadacitinib group, n = 42; placebo, n = 41); 166 were analyzed for safety (each upadacitinib group, n = 42; placebo, n = 40). The mean (SE) primary efficacy end point was 39% (6.2%), 62% (6.1%), and 74% (6.1%) for the upadacitinib 7.5-, 15-, and 30-mg groups, respectively, versus 23% (6.4%) for placebo ($P = .03$, $<.001$, and $<.001$). Serious adverse events occurred in 4.8% (2 of 42), 2.4% (1 of 42), and 0% (0 of 42) of upadacitinib groups (vs 2.5% [1 of 40] for placebo).

Conclusions: A dose-response relationship was observed for upadacitinib efficacy; the 30-mg once-daily dose showed the greatest clinical benefit. Dose-limiting toxicity was not observed. (*J Allergy Clin Immunol* 2020;145:877-84.)

Key words: Atopic dermatitis, randomized clinical trial, eczema, efficacy, Janus kinase, placebo-controlled, upadacitinib, safety

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Abbreviations used

AD:	Atopic dermatitis
AE:	Adverse event
ALT:	Alanine aminotransferase
AST:	Aspartate aminotransferase
BSA:	Body surface area
EASI 90:	≥90% improvement in Eczema Area and Severity Index
IGA:	Investigator Global Assessment
IGA 0/1:	Investigator Global Assessment of 0 or 1
JAK:	Janus kinase
NRS:	Numeric rating scale
POEM:	Patient-Oriented Eczema Measure
QD:	Once daily
SCORAD:	SCORing Atopic Dermatitis

Atopic dermatitis (AD) is a common inflammatory skin disease characterized by recurrent eczematous lesions,¹ which are associated with intense pruritus that greatly interferes with quality of life and sleep,² particularly in those with moderate to severe disease (16%-71% of patients across different ages and regions).³ AD in adults may persist from childhood⁴ or may begin or reoccur in adulthood.⁵ Corticosteroids are an orally administered systemic treatment widely used for patients with AD,⁶ but there is risk of exposure-associated adverse effects with long-term and short-term use.⁷ In some countries, cyclosporine A is approved for use for patients with severe AD but generally as short-term rescue therapy (≤1 year) because of cumulative nephrotoxicity. The paucity of approved treatments has led to recommendations for the use of other agents not approved for AD (eg, methotrexate and azathioprine)⁸ and motivated discovery and development of new compounds. Dupilumab, an approved injectable biologic for the treatment of moderate to severe AD, blocks binding of the T_H2 cytokines IL-4 and IL-13 to IL-4 receptor α .⁹ Dupilumab administered every other week provided significant benefit compared with placebo in phase 2 and 3 trials by week 16; however, less than or equal to 40% of patients achieved clear or almost clear skin (as defined by ≥90% improvement in Eczema Area and Severity Index [EASI 90] or Investigator Global Assessment of 0 or 1 [IGA 0/1]).⁹⁻¹¹ Thus, there remains a large unmet need for treatments with better efficacy and a safety profile that is acceptable for long-term use.

Similar to psoriasis, AD is associated with T-cell activation in the skin and blood but is a more heterogeneous disease.¹² In AD, the T_H2 and T_H22 cytokine pathways are activated, and some disease subtypes also appear to involve T_H1 and T_H17 cells.¹³⁻¹⁵ Thus, targeting multiple cytokine axes may be required to achieve broad efficacy.¹³ Many cytokines implicated in the pathogenesis of AD (eg, T_H2 cytokines [IL-4, IL-5, IL-13], IL-22, IL-31, IL-33, chemokines, thymic stromal lymphopoietin, and IFN- γ) exert their effects via intracellular signaling that involves the Janus kinase (JAK) and signal transducer and activator of transcription pathways.^{15,16}

Preclinical research shows that disruption of JAK1 signaling reduces chronic itch by mechanisms involving T_H2 cytokines, which may also directly stimulate neurons to elicit itching¹⁷ and supports a potential role for JAK inhibitors in the treatment of AD. Upadacitinib is an oral reversible JAK1 inhibitor engineered for increased selectivity for JAK1 over JAK2, JAK3, and

tyrosine kinase²¹⁸ and is currently being investigated for several immune-mediated inflammatory diseases. Minimizing inhibition of JAK2 and JAK3 may reduce adverse effects, such as anemia and infections.¹⁹

The objective of this study was to evaluate the safety and efficacy of multiple doses of upadacitinib versus placebo in adults with moderate to severe AD. Several other studies have tested JAK inhibitors for the treatment of AD²⁰; however, interpretation of the results was complicated by concomitant use of topical corticosteroids (eg, in the case of baricitinib).²¹ Ours was the first study to examine selective JAK1-inhibitor monotherapy for the treatment of AD.

METHODS

Study design

This is a phase 2b, double-blind, randomized, parallel-group, dose-ranging trial conducted at clinical centers in Australia, Canada, Finland, Germany, Japan, the Netherlands, Spain, and the United States. Results from the 16-week, double-blind, randomized treatment period are reported on the basis of an interim database lock for the prespecified final efficacy analysis for this period. A subsequent 72-week, double-blind, randomized withdrawal period is ongoing. The study is being conducted in accordance with International Council for Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. An independent ethics committee or institutional review board at each study center approved the study protocol and other study-related documents before procedures began. Patients provided written informed consent before beginning the study.

Patients

Eligible patients were 18 to 75 years old at screening, with a dermatologist-confirmed diagnosis of AD according to Hanifin and Rajka criteria (≥3 of 4 major features and ≥3 of 23 minor features),²² with symptoms for 1 year or more before baseline. The patients had moderate to severe AD, defined as EASI value of 16 or more, affected body surface area (BSA) greater than or equal to 10%, and IGA 3 or more, at baseline. They had inadequate response to topical corticosteroids or topical calcineurin inhibitors within 1 year before screening, or were patients for whom topical treatments were otherwise medically inadvisable (eg, because of important side effects or safety risks). All patients were to use an additive-free bland emollient twice daily for 7 days or more before baseline and during the study (for details, see this article's [Methods](#) section in the Online Repository at www.jacionline.org).

Randomization and masking

An interactive response system referring to a schedule previously generated via computer by statisticians from the study sponsor was used to randomize qualifying patients 1:1:1:1, stratified by geographic region (United States, Puerto Rico, and Canada; European Union and Australia; and Japan). Patients, investigators, and the sponsor were blinded to allocation. Each study drug kit was labeled with a unique code that was linked to the randomization schedule. The placebo and upadacitinib tablets were identical in appearance to maintain blinding of treatment assignment.

Procedures

Patients received placebo or extended-release upadacitinib (manufactured by the study sponsor) 7.5, 15, or 30 mg once daily (QD) by mouth. After the baseline visit, patients returned to the clinic at weeks 2, 4, 8, 12, and 16. Discontinuation of study drug (placebo or upadacitinib) was required if a patient's EASI worsened by greater than or equal to 25% from baseline at 2 consecutive visits between weeks 4 and 12.

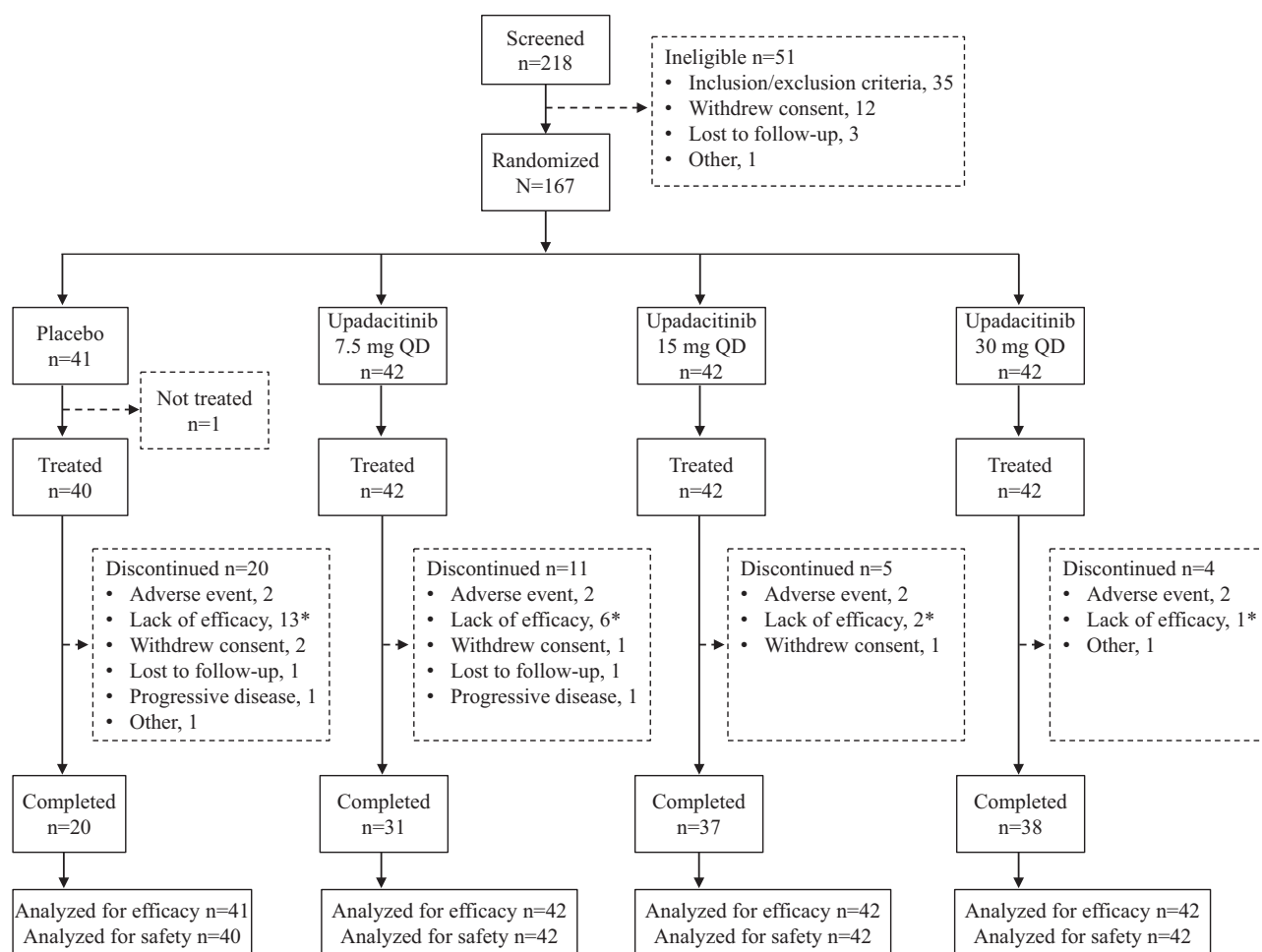


FIG 1. Patient disposition with primary reasons for discontinuation of study drug. *May include meeting criteria for greater than or equal to 25% worsening of Eczema Area and Severity Index, resulting in discontinuation of study drug according to the protocol.

Efficacy assessments, recorded at baseline and during clinic visits at weeks 2, 4, 8, 12, and 16, included EASI, IGA, pruritus numeric rating scale (NRS; weekly average of daily patient assessments), SCORing Atopic Dermatitis (SCORAD),²³ BSA, and Patient-Oriented Eczema Measure (POEM).²⁴ For details, see this article's [Methods](#) section in the Online Repository.

Safety monitoring included treatment-emergent adverse events (AEs), physical examinations, vital signs, and clinical laboratory assessments. AEs, vital signs, and clinical laboratory assessments were recorded at each clinic visit. Physical examinations were made at baseline and week 16.

Outcomes

Primary and secondary outcomes were prespecified. The primary end point was percentage improvement from baseline at week 16 in EASI. Secondary end points were proportions of patients achieving improvement of greater than or equal to 50%/greater than or equal to 75%/greater than or equal to 90% from baseline in EASI (EASI 50/75/90) at weeks 8 and 16; proportions of patients achieving IGA 0/1 at week 16; percentage improvement from baseline in EASI at week 8; percentage improvement from baseline in pruritus NRS by week and proportions of patients achieving pruritus NRS improvement from baseline of 4 points or more at each visit (among patients with baseline NRS ≥ 4 points); percentage improvement from baseline in SCORAD at weeks 8 and 16; proportions of patients achieving greater than or equal to 50%/greater than or equal to 75%/greater than or equal to 90% improvement from baseline in SCORAD (SCORAD 50/75/90) at weeks 8 and 16; and change from

baseline in BSA at week 16. The primary and secondary variables were also analyzed for all study visits at which they were assessed. Additional end points included percentage improvement from baseline in BSA at each visit, proportions of patients achieving EASI 100 at each visit, and change from baseline in POEM at weeks 4 and 16. Dermatology Life Quality Index outcomes (proportion of patients achieving score 0/1 and change from baseline) were defined but are not reported because of an error in the programming of the electronic device used to administer the questionnaire that precluded determination of these outcomes.

Upadacitinib plasma concentrations were quantitated as previously described.²⁵

AEs were coded according to Medical Dictionary for Regulatory Activities, version 20.0. Changes from baseline in physical examination findings, vital signs, and clinical laboratory values were recorded. Assessment of the severity of AEs and laboratory changes was based on Common Terminology Criteria for Adverse Events (version 4.0) developed by the National Cancer Institute.

Statistical analysis

Forty patients per treatment arm were targeted for enrollment. Assuming that improvements of 35%, 45%, 60%, and 70% would occur for the primary end point in the placebo and upadacitinib 7.5-, 15-, and 30-mg QD groups, respectively, with an SD of 40%, this sample size provides 99% average power to detect a dose effect at a 5% level of

TABLE I. Patients' demographic and baseline characteristics

Characteristic	Placebo (n = 41)	Upadacitinib 7.5 mg QD (n = 42)	Upadacitinib 15 mg QD (n = 42)	Upadacitinib 30 mg QD (n = 42)
Sex: female, n (%)	17 (41)	14 (33)	12 (29)	20 (48)
Age, y, mean $\pm$ SD	39.9 $\pm$ 17.5	41.5 $\pm$ 15.4	38.5 $\pm$ 15.2	39.9 $\pm$ 15.3
Race, n (%)				
White	28 (68)	24 (57)	21 (50)	23 (55)
Black or African American	6 (15)	7 (17)	10 (24)	6 (14)
Asian	7 (17)	9 (21)	9 (21)	13 (31)
Native Hawaiian or other Pacific Islander	0	2 (4.8)	1 (2.4)	0
American Indian or Alaska Native	0	0	1 (2.4)	0
Hispanic or Latino ethnicity, n (%)	0	2 (4.8)	2 (4.8)	1 (2.4)
BMI (kg/m ²), mean $\pm$ SD	26.2 $\pm$ 6.8	27.9 $\pm$ 6.3	27.4 $\pm$ 6.7	27.4 $\pm$ 6.0
Region, n (%)				
USA/PR/Canada	29 (71)	29 (69)	29 (69)	29 (69)
EU/Australia	10 (24)	11 (26)	10 (24)	10 (24)
Japan	2 (4.9)	2 (4.8)	3 (7.1)	3 (7.1)
Duration since AD diagnosis (y), mean $\pm$ SD	26.8 $\pm$ 18.8*	30.4 $\pm$ 18.1	22.6 $\pm$ 15.8	24.2 $\pm$ 13.6
Duration of AD symptoms (y), mean $\pm$ SD	30.6 $\pm$ 18.6*	33.9 $\pm$ 18.0	23.6 $\pm$ 15.2†	26.7 $\pm$ 15.7†
History of asthma, n (%)	14 (34)	15 (36)	11 (26)	14 (33)
Eosinophils ($\times 10^9/L$), mean $\pm$ SD	0.556† $\pm$ 0.497	0.575 $\pm$ 0.683	0.446 $\pm$ 0.475	0.518 $\pm$ 0.385
EASI, mean $\pm$ SD‡	32.6 $\pm$ 14.5	31.4 $\pm$ 15.8	31.4 $\pm$ 12.3	28.2 $\pm$ 11.6
BSA (%), mean $\pm$ SD	45.7 $\pm$ 22.8	46.9 $\pm$ 24.9	50.6 $\pm$ 21.5	42.1 $\pm$ 20.4
IGA, n (%)§				
Moderate (IGA = 3)	18 (44)	29 (69)	19 (45)	31 (74)
Severe (IGA = 4)	23 (56)	13 (31)	23 (55)	11 (26)
Pruritus NRS, mean $\pm$ SD	6.5 $\pm$ 1.9†	6.8 $\pm$ 1.8†	6.4 $\pm$ 1.7¶	6.3 $\pm$ 2.1

BMI, Body mass index; PR, Puerto Rico.

*Data missing for 1 patient.

†Data missing for 2 patients.

‡Full scale ranges from 0 (none) to 72 (most severe).

§Full scale ranges from 0 (clear) to 4 (severe).

||Full scale ranges from 0 (no itch) to 10 (worst imaginable itch).

¶Data missing for 5 patients.

significance (1-sided) to characterize the dose-response for upadacitinib. This sample size also provided 97% power to detect a difference for upadacitinib 30 mg QD compared with placebo and 78% power to detect a difference for upadacitinib 15 mg QD compared with placebo at a 2-sided significance level of 5%. Between-group statistical comparisons of continuous efficacy end points were made by analysis of covariance, with stratum (geographic region), baseline value, and treatment in the model. Between-group statistical comparisons of categorical efficacy end points were made with the Cochran-Mantel-Haenszel test, adjusted for stratum (geographic region). All efficacy analyses were conducted in the intention-to-treat population, comprising all randomized patients, based on treatment assigned. Missing efficacy data were analyzed by last observation carried forward (continuous variables) and by nonresponder imputation (categorical variables). The dose-response relationships among the 3 upadacitinib treatment groups and the placebo group were characterized for the primary end point using a multiple comparison procedures and modeling approach that also controlled for overall type I error. Secondary end points and other efficacy end points were analyzed at the nominal alpha level of 5%. Safety was analyzed in all randomized patients who received 1 or more doses of study medication, based on actual treatment received. A data monitoring committee oversaw unblinded safety results during the study. Cardiovascular events were adjudicated by a blinded, independent adjudication committee according to predefined criteria. Treatment-emergent AEs (ie, those that occurred after starting study drug through 30 days after the last dose) were summarized with descriptive statistics; between-group statistical comparisons of laboratory measures were made by using a contrast within a 1-way ANOVA. Analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC). The study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02925117) (no. NCT02925117).

RESULTS

Patients

Between October 25, 2016, and March 16, 2017, 218 patients were assessed for eligibility, of whom 167 were found eligible and enrolled to the study, and 166 received placebo or upadacitinib (Fig 1). The first patient was enrolled on November 21, 2016, and the last on April 20, 2017. Premature discontinuation was more common with placebo (primarily due to lack of efficacy) than with upadacitinib. Patient demographic and baseline characteristics were generally well balanced among treatment arms, except that numerically fewer patients had an IGA of 4 (severe AD) in the upadacitinib 7.5- and 30-mg groups compared with the placebo and upadacitinib 15-mg groups (Table I).

Efficacy

All upadacitinib doses (7.5, 15, and 30 mg) showed significantly higher mean (SE) percentage improvement from baseline at week 16 in EASI versus placebo (39% [6.2%], $P = .03$; 62% [6.1%], $P < .001$; and 74% [6.1%], $P < .001$ vs 23% [6.4%], respectively), with a clear dose-response relationship (Fig 2). Mean (95% CI) difference versus placebo for percentage improvement from baseline at week 16 in EASI was 16% (1.4%-31%), 39% (24%-54%), and 51% (36%-67%), for upadacitinib 7.5, 15, and 30 mg, respectively. The dose-response relationship for upadacitinib doses (7.5, 15, and 30 mg) was

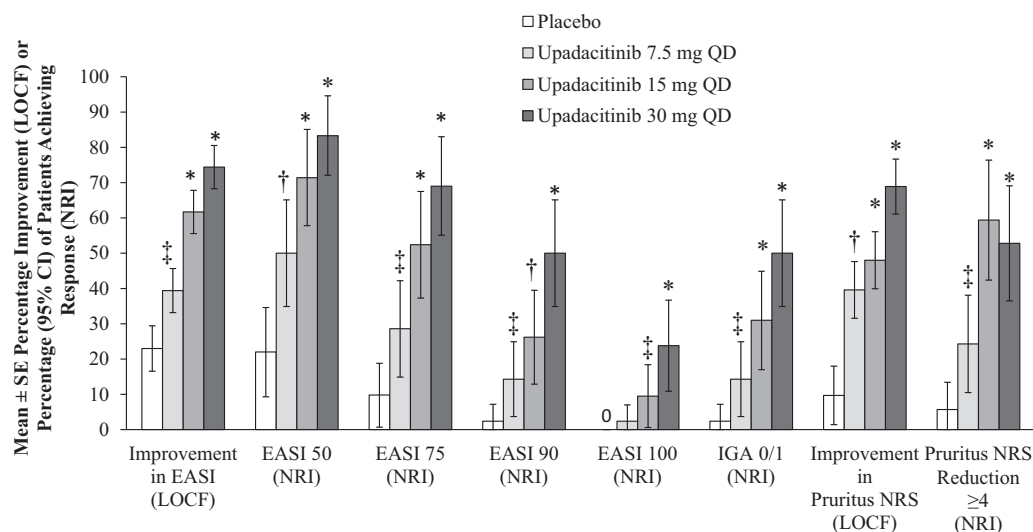


FIG 2. EASI, IGA 0/1, and pruritus NRS outcomes at week 16. EASI 50/75/90/100, Greater than or equal to 50%/greater than or equal to 75%/greater than or equal to 90%/100% improvement in EASI; LOCF, last observation carried forward; NRI, nonresponder imputation. * $P \leq .001$, † $P \leq .01$, and ‡ $P \leq .05$ for upadacitinib vs placebo.

consistently demonstrated for this end point in the subgroups of patients with baseline IGA of 3 (40% [8.3%], $P = .23$; 63% [9.6%], $P = .004$; and 73% [7.6%], $P < .001$ vs 27% [10%] for placebo) and baseline IGA of 4 (35% [10%], $P = .19$; 59% [8.3%], $P < .001$; and 75% [11%], $P < .001$ vs 19% [8.5%] for placebo), confirming that treatment response was not affected by the numerical imbalance in baseline IGA among the treatment groups. Statistical significance in favor of all upadacitinib doses in EASI 50, EASI 75, and EASI 90 responses was also achieved at week 16; EASI 100 was achieved by 2.4% (1 of 42; $P = .43$), 9.5% (4 of 42; $P = .05$), and 24% (10 of 42; $P = .001$) of patients in the upadacitinib 7.5-, 15-, and 30-mg groups, respectively, versus none (0 of 41) in the placebo group. Each upadacitinib dose level was significantly superior to placebo for investigator assessment (IGA 0/1) and patient assessment of pruritus (improvement in NRS and achievement of NRS reduction ≥ 4) at week 16. Efficacy at the studied doses was generally demonstrated by week 1 to 4, with peak values reached and maintained after week 4 or 8 (Fig 3; see Fig E1 in this article's Online Repository at www.jacionline.org). SCORAD outcomes at weeks 8 and 16 favored upadacitinib compared with placebo, reaching statistical significance for most comparisons (see Fig E2 in this article's Online Repository at www.jacionline.org). Mean percentage reductions in BSA were significantly greater in all upadacitinib groups compared with placebo at every assessment (weeks 2, 4, 8, 12, and 16; see Fig E3 in this article's Online Repository at www.jacionline.org), with the exception of the last assessment in the upadacitinib 7.5-mg group. POEM scores at weeks 4 and 16 improved significantly more in all upadacitinib groups compared with the placebo group (see Fig E4 in this article's Online Repository at www.jacionline.org).

Pharmacokinetics

Upadacitinib exposures were approximately dose proportional over the 7.5- to 30-mg dose range. Upadacitinib median (interquartile range) plasma concentrations around peak and

trough times were consistent with exposures previously observed for the evaluated doses in healthy volunteers (7.5-mg dose: 10.6 [0.8-21.0] and 2.8 [1.4-4.5] ng/mL, respectively; 15-mg dose: 32.5 [22.7-39.3] and 3.6 [1.8-7.0] ng/mL; 30-mg dose: 57.0 [28.1-94.8] and 8.1 [6.6-16.6] ng/mL).²⁶

Safety

Exposure to study drug was lower in the placebo group (Table II) because of the higher rate of study discontinuation (Fig 1) in this group compared with the upadacitinib groups. AEs were reported in 71% (30 of 42), 74% (31 of 42), and 79% (33 of 42) of patients receiving upadacitinib 7.5, 15, and 30 mg, respectively, versus 63% (25 of 40) of patients receiving placebo (Table II). The most frequently reported AEs ($\geq 10\%$ in any group) were upper respiratory tract infection, AD worsening, and acne (all reported as mild or moderate in severity). There was no relationship between the dose of upadacitinib and the occurrence of particular AEs.

Serious AEs were infrequent and occurred in no more than 2 patients in any treatment group (Table II). In the placebo group, a serious AE of atrial fibrillation occurred in a 71-year-old man with a history of atrial fibrillation, sick sinus syndrome, hypertension, asthma, emphysema/chronic obstructive pulmonary disease, obstructive sleep apnea, and smoking (30 years). Two patients in the upadacitinib 7.5-mg group had serious AEs: a 35-year-old man with a history of repeated tooth infections experienced lower jaw pericoronitis, and a 20-year-old woman experienced worsening AD (skin infection and exacerbation of AD) in the context of contact dermatitis. In the upadacitinib 15-mg group, 1 serious AE of appendicitis was reported in a 66-year-old man. No serious AEs occurred in patients allocated to upadacitinib 30 mg. All serious AEs resolved with treatment in patients who received upadacitinib. The number of AEs leading to discontinuation was low across the placebo and upadacitinib treatment groups ($n = 3$, $n = 4$, $n = 2$, and $n = 4$ in the placebo and upadacitinib 7.5-, 15-, and 30-mg groups).

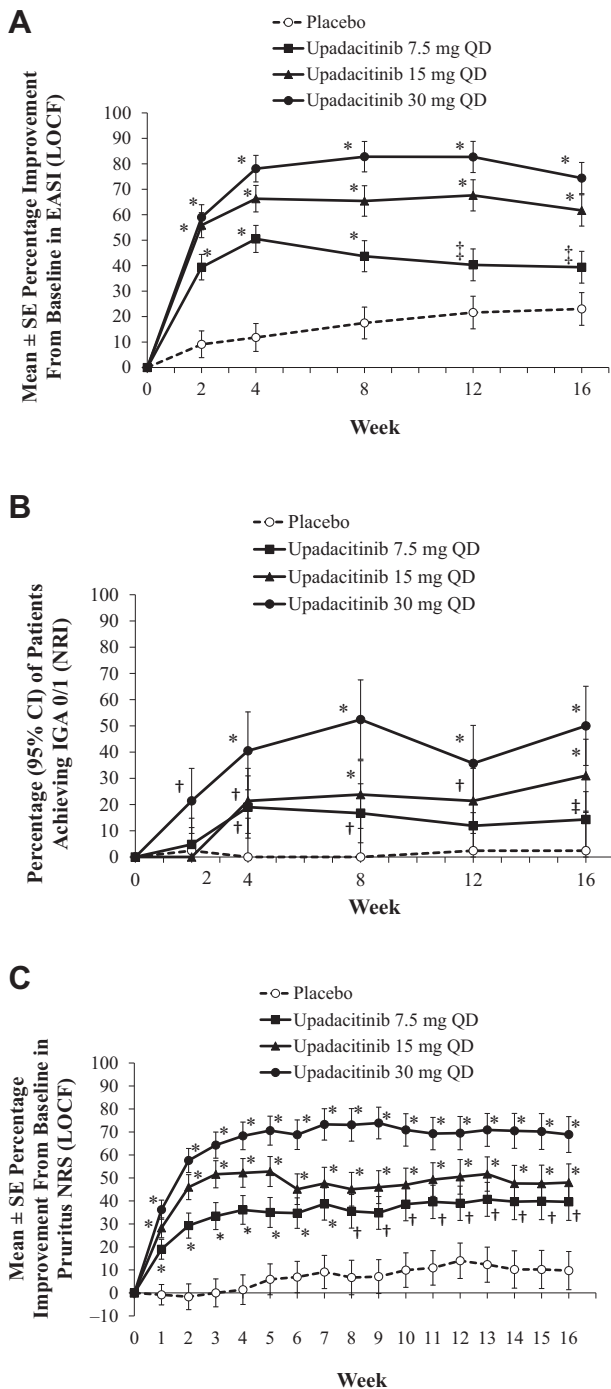


FIG 3. EASI (A), IGA 0/1 (B), and pruritus NRS (C) over time. LOCF, Last observation carried forward. * $P \leq .001$, † $P \leq .01$, and ‡ $P \leq .05$ for upadacitinib vs placebo.

There were no deaths, opportunistic infections, malignancies, gastrointestinal perforations, AEs of herpes zoster, renal dysfunction, active or latent tuberculosis, adjudicated cardiovascular events, or thromboembolic events. Infections were more common with upadacitinib than with placebo, but there were few serious infections (Table II). Although 63 of 167 patients (38%) had a history of asthma, no AEs of asthma exacerbation were reported during the study.

Mean laboratory values remained within normal ranges (see Fig E5 in this article's Online Repository at www.jacionline.org), and grade 3 and 4 laboratory abnormalities were uncommon (see Table E1 in this article's Online Repository at www.jacionline.org). Hepatic disorder AEs, none serious, were reported in 3 patients during the study (Table II; alanine aminotransferase [ALT] and aspartate aminotransferase [AST] increased in 1 patient in the placebo group [neither event with grade ≥ 2 laboratory increase]; blood bilirubin increased in 1 patient in the upadacitinib 15-mg group [grade 2 laboratory increase]; and hepatic steatosis in another patient in the upadacitinib 15-mg group [associated with grade 2 ALT increase]). All hepatic disorder AEs were considered mild and resolved without dosing changes. Mean changes in ALT and AST levels were similar among treatment groups, and no grade 3 or 4 ALT or AST elevations occurred in patients receiving upadacitinib. All AEs of creatine phosphokinase elevation were asymptomatic in patients receiving upadacitinib and reported as mild to moderate in severity (Table E1). Mean hemoglobin levels decreased more with upadacitinib compared with placebo but remained at 133 to 145 g/L, which is within the normal ranges for both women and men. No patients had hemoglobin abnormalities of grade 3 or more. No decrease in mean absolute lymphocyte counts was observed in any upadacitinib treatment group, and no patients had lymphocyte abnormalities of grade 3 or more. Decreases in mean neutrophil counts were small and generally similar between upadacitinib and placebo. There were increases in mean concentrations of low-density and high-density lipoprotein cholesterol in the upadacitinib groups compared with the placebo group, but lipid ratios showed no clear pattern of change (see Table E2 in this article's Online Repository at www.jacionline.org).

DISCUSSION

In this first study to investigate the efficacy and safety of the JAK1-selective inhibitor upadacitinib as monotherapy for the treatment of adults with moderate to severe AD inadequately controlled by topical medications, upadacitinib was efficacious and appeared to exhibit a favorable benefit/risk profile compared with placebo. This phase 2b clinical trial enrolled a population of patients with long-standing AD whose baseline severity was comparable to that in the dupilumab phase 3 studies.⁹⁻¹¹ The primary efficacy end point of percentage improvement from baseline to week 16 in EASI and multiple other end points (eg, EASI 50, EASI 75, EASI 90, and IGA 0/1) were statistically significantly better at each upadacitinib dose level compared with placebo, with a clear dose response. Achievement of EASI 100 was significantly higher in the upadacitinib 15-mg and 30-mg groups versus placebo at week 16. We also noted marked improvement from baseline at week 16 in pruritus, SCORAD, BSA, and POEM with each upadacitinib dose regimen. Signs and symptoms showed rapid improvements with upadacitinib compared with placebo; pruritus improved significantly at first assessment (week 1), as did clinical efficacy end points (first assessments at week 2). The alleviation of pruritus may be particularly important because itching worsens the quality of life (including loss of sleep and suicidal thoughts) of patients with AD.² Maximal efficacy for percentage improvement in EASI, EASI 50, and EASI 75 was reached at week 4 and maintained through week 16. More stringently defined end points (EASI 90 and IGA 0/1) plateaued between weeks 8 and 16, although the EASI 100 response was

TABLE II. AE summary*

Treatment-emergent AE, n (%)	Placebo (n = 40)	Upadacitinib 7.5 mg QD (n = 42)	Upadacitinib 15 mg QD (n = 42)	Upadacitinib 30 mg QD (n = 42)
Any AE	25 (63)	31 (74)	32 (76)	33 (79)
Serious AE	1 (2.5)	2 (4.8)	1 (2.4)	0
AE leading to discontinuation of study drug	3 (7.5)	4 (9.5)	2 (4.8)	4 (9.5)
Infection	8 (20)	22 (52)	18 (43)	17 (41)
Serious infection	0	2 (4.8) [†]	1 (2.4) [‡]	0
Hepatic disorder	1 (2.5) [§]	0	2 (4.8)	0
Anemia	0	0	0	1 (2.4)
Neutropenia	0	1 (2.4)	2 (4.8)	2 (4.8)
Lymphopenia	0	0	1 (2.4)	0
AE in ≥5% of patients in any group				
URTI	4 (10)	7 (17)	5 (12)	5 (12)
AD worsening	2 (5.0)	6 (14)	2 (4.8)	4 (9.5)
Acne	1 (2.5)	4 (9.5)	2 (4.8)	6 (14)
Headache	1 (2.5)	3 (7.1)	3 (7.1)	4 (9.5)
Nasopharyngitis	1 (2.5)	2 (4.8)	4 (9.5)	3 (7.1)
Blood CPK increased	2 (5.0)	0	3 (7.1)	4 (9.5)
Nausea	1 (2.5)	3 (7.1)	1 (2.4)	3 (7.1)
Diarrhea	2 (5.0)	2 (4.8)	2 (4.8)	0
Influenza	0	3 (7.1)	0	0
Oropharyngeal pain	0	3 (7.1)	0	0
Contact dermatitis	2 (5.0)	0	1 (2.4)	1 (2.4)
Hematuria	2 (5.0)	0	0	0
Proteinuria	2 (5.0)	0	0	0
Ligament sprain	2 (5.0)	0	0	0

CPK, Creatine phosphokinase; URTI, upper respiratory tract infection.

*Mean ± SD exposure to study drug in the placebo, upadacitinib 7.5-mg, upadacitinib 15-mg, and upadacitinib 30-mg groups was 81.6 ± 41.2, 101.3 ± 28.5, 104.2 ± 24.5, and 108.9 ± 16.4 days, respectively.

[†]One event each of skin infection and pericoronitis.

[‡]One event of appendicitis.

[§]One patient with ALT increased and AST increased.

^{||}One patient with blood bilirubin increased; 1 patient with hepatic steatosis.

still increasing at week 16. In this phase 2b study, there were no dose-limiting safety events or unexpected safety findings that would preclude further evaluation of upadacitinib in AD.

A clear dose response was observed for the primary end point and most secondary end points. Upadacitinib 30 mg QD was associated with the greatest reduction in EASI and appeared to present the best benefit/risk profile; the EASI 90 and IGA 0/1 results with upadacitinib 30 mg (both end points, 50.0% at week 16) are high for a systemic monotherapy in this patient population. A threshold of response, EASI 100, that had not previously been reported before this study began was defined and observed with upadacitinib. The improvement in pruritus with JAK1 inhibition in this trial may have been mediated by blocking the effects of IL-31 and factors that directly induce itching in sensory neurons.¹⁷ More broadly, the efficacy observed in this trial may reflect the fact that JAK1 inhibition targets additional cytokine pathways involved in chronic AD¹⁵ beyond just T_H2 and T_H22 cytokines.¹⁶ Further research may reveal whether JAK1 inhibition might be beneficial in atopic diseases other than AD.

In this study with a limited population size that might not be representative of all potential AD populations, no dose-limiting safety events nor any new safety concerns compared with the ongoing upadacitinib rheumatoid arthritis phase 3 program were observed, even though safety analyses were not adjusted for the greater rate of discontinuation in the placebo group. No dose relationship was observed in the overall rate of AEs. Infections (but not serious infections) were more common with upadacitinib

compared with placebo. The events of acne, diagnosed by the dermatologist investigators, were unexpected; however, as none of those AEs was serious, no further details, for example, the type of acne, are available. No deaths, herpes zoster, malignancies, or thromboembolic events were reported. Dose-dependent decreases in mean hemoglobin levels were small and remained within the normal ranges for women and men; no grade 3 or 4 decreases in hemoglobin were reported. A small number of asymptomatic creatine phosphokinase abnormalities were observed but did not require permanent discontinuation in study drug dosing.

A limitation of this report is the 16-week duration of treatment. Although efficacy appeared to stabilize within the 16-week period (except EASI 100, which was still increasing), the ongoing 72-week period of this study will provide information on longer-term efficacy and safety. Another limitation is that a dose-limiting toxicity was not defined and therefore complete dose ranging was not accomplished. In fact, efficacy did not plateau with the tested doses so it is possible that higher doses might have produced even greater efficacy. However, unprecedented efficacy in patients with AD was demonstrated with upadacitinib 30 mg in this study, and small dose-dependent changes, not considered to be clinically meaningful, in hemoglobin, neutrophils, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol over time were observed. Overall, based on the phase 2 data, the 30-mg QD upadacitinib dose appears to have a favorable benefit/risk profile in AD.

Overall, upadacitinib showed rapid clinical improvement in the primary and secondary study outcomes at every dose studied, with particularly robust efficacy at the 2 highest doses. Because of these results, upadacitinib is the first oral agent granted breakthrough therapy designation by the US Food and Drug Administration for development in AD.

Conclusions

Upadacitinib monotherapy was efficacious and demonstrated a favorable benefit/risk profile compared with placebo in adults with moderate to severe AD and inadequate response to topical treatments, supporting initiation of larger randomized, controlled, phase 3 studies to confirm its potential as an effective treatment for this population.

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These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the AbbVie data and information sharing website: <https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html>.

Clinical implication: The favorable benefit/risk profile of upadacitinib supported initiation of phase 3 trials in atopic dermatitis.

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Online Repository

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Methods

Patients

Patients were excluded from the study if they had prior exposure to any Janus kinase (JAK) inhibitor or dupilumab; treatment within 10 days before baseline with topical corticosteroids, topical calcineurin inhibitors, prescription moisturizers, or moisturizers with additives (e.g., ceramide, hyaluronic acid, urea, or filaggrin); exposure to any investigational systemic treatment within 30 days or 5 half-lives of baseline, whichever was longer, or current enrollment in another clinical study; exposure to systemic treatment for atopic dermatitis (AD), including but not limited to corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 inhibitors, and mycophenolate mofetil, within 4 weeks before baseline; or phototherapy, tanning booth use, or extended sun exposure that could affect disease severity or interfere with disease measurements, within 4 weeks of baseline.

Concomitant medications for the treatment of AD, other than an additive-free bland emollient and orally administered antibiotics for superficial skin infections, were prohibited during the 16-week, randomized, double-blind part of the study reported here. The following were prohibited during the study period: JAK inhibitors (other than upadacitinib) and other non-biologic systemic treatments for AD; all biologic therapies, corticosteroids, phototherapy, and forms of extensive light exposure that could have affected study outcomes; all topical therapies, investigational drugs, live vaccines, cannabis, and strong inducers and inhibitors of cytochrome P450 3A; and traditional Chinese medicine. Rescue treatment, including topical therapy, was not allowed until after the end of the 16-week, randomized, double-blind period.

Efficacy Assessments

The Dermatology Life Quality Index was administered at baseline and weeks 4 and 16. For the Eczema Area and Severity Index, the investigator scored the extent and severity of AD over 4 body regions (head and neck, trunk [including lower extremities], upper limbs, and lower limbs); the score could range from 0 (none) to 72 (most severe). For the Investigator Global Assessment, the investigator scored the patient's AD as 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), or 4 (severe). For the daily numeric rating scale (which was averaged over each 7-day week), the patient electronically scored pruritus over the past 24 hours on an 11-point scale ranging from 0 (no itch) to 10 (worst imaginable itch). The affected body surface area from 0% to 100% was estimated by the investigator. For the SCORing Atopic Dermatitis assessments, the investigator scored the extent of AD over 6 body regions (head and neck, upper limbs, lower limbs, anterior trunk, back, and genitals) and the severity in a representative area; the patient scored pruritus and loss of sleep over the past 3 days on a 10-cm visual analog scale. The score could range from 0 (none) to 103 (most severe). For the Patient-Oriented Eczema Measure, the patient answered seven questions about the frequency with which AD symptoms had occurred in the past week (no days [score=0], 1–2 days [score=1], 3–4 days [score=2], 5–6 days [score=3], or every day [score=4]); the score could range from 0 to 2 (clear or almost clear) to 25 to 28 (very severe eczema).

Measurement of Upadacitinib Plasma Concentrations

Upadacitinib plasma concentrations were assessed in plasma obtained from blood samples collected throughout the study (1 sample per post-baseline visit).

Table E1. Summary of Laboratory Abnormalities*

Laboratory Abnormalities by CTCAE Grade ≥2, n (%)	Placebo (n=39[†])	Upadacitinib 7.5 mg QD (n=42[†])	Upadacitinib 15 mg QD (n=42[†])	Upadacitinib 30 mg QD (n=42[†])
ALT				
Grade 2 (>3 to 5 ×ULN)	1 (2.6)	0	1 (2.4)	0
Grade 3 (>5 to 20 ×ULN)	0	0	0	0
Grade 4 (>20 ×ULN)	0	0	0	0
AST				
Grade 2 (>3 to 5 ×ULN)	0	0	0	0
Grade 3 (>5 to 20 ×ULN)	1 (2.6)	0	0	0
Grade 4 (>20 ×ULN)	0	0	0	0
CPK [‡]				
Grade 2 (>2.5 to 5 ×ULN)	2 (5.1)	4 (9.5)	4 (9.5)	2 (4.8)
Grade 3 [§] (>5 to 10 ×ULN)	0	0	1 (2.4)	1 (2.4)
Grade 4 (>10 ×ULN)	1 (2.6)	0	0	1 (2.4)
Hemoglobin				
Grade 2 (80 to <100 g/L)	1 (2.6)	1 (2.4)	0	1 (2.4)
Grade 3 (<80 g/L)	0	0	0	0
Grade 4 (life-threatening consequences)	0	0	0	0
Lymphocytes				
Grade 2 (0.5 to <0.8 ×10 ⁹ /L)	3 (7.7)	2 (4.8)	1 (2.4)	0
Grade 3 (0.2 to <0.5 ×10 ⁹ /L)	0	0	0	0
Grade 4 (<0.2 ×10 ⁹ /L)	0	0	0	0
Neutrophils				
Grade 2 (1.0 to <1.5 ×10 ⁹ /L)	0	3 (7.1)	2 (4.8)	2 (4.8)
Grade 3 (0.5 to <1.0 ×10 ⁹ /L)	0	0	0	1 (2.4)
Grade 4 (<0.5 ×10 ⁹ /L)	0	0	0	0

CPK, creatine phosphokinase; CTCAE, Common Terminology Criteria for Adverse Events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; QD, once daily; ULN, upper limit of normal.

*Includes any patient with at least 1 occurrence of a grade 2, 3, or 4 event that was worse than at baseline.

[†]Includes patients with at least 1 postbaseline observation.

[‡]The highest CPK value (>40,000 U/L) was reported in a patient from the placebo group during an influenza-like illness; all CPK elevations in patients receiving upadacitinib were ≤3505 U/L.

[§]Includes one man receiving upadacitinib 15 mg, with elevated baseline CPK whose work required heavy lifting, and one woman with no predisposing factors, receiving upadacitinib 30 mg.

^{||}Patient had an isolated grade 3 neutrophil abnormality, in the context of mild impetigo that normalized 8 days later without intervention.

Table E2. Lipoprotein Ratios

Lipid Ratio, mean (SD)	Placebo	Upadacitinib 7.5 mg QD	Upadacitinib 15 mg QD	Upadacitinib 30 mg QD
LDL-C/HDL-C				
Baseline	n=39	n=42	n=42	n=42
	1.942 (0.746)	2.165 (0.835)	2.038 (0.806)	1.959 (0.705)
Week 16	n=23	n=31	n=38	n=39
	1.951 (0.642)	1.969 (0.720)	2.046 (0.854)	1.849 (0.725)
TC/HDL-C				
Baseline	n=39	n=42	n=42	n=42
	3.407 (0.946)	3.797 (1.223)	3.535 (0.997)	3.438 (0.908)
Week 16	n=23	n=33	n=38	n=40
	3.473 (0.752)	3.644 (1.272)	3.567 (1.042)	3.344 (1.037)

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; QD, once daily.

All $P > 0.05$ for differences between treatment groups in baseline and mean change from baseline using a contrast within a 1-way analysis of variance.

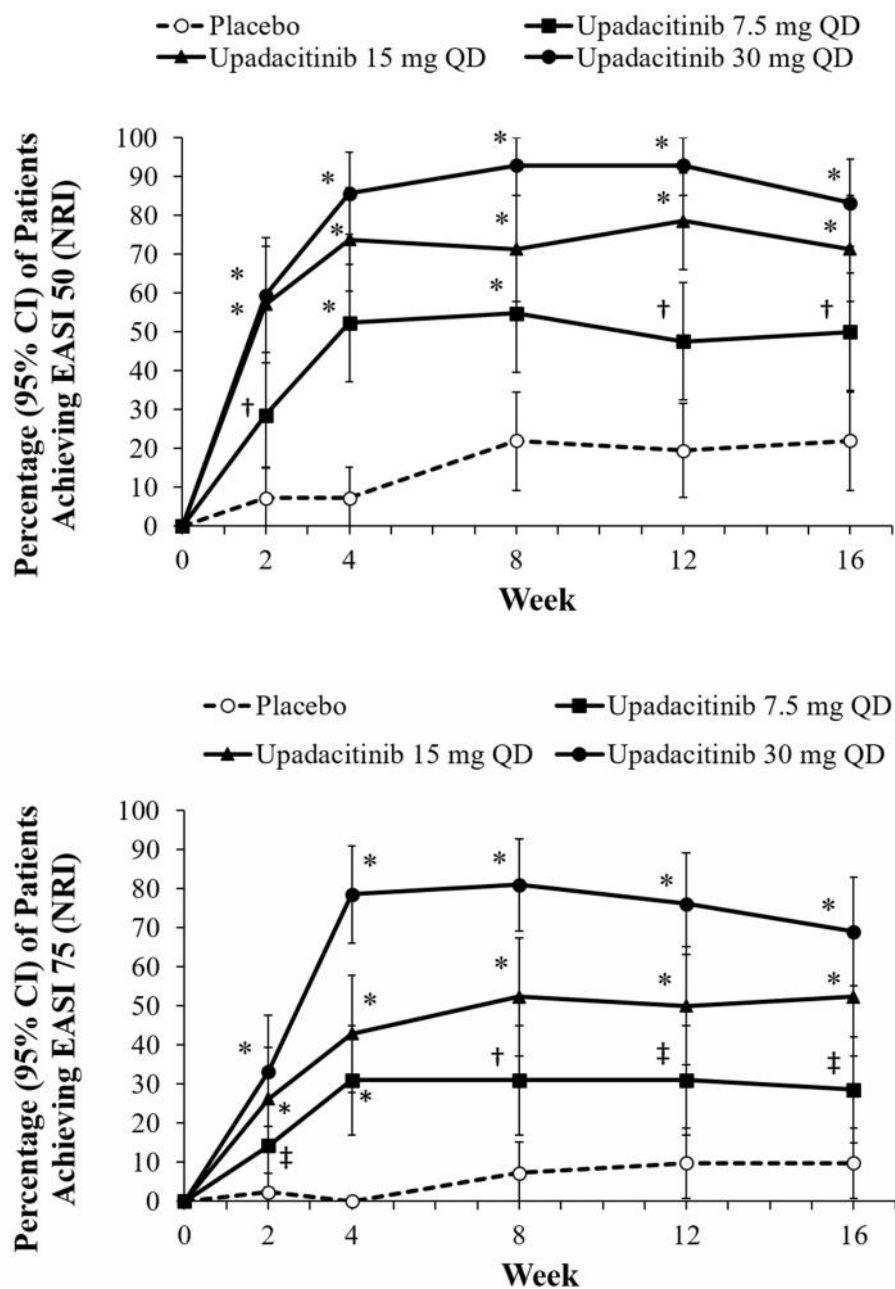


Figure E1. EASI 50/75/90 and pruritus NRS improvement ≥ 4 over time.

EASI, Eczema Area and Severity Index; EASI 50/75/90, $\geq 50\%$ / $\geq 75\%$ / $\geq 90\%$ improvement in EASI; NRI, non-responder imputation; NRS, numeric rating scale; QD, once daily. * $P \leq 0.001$, $^{\dagger}P \leq 0.01$, and $^{\ddagger}P \leq 0.05$ for upadacitinib vs placebo.

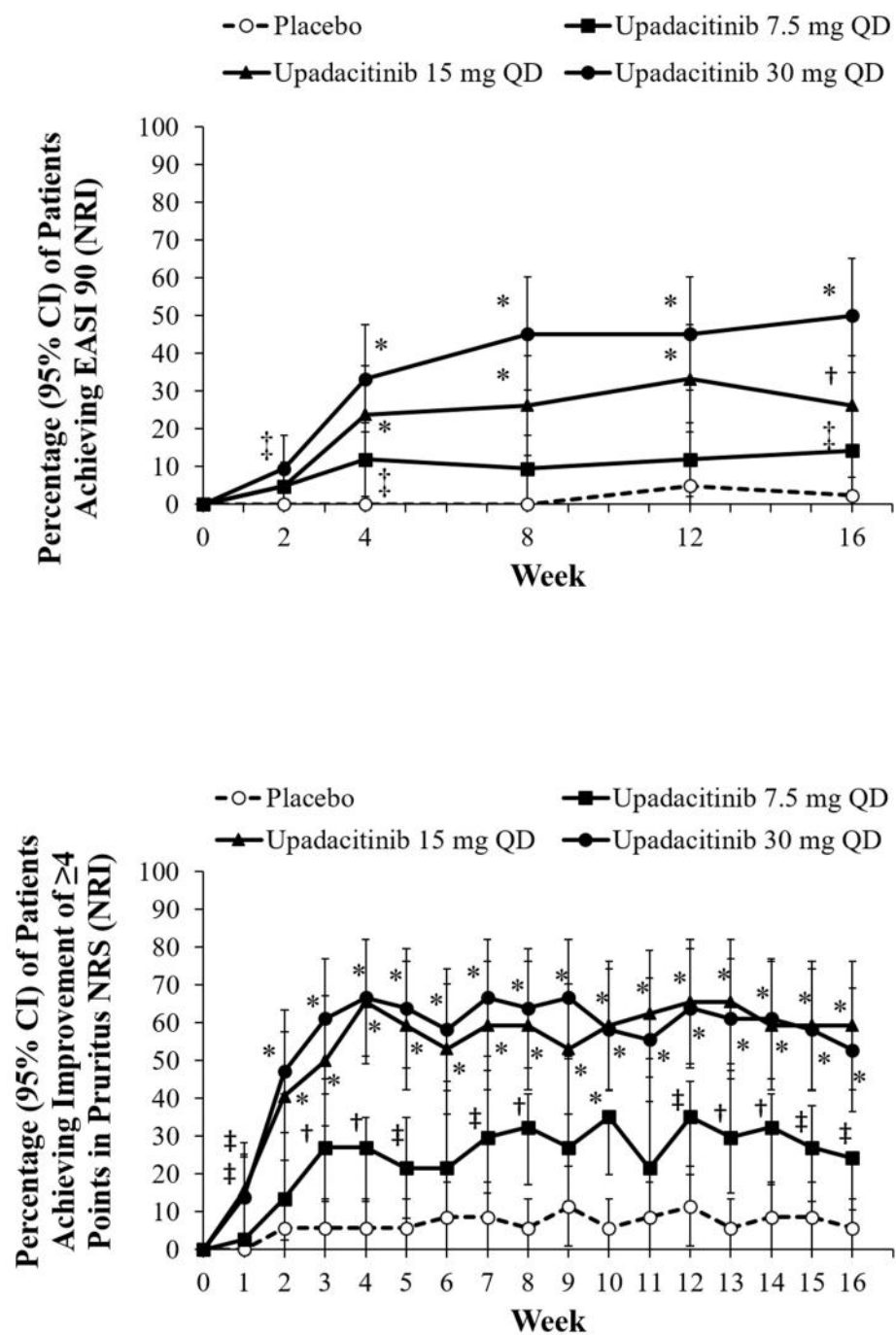


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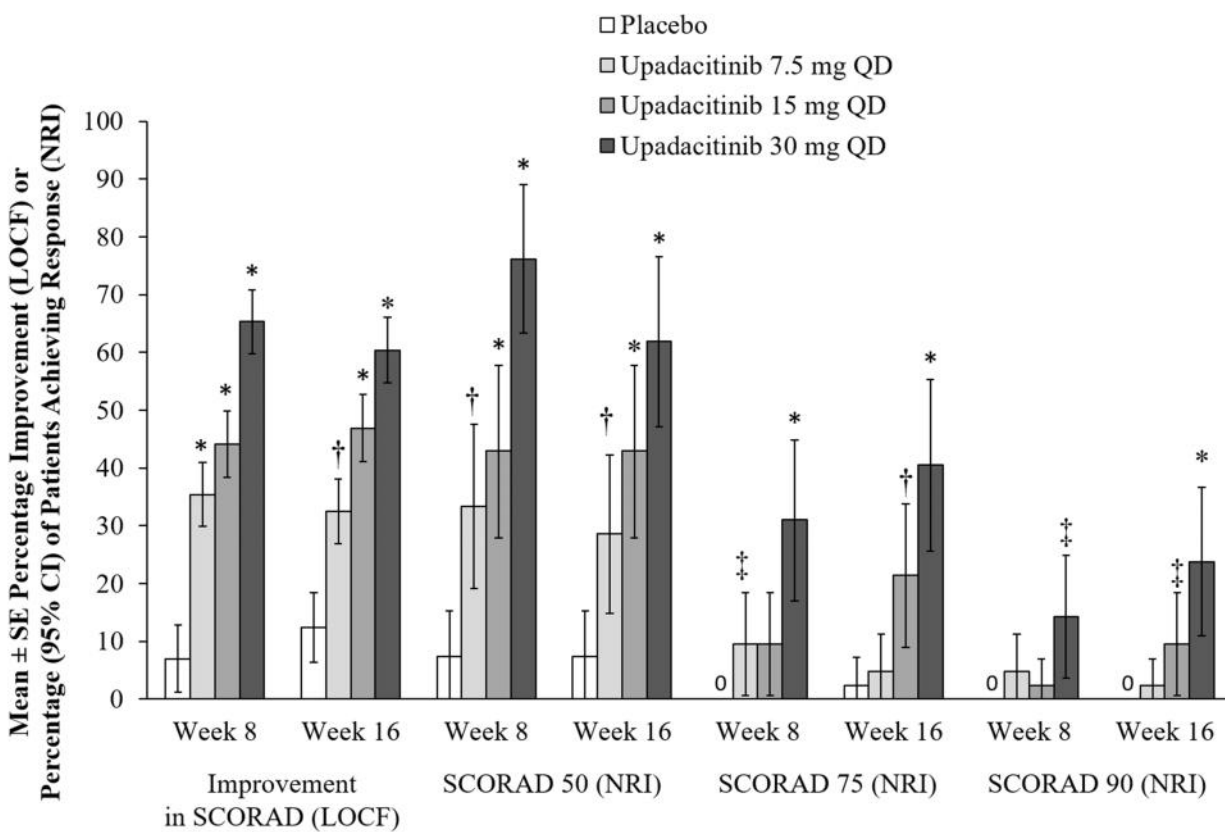


Figure E2. SCORAD outcomes at weeks 8 and 16.

LOCF, last observation carried forward; NRI, non-responder imputation; QD, once daily; SCORAD, SCORing Atopic Dermatitis; SCORAD 50/75/90, $\geq 50\%$ / $\geq 75\%$ / $\geq 90\%$ improvement in SCORAD. * $P \leq 0.001$, $^{\dagger}P \leq 0.01$, and $^{\ddagger}P \leq 0.05$ for upadacitinib vs placebo.

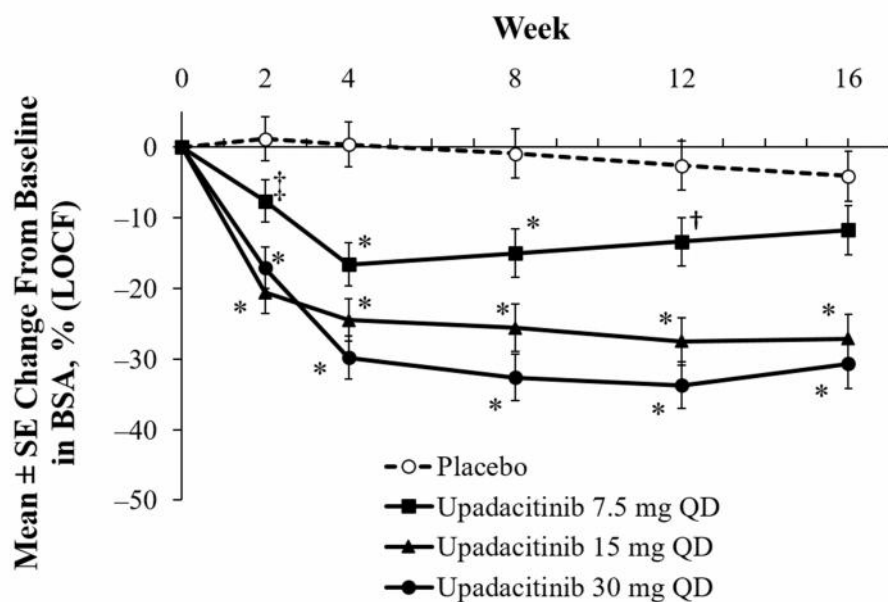


Figure E3. Change in BSA over time.

BSA, affected body surface area; LOCF, last observation carried forward; QD, once daily. * $P \leq 0.001$, † $P \leq 0.01$, and ‡ $P \leq 0.05$ for upadacitinib vs placebo.

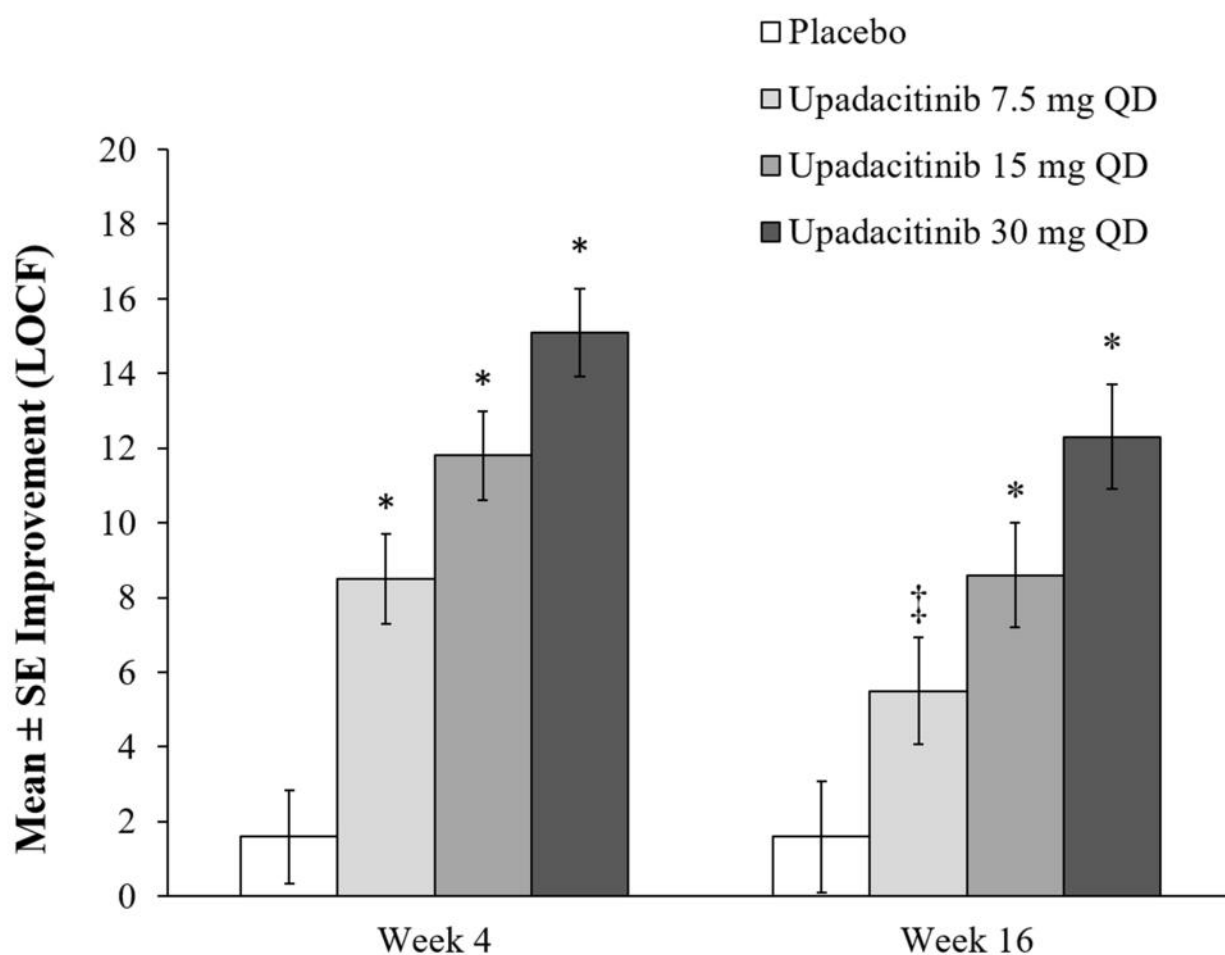


Figure E4. Change in POEM scores at weeks 4 and 16.

LOCF, last observation carried forward; POEM, Patient-Oriented Eczema Measure; QD, once daily. * $P \leq 0.001$, [†] $P \leq 0.01$, and [‡] $P \leq 0.05$ for upadacitinib vs placebo.

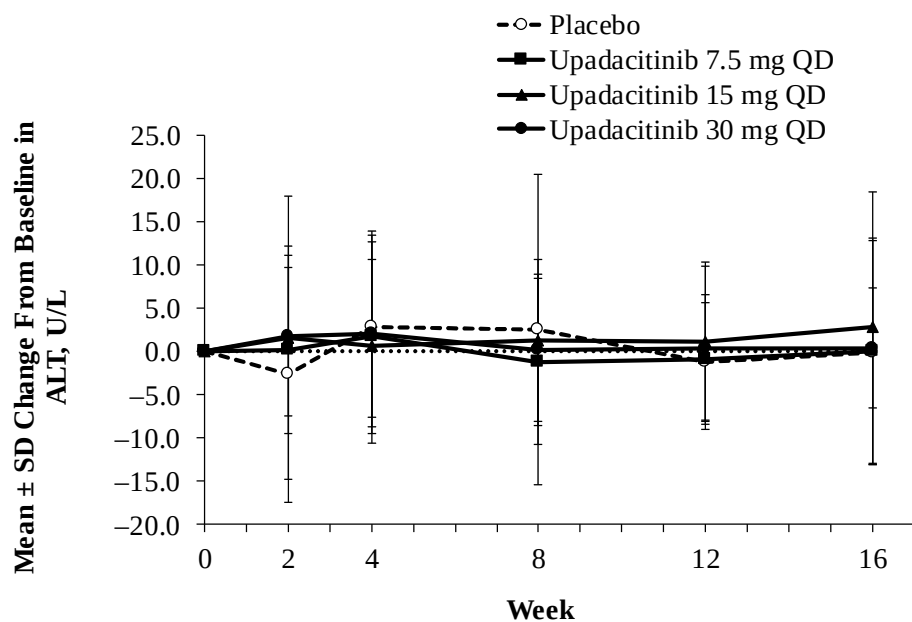
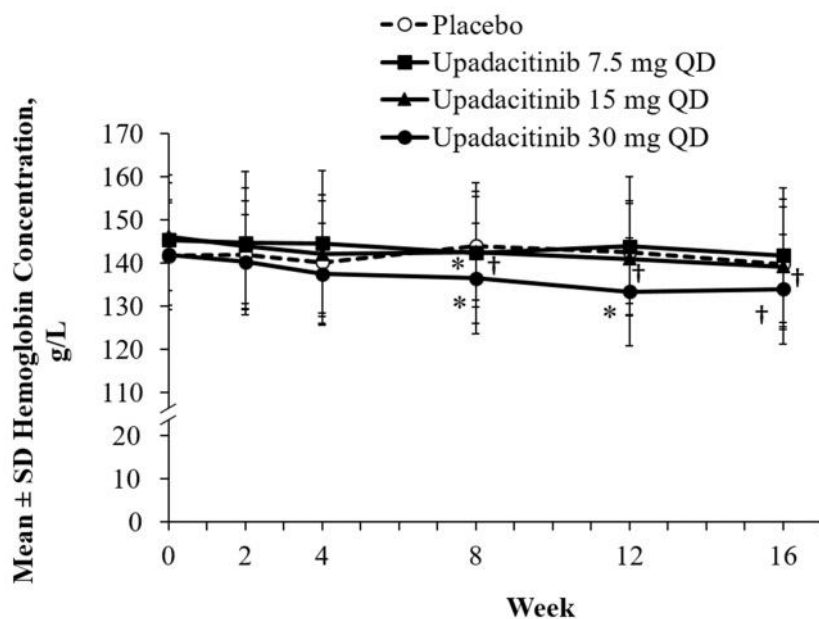
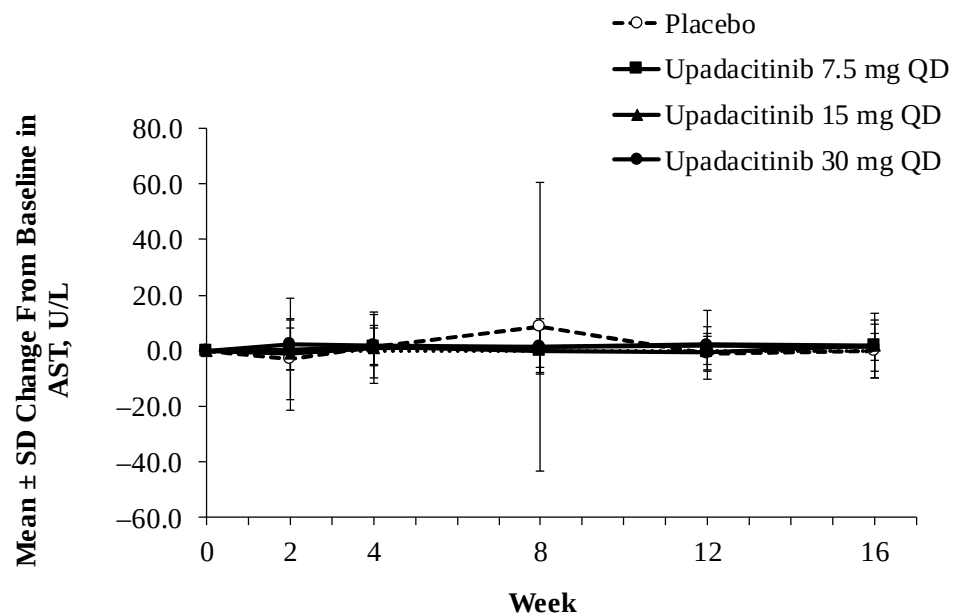
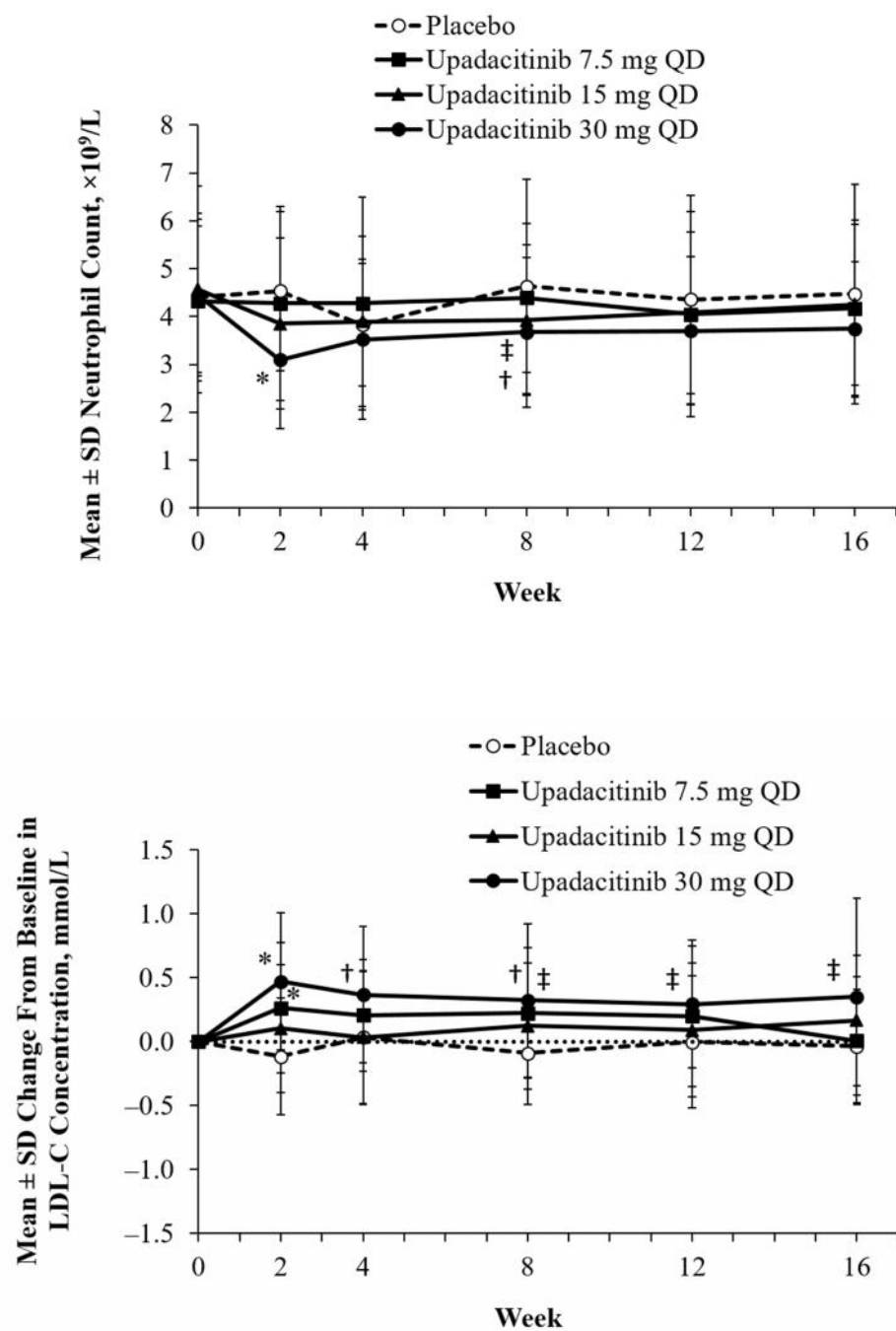


Figure E5. Laboratory values over time.

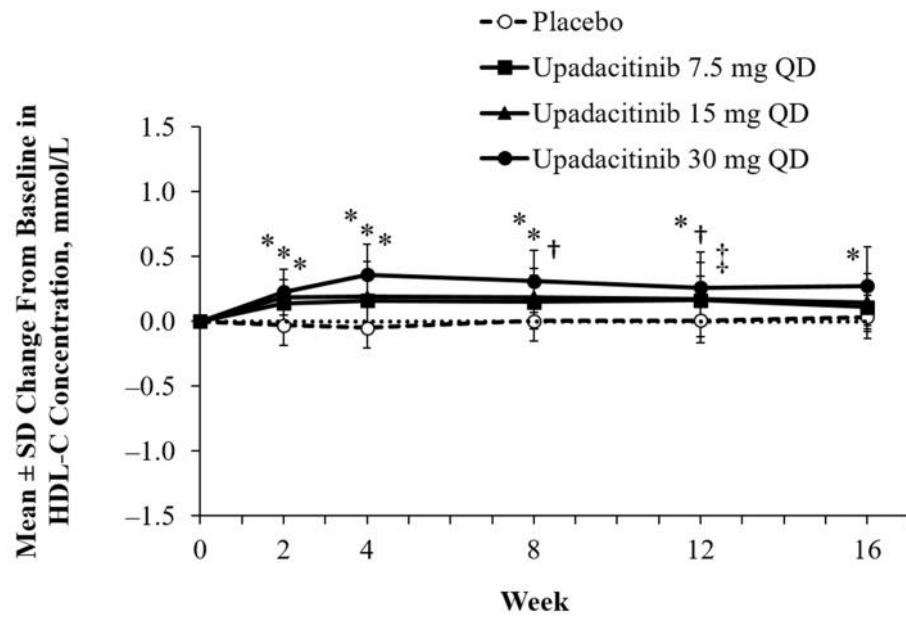
ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; QD, once daily. * $P \leq 0.001$, $^{\dagger}P \leq 0.01$, and $^{\ddagger}P \leq 0.05$ for upadacitinib vs placebo based on between-group comparisons of mean changes from baseline. The normal range for hemoglobin is 132–170 g/L in men and 115–155 g/L in women.



Supplementary Figure E5 continued.



Supplementary Figure E5 continued.



Supplementary Figure E5 continued.