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

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Emma Guttman-Yassky, MD,a Diamant Thaçi, MD,b Aileen L. Pangan, MD,c H. Chih-ho Hong, MD,d Kim A. Papp, MD,e Kristian Reich, MD,f Lisa A. Beck, MD,g Mohamed-Eslam F. Mohamed, PhD,h Ahmed A. Othman, PhD,h Jaclyn K. Anderson, DO,i Yihua Gu, MS,j Henrique D. Teixeira, PhD,k and Jonathan I. Silverberg, MDl

Washington, DC; Lübeck and Hamburg, Germany; North Chicago, Ill; Surrey, British Columbia, and Waterloo, Ontario, Canada; and Washington, DC

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, 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.

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

From a the Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York; b the Institute and Comprehensive Center Inflammation Medicine, University of Lübeck, Lübeck; c Immunology Clinical Development, AbbVie Inc, North Chicago; d the Department of Dermatology and Skin Science, University of British Columbia and Probiy Medical Research, Surrey, British Columbia; e Probiy Medical Research and K Papp Clinical Research, Waterloo, Ontario; f Translational Research in Inflammatory Skin Diseases, Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, and Skinflammation Center, Hamburg; g the Department of Dermatology, University of Rochester Medical Center, Rochester; h Clinical Pharmacology and Pharmacoepidemiometrics, AbbVie Inc, North Chicago; i Data and Statistical Sciences, AbbVie Inc, North Chicago; and the Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington.

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Corresponding author: Emma Guttman-Yassky, MD, PhD, Department of Dermatology, Icahn School of Medicine at Mount Sinai, 5 East 98th St, New York, NY 10029. E-mail: emma.guttman@mountsinai.org.

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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 \((16\%-71\% \text{ of patients across different ages and regions).}^3\) AD in adults may persist from childhood \(^4\) or may begin or reoccur in adulthood. \(^3\) Corticosteroids are an orally administered systemic treatment widely used for patients with AD, \(^5\) but there is risk of exposure-associated adverse effects with long-term and short-term use. \(^6\) In some countries, cyclosporine A is approved for use for patients with severe AD but generally as short-term rescue therapy \((\leqslant 1 \text{ year})\) 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) \(^7\) 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 \(\alpha\). \(^8\) 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 \(\geqslant 90\%\) improvement in Eczema Area and Severity Index \((EASI))\) or investigator Global Assessment of 0 or 1 \((IGA))\). \(^9\) 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. \(^1\) 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-\(\gamma\)) 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, \(^17\) which may also directly stimulate neurons to elicit itching \(^17\) 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 kinase \(^18\) 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 AD \(^20\); 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 \((\geqslant 3 \text{ of } 4 \text{ major features and } \geqslant 3 \text{ of } 23 \text{ minor features}),\) \(^22\) 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 \((\text{BSA})\) 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 \((\text{QD})\) 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.

Abbreviations used

- **AD**: Atopic dermatitis
- **AE**: Adverse event
- **ALT**: Alanine aminotransferase
- **AST**: Aspartate aminotransferase
- **BSA**: Body surface area
- **EASI 90**: \(\geqslant 90\%\) 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
- **SCORing Atopic Dermatitis**
- **BSA**: Body surface area
- **IGA**: Investigator Global Assessment
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), BSA, and Patient-Oriented Eczema Measure (POEM). 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 at weeks 8 and 16; 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.

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
significant (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 (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).

### 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 at a 2-sided significance (1-sided) to characterize the dose-response for upadacitinib.
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 (IGA 0/1) and patient assessment of pruritus (improvement in NRS) outcomes at weeks 8 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). 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 [8.8-21.0] 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 (≥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).


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/SCORAD, BSA, and POEM) showed no clear pattern of change (see Table E2 in this article’s Online Repository at www.jacionline.org). The alleviation of itching 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 stringent end points (EASI 90 and IGA 0/1) plateaued between weeks 8 and 16, although the EASI 100 response was generally defined end points (EASI 90 and IGA 0/1) plateaued between weeks 8 and 16, although the EASI 100 response was not achieved by the upadacitinib 15- or 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 level compared with placebo, but lipid ratios showed no clear pattern of change (see Table E2 in this article’s Online Repository at www.jacionline.org).

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).

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.
One patient with ALT increased and AST increased. (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.

In this study with a limited population size that might not be representative of all potential AD populations, 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 T17L2 and T17L22 cytokines.18 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.

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### Table II. AE summary*

<table>
<thead>
<tr>
<th>Treatment-emergent AE, n (%)</th>
<th>Placebo (n = 40)</th>
<th>Upadacitinib 7.5 mg QD (n = 42)</th>
<th>Upadacitinib 15 mg QD (n = 42)</th>
<th>Upadacitinib 30 mg QD (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>25 (63)</td>
<td>31 (74)</td>
<td>32 (76)</td>
<td>33 (79)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1 (2.5)</td>
<td>2 (4.8)</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>AE leading to discontinuation of study drug</td>
<td>3 (7.5)</td>
<td>4 (9.5)</td>
<td>2 (4.8)</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>Infection</td>
<td>8 (20)</td>
<td>22 (52)</td>
<td>18 (43)</td>
<td>17 (41)</td>
</tr>
<tr>
<td>Serious infection</td>
<td>0</td>
<td>2 (4.8)†</td>
<td>1 (2.4)‡</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic disorder</td>
<td>1 (2.5)§</td>
<td>0</td>
<td>2 (4.8)§</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>1 (2.4)</td>
<td>2 (4.8)</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0</td>
<td>0</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

*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 of each 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.
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.

REFERENCES
