Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background Systemic therapies are typically combined with topical corticosteroids for the management of moderate-to-severe atopic dermatitis. Upadacitinib is an oral Janus kinase (JAK) inhibitor with greater inhibitory potency for JAK1 than JAK2, JAK3, or tyrosine kinase 2 that is being tested for atopic dermatitis. We aimed to assess the efficacy and safety of upadacitinib plus topical corticosteroids compared with placebo for the treatment of moderate-to-severe atopic dermatitis.

Methods In this randomised, double-blind, placebo-controlled, phase 3 trial (AD Up) adults (aged 18–75 years) and adolescents (aged 12–17 years) with chronic atopic dermatitis that was moderate to severe (≥10% of body surface area affected, Eczema Area and Severity Index [EASI] score of ≥16, validated Investigator's Global Assessment for atopic dermatitis [vIGA-AD] score of ≥3, and weekly average Worst Pruritus Numerical Rating Scale score of ≥4 at baseline) were enrolled at 171 clinical centres across 22 countries in the Asia-Pacific region, Europe, the Middle East, North America, and Oceania. Patients were randomly assigned (1:1:1) to receive upadacitinib 15 mg, upadacitinib 30 mg, or placebo once daily, all in combination with topical corticosteroids for 16 weeks. Randomisation was done using an interactive response technology system, stratified by baseline disease severity, geographical region, and age. Study investigators, study site personnel, and patients were masked to study treatment. The coprimary endpoints were the proportion of patients who had achieved at least a 75% reduction in EASI score from baseline (EASI-75) and the proportion of patients who had achieved a vIGA-AD response (defined as a vIGA-AD score of 0 [clear] or 1 [almost clear] with ≥2 grades of improvement from baseline) at week 16. Efficacy was analysed in the intention-to-treat population and safety was analysed in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, NCT03568318, and is active, but not recruiting.

Findings Between Aug 9, 2018, and Dec 20, 2019, 901 patients were randomly assigned to receive upadacitinib 15 mg plus topical corticosteroids (n=300), upadacitinib 30 mg plus topical corticosteroids (n=297), or placebo plus topical corticosteroids (n=304). At week 16, the proportion of patients who had achieved EASI-75 was significantly higher in the upadacitinib 15 mg plus topical corticosteroid group (194 [65%] of 300 patients) and the upadacitinib 30 mg plus topical corticosteroids group (229 [77%] of 297 patients) than the placebo group (80 [26%] of 304 patients; adjusted difference in EASI-75 response rate *vs* placebo, 38·1% [95% CI 30·8–45·4] for the upadacitinib 15 mg group and 50·6% [43·8–57·4] for the upadacitinib 30 mg group; p<0·0001 for both doses). The proportion of patients who had achieved a vIGA-AD response at week 16 was significantly higher in the upadacitinib 15 mg plus topical corticosteroid group (119 [40%] patients) and upadacitinib 30 mg plus topical corticosteroid group (174 [59%] patients) than the placebo group (33 [11%] patients; adjusted difference in vIGA-AD response *vs* placebo, 28·5% [22·1–34·9] for the upadacitinib 15 mg group and 47·6% [41·1–54·0] for the upadacitinib 30 mg group; p<0·0001 for both doses). During the double-blind period, upadacitinib 15 and 30 mg were well tolerated in combination with topical corticosteroids. The most frequently reported treatment-emergent adverse events (≥5% in any treatment group) were acne, nasopharyngitis, upper respiratory tract infection, oral herpes, elevation of blood creatine phosphokinase levels, headache, and atopic dermatitis. The incidence of acne was higher in the upadacitinib 15 mg (30 [10%] of 300 patients) and upadacitinib 30 mg (41 [14%] of 297 patients) groups than the placebo group (six [2%] of 304 patients). The incidence of adverse events leading to discontinuation of study drug (four [1%] patients in the upadacitinib 15 mg plus topical corticosteroids group, four [1%] patients in the upadacitinib 30 mg plus topical corticosteroids group, and seven [2%] patients in the placebo plus topical corticosteroids group) and serious adverse events (seven [2%] patients, four [1%] patients, and nine [3%] patients) were similar among treatment groups. No deaths were reported in any treatment group.

Interpretation Upadacitinib plus topical corticosteroids was well tolerated and superior to placebo plus topical corticosteroids. Upadacitinib as combination therapy had a positive benefit–risk profile in adults and adolescents with moderate-to-severe atopic dermatitis.

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Introduction

Atopic dermatitis, also known as atopic eczema, is the major cause of skin-related disability globally,[1] and is characterised by recurrent eczematous lesions and intense itch (pruritus).[2] The understanding of atopic dermatitis pathophysiology has evolved from early concepts that atopic dermatitis lesions were T-helper-2 (Th2) cell-driven in the acute phase, shifting to Th1 cell-driven in the chronic phase, to current understanding that atopic dermatitis lesions are associated with broad and progressive immune activation involving Th2, Th17, Th1, and Th22 pathways as lesions progress from acute to chronic.[3] For many patients with moderate-to-severe atopic dermatitis, systemic therapy in addition to topical corticosteroids has been typically recommended to control symptoms.[4] This combined treatment framework is

Research in context

Evidence before this study

Upadacitinib is an oral selective Janus kinase (JAK) inhibitor with greater inhibitory potency for JAK1 than JAK2, JAK3, or tyrosine kinase 2, which is approved in the USA, Europe, and other countries to treat moderately or severely active rheumatoid arthritis and is under investigation for atopic dermatitis and other immune-mediated inflammatory conditions. Results from a phase 2b study (NCT02925117) showed that monotherapy with upadacitinib is well tolerated and effective in treating patients with moderate-to-severe atopic dermatitis. For many patients with moderate-to-severe atopic dermatitis, systemic therapy in addition to topical corticosteroids is recommended to control symptoms. This combination treatment framework is largely based on the poor efficacy of systemic therapies as monotherapy observed to date. Use of systemic immunosuppressive treatments are limited by the risk of adverse events and the potential for cumulative toxicity.

We searched ClinicalTrials.gov for clinical trials done on or before Nov 5, 2020, using the search terms "TCS" and "combination" with "interventional phase 3 studies in atopic dermatitis". Our search yielded ten studies: one study was not yet recruiting, two studies did not have published results, one study was done in children, three studies were in adults who were not adequately controlled with or had contraindications for ciclosporin A, and three studies were in a population similar to that of AD Up (adolescents or adults with moderate-to-severe atopic dermatitis). In the LIBERTY AD CHRONOS study, the addition of topical corticosteroids to dupilumab, an anti-interleukin (IL)-4 receptor α monoclonal antibody, increased the response rate compared with that for dupilumab monotherapy by approximately 10–20% in patients with moderate-to-severe atopic dermatitis. Similarly in the ECZTRA 3 and BREEZE-AD7 studies, the addition of topical corticosteroids to tralokinumab, an anti-IL-13 monoclonal antibody, or baricitinib, a selective JAK1 and JAK2 inhibitor, increased response rates by approximately 20–30% when compared with either drug as monotherapy.

Added value of this study

This study provides evidence for the safety and efficacy of upadacitinib in combination with topical corticosteroids, which is the current treatment framework for moderate-to-severe atopic dermatitis. Upadacitinib 15 mg and 30 mg plus topical corticosteroids were superior to placebo plus topical corticosteroids for the coprimary endpoints and all key secondary endpoints, with upadacitinib 30 mg plus topical corticosteroids showing numerically better results than upadacitinib 15 mg plus topical corticosteroids for all.

A substantial proportion of patients achieved the stringent endpoint of at least a 90% improvement in Eczema Area and Severity Index score from baseline at week 16 in both upadacitinib groups (15 mg or 30 mg plus topical corticosteroids); 63% of patients in the upadacitinib 30 mg plus topical corticosteroids group achieved this endpoint, demonstrating a depth of response that has not previously been reported in studies of other atopic dermatitis therapies.

Both doses of upadacitinib were well tolerated in combination with topical corticosteroids and no new important safety signals were observed beyond the known safety profile of upadacitinib in patients with rheumatoid arthritis; however, more patients given upadacitinib reported acne than did patients given placebo in this study. No patients had active tuberculosis, lymphoma, adjudicated gastrointestinal perforations, or adjudicated venous thromboembolisms.

Implications of all the available evidence

The results of this study support the potential of upadacitinib as a treatment option for adults and adolescents with moderate-to-severe atopic dermatitis. The magnitude of the clinical responses observed were generally similar to those observed for upadacitinib monotherapy, which might indicate that the incremental benefit of adding topical corticosteroids to upadacitinib is minimal compared with upadacitinib as monotherapy. A substantial proportion of patients were able to discontinue topical corticosteroids while maintaining a strong treatment response at week 16, suggesting that upadacitinib therapy could align with steroid-sparing treatment goals. These results challenge the current standard of care that asserts combination therapy with topical corticosteroids is essential to optimise outcomes.

based largely on the poor efficacy of systemic therapies used as monotherapy observed to date. Use of systemic immunosuppressive treatments such as ciclosporin A, azathioprine, and oral corticosteroids is restricted because of the risk of adverse events and the potential for cumulative toxicity, which is reflected by the high proportion of patients who discontinue treatment in clinical practice due to side-effects.[5,6] Less than half of patients given the anti-interleukin (IL)-4 receptor α monoclonal antibody dupilumab achieve clear or almost clear skin after 16 weeks of monotherapy treatment with maximal response achieved after week 8.[7] The addition of topical corticosteroids to dupilumab increases the response rate compared with that observed for monotherapy by approximately 10–20%.[7,8] Similarly, the addition of topical corticosteroids to tralokinumab, an anti-IL-13 monoclonal antibody, or baricitinib, a selective Janus kinase 1 (JAK1) and JAK2 inhibitor, increased response rates by approximately 20–30% compared with that observed with either drug as monotherapy.[9–12]

There is a need for additional atopic dermatitis treatment options that can provide clinical responses (ie, Investigator's Global Assessment [IGA] of 0 [clear] or 1 [almost clear] with ≥2 grades of improvement and ≥75% improvement in Eczema Area and Severity Index score from baseline [EASI-75]) in more patients and more extensive (ie, at least a 90% reduction in EASI score [EASI-90] and at least a 100% reduction in EASI score [EASI-100]) and more rapid responses. The efficacy of dupilumab and other targeted therapies directed against specific cytokine pathways might be lower than therapies that inhibit multiple inflammatory pathways involved in atopic dermatitis. Many of the proinflammatory cytokines implicated in the pathophysiology of atopic dermatitis use JAK1 to mediate their effects, which include Th2 axis activation (IL-4, IL-13, and thymic stromal lymphopoietin), epidermal thickening and skin barrier dysfunction (IL-4, IL-13, IL22, and interferon-γ), and itch (IL–4, IL-13, IL-31, and thymic stromal lymphopoietin).[13]

Upadacitinib is an oral selective JAK inhibitor with greater inhibitory potency for JAK1 than JAK2, JAK3, or tyrosine kinase 2, and is approved in the USA, Europe, and other countries to treat moderately or severely active rheumatoid arthritis, and is under investigation for the treatment of atopic dermatitis and other immune-mediated inflammatory conditions.[14] Upadacitinib was designed to occupy the so-called closed glycine-rich P-loop of JAK1 (as opposed to the more open confirmation of JAK2) via tight van der Waals interactions using its small and highly polar trifluoroethyl group, which confers increased metabolic stability and membrane permeability.[14,15] Results from a phase 2b study[16] and contemporaneous phase 3 studies[17] demonstrated that monotherapy with once-daily upadacitinib 15 mg or 30 mg is an effective and well tolerated treatment option for patients with moderate-to-severe atopic dermatitis. Since systemic atopic dermatitis treatments are often prescribed in combination with topical corticosteroids, it is important to assess the safety and efficacy of combination therapy for any new systemic atopic dermatitis treatment. Considering that treatment practices for atopic dermatitis vary with respect to topical corticosteroids use, here, we report the primary results from a phase 3 trial of upadacitinib in combination with topical corticosteroids in adults and adolescents with moderate-to-severe atopic dermatitis.

Methods

Study design and participants

AD Up (NCT03568318) was a randomised, double-blind, placebo-controlled, phase 3 trial done at 171 clinical centres across 22 countries in the Asia-Pacific region, Europe, Middle East, North America, and Oceania. The study consisted of a main study and an adolescent substudy (for which data acquisition is ongoing; results will be reported elsewhere). The main study consisted of a 35-day screening period and 16-week double-blind treatment period, followed by a 120-week blinded extension period for up to 260 weeks of treatment with a 30-day follow-up period (for which data acquisition is ongoing; results will be reported elsewhere; appendix p 1). Eligible patients were adults (aged 18–75 years) and adolescents (aged 12–17 years; bodyweight ≥40 kg) with chronic atopic dermatitis (onset ≥3 years before baseline) diagnosed as per Hanifin and Rajka criteria[18] that was moderate to severe (defined as ≥10% of body surface area affected by atopic dermatitis, EASI score of ≥16, validated IGA for atopic dermatitis [vIGA-AD][19] score of ≥3, and weekly average Worst Pruritus Numerical Rating Scale [WP-NRS] score of ≥4 at baseline). Full eligibility criteria, including washout requirements, are listed in the appendix (pp 2–3).

See Online for appendix

Independent ethics committees or institutional review boards at each study site approved the study protocol (appendix p 13), informed consent forms, and recruitment materials before patient enrolment. The study was done in accordance with the International Conference for Harmonisation guidelines, applicable regulations, and the Declaration of Helsinki. Adult patients and parents or legal guardians of adolescent patients provided written informed consent before screening. The adolescent substudy was added after the protocol was initiated to allow enrolment of additional adolescents to fulfil a regulatory commitment. Operational accommodations implemented due to the COVID-19 pandemic are in the appendix (p 4).

Randomisation and masking

Patients were randomly assigned (1:1:1) to receive upadacitinib 15 mg, upadacitinib 30 mg, or placebo once daily, all in combination with topical corticosteroids, stratified by baseline vIGA-AD score (3 *vs* 4), geographical region (USA, Puerto Rico, or Canada *vs* Japan *vs* China *vs* other), and age group (adolescents *vs* adults). Randomisation was done using an interactive response

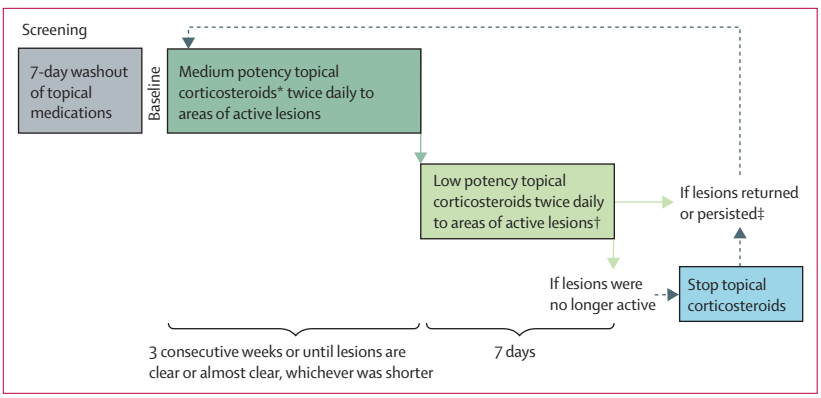

Figure 1: **52-week topical corticosteroids step-down regimen**
*Low potency topical corticosteroids or topical calcineurin inhibitor once daily for sensitive skin areas. †For sensitive skin areas, low potency topical corticosteroids or topical calcineurin inhibitors were tapered and stopped. ‡If lesions returned or persisted, the topical corticosteroid step-down regimen had to be repeated until lesion resolution in the absence of signs of local systemic topical corticosteroids toxicity.

technology system according to a schedule generated by statisticians at AbbVie. Study investigators, study site personnel, and patients remained masked to treatment allocation throughout the study: upadacitinib 15 mg, upadacitinib 30 mg, and placebo tablets were identical in appearance to maintain blinding.

Procedures

During the 16-week double-blind treatment period, patients received orally administered upadacitinib 15 mg, or upadacitinib 30 mg, or placebo (AbbVie, North Chicago, IL, USA) once daily. From the screening visit, patients were required to apply an additive-free, bland emollient twice daily for at least 7 days before baseline, and during the study until week 52.

Protocol-mandated topical corticosteroids were to be applied per the following step-down regimen: step 1, medium potency topical corticosteroids (low potency topical corticosteroids or topical calcineurin inhibitor to sensitive skin areas) once daily to areas with active lesions until lesions were clear or almost clear, or for 3 consecutive weeks, whichever was shorter; step 2, low potency topical corticosteroids once daily for 7 days and stopped if lesions were no longer active (for sensitive skin areas, low potency topical corticosteroids or topical calcineurin inhibitor were tapered and stopped); step 3, if lesions returned or persisted, this step-down approach had to be repeated until lesion resolution or there was evidence of local or systemic topical corticosteroids toxicity (eg, striae, skin atrophy, or bruising; figure 1). Choice of topical corticosteroids aligned with potency was at the investigator's discretion; the protocol recommended triamcinolone acetonide 0·1% cream or fluocinolone acetonide 0·025% ointment as medium potency topical corticosteroids and hydrocortisone 1% cream as low potency topical corticosteroids.

From week 4, rescue therapy was permitted if certain disease activity criteria were met (appendix p 4).

Efficacy and safety were assessed at study visits done at weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, and 52, and every 12 weeks between week 64 and 260.

Outcomes

The coprimary efficacy endpoints were the proportion of patients who had achieved EASI-75 and the proportion of patients who had achieved a vIGA-AD response (defined as scores of 0 [clear] or 1 [almost clear] with ≥2 grades of improvement from baseline) at week 16. Secondary efficacy endpoints were the proportion of patients who had achieved a 4-point or greater improvement in WP-NRS score from baseline at weeks 1, 4, and 16 among patients with a WP-NRS score of 4 or higher at baseline; the proportion of patients who had achieved EASI-90 at week 4 and week 16; the proportion of patients who had achieved EASI-75 at week 2 and week 4; and the proportion of patients in the upadacitinib 30 mg group who had achieved EASI-100 at week 16. Additional secondary endpoints prespecified for European Medicines Agency regulatory purposes were percentage change in WP-NRS score from baseline at week 16 and percentage change in EASI score from baseline at week 16.

Prespecified additional endpoints were all primary and secondary endpoints assessed at all other study visits, the mean number of topical corticosteroid-free days with EASI-75 response at week 16, and the median time to first discontinuation of topical corticosteroid treatment (defined as discontinuation of topical corticosteroid use for >7 consecutive days) with EASI-75 response at week 16.

Treatment-emergent adverse events (defined as new or worsening adverse events after the first dose of study drug but within 30 days after the last dose), serious adverse events, deaths, adverse events leading to discontinuation, and adverse events of special interest were assessed over the course of the study. Prespecified adverse events of special interest were based on the known safety profile of upadacitinib[20] and previous safety observations with upadacitinib in atopic dermatitis,[16] and other JAK inhibitors.[13] Mean change from baseline and the proportion of patients who met criteria for potentially clinically significant laboratory assessments (ie, National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] grade 3 or higher, and increase in NCI CTCAE grade from baseline) and vital signs were also recorded.

Statistical analysis

On the basis of the maximum response rate of patients given placebo in previous trials,[2,3] assuming 24% of patients achieved an EASI-75 response and 13% achieved a vIGA-AD response in the placebo group, a sample size of 810 patients (270 per treatment group) would provide more than 90% power to detect a treatment difference of 38% in EASI-75 response and 20% in vIGA-AD response at a two-sided 5% significance level. Efficacy analyses

were done after all patients in the main study had completed the 16-week, double-blind period. Efficacy was assessed in the intention-to-treat population, which included all patients who were randomly assigned at baseline. Safety was assessed in the safety population, which included all randomly assigned patients who received at least one dose of study drug.

Categorical endpoints were analysed using the Cochran-Mantel-Haenszel model, adjusted for baseline vIGA-AD categories (vIGA-AD score 3 *vs* 4) and age (adolescent *vs* adult), with non-responder imputation incorporating multiple imputation for missing values due to COVID-19 (NRI-C; appendix p 5); continuous endpoints were analysed using a mixed-effect model with repeated measures. The initial non-responder imputation approach was revised to NRI-C in response to the COVID-19 pandemic, which might have prevented visits due to logistical restrictions; non-responder imputation was retained as a sensitivity analysis for the coprimary and all categorical secondary endpoints. All assessments done after the initation of rescue medications were not included in the analyses; patients were defined as non-responders after initiation of rescue medication and were not imputed by multiple imputation. The overall type I error rate of the coprimary and all key secondary endpoints for upadacitinib 15 mg and upadacitinib 30 mg was controlled at the 0·05 level using a graphical multiple testing procedure (appendix p 6). All statistical tests were two-sided. All statistical analysis were done using SAS (version 9.4 or higher). An external data monitoring committee oversaw the study.

Safety data, rescue medication use, and proportion of patients with potentially clinically significant values in laboratory assessments were reported using descriptive statistics only.

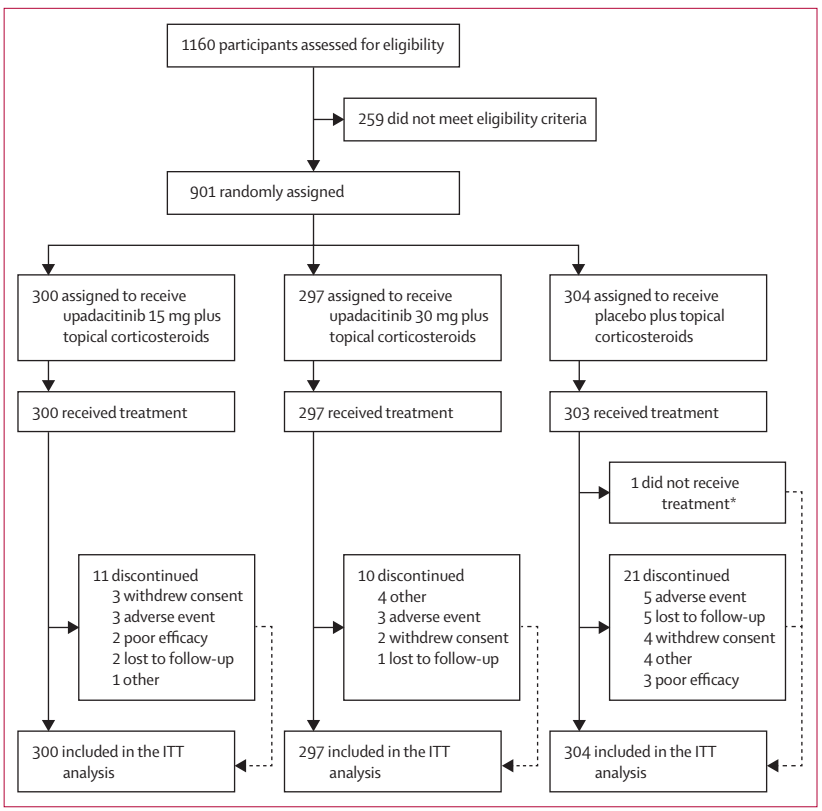

Figure 2: **Trial profile**
ITT=intention-to-treat. *Consent was withdrawn after randomisation.

Role of the funding source

The study funder was involved in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Aug 9, 2018, and Dec 20, 2019, 1160 patients were screened, of whom 901 (785 adults and 116 adolescents) were randomly assigned to receive upadacitinib 15 mg plus topical corticosteroids (n=300), upadacitinib 30 mg plus topical corticosteroids (n=297), or placebo plus topical corticosteroids (n=304; figure 2). 287 (96%) of 300 patients in the upadacitinib 15 mg plus topical corticosteroids group, 287 (97%) of 297 patients in the upadacitinib 30 mg plus topical corticosteroids group, and 280 (92%) of 304 patients in the placebo plus topical corticosteroids group completed 16 weeks of treatment. No patients discontinued study or treatment because of COVID-19 during the double-blind treatment period. Missing data for EASI-75 and vIGA-AD for six patients were imputed using multiple imputation due to COVID-19 at week 16; no data for the 4-point or more improvement in WP-NRS score at week 16 were missing due to COVID-19. Rescue medication use was most frequent in the placebo plus topical corticosteroids group (78 [26%] of 304 patients); the proportion of patients who initiated rescue medication was similar between the upadacitinib 15 mg plus topical corticosteroids (16 [5%] of 300) and the upadacitinib 30 mg plus topical corticosteroids (16 [5%] of 297) groups (appendix p 7). The cumulative proportion of patients who received rescue medication increased between baseline and week 8 in all groups (12 [4%] of 300 patients in the upadacitinib 15 mg plus topical corticosteroids group; 12 [4%] of 297 patients in the upadacitinib 30 mg plus topical corticosteroids group; 69 [23%] of 304 patients in the placebo plus topical corticosteroids group) and remained largely unchanged thereafter for patients in the upadacitinib plus topical corticosteroids groups, but continued to increase for patients in the placebo plus topical corticosteroids group (appendix p 8). Demographics and baseline characteristics were balanced between the treatment groups, including baseline EASI score and the proportion of patients with severe vIGA-AD (table 1).

At week 16, the proportion of patients who had achieved EASI-75 was significantly higher in the upadacitinib 15 mg plus topical corticosteroids and upadacitinib

	Upadacitinib 15 mg plus topical corticosteroids (n=300)	Upadacitinib 30 mg plus topical corticosteroids (n=297)	Placebo plus topical corticosteroids (n=304)
Sex			
Male	179 (60%)	190 (64%)	178 (59%)
Female	121 (40%)	107 (36%)	126 (41%)
Age, years	32·5 (13–74)	35·5 (12–72)	34·3 (12–75)
Age group			
<18 years	39 (13%)	37 (12%)	40 (13%)
≥18 years	261 (87%)	260 (88%)	264 (87%)
Race			
White	204 (68%)	218 (73%)	225 (74%)
Asian	64 (21%)	61 (21%)	60 (20%)
Black or African American	19 (6%)	13 (4%)	18 (6%)
American Indian or Alaska Native	2 (1%)	3 (1%)	1 (<1%)
Native Hawaiian or other Pacific Islander	3 (1%)	1 (<1%)	0
Multiracial	8 (3%)	1 (<1%)	0
Ethnicity			
Hispanic or Latino	32 (11%)	20 (7%)	26 (9%)
Not Hispanic or Latino	268 (89%)	277 (93%)	278 (91%)
Geographical region			
North America	108 (36%)	106 (36%)	108 (36%)
Japan	16 (5%)	17 (6%)	18 (6%)
China	17 (6%)	16 (5%)	18 (6%)
Other*	159 (53%)	158 (53%)	160 (53%)
Body-mass index, kg/m²	25·8 (6·2)	25·7 (5·4)	25·9 (5·7)
Disease duration since diagnosis, years	22·9 (13·9)	23·1 (16·1)	24·3 (15·2)
Body surface area affected, %	46·7 (21·6)	48·5 (23·1)	48·6 (23·1)
vIGA-AD score			
3 (moderate)	143 (48%)	140 (47%)	141 (46%)
4 (severe)	157 (52%)	157 (53%)	163 (54%)
EASI score	29·2 (11·8)	29·7 (11·8)	30·3 (13·0)
Weekly WP-NRS score	7·1 (1·8)	7·4 (1·6)	7·1 (1·6)
POEM total score	21·0 (5·0)	21·5 (5·3)	21·1 (5·1)
DLQI total score†	16·4 (7·2)	17·1 (7·0)	16·3 (7·0)
Previous systemic treatment	171 (57%)	172 (58%)	157 (52%)
Medical history			
Acne	26 (9%)	21 (7%)	21 (7%)
Asthma	130 (43%)	140 (47%)	138 (45%)
Chronic sinusitis	1 (<1%)	2 (1%)	0
Allergic conjunctivitis	22 (7%)	17 (6%)	21 (7%)
Eosinophilic oesophagitis	2 (1%)	3 (1%)	0
Food allergy	112 (37%)	101 (34%)	89 (29%)
Nasal polyps	5 (2%)	7 (2%)	3 (1%)
Allergic rhinitis	96 (32%)	104 (35%)	108 (36%)

Data are n (%), mean (range), or mean (SD). Data are based on non-missing values from randomly assigned patients. vIGA-AD=validated Investigator's Global Assessment for Atopic Dermatitis. EASI=Eczema Area and Severity Index. WP-NRS=Worst Pruritus Numerical Rating Scale. POEM=Patient Oriented Eczema Measure. DLQI=Dermatology Life Quality Index. *Includes Europe, Middle East, and Oceania. †Assessed in patients aged ≥16 years (276 patients in the upadacitinib 15 mg plus topical corticosteroids group, 273 patients in the upadacitinib 30 mg plus topical corticosteroids group, and 276 patients in the placebo plus topical corticosteroids group).

Table 1: **Demographics and baseline characteristics of the intention-to-treat population**

30 mg plus topical corticosteroids groups than the placebo plus topical corticosteroids group (194 [65%] of 300 patients and 229 [77%] of 297 patients *vs* 80 [26%] of 304 patients; adjusted difference *vs* placebo 38·1% [95% CI 30·8–45·4] for the upadacitinib 15 mg group and 50·6% [43·8–57·4] for the upadacitinib 30 mg group; p<0·0001 for both doses; table 2). At week 16, the proportion of patients who had achieved a vIGA-AD response was significantly higher in the upadacitinib 15 mg plus topical corticosteroids and upadacitinib 30 mg plus topical corticosteroids groups than the placebo plus topical corticosteroids group (119 [40%] and 174 [59%] *vs* 33 [11%]; adjusted difference *vs* placebo, 28·5% [22·1–34·9] for the upadacitinib 15 mg group and 47·6% [41·1–54·0] for the upadacitinib 30 mg group; p<0·0001 for both doses; table 2). Similarly, the proportion of patients with a response for all key secondary endpoints was significantly higher in the upadacitinib 15 mg and upadacitinib 30 mg groups than the placebo group (p<0·0001 for all; table 2). The number of patients who met each endpoint was calculated on the basis of the response rate using NRI-C; the NRI-C-based results were consistent with those based on NRI (data not shown).

The rapidity of response with upadacitinib plus topical corticosteroids was observed across endpoints. The proportion of patients who had achieved EASI-75 at week 2 was significantly higher in the upadacitinib groups than the placebo group (p<0·0001 for both doses), the proportion of patients who had achieved a vIGA-AD response at week 2 was significantly higher in the upadacitinib groups than the placebo group (p<0·01 for both doses), and the proportion of patients who had achieved at least a 4-point improvement in WP-NRS score at week 1 was significantly higher in the upadacitinib groups than the placebo group (p<0·0001 for both doses; figure 3A–C). Similarly, a higher proportion of patients in the upadacitinib 15 mg plus topical corticosteroids and upadacitinib 30 mg plus topical corticosteroids groups achieved EASI-90 by week 2 and EASI-100 by week 4 than patients in the placebo group (p=0·0012 for the upadacitinib 15 mg group and p<0·0001 for the upadacitinib 30 mg group for EASI-90; p=0·0012 for the upadacitinib 15 mg group and p<0·0001 for the upadacitinib 30 mg group for EASI-100; appendix p 9).

The proportion of patients who had achieved these efficacy endpoints in skin clearance (EASI-90 and EASI-100) and itch reduction (WP-NRS response) at week 4 continued to increase between week 4 and 12 and was maintained until week 16. Between week 4 and week 16, 176 (59%) of 300 patients in the upadacitinib 15 mg plus topical corticosteroids group and 215 (72%) of 297 patients in the upadacitinib 30 mg plus topical corticosteroids group achieved EASI-75 (figure 3A). Between week 8 and week 16, 108 (36%) of 300 patients in the upadacitinib 15 mg plus topical

	Upadacitinib 15 mg plus topical corticosteroids (n=300)	Upadacitinib 30 mg plus topical corticosteroids (n=297)	Placebo plus topical corticosteroids (n=304)
Coprimary endpoints			
EASI-75 at week 16			
Responders, n (%; 95% CI)	194 (64·6%; 59·1 to 70·0)	229 (77·1%; 72·3 to 81·9)	80 (26·4%; 21·5 to 31·4)
Adjusted percentage difference compared with placebo (95% CI)	38·1 (30·8 to 45·4); p<0·0001	50·6 (43·8 to 57·4); p<0·0001	..
vIGA-AD response at week 16*			
Responders, n (%; 95% CI)	119 (39·6%; 34·1 to 45·2)	174 (58·6%; 53·0 to 64·2)	33 (10·9%; 7·4 to 14·4)
Adjusted percentage difference compared with placebo (95% CI)	28·5 (22·1 to 34·9); p<0·0001	47·6 (41·1 to 54·0); p<0·0001	..
Key secondary endpoints			
EASI-90 at week 16			
Responders, n (%; 95% CI)	128 (42·8%; 37·2 to 48·4)	187 (63·1%; 57·6 to 68·6)	40 (13·2%; 9·4 to 17·0)
Adjusted percentage difference compared with placebo (95% CI)	29·5 (22·8 to 36·3); p<0·0001	49·9 (43·3 to 56·4); p<0·0001	..
EASI-90 at week 4			
Responders, n (%; 95% CI)	85 (28·3%; 23·2 to 33·4)	130 (43·8%; 38·1 to 49·4)	15 (4·9%; 2·5 to 7·4)
Adjusted percentage difference compared with placebo (95% CI)	23·3 (17·7 to 28·9); p<0·0001	38·8 (32·8 to 44·8); p<0·0001	..
EASI-100 at week 16			
Responders, n (%; 95% CI)	NA†	67 (22·6%; 17·8 to 27·3)	4 (1·3%; 0·0 to 2·6)
Adjusted percentage difference compared with placebo (95% CI)	NA†	21·2 (16·3 to 26·1); p<0·0001	..
EASI-75 at week 4			
Responders, n (%; 95% CI)	176 (58·7%; 53·1 to 64·2)	215 (72·4%; 67·3 to 77·5)	45 (14·8%; 10·8 to 18·8)
Adjusted percentage difference compared with placebo (95% CI)	43·8 (37·0 to 50·5); p<0·0001	57·6 (51·2 to 63·9); p<0·0001	..
EASI-75 at week 2			
Responders, n (%; 95% CI)	93 (31·0%; 25·8 to 36·2)	131 (44·1%; 38·5 to 49·8)	21 (6·9%; 4·1 to 9·8)
Adjusted percentage difference compared with placebo (95% CI)	24·0 (18·1 to 29·9); p<0·0001	37·2 (31·0 to 43·3); p<0·0001	..
Change in EASI score from baseline at week 16			
n	275	276	206
Least squares mean change from baseline (95% CI)	−78·0 (−74·1 to −81·9)	−87·3 (−83·4 to −91·2)	−45·9 (−41·6 to −50·1)
Adjusted least squares mean difference compared with placebo (95% CI)	−32·1 (−26·9 to −37·4); p<0·0001	−41·5 (−36·2 to −46·7); p<0·0001	..
WP-NRS response‡§			
Responders at week 16, n/N (%; 95% CI)	149/288 (51·7%; 46·0 to 57·5)	186/291(63·9%; 58·4 to 69·4)	44/294 (15·0%; 10·9 to 19·0)
Adjusted percentage difference compared with placebo (95% CI)	36·8 (29·7 to 43·8); p<0·0001	48·8 (41·9 to 55·7) p<0·0001	..
Responders at week 4, n/N (%; 95% CI)	151/288 (52·4%; 46·7 to 58·2)	191/291 (65·6%; 60·2 to 71·1)	44/294 (15·0%; 10·9 to 19·0)
Adjusted percentage difference compared with placebo (95% CI)	37·4 (30·4 to 44·3); p<0·0001	50·6 (43·8 to 57·3); p<0·0001	..
Responders at week 1, n/N (%; 95% CI)	35/288 (12·2%; 8·4 to 15·9)	56/291 (19·2%; 14·7 to 23·8)	9/294 (3·1%; 1·1 to 5·0)
Adjusted percentage difference compared with placebo (95% CI)	9·2 (4·9 to 13·4); p<0·0001	16·2 (11·3 to 21·1); p<0·0001	..
Change in WP-NRS from baseline at week 16‡			
n	260	247	184
Least squares mean percentage change from baseline (95% CI)	−58·1 (−52·1 to −64·2)	−66·9 (−60·7 to −73·0)	−25·1 (−18·5 to −31·6)
Adjusted difference in least squares mean compared with placebo (95% CI)	−33·1 (−24·4 to −41·7); p<0·0001	−41·8 (−33·1 to −50·5); p<0·0001	..

n is the estimation of the number of responders based on NRI-C. EASI-75=at least a 75% improvement in Eczema Area and Severity Index score from baseline. vIGA-AD=validated Investigator's Global Assessment for Atopic Dermatitis. EASI-90=at least 90% improvement in EASI score from baseline. EASI-100=100% improvement in EASI score from baseline. NA=not applicable. WP-NRS=Worst Pruritus Numerical Rating Scale. NRI-C=non-responder imputation incorporating multiple imputation to address missing data due to COVID-19. *Defined as a vIGA-AD score of 0 (clear) or 1 (almost clear) with ≥2 grades of reduction from baseline. †EASI-100 at week 16 in the upadacitinib 15 mg plus topical corticosteroids group was not a secondary endpoint. ‡Based on weekly average. §Defined as a 4-point or more improvement in WP-NRS from baseline, assessed in patients with a WP-NRS score of ≥4 at baseline.

Table 2: **Coprimary and key secondary endpoints in the intention-to-treat population**

corticosteroids group and 163 (55%) of 297 patients in the upadacitinib 30 mg plus topical corticosteroids group achieved a vIGA-AD response (figure 3B). From week 4 to week 16, among patients who had a WP-NRS score of 4 or higher at baseline, 149 (52%) of 288 patients in the upadacitinib 15 mg plus topical corticosteroids group and 186 (64%) of 291 patients in the upadacitinib 30 mg plus topical corticosteroids group had at least a 4-point improvement in WP-NRS score (figure 3C). Between week 12 and week 16, 123 (41%) of 300 patients in the upadacitinib 15 mg plus topical corticosteroids group achieved EASI-90; between week 8 and week 16, 186 (63%) of 297 patients in the upadacitinib 30 mg plus topical corticosteroids group achieved EASI-90 (appendix p 9). At weeks 12 and 16, 12% of patients in the upadacitinib 15 mg plus

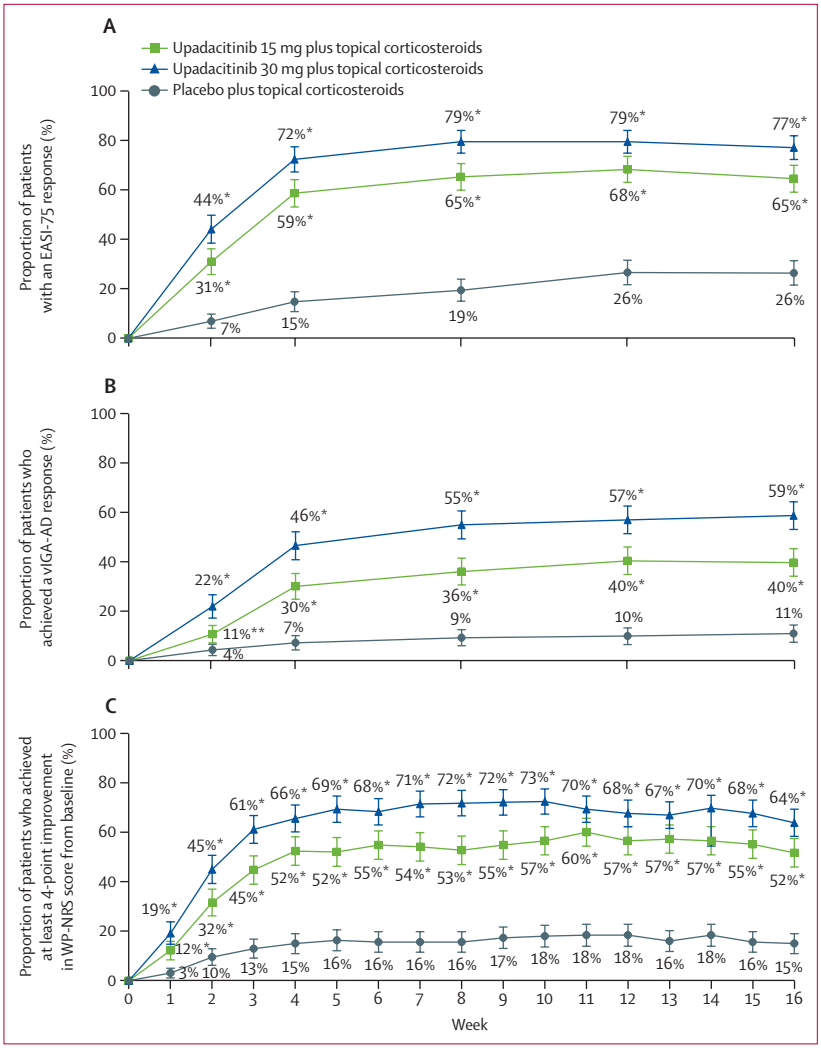

Figure 3: **Proportion of patients who had achieved EASI-75 (A), a vIGA-AD response (B), and a ≥4-point improvement in weekly average WP-NRS score from baseline (C) in the intention-to-treat population**
vIGA-AD response was defined as vIGA-AD score of clear or almost clear with ≥2 grades of improvement (reduction) from baseline. Error bars show 95% CIs. EASI-75=at least a 75% improvement in Eczema Area and Severity Index score from baseline. vIGA-AD=validated Investigator's Global Assessment for Atopic Dermatitis. WP-NRS=Worst Pruritus Numerical Rating Scale. *=p<0·001 versus placebo plus topical corticosteroids, **=p<0·01 versus placebo plus topical corticosteroids; p values were multiplicity controlled for EASI-75 at weeks 2, 4, and 16; for vIGAAD at week 16; and for WP-NRS at weeks 1, 4, and 16; p values were nominal at all other timepoints.

topical corticosteroids group and more than 21% of patients in the upadacitinib 30 mg plus topical corticosteroid group achieved EASI-100 (appendix p 9).

The EASI-75, EASI-90, EASI-100, and WP-NRS responses were further supported by the marked percentage change from baseline in EASI and WP-NRS scores observed starting at week 2 in the upadacitinib 15 mg plus topical corticosteroids and upadacitinib 30 mg plus topical corticosteroids groups compared with the placebo plus topical corticosteroid group. At week 2, the least squares mean percentage change in EASI score from baseline was –57·6% (95% CI –61·4 to –53·9) in the upadacitinib 15 mg group and –65·9% (–69·6 to –62·1) in the upadacitinib 30 mg group compared with –25·0% (–28·7 to –21·3) in the placebo group, and this difference was maintained at week 16. At week 1, the least squares mean percentage change in WP-NRS from baseline was –25·5% (–28·7 to –22·3) in the upadacitinib 15 mg group and –30·4% (–33·6 to –27·2) in the upadacitinib 30 mg group compared with –8·9% (–12·1 to –5·7) in the placebo group, and was maintained at week 16 (appendix p 10). Efficacy in the adolescent population was consistent with that observed in the overall population (data not shown).

The mean number of topical corticosteroid-free days with EASI-75 response at week 16 was greater for patients in the upadacitinib 15 mg plus topical corticosteroids group (33·5 [SD 35·3]) and upadacitinib 30 mg plus topical corticosteroids group (47·5 [38·4]) than the placebo plus topical corticosteroids group (7·9 [19·1]; nominal p<0·0001 for both doses). Median time to first discontinuation of topical corticosteroids treatment (defined as discontinuation of topical corticosteroids use for >7 consecutive days) with EASI-75 response was significantly shorter for the upadacitinib 15 mg plus topical corticosteroids group (88 days [IQR 73–not estimable]) and upadacitinib 30 mg plus topical corticosteroids group (57 days [41–59]) than the placebo plus topical corticosteroids group (not estimable [120–not estimable], p<0·0001 for both; figure 4).

During the double-blind period, upadacitinib 15 mg and 30 mg in combination with topical corticosteroids were both well tolerated in the overall population (table 3). The incidence of adverse events leading to discontinuation of study drug and serious adverse events was similar among treatment groups (table 3). Serious adverse events of retinal detachment, appendicitis, peritonsillar abscess, streptococcal pharyngitis, drug overdose (paracetamol, ibuprofen, or tramadol), hydronephrosis, nephrolithiasis, asthma, oropharyngeal pain, pleural effusion, and severe asthma exacerbation were reported for one (<1%) patient each in the upadacitinib 15 mg plus topical corticosteroids group; pancytopenia, congestive cardiac failure, anaphylactic reaction, and adenocarcinoma of the colon were reported for one patient each (<1%) in the upadacitinib 30 mg plus topical corticosteroids group; and rhegmatogenous retinal detachment, vascular stent thrombosis, anaphylactic reaction, anal abscess, pneumonia, staphylococcal sepsis, urinary tract infection, acute respiratory failure, generalised exfoliative dermatitis, eczema, erythrodermic atopic dermatitis, and haematoma were reported for one (<1%) patient each in the placebo plus topical corticosteroids group.

The most common treatment-emergent adverse events were acne (30 [10%] of 300 patients in the upadacitinib 15 mg plus topical corticosteroids group, 41 [14%] of 297 patients in the upadacitinib 30 mg plus topical corticosteroids group, and 6 [2%] of 303 patients in the placebo plus topical corticosteroids group) and nasopharyngitis (37 [12%] patients in the upadacitinib

15 mg plus topical corticosteroids group, 40 [14%] patients in the upadacitinib 30 mg plus topical corticosteroids group, and 34 [11%] patients in the placebo plus topical corticosteroids group; table 3). The incidence of atopic dermatitis was highest in the placebo plus topical corticosteroids group (20 [7%] of 303 patients *vs* 11 [4%] of 300 patients in the upadacitinib 15 mg plus topical corticosteroids group and two [1%] of 297 patients in the upadacitinib 30 mg plus topical corticosteroids group). The incidence of treatment-emergent adverse events associated with other atopic conditions was similar between groups including for asthma (six [2%] of 300 patients in the upadacitinib 15 mg plus topical corticosteroids group, two [1%] of 297 patients in the upadacitinib 30 mg plus topical corticosteroids group, and five [2%] of 304 patients in the placebo plus topical corticosteroids group), allergic rhinitis (no patients in the upadacitinib 15 mg plus topical corticosteroids group, two patients [1%] in the upadacitinib 30 mg plus topical corticosteroids group, two patients [1%] in the placebo plus topical corticosteroids group), and allergic conjunctivitis (no patients in the upadacitinib 15 mg plus topical corticosteroids group, two patients [1%] in the upadacitinib 30 mg plus topical corticosteroids group, one patient [<1%] in the placebo plus topical corticosteroids group). Among the most frequently reported treatment-emergent adverse events, dose-related increases in the incidence of acne and oral herpes were observed (table 3). Most treatment-emergent adverse events of acne (61 [79%] of 77 events) were grade 1 (the remainder were grade 2) and consisted primarily of inflammatory papules, pustules, and comedones, typically involving the face. None of the treatment-emergent adverse events of acne were considered serious and none led to treatment discontinuation. Most treatment-emergent adverse events of oral herpes (30 [79%] of 38 events) were grade 1 and none led to treatment discontinuation.

Among adverse events of special interest, no active tuberculosis infections, lymphomas, adjudicated gastrointestinal perforations, adjudicated major adverse cardiovascular events, or adjudicated venous thromboembolic events were observed (table 3). One event of arterial thrombosis was reported for a patient in the placebo plus topical corticosteroids group.

During the double-blind treatment period, the incidence of serious infections was similar between the treatment groups (table 3). All opportunistic infections reported, excluding tuberculosis and herpes zoster, were cases of eczema herpeticum (or synonymous Kaposi's varicelliform eruption). The incidence of treatment-emergent adverse events of eczema herpeticum was similar between both upadacitinib plus topical corticosteroids groups, and greater than treatment-emergent adverse events of eczema herpeticum reported in the placebo plus topical corticosteroids group (table 3). All treatment-emergent adverse events of eczema herpeticum were mild or moderate; none were considered serious and none led to treatment discontinuation. The incidence of herpes zoster was similar among groups (table 3). All treatment-emergent adverse events of herpes zoster were non-serious, and none led to discontinuation of study drug. Most of the events were mild or moderate (ten [91%] of 11 cases) and involved a single dermatome (nine [82%] of 11 cases). No cases of disseminated herpes zoster or cases with ophthalmic or CNS involvement were reported. Two malignancies were reported: one non-melanoma skin cancer (keratoacanthoma) identified on treatment day 45 and one adenocarcinoma of the colon identified on treatment day 7, both in the upadacitinib 30 mg plus topical corticosteroids group. The case of colon adenocarcinoma was considered serious and not associated with treatment, but did lead to discontinuation of study medication. The incidence of treatment-emergent hepatic disorders was similar among treatment groups (table 3). Most of the hepatic disorders were asymptomatic elevations in aminotransferase levels that were transient and did not lead to study medication discontinuation. No cases of Hy's Law[21] were identified. A dose-related increase in the incidence of elevations in creatine phosphokinase levels was observed, the majority of which were asymptomatic, self-limited, and due to exercise or other vigorous activity (table 3). Treatment-emergent anaemia was reported for four patients (three in the upadacitinib 30 mg plus topical corticosteroids group

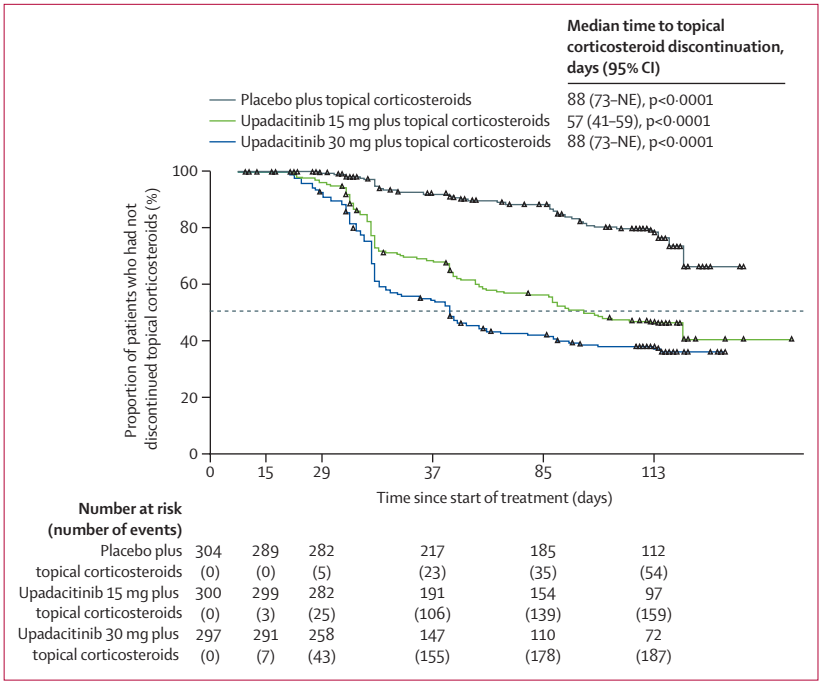

Figure 4: **Time to first topical corticosteroids discontinuation (>7 consecutive days) among patients with an EASI-75 response in the intention-to-treat population**

Topical corticosteroid-free with EASI-75 response refers to the first time a patient did not take any topical corticosteroids medication, and had achieved an EASI-75 response. Triangles show censored values. Nominal p values are for the comparison with the placebo plus topical corticosteroids group. EASI-75=at least a 75% improvement in Eczema Area and Severity Index score from baseline. NE=not estimable.

	Upadacitinib 15 mg plus topical corticosteroids (n=300)	Upadacitinib 30 mg plus topical corticosteroids (n=297)	Placebo plus topical corticosteroids (n=303)
Any treatment-emergent adverse event	200 (67%)	215 (72%)	190 (63%)
Serious adverse events	7 (2%)	4 (1%)	9 (3%)
Adverse events leading to discontinuation of study drug	4 (1%)	4 (1%)	7 (2%)
Deaths	0	0	0
Adverse events of special interest			
Serious infections	3 (1%)	0	3 (1%)
Opportunistic infections excluding tuberculosis and herpes zoster	3 (1%)	4 (1%)	0
Eczema herpeticum (Kaposi's varicelliform eruption)	3 (1%)	4 (1%)	0
Herpes zoster	3 (1%)	5 (2%)	3 (1%)
Active tuberculosis	0	0	0
Non-melanoma skin cancer	0	1 (<1%)	0
Malignancy (excluding non-melanoma skin cancer)	0	1 (<1%)	0
Lymphoma	0	0	0
Hepatic disorder†	6 (2%)	3 (1%)	5 (2%)
Adjudicated gastrointestinal perforation	0	0	0
Anaemia†	0	3 (1·0)	1 (0·3)
Neutropenia†	2 (1%)	3 (1%)	0
Lymphopenia†	0	0	1 (0·3)
Creatine phosphokinase elevation†	13 (4%)	18 (6%)	7 (2%)
Renal dysfunction†	1 (<1%)	0	0
Adjudicated major adverse cardiovascular event	0	0	0
Adjudicated venous thromboembolic event	0	0	0
Most frequently reported treatment-emergent adverse events (≥5% in any treatment group)			
Acne	30 (10%)	41 (14%)	6 (2%)
Nasopharyngitis	37 (12%)	40 (13%)	34 (11%)
Upper respiratory tract infection	21 (7%)	23 (8%)	22 (7%)
Oral herpes	10 (3%)	23 (8%)	5 (2%)
Blood creatine phosphokinase elevation†	13 (4%)	18 (6%)	7 (2%)
Headache	15 (5%)	14 (5%)	15 (5%)
Atopic dermatitis	11 (4%)	2 (1%)	20 (7%)

Data are n (%). *Safety in the main study during the double-blinded period. †Includes laboratory investigations reported as treatment-emergent adverse events.

Table 3: **Treatment-emergent adverse events in the safety population***

[two grade 1 events and one grade 3 event], and one in the placebo plus topical corticosteroids group [grade 1]). Treatment-emergent neutropenia was reported in the upadacitinib plus topical corticosteroids treatment groups with similar rates between doses (three patients in the upadacitinib 30 mg plus topical corticosteroids group and two patients in the upadacitinib 15 mg plus topical corticosteroids group); no cases of treatment-emergent neutropenia were reported in the placebo plus topical corticosteroids group. All cases of treatment-emergent neutropenia were mild or moderate in severity and one led to treatment discontinuation in a patient in the upadacitinib 30 mg plus topical corticosteroids group. No cases of treatment-emergent lymphopenia were reported for either upadacitinib group (table 3).

The proportion of patients who met criteria for potentially clinically important laboratory values (NCI CTCAE grade 3 or higher; including those for haematological and liver function assessments) was low and generally balanced across treatment groups (appendix p 11). No grade 3 or grade 4 thrombocytopenia events were observed (appendix p 11). One (<1%) of 300 patients in the upadacitinib 15 mg plus topical corticosteroids group and three (1%) of 297 patients in the upadacitinib 30 mg plus topical corticosteroids group had grade 3 or higher low absolute neutrophil counts and seven (2%) patients in the upadacitinib 15 mg group and 11 (4%) patients in the upadacitinib 30 mg group had grade 3 or higher elevations in creatine phosphokinase levels, with a dose-related increase observed across the groups compared with the placebo plus topical corticosteroids group (no cases of low absolute neutrophil counts events and five [2%] of 304 patients had creatine phosphokinase elevations).

Discussion

Upadacitinib 15 mg plus topical corticosteroids and upadacitinib 30 mg plus topical corticosteroids were superior to placebo plus topical corticosteroids for the coprimary endpoints. Although no statistical comparisons were done between the upadacitinib 15 mg and 30 mg groups, the number of responders in the upadacitinib 30 mg plus topical corticosteroids group was consistently numerically higher than that in the upadacitinib 15 mg plus topical corticosteroids group for all key endpoints. The proportion of patients who had achieved EASI-90 and EASI-100 was significantly higher in the upadacitinib 15 mg plus topical corticosteroids and upadacitinib 30 mg plus topical corticosteroids groups than the placebo plus topical corticosteroids group from the first post-baseline assessments (week 1 or 2), increased until week 4 or 8, and was maintained at week 16 ($p<0·0001$ for both doses for each endpoint at all timepoints [nominal p values for all other timepoints], with the exception of EASI-100 for upadacitinib 15 mg plus topical corticosteroids at week 2). Together, these results indicate a rapidity and depth of response in skin improvement and itch reduction that were also demonstrated with upadacitinib monotherapy.[17]

A higher proportion of patients given placebo in combination with topical corticosteroids in this study had a response than did patients given upadacitinib in monotherapy studies. The magnitudes of the responses achieved with upadacitinib plus topical corticosteroids were similar to that achieved for the same endpoints with upadacitinib monotherapy.[17] For example, the proportion of patients who had achieved EASI-75 with upadacitinib 15 mg (60·1–69·6%) and upadacitinib 30 mg (72·9–79·7%) as monotherapy were similar to

those observed with upadacitinib 15 mg plus topical corticosteroids (65%) and upadacitinib 30 mg plus topical corticosteroids (77%). The similarity of results in skin improvement and itch reduction suggests that topical corticosteroids provided little additional contribution to the efficacy of upadacitinib, challenging the current treatment practice of combining systemic therapy with topical corticosteroids for additive results. These results contrast with the incremental benefit observed for adding topical corticosteroids to other systemic treatments[7–12] and to the best of our knowledge, this is the first time that a small effect has been observed for an atopic dermatitis treatment. In LIBERTY AD CHRONOS,[8] approximately 20% more patients treated with dupilumab in combination with topical corticosteroids achieved EASI-75 at week 16 than did patients treated with dupilumab monotherapy in SOLO 1 and SOLO 2,[7] although direct comparisons between studies are not possible because of differences in patient populations. The topical corticosteroids regimen used in AD Up and LIBERTY AD CHRONOS had a similar protocol for continuing topical corticosteroids use for active atopic dermatitis lesions, with the exception that in AD Up, per-protocol topical corticosteroids step-down treatment with low potency topical corticosteroids was to be attempted after every 3 weeks of medium potency topical corticosteroids in patients whose atopic dermatitis lesions persisted. In AD Up, the mean number of topical corticosteroid-free days with EASI-75 response was higher for both upadacitinib groups than the placebo group and the time to discontinuation of topical corticosteroids while maintaining response was shorter, demonstrating a substantial steroid-sparing effect of upadacitinib. This suggests synergy with treatment goals that aim to avoid the long-term use of steroids. The absence of incremental benefit with topical corticosteroids could be because optimal atopic dermatitis improvement is achievable with upadacitinib alone, or because the substantial proportion of patients who were able to discontinue topical corticosteroids were able to do so as a result of the steroid-sparing effects of upadacitinib, which might confound the incremental benefit of adding topical corticosteroids to upadacitinib.

During the double-blind period of the AD Up study, both upadacitinib doses in combination with topical corticosteroids were well tolerated and no new important safety signals were observed that impacted the benefit–risk ratio compared with the safety profile of upadacitinib in patients with rheumatoid arthritis.[20] No active tuberculosis, adjudicated gastrointestinal perforations, or adjudicated venous thromboembolisms were observed in this study. The incidence of acne was higher than that observed in previous studies in rheumatoid arthritis (SELECT EARLY[22] and SELECT-MONOTHERAPY[23]), which might reflect the younger age of patients overall in the atopic dermatitis studies and directed skin examinations by dermatologists that might have increased the likelihood of acne detection. Although acne might be associated with topical corticosteroid use on the face,[24] since a similar incidence of acne was observed in the upadacitinib monotherapy studies,[16,17] the higher incidence of acne in this study is unlikely to be attributable to concomitant topical corticosteroids use. Additionally, in a previous study, no association was identified between atopic dermatitis and acne prevalence.[25] Acne has also been reported in trials of other JAK inhibitors in dermatological conditions (eg, abrocitinib and baricitinib).[26–28] Eczema herpeticum is a frequently reported viral infection in atopic dermatitis;[29,30] in this study, the incidence of eczema herpeticum was similar between upadacitinib 15 mg plus topical corticosteroids (1%) and upadacitinib 30 mg plus topical corticosteroids groups (1%), and no patients in the placebo plus topical corticosteroids group had eczema herpeticum. Despite the greater inhibitory activity of upadacitinib for JAK1 than other members of the family, neutropenia events were observed more frequently in the upadacitinib plus topical corticosteroids groups than the placebo plus topical corticosteroids group. Although JAK2 is thought to be primarily involved with haematopoietic signalling,[13] effects of JAK inhibition on neutrophil counts and function in patients might be more complex and multifactorial.[31] With regard to the effects of upadacitinib on elevation of creatine phosphokinase concentrations, the underlying basis for this finding is not clear but JAK1 inhibition has been reported to stimulate myoblast differentiation resulting in increased creatine phosphokinase expression.[32]

These results must be evaluated in the context of several limitations. Operational limitations precluded the detailed collection of the amounts of topical corticosteroids used due to the heterogeneity of topical corticosteroids prescribed; although the protocol required specific potencies of topical corticosteroids, the selection and formulation of topical corticosteroids used was per investigator choice. Although this restricted the measurement of topical corticosteroids amounts, it allowed selection of topical corticosteroids more closely reflecting clinical practice. Additionally, the strength of this analysis is limited by the 16-week duration of the double-blind treatment period. However, AD Up is ongoing and will provide more than 2 years of efficacy and safety data for upadacitinib in combination with topical corticosteroids when complete. Black or African American and Asian patients were under-represented in this study, reducing the applicability of these results to people with skin of colour. Although the main study population included 116 adolescents, an ongoing substudy aims to complete the enrolment of approximately 180 adolescents into AD Up, providing additional efficacy and safety data in this paediatric population with unmet need for systemic atopic dermatitis treatments.

Overall, upadacitinib was well tolerated and effective in combination with topical corticosteroids in adolescent and adult patients with moderate-to-severe atopic dermatitis. The upadacitinib efficacy and safety data in atopic dermatitis demonstrates a favourable benefit–risk profile for both the upadacitinib 15 mg and 30 mg oral once-daily doses in adults. The utility of adding topical corticosteroids to upadacitinib treatment will continue to be investigated in the ongoing long-term masked extension and adolescent substudy of AD Up to gain further insight into the maintenance of efficacy and safety of upadacitinib while attempting to align with steroid-sparing treatment goals in atopic dermatitis.

Contributors

HDT, BL, ADC, and BAH conceptualised the study. KR, MdB-W, TB, WS, KK, TW, JIS, HDT, BL, and ADC participated in data acquisition. HDT and ADC accessed and verified the data. JZ, XHua, and XHu participated in statistical analysis. All authors participated in data interpretation and critically reviewed this manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

KR has served as an adviser, paid speaker, or has participated in clinical trials sponsored by AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Bausch Health (Valeant), Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Centocor, Covagen, Dermira, Forward Pharma, Fresenius, Galapagos, GlaxoSmithKline, Janssen, Kyowa Kirin, LEO Pharma, Lilly, Medac, Merck, Novartis, Miltenyi Biotec, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB, and XenoPort. HDT, JZ, XHua, XHu, BAH, BL, and ADC are full-time employees of AbbVie, and might hold AbbVie stock or stock options. MdB-W has been a consultant, advisory board member, or speaker for AbbVie, Almirall, Galderma, Janssen, LEO Pharma, Lilly, Pfizer, Regeneron, Sanofi Genzyme, and UCB. TB is an adviser, speaker, and researcher for AbbVie, Allmiral, AnaptysBio, Arena, Asana Biosciences, Astellas, Bayer, BioVersys, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Dermavant/Roivant, Dermtreat, Domain Therapeutics, DS Biopharma, RAPT Therapeutics (FLX Bio), Galapagos/MorphoSys, Galderma, Glenmark, GlaxoSmithKline, Incyte, Kymab, LEO Pharma, Lilly, L'Oréal, Menlo Therapeutics, Novartis, Pfizer, Pierre Fabre, Sanofi/Regeneron, and UCB. WS is a consultant for AbbVie, Pfizer, Regeneron, and Sanofi; a speaker for Regeneron and Sanofi; and has received research grants from AbbVie, AB Biosciences, Genentech, Glenmark, LEO Pharma, Regeneron, Sanofi, and Vanda. KK has received consulting fees, honoraria, or grant support or lecturing fees from AbbVie, Japan Tobacco, LEO Pharma, Maruho, Mitsubishi Tanabe Pharma, Ono Pharmaceutical, Procter & Gamble, Sanofi, Taiho Pharmaceutical, and Torii Pharmaceutical. TW has received lecture or consultancy fees from AbbVie, Almirall, Astellas, Galderma, Janssen/Johnson & Johnson, LEO Pharma, Lilly, Novartis, Pfizer, and Regeneron/Sanofi. JIS is an adviser, speaker, or consultant for AbbVie, Asana Biosciences, Dermavant, Galderma, GlaxoSmithKline, Glenmark, Kiniksa, LEO Pharma, Lilly, Menlo Therapeutics, Novartis, Pfizer, Realm Pharma, and Regeneron-Sanofi; and is a researcher for GlaxoSmithKline.

Data sharing

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual, and trial-level data (analysis datasets), as well as other information (eg, protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This 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, see https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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