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Simpson, E.L., Sinclair, R., Forman, S. et al. (2020) Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet, 396 (10246). pp. 255-266. ISSN: 0140-6736

https://doi.org/10.1016/s0140-6736(20)30732-7

19TL6530

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THELANCET-D-19-06530R1

S0140-6736(20)30732-7

Embargo: [add date when known]

Doctopic: Primary Research

Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 clinical trial

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Summary

Background Abrocitinib, an oral selective Janus kinase 1 inhibitor, was effective and well tolerated in adults with moderate-to-severe atopic dermatitis in a phase 2b trial. We aimed to assess the efficacy and safety of abrocitinib monotherapy in adolescents and adults with moderate-to-severe atopic dermatitis.

Methods In this multicentre, double-blind, randomised phase 3 trial (JADE MONO-1), patients (aged ≥12 years) with moderate-to-severe atopic dermatitis (Investigator Global Assessment score ≥3, Eczema Area and Severity Index [EASI] score ≥16, percentage of body surface area affected ≥10%, and Peak Pruritus Numerical Rating Scale [PP-NRS] score ≥4) with a bodyweight of 40 kg or more, were enrolled at 69 sites in Australia, Canada, Europe, and the USA. Patients were randomly assigned (2:2:1) to oral abrocitinib 100 mg, abrocitinib 200 mg, or placebo once daily for 12 weeks. Randomisation was done using an interactive response technology system, stratified by baseline disease severity and age. Patients, investigators, and the funder of the study were masked to study treatment. The coprimary endpoints were the proportion of patients who had achieved an Investigator Global Assessment response (score of 0 [clear] or 1 [almost clear] with a ≥2-grade improvement from baseline), and the proportion of patients who achieved at least a 75% improvement in EASI score from baseline (EASI-75) score, both assessed at week 12. Efficacy was assessed in the full analysis set, which included all randomised patients who received at least one dose of study medication. Safety was assessed in all randomised patients. This study is registered with ClinicalTrials.gov, NCT03349060.

Findings Between Dec 7, 2017, and March 26, 2019, 387 patients were enrolled: 156 were assigned to abrocitinib 100 mg, 154 to abrocitinib 200 mg, and 77 to placebo. All enrolled patients received at least one dose of study treatment and thus were evaluable for 12-week efficacy. Of the patients with available data for the coprimary endpoints at week 12 [A: edit ok?], the proportion of patients who had achieved an Investigator Global Assessment response was significantly higher in the abrocitinib 100 mg group than in the placebo group (37 [24%] of 156 patients *vs* six [8%] of 76 patients; p=0·0037) and in the abrocitinib 200 mg group compared with the placebo group (67 [44%] of 153 patients vs *vs* six [8%] of 76 patients; p<0·0001). Of the patients with available data for the coprimary endpoints at week 12 [A: edit ok?], compared with the placebo group, the proportion of patients who had achieved an EASI-75 response was significantly higher in the abrocitinib 100 mg group (62 [40%] of 156 patients *vs* nine [12%] of 76 patients; p<0·0001) and abrocitinib 200 mg group (96 [63%] of 153 patients *vs* nine [12%] of 76 patients; p<0·0001). Adverse events were reported in 108 (69%) of 156 patients in the abrocitinib 100 mg group, 120 (78%) of 154 patients in the abrocitinib 200 mg group, and 44 (57%) of 77 patients in the placebo group. Serious adverse events were reported in five (3%) of 156 patients in the abrocitinib 100 mg group, five (3%) of 154 patients in the abrocitinib 200 mg group, and three (4%) of 77 patients in the placebo group. No treatment-related deaths were reported.

Interpretation Monotherapy with oral abrocitinib once daily was effective and well tolerated in adolescents and adults with moderate-to-severe atopic dermatitis.

Funding Pfizer.

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Introduction

Atopic dermatitis is a chronic and relapsing inflammatory skin condition with a complex pathophysiology that involves the interplay of impaired skin barrier function, immune dysregulation, genetic susceptibility, and environmental factors.[1] Atopic dermatitis is characterised by intense pruritus.[2] Although estimates vary widely, atopic dermatitis has been reported to affect up to 20% of children and adolescents and up to 10% of adults, and is

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Research in context

Evidence before this study

Atopic dermatitis is a chronic and recurrent inflammatory skin condition characterised by intense pruritus. At present, the available systemic treatments for patients with moderate-to-severe atopic dermatitis are limited by their short-term and long-term side-effects. Dupilumab is a subcutaneous systemic drug recently approved in adolescents and adults with moderate-to-severe atopic dermatitis. Not all patients with moderate-to-severe atopic dermatitis respond to dupilumab, and treatment is associated with a risk of conjunctivitis. Furthermore, the use of dupilumab is limited in patients who are unwilling to receive injections. Hence, there is a need for an efficacious, oral treatment with a favourable benefit–risk profile for patients with moderate-to-severe atopic dermatitis.
We searched PubMed on June 4, 2020, for studies published in English between 2010 and 2019, using the search terms "atopic dermatitis" or "eczema" AND "treatment" or "moderate to severe" or "moderate-to-severe" AND "phase 3" or "phase III". Our search yielded nine clinical trials of systemic therapy.

Added value of this study

This phase 3 trial investigated the efficacy and safety of oral abrocitinib in adolescents and adults with moderate-to-severe atopic dermatitis. Abrocitinib 200 mg and 100 mg significantly improved signs and symptoms of moderate-to-severe atopic dermatitis compared with placebo. At week 12, the proportion of patients in the abrocitinib 100 mg and 200 mg groups who had achieved an Investigator Global Assessment response and 75% improvement in Eczema Area and Severity Index score was significantly higher than in the placebo group. Improvements in pruritus were observed at the first post-baseline assessment. Abrocitinib had a favourable safety profile in this 12-week study, and no cases of venous thromboembolism, malignancy, major adverse cardiovascular events, or deaths were observed.

Implications of all the available evidence

Oral abrocitinib 100 mg or 200 mg monotherapy administered once daily was effective in patients with moderate-to-severe atopic dermatitis with a favourable safety profile. Our results suggest that abrocitinib was well tolerated and could present an efficacious oral systemic drug for the treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older.

associated with considerable impairment in quality of life, sleep, depression, anxiety, and work absenteesm.[3–6]

Management of moderate-to-severe atopic dermatitis often necessitates systemic therapy; however, few options are available and, of those that are available, most are not approved for atopic dermatitis and can be limited by their risk of adverse effects. Systemic corticosteroids might offer higher efficacy than topical treatments in patients with moderate-to-severe atopic dermatitis, but their effect is often accompanied with short-term and long-term side-effects, and long-term use is not recommended.[7] Other treatment options include immunosuppressive drugs, such as ciclosporin, methotrexate, azathioprine, and mycophenolate mofetil. None of these drugs are approved for the treatment of moderate-to-severe atopic dermatitis in the USA or Europe; however, ciclosporin is licensed in many European countries for the treatment of severe atopic dermatitis. These drugs have been reported to have a broad adverse event profile and poor tolerability, especially when used long-term.[7]

Dupilumab is a fully human monoclonal immunoglobulin G4 antibody that binds to the shared α chain of interleukin-4 (IL-4) and IL-13 receptors, partly restricting T-helper-2 (Th2) cell-driven inflammatory activity.[8,9] Dupilumab is approved by the US Food and Drug Administration and European Medicines Agency for the treatment of adolescents and adults with moderate-to-severe atopic dermatitis. Some patients do not respond sufficiently to dupilumab, whereas others lose response over time[10] (potentially as a result of drug-neutralising antibodies).[11] In clinical trials, conjunctivitis was recorded as an adverse event with dupilumab treatment, which can lead to treatment cessation and the need for ophthalmological care.[12,13] Furthermore, dupilumab is administered subcutaneously, which could prevent use in patients who are unwilling to receive injections.[14] Hence, a need exists for an efficacious oral treatment with a favourable benefit-risk profile for patients with moderate-to-severe atopic dermatitis. The Janus kinase (JAK) family are a group of cytoplasmic tyrosine kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2), which bind cytokine receptor intracellular chains to form functional signalling complexes. JAKs associate with receptor chains, and on receptor activation dimerise (as homodimers or heterodimers) to form receptor complexes. Various cytokines relevant to the pathophysiology of atopic dermatitis, including IL-4, IL-13, IL-22, IL-31, and thymic stromal lymphopoietin[15–17] activate JAK1-containing heterodimeric receptors, thereby mediating Th2 cell differentiation and itch via downstream effects. JAK2 forms homodimeric receptor complexes involved in hematopoiesis.[18] Therefore, selective inhibition of JAK1 is a desirable target to modulate a broad range of cytokines involved in the pathogenesis of atopic dermatitis while avoiding the undesirable effects of JAK2 inhibition, such as neutropenia and anaemia.

Abrocitinib (formerly known as PF-04965842) is an oral, JAK1 selective inhibitor under investigation for the treatment of atopic dermatitis. Monotherapy with oral abrocitinib 100 mg or 200 mg once daily was effective and

well tolerated in a dose-ranging phase 2b study in adults with moderate-to-severe atopic dermatitis.[19] At week 12, the proportion of patients who had achieved the primary endpoint of Investigator Global Assessment response (0 [clear] or 1 [almost clear] with ≥2-grade improvement from baseline) was 43·8% for the 200 mg dose and 29·6% for the 100 mg dose compared with 5·8% for placebo ($p<0·05$ for both). Additionally, reductions in Eczema Area and Severity Index (EASI) score[20] and pruritus numeric rating scale were observed in the abrocitinib 200 mg and 100 mg groups. Abrocitinib had a favourable safety profile, with most adverse events being mild and considered unrelated to treatment. On the basis of the positive benefit to risk ratio of the abrocitinib 200 mg and 100 mg doses, a phase 3 trial was designed to assess these doses further.

Here, we report results from the phase 3 trial JADE MONO-1, which investigated monotherapy with oral abrocitinib in adolescent and adult patients with moderate-to-severe atopic dermatitis.

Methods

Study design and participants

JADE MONO-1 was a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial done at 69 hospitals and clinics in Australia, Canada, Europe, and the USA. Eligible patients were aged 12 years or older, with a bodyweight of 40 kg or more. Adolescent patients aged younger than 18 years were eligible on a country-by-country basis as approved by the country or regulatory health authority. All eligible patients had a confirmed diagnosis of atopic dermatitis for at least 1 year before randomisation (according to Hanifin and Rajka diagnostic criteria[21]); had moderate-to-severe atopic dermatitis (Investigator Global Assessment score ≥3, EASI score ≥16, percentage of body surface area affected ≥10%, and Peak Pruritus Numerical Rating Scale [PP-NRS] score ≥4) at the baseline visit. The PP-NRS score used with the permission of Regeneron Pharmaceuticals (Tarrytown, NY, USA) and Sanofi SA (Paris, France)[22] **[A: Moved info about permission here, so that the information in parantheses is clearer for readers, ok?]**. Eligible patients also had a documented recent history (in the 6 months before screening) of inadequate response to treatment with topical corticosteroids or topical calcineurin inhibitors given for at least 4 weeks, or were patients for whom topical treatments were otherwise medically inadvisable, or required systemic therapies to control their disease. Patients with acute or chronic medical or psychiatric conditions (including active suicidal ideation or behaviour) or laboratory abnormalities in the past year

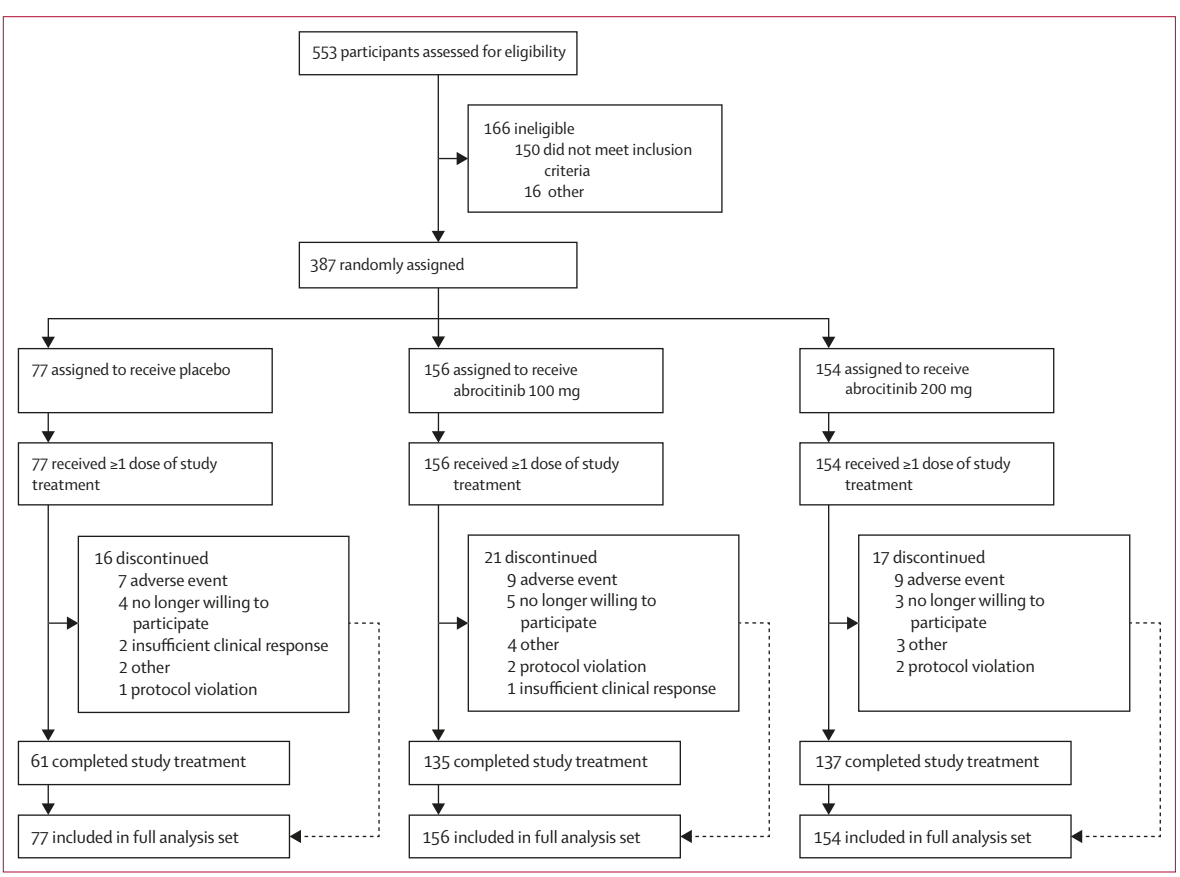

Figure 1: **Trial profile**

See Online for appendix

that might increase the risk associated with study participation or that might have interfered with the interpretation of results) or with current or past medical history of conditions associated with thrombocytopenia, coagulopathy, or platelet dysfunction were excluded. Patients with any previous systemic JAK inhibitor use, systemic corticosteroid use within 4 weeks of study initiation, or treatment with dupilumab within 6 weeks of study initiation were also excluded. Patients were permitted to use oral antihistamines and topical non-medicated emollients during the study. Use of topical therapies for atopic dermatitis (corticosteroids, calcineurin inhibitors, tars, antibiotic creams, and topical antihistamines) and rescue medication was not permitted. Full inclusion and exclusion criteria are shown in the appendix (pp 2–9).

This study was done in accordance with the Declaration of Helsinki and International Council for Harmonization Good Clinical Practice Guidelines. All local regulatory requirements were followed. The study protocol was approved by institutional review boards or ethics committees at each study site. Internal and external review committees monitored the safety of patients throughout the study. All patients provided written informed consent. The study protocol is available online.

	Placebo (n=77)	Abrocitinib 100 mg (n=156)	Abrocitinib 200 mg (n=154)
Age, years	31·5 (14·4)	32·6 (15·4)	33·0 (17·4)
Age group, years			
<18	17 (22%)	34 (22%)	33 (21%)
18–65	59 (77%)	118 (76%)	110 (71%)
≥65	1 (1%)	4 (3%)	11 (7%)
Sex			
Men	49 (64%)	90 (58%)	81 (53%)
Women	28 (36%)	66 (42%)	73 (47%)
Race			
White	62 (81%)	113 (72%)	104 (68%)
Black or African American	6 (8%)	15 (10%)	11 (7%)
Asian	6 (8%)	26 (17%)	26 (17%)
Other*	2 (3%)	2 (1%)	11 (7%)
Not reported	1 (1%)	0	2 (1%)
Ethnicity			
Hispanic or Latino	6 (8%)	10 (6%)	4 (3%)
Not Hispanic or Latino	71 (92%)	144 (92%)	149 (97%)
Not reported	0	2 (1%)	1 (1%)
Disease duration, years	22·5 (14·4)	24·9 (16·1)	22·7 (14·5)
Previous medication for atopic dermatitis†			
Any previous medication	77 (100%)	155 (99%)	154 (100%)
Topical drugs alone‡	34 (44%)	69 (44%)	82 (53%)
Systemic medication with or without topical drugs§	41 (53%)	78 (50%)	68 (44%)
Dupilumab	8 (10%)	13 (8%)	9 (6%)
Investigator Global Assessment score			
3 (moderate disease)	46 (60%)	92 (59%)	91 (59%)
4 (severe disease)	31 (40%)	64 (41%)	63 (41%)
EASI score	28·7 (12·5)	31·3 (13·6)	30·6 (14·1)
Body surface area affected, %	47·4 (22·7)	50·8 (23·4)	49·9 (24·4)
SCORAD score	64·5 (13·2)	67·1 (13·7)	64·3 (13·1)
PP-NRS score¶	7·0 (1·8)	6·9 (2·0)	7·1 (1·9)
PSAAD total score‖	5·5 (2·0)	5·3 (2·3)	5·4 (2·1)
DLQI total score**	13·9 (7·3)	14·6 (6·5)	14·6 (6·8)
CDLQI total score††	13·6 (7·0)	11·7 (6·6)	13·2 (5·5)
POEM total score‡‡	19·9 (6·1)	19·5 (6·5)	19·6 (5·9)

Data are mean (SD) or n (%). EASI=Eczema Area and Severity Index. SCORAD=SCORing Atopic Dermatitis. PP-NRS=Peak Pruritus Numerical Rating Scale. PSAAD= Pruritus and Symptoms Assessment for Atopic Dermatitis. DLQI=Dermatology Life Quality Index. CDLQI=Children's Dermatology Life Quality Index. POEM=Patient Oriented Eczema Measure. *Includes patients that were American Indian or Alaskan Native, Native Hawaiian or Pacific Islander, or multiracial. †Patients were counted for each main category (ie, topical agents or systemic agents) in an exclusive manner. ‡Topical agents includes corticosteroids and calcineurin inhibitors. §Systemic agents includes mycophenolate mofetil, methotrexate, azathioprine, corticosteroids, ciclosporin, and dupilumab. ¶Data were available for 77 patients in the placebo group, 155 patients in the abrocitinib 100 mg group, and 154 patients in the abrocitinib 200 mg group. ‖Data were available for 68 patients in the placebo group, 137 patients in the abrocitinib 100 mg group, and 138 patients in the abrocitinib 200 mg group. **Assessed in patients aged ≥18 years; data were available for 60 patients in the placebo group, 121 patients in the abrocitinb 100 mg group, and 119 patients in the abrocitinb 200 mg group. ††Assessed in patients aged <18 years; data were available for 16 patients in the placebo group, 32 patients in the abrocitinb 100 mg group, and 32 patients in the abrocitinb 200 mg group. ‡‡Data were available for 77 patients in the placebo group, 153 patients in the abrocitinib 100 mg group, and 153 patients in the abrocitinib 200 mg group.

Table 1: **Demographic and baseline characteristics**

Randomisation and masking

Patients were randomly assigned (2:2:1) to receive oral abrocitinib 100 mg, abrocitinib 200 mg, or matching placebo, using a central randomisation scheme provided by an interactive response technology system. Randomisation was stratified by baseline disease severity (Investigator Global Assessment score 3 or 4) and age group (<18 years or ≥18 years). Patients, investigators, and the funder of the study were masked to study treatment. The placebo tablets were identical to the abrocitinib 100 mg tablets in size, colour, shape, and odour. Patients were given two bottles, and were instructed to take one tablet from each bottle: for the 100 mg group, one bottle contained placebo and the other contained abrocitinib 100 mg tablets; for the 200 mg group, both bottles contained abrocitinib 100 mg tablets; and for the placebo group, both bottles contained placebo tablets.

Procedures

Patients were screened within 28 days of the first dose of study drug. Screening consisted of laboratory assessment (neutrophil, haemoglobin, platelet, and lymphocyte counts; and creatinine, aspartate aminotransferase or alanine aminotransferase, and bilirubin levels); complete blood count and blood chemistry, lipid panels, vital signs, and electrocardiogram; and hepatitis and tuberculosis testing. Chest x-rays were also done as appropriate. Patients received oral abrocitinib 100 mg, abrocitinib 200 mg, or matching placebo once daily for 12 weeks. Follow-up efficacy, safety, and laboratory assessments were done at weeks 2, 4, 6, 8, and 12 through clinical examinations and patient-reported

questionnaires.

Outcomes

The coprimary endpoints were the proportion of patients who had achieved an Investigator Global Assessment response (score of 0 [clear] or 1 [almost clear] and a ≥2-grade improvement from baseline), and the proportion of patients who had achieved at least a 75% improvement in EASI score from baseline (EASI-75) at week 12 of treatment. Both coprimary endpoints must have achieved statistically significant difference from placebo to meet the primary objective.

Multiplicity-controlled key secondary endpoints were the proportion of patients who achieved a PP-NRS response (≥4 point improvement from baseline in PP-NRS score) at weeks 2, 4, and 12, and least squares mean change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD; 11-item questionnaire developed to measure daily symptoms of atopic dermatitis) total score[23] at week 12. Other secondary endpoints were: the proportion of patients who achieved an Investigator Global Assessment response at all other scheduled timepoints (weeks 2, 4, and 8); proportion of patients who achieved EASI-75 at all other scheduled timepoints (weeks 2, 4, and 8); the proportion of patients who achieved EASI-50 (≥50% improvement from baseline) and EASI-90 (≥90% improvement from baseline) at all scheduled timepoints; the proportion of patients who achieved a PP-NRS response at week 8; time from baseline to PP-NRS response; and the proportion of patients who achieved an improvement of 75% or more in SCORing Atopic Dermatitis (SCORAD)[24] score from baseline at all scheduled timepoints. The other secondary endpoints, which will be reported elsewhere, were: the proportion of patients who achieved an improvement of 50% or more in SCORAD score from baseline at all scheduled timepoints; change from baseline in percentage body surface area affected at all timepoints; and change from baseline in SCORAD subjective assessments of itch and sleep loss at all scheduled timepoints. Patient-reported outcomes were change from baseline in Patient-Oriented Eczema Measure (POEM)[25] total score and Dermatology Life Quality Index (DLQI; assessed in patients aged ≥18 years)[26] or children's DLQI (CDLQI; assessed in patients aged <18 years)[27] total score at week 12 and all other timepoints. The other patient-reported outcomes, which will be reported elsewhere, were: Hospital Anxiety and Depression Scale, and Patient Global Assessment, EuroQol Quality of Life 5-Dimension 5-Level Scale or EuroQol Quality of Life 5-Dimension Youth Scale, Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) or Pediatric FACIT-F, and Short Form 36 Health Survey version 2 (SF-36v2) at week 12 and all other timepoints. Pharmacokinetic analysis will also be reported elsewhere.

Adverse events, serious adverse events, and adverse events leading to discontinuation from the first dose of study drug were assessed over the 12-week treatment period until 28 days after the last dose of study drug. The incidence of clinical abnormalities, change from baseline in clinical laboratory values, electrocardiogram (ECG) measurements, and vital signs were also recorded.

Statistical analysis

A sample size of 375 patients (150, 150, and 75 patients randomly assigned to **[A: I have not added 'to receive' here because we are talking about the groups]** 100 mg, 200 mg, and placebo groups, respectively) was required to provide at least 95% power to detect at least 20% difference in Investigator Global Assessment response rates between either abrocitinib dose and placebo, assuming a response rate of 6% in the placebo group at week 12, and at least 99% power to detect a difference in EASI-75 response rate of at least 30% between either abrocitinib dose and placebo, assuming a response rate of 15% in the placebo group at week 12. The type-1 error for testing each individual coprimary endpoint was set at

For the **study protocol** see https://clinicaltrials.gov/ProvidedDocs/60/NCT03349060/Prot_001.pdf

	Placebo (n=77)	Abrocitinib 100 mg (n=156)	Abrocitinib 200 mg (n=154)
Coprimary endpoints			
Investigator Global Assessment response at 12 weeks			
Responders, n/N (%)	6/76 (8%)	37/156 (24%)	67/153 (44%)
Percentage difference compared with placebo (95% CI)	..	15·8 (6·8 to 24·8)	36·0 (26·2 to 45·7)
p value	..	0·0037	<0·0001
EASI-75 response at 12 weeks			
Responders, n/N (%)	9/76 (12%)	62/156 (40%)	96/153 (63%)
Percentage difference compared with placebo (95% CI)	..	27·9 (17·4 to 38·3)	51·0 (40·5 to 61·5)
p value	..	<0·0001	<0·0001
Key secondary endpoints			
PP-NRS response*			
Responders at week 2, n/N (%)	2/74 (3%)	30/147 (20%)	67/147 (46%)
Percentage difference compared with placebo (95% CI)	..	18·0 (10·2 to 25·8)	42·5 (33·6 to 51·4)
p value	..	0·0004	<0·0001
Responders at week 4, n/N (%)	13/74 (17%)	47/147 (32%)	86/147 (59%)
Percentage difference compared with placebo (95% CI)	..	15·0 (1·9 to 28·0)	41·1 (27·8 to 54·4)
p value	..	0·0251	<0·0001
Responders at week 12, n/N (%)	11/74 (15%)	55/147 (38%)	84/147 (57%)
Percentage difference compared with placebo (95% CI)	..	22·5 (10·3 to 34·8)	41·7 (29·6 to 53·9)
p value	..	0·0003	<0·0001
PSAAD total score change from baseline at week 12			
n	68	137	138
Least squares mean change from baseline (95% CI)	−1·1 (−1·7 to −0·6)	−2·2 (−2·6 to −1·9)	−3·2 (−3·6 to −2·8)
Difference in least squares mean change compared with placebo (95% CI)	–	−1·1 (−1·7 to −0·4)	−2·1 (−2·7 to −1·4)
p value	–	0·0010	<0·0001

(Table 2 continues on next page)

	Placebo (n=77)	Abrocitinib 100 mg (n=156)	Abrocitinib 200 mg (n=154)
(Continued from previous page)			
Other secondary endpoints			
EASI-90 response at week 12			
Responders, n/N (%)	4/76 (5%)	29/156 (19%)	59/153 (39%)
Percentage difference compared with placebo (95% CI)	..	13·3 (5·4 to 21·2)	33·4 (24·3 to 42·5)
EASI-50 response at week 12			
Responders, n/N (%)	17/76 (22%)	90/156 (58%)	116/153 (76%)
Percentage difference compared with placebo (95% CI)	..	35·3 (23·3 to 47·4)	53·5 (42·0 to 65·0)
PP-NRS response* at week 8			
Responders, n/N (%)	11/74 (14%)	50/147 (34%)	88/147 (60%)
Percentage difference compared with placebo (95% CI)	..	20·0 (7·4 to 32·7)	45·3 (32·7 to 57·8)
Change in DLQI total score from baseline at week 12			
Patients assessed, n	60	121	119
Least squares mean change from baseline (95% CI)	−4·2 (−5·9 to −2·5)	−7·0 (−8·1 to −5·8)	−9·1 (−10·3 to −8·0)
Least squares mean difference compared with placebo (95% CI)	..	−2·8 (−4·8 to −0·8)	−4·9 (−6·9 to −2·9)
Change in CDLQI total score from baseline at week 12			
Patients assessed, n	16	32	32
Least squares mean change from baseline (95% CI)	−3·9 (−6·1 to −1·7)	−6·4 (−7·9 to −5·0)	−7·5 (−8·9 to −6·0)
Least squares mean difference compared with placebo (95% CI)	..	−2·5 (−5·2 to 0·1)	−3·6 (−6·2 to −0·9)
Change in POEM total score from baseline at week 12			
Patients assessed, n	77	153	153
Least squares mean change from baseline (95% CI)	−3·7 (−5·5 to −1·9)	−6·8 (−8·0 to −5·6)	−10·6 (−11·8 to −9·4)
Least squares mean difference compared with placebo (95% CI)	..	−3·1 (−5·2 to −0·9)	−6·9 (−9·0 to −4·7)

p values for coprimary and key secondary efficacy endpoints were adjusted for multiplicity. Testing of secondary endpoints was not controlled for multiplicity; thus, p values are not provided. For PP-NRS responses, the estimated number of responders, response rates, and 95% CIs were obtained from a multiple imputation procedure accounting for any other missing data that were not already handled by non-responder imputation. EASI=Eczema Area and Severity Index. EASI-75=Improvement of at least 75% in EASI score from baseline. PP-NRS=Peak Pruritus Numeric Rating Scale. PSAAD=Pruritus and Symptoms Assessment for Atopic Dermatitis. EASI-90=Improvement of at least 90% in EASI score from baseline. EASI-50=Improvement of at least 50% in EASI score from baseline. DLQI=Dermatology Life Quality Index. CDLQI= Children's Dermatology Life Quality Index. POEM=Patient Oriented Eczema Measure. *Defined as a 4-point or greater improvement from baseline in PP-NRS score.

Table 2: **Summary of efficacy endpoints and 12-week patient-reported outcomes**

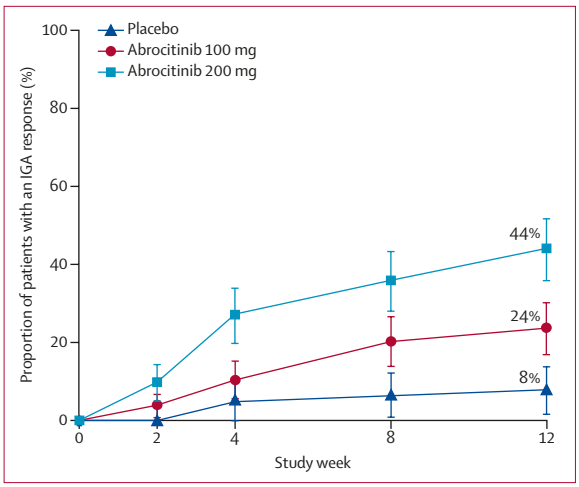

Figure 2: **Proportion of patients who achieved an IGA response over the 12-week treatment period**
Error bars show 95% CI. IGA=Investigator Global Assessment.

5%. The coprimary endpoints tested the hypotheses of superiority of each abrocitinib dose compared with placebo in both Investigator Global Assessment and EASI-75 response at week 12 (two hypotheses). The key secondary endpoints tested the hypothesis of superiority of each abrocitinib dose compared with placebo in PP-NRS response at weeks 2, 4, and 12, and the change from baseline in PSAAD total score at week 12 (8 hypotheses). The familywise type-1 error rate for testing the coprimary and key secondary endpoints was controlled at 5% using a sequential, Bonferroni-based procedure. Testing of all other secondary endpoints was done at the nominal 5% significance level and was not controlled for multiplicity.

The primary analysis population for efficacy data was the full analysis set, which included all randomised patients who received at least one dose of study medication. The coprimary and key secondary endpoints were analysed using the Cochran-Mantel-Haenszel test, adjusted for randomisation strata (baseline disease severity and age group). All other binary endpoints were analysed using the same methods. Missing responses for patients who permanently discontinued the study (including those who discontinued due to use of protocol-prohibited atopic dermatitis medication, such as topical corticosteroids) were defined as non-responders at all visits after discontinuation. We also did sensitivity analyses, in which the coprimary endpoints were analysed using the per-protocol analysis set and using a tipping point analysis based on the full analysis set. Patients with major protocol violations and who had missing responses for the coprimary endpoints were excluded from the per-protocol analysis; the tipping point analysis imputed all missing responses using a multiple imputation approach. All continuous endpoints were analysed using a mixed-effect model with repeated measures (MMRM) on the basis of all observed data. The model included factors (fixed effects) for treatment group, randomisation strata (age group, baseline disease severity), visit, treatment-by-visit interaction, and relevant baseline value. Within the framework of MMRM, treatment difference was tested at the prespecified primary timepoint (week 12) and at the other timepoints (weeks 2, 4, and 8) by time-point-specific contrasts from the MMRM model. No explicit imputations were made for missing data, and the MMRM model yields valid inferences under the assumption of a missing at random mechanism. Safety was assessed in all patients who received study medication. All safety data were summarised using descriptive statistics. SAS software (version 9.4) was used

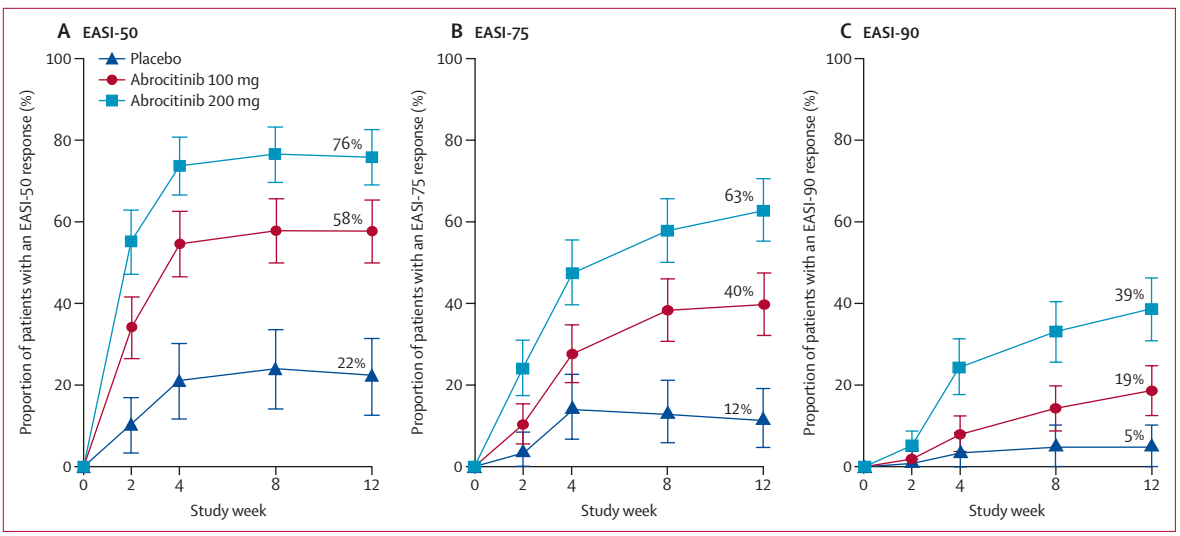

Figure 3: **Proportion of patients who achieved an EASI-50 (A), EASI-75 (B), and EASI-90 (C) response over the 12-week treatment period**
Error bars show 95% CI. EASI=Eczema Area and Severity Index. EASI-50=Improvement of at least 50% in EASI score from baseline. EASI-75=Improvement of at least 75% in EASI score from baseline. EASI-90=Improvement of at least 90% in EASI score from baseline.

for all statistical analysis. This study is registered with ClinicalTrials.gov, NCT03349060.

Role of the funding source

The study was designed, funded, and managed by the funder. The funder collected, managed data, and analysed data. All authors participated in interpretation of the data, preparation, review, and approval of the manuscript and decision to submit the manuscript for publication. Medical writing and editorial support were provided and funded by the funder.

Results

Between Dec 7, 2017, and March 26, 2019, we screened 553 patients, of whom 387 were randomly assigned to receive abrocitinib 100 mg (n=156), abrocitinib 200 mg (n=154), or placebo (n=77). 61 patients in the placebo group, 135 patients in the abrocitinib 100 mg group, and 137 patients in the abrocitinib 200 mg group completed the study (figure 1). The most common reason for discontinuation of the study in the abrocitinib 100 mg and 200 mg groups was adverse events. The proportion of patients who discontinued due to adverse events was lower in both abrocitinib groups than in the placebo group (figure 1).

Demographics and baseline characteristics were balanced across the treatment groups (table 1). Most patients in the study were men (57%), with a mean age of 32·5 years (SD 16·0). Black (8%) and Asian (15%) patients were well represented in the study. The proportion of patients with moderate disease (59%) was higher than the proportion of patients with severe disease (41%), as measured by Investigator Global Assessment score. Most patients had received previous treatment for atopic dermatitis before the study

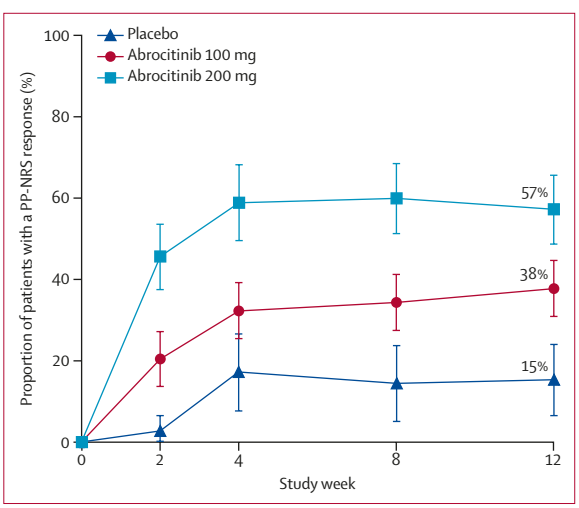

Figure 4: **Proportion of patients who achieved a PP-NRS response* over the 12-week treatment period**
Error bars show 95% CI. PP-NRS=Peak Pruritus Numerical Rating Scale. *Defined as a ≥4-point improvement from baseline in PP-NRS score.

(187 [48%] of 387 patients had received systemic medication with or without topical drugs and 185 [48%] had received topical drugs alone).

All 156 randomly assigned patients in the abrocitinib 100 mg group, 154 patients in the abrocitinib 200 mg group and 77 patients in the placebo group received at least one dose of study drug and thus were included in the full analysis set. One patient in the 200 mg abrocitinib group and one patient in the placebo group were not assessed for the coprimary endpoints at the 12-week timepoint, and hence were included in the analysis of the coprimary endpoints **[A: correct as edited?]**. Of the patients with available data at week 12 **[A: ok?]**, 37 (24%) of 156 patients in the abrocitinib 100 mg group, 67 (44%) of 153 patients in

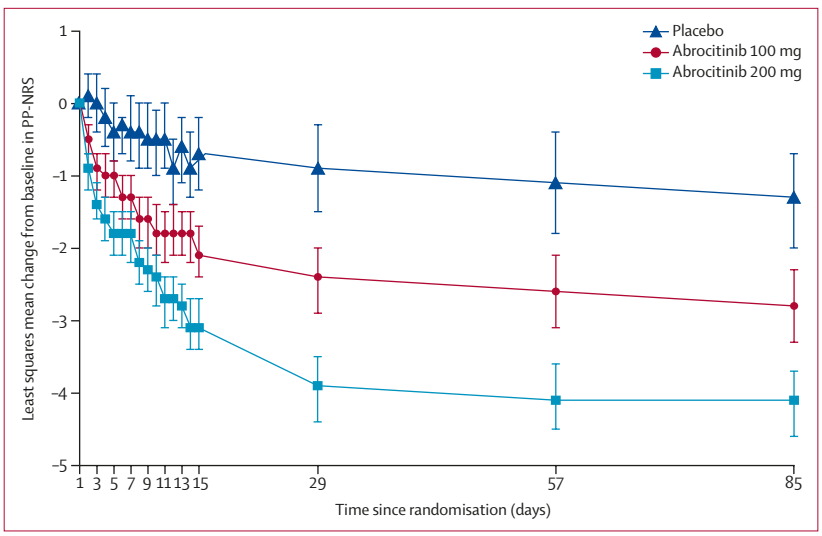

Figure 5: **Least squares mean change from baseline in PP-NRS score over the 12-week treatment period**
Error bars show 95% CI. PP-NRS=Peak Pruritus Numerical Rating Scale.

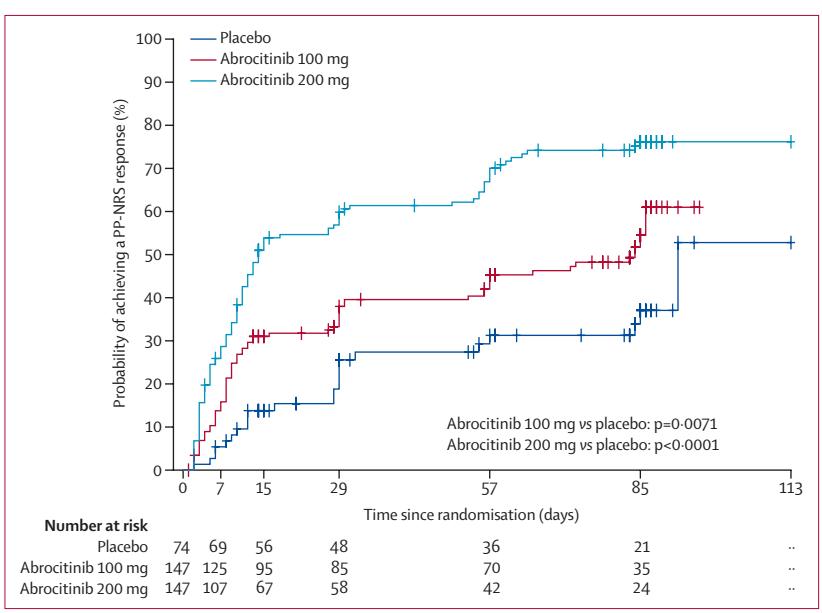

Figure 6: **Kaplan-Meier plot of estimated probability of achieving a PP-NRS response***
Plot is based on observed data only (no imputations) and times to event were censored at treatment discontinuation, or last observation for patients who had not achieved a response. 23 patients in the placebo group, 73 patients in the abrocitinib 100 mg group, and 106 patients in the abrocitinib 200 mg group had achieved a response by 16 weeks. PP-NRS=Peak Pruritus Numerical Rating Scale. *Defined as a ≥4-point improvement from baseline in PP-NRS score.

the abrocitinib 200 mg group, and six (8%) of 76 patients in the placebo group had achieved an Investigator Global Assessment response (table 2). The difference in the investigator global assessment response rate between the placebo and abrocitinib 100 mg group was 15·8% (95% CI 6·8 to 24·8; p=0·0037) and 36·0% (95% CI 26·2 to 45·7; p<0·0001) for the abrocitinib 200 mg group (table 2). Of the patients with available data at week 12 **[A: ok?]**, 62 (40%) of 156 patients in the abrocitinib 100 mg group, 96 (63%) of 153 patients in the abrocitinib 200 mg group, and nine (12%) of 76 patients in the placebo group had an EASI-75 response (table 2). The difference in EASI-75 response rate between the placebo group and abrocitinib 100 mg group was 27·9% (95% CI 17·4 to 38·3; p<0·0001) and 51·0% (95% CI 40·5 to 61·5; p<0·0001) for the abrocitinib 200 mg group (table 2). Sensitivity analyses done for the coprimary endpoints yielded similar results. The proportion of patients who had achieved an Investigator Global Assessment and EASI-75 responses at 12 weeks was higher for both 100 mg and 200 mg abrocitinib groups than for the placebo group for adolescent and adult patients and patients with moderate and severe baseline disease severity (appendix pp 10–11). The proportion of patients who had achieved an Investigator Global Assessment response was higher in the abrocitinib groups than in the placebo group at each timepoint, and increased between treatment initiation and week 12 (figure 2). The proportion of patients who achieved EASI-50, EASI-75, and EASI-90 responses was higher for both abrocitinib groups than for the placebo group at each timepoint, and increased between treatment initiation and week 12 (table 2; figure 3).

The proportion of patients achieving a PP-NRS response increased between week 2 and week 12 for both abrocitinib groups, with significant differences identified between abrocitinib groups and placebo at weeks 2, 4, and 12 (table 2; figure 4). PP-NRS scores decreased between baseline and week 12 for both abrocitinib doses compared with placebo (figure 5), and this reduction was observed within 1 day of the first dose of treatment (appendix p 27). The median time to PP-NRS response was 84·0 days (IQR 10·0–not evaluable [NE]) in the abrocitinib 100 mg group, 14·0 days (6·0–84·0) in the abrocitinib 200 mg group, and 92·0 days (29·0–NE) in the placebo group (figure 6).

At week 12, the difference in least squares mean change from baseline in PSAAD total scores between the abrocitinib 100 mg group and the placebo group was −1·1 (95% CI −1·7 to −0·4; p=0·0010) and the difference between the 200 mg group and the placebo group was −2·1 (−2·7 to −1·4; p<0·0001; table 2; appendix p 27). The proportion of patients who achieved a SCORAD-75 response increased between treatment initiation and week 12 for both abrocitinib groups. A significant difference in SCORAD-75 response rate was identified between the abrocitinib 200 mg and the placebo group at all timepoints and between the abrocitinib 100 mg group and placebo group at weeks 8 and 12 (appendix p 28).

At week 12, among adult patients (aged ≥18 years), the difference in least squares mean change from baseline in DLQI total score was −7·0 (95% CI −8·1 to −5·8) in the abrocitinib 100 mg group, −9·1 (−10·3 to −8·0) in the abrocitinib 200 mg group, and −4·2 (−5·9 to −2·5) in the placebo group (table 2). Reductions in DLQI total score were observed between week 2 to 12 for all groups

(appendix p 29). At week 12, among adolescent patients (aged <18 years), the difference in least squares mean change from baseline in CDLQI total score, was –6·4 (–7·9 to –5·0) in the abrocitinib 100 mg group, –7·5 (–8·9 to –6·0) in the abrocitinib 200 mg group, and –3·9 (–6·1 to –1·7) in the placebo group (table 2). Reductions in CDLQI total score were observed between week 2 and 12 for all groups (appendix p 29). For POEM total score, the difference in least squares mean change from baseline at week 12 was –6·8 (–8·0 to –5·6) for the abrocitinib 100 mg group, –10·6 (–11·8 to –9·4) for the abrocitinib 200 mg group, and –3·7 (–5·5 to –1·9) for the placebo group (table 2). Patients in the abrocitinib 100 mg and abrocitinib 200 mg groups had significant improvement in POEM score compared with placebo between week 2 and 12 (appendix p 30).

Overall, 108 (69%) of 156 patients in the abrocitinib 100 mg group, 120 (78%) of 154 patients in the abrocitinib 200 mg group, and 44 (57%) of 77 patients in the placebo group reported adverse events (appendix p 13). The most frequently reported treatment-emergent adverse events in the abrocitinib 100 mg and 200 mg groups were nausea and nasopharyngitis; the most frequently reported treatment-emergent adverse events in the placebo group was dermatitis atopic (table 3). The median duration of nausea was 13·0 days (IQR 5·0–NE) in the abrocitinib 100 mg group and 39·0 days (4·0–NE) in the abrocitinib 200 mg group. The median duration of headache was 4·0 days (IQR 1·5–22·0) in the abrocitinib 100 mg group and 3·0 days (1·0–6·0) in the abrocitinib 200 mg group. One (1%) of 156 patients in the abrocitinib 100 mg group discontinued treatment due to nausea, with no discontinuations due to this adverse event observed in the abrocitinib 200 mg or placebo groups. No patients discontinued treatment due to headache.

Serious adverse events were reported in five (3%) of 156 patients in the abrocitinib 100 mg group, five (3%) of 154 patients in the abrocitinib 200 mg group, and three (4%) of 77 patients in the placebo group (table 3). Among these patients, only two serious adverse events were considered treatment-related (table 4): one patient in the abrocitinib 200 mg group developed chronic inflammatory bowel disease during the treatment period, abrocitinib was permanently discontinued, and the patient recovered; the other patient was in the abrocitinib 100 mg group and developed acute pancreatitis during the treatment period, abrocitinib was permanently discontinued, and the patient recovered. No cases of venous thromboembolism, malignancies, major adverse cardiovascular events, or deaths were observed (table 3).

A total of nine (6%) of 156 patients in the abrocitinib 100 mg group, nine (6%) of 154 patients in the abrocitinib 200 mg group, and seven (9%) of 77 patients in placebo group discontinued treatment due to adverse events. The most common adverse events leading to treatment discontinuation were atopic dermatitis (four [3%] of 156 patients) in the abrocitinib 100 mg group,

	Placebo (n=77)	Abrocitinib 100 mg (n=156)	Abrocitinib 200 mg (n=154)
Deaths	0	0	0
Serious adverse events	3 (4%)	5 (3%)	5 (3%)
Most frequently reported treatment-emergent adverse events (≥5% in any treatment group)			
Nausea	2 (3%)	14 (9%)	31 (20%)
Nasopharyngitis	8 (10%)	23 (15%)	18 (12%)
Headache	2 (3%)	12 (8%)	15 (10%)
Upper respiratory tract infection	5 (7%)	11 (7%)	11 (7%)
Atopic dermatitis	13 (17%)	22 (14%)	8 (5%)
Treatment-emergent herpes viral infection			
Any	0	5 (3%)	4 (3%)
Herpes simplex	0	1 (1%)	3 (2%)
Herpes zoster	0	1 (1%)	2 (1%)
Oral herpes	0	3 (2%)	1 (1%)
Eczema herpeticum	1 (1%)	2 (1%)	0

Data are n (%).

Table 3: **Adverse events**

	Placebo (n=77)	Abrocitinib 100 mg (n=156)	Abrocitinib 200 mg (n=154)
General disorders and administration site conditions or condition aggravated	1 (1%)	0	0
Appendicitis	1 (%)	0	0
Meniscal degeneration	1 (1%)	0	0
Atopic dermatitis	1 (1%)	0	0
Appendicitis	0	1 (1%)	0
Dizziness	0	1 (%)	0
Seizure	0	1 (1%)	0
Retinal detachment	0	1 (1%)	0
Acute pancreatitis	0	1 (1%)*	0
Inflammatory bowel disease	0	0	1 (1%)*
Peritonsillitis	0	0	1 (1%)
Dehydration	0	0	1 (1%)
Asthma	0	0	2 (1%)

Data are n (%). *Serious adverse event related to treatment.

Table 4: **Serious adverse events**

gastrointestinal disorders (three [2%] of 154 patients; abdominal pain [n=1], inflammatory bowel disease [n=1], and vomiting [n=1]) in the abrocitinib 200 mg group, and atopic dermatitis (three [4%] of 77 patients) in the placebo group (appendix p 12).

Herpes virus infections were reported in all treatment groups. One (1%) of 156 patients in the abrocitinib 100 mg group, and three (2%) of 154 patients in the abrocitinib 200 mg group had herpes simplex infection. Herpes zoster infection was reported in one (1%) of 156 patients in the abrocitinib 100 mg group and two (1%) of 154 patients in the abrocitinib 200 mg group. Three (2%) of 156 patients in the abrocitinib 100 mg group and one (1%) of 154 patients in the abrocitinib 200 mg group had oral herpes (table 3). Eczema herpeticum was

reported in two (1%) of 156 patients in the abrocitinib 100 mg group and one (1%) of 77 patients in the placebo group. Conjunctivitis was reported in four (3%) of 156 patients in the abrocitinib 100 mg group and four (3%) of 154 patients in the abrocitinib 200 mg group; no cases were reported in the placebo group (appendix p 17).

Dose-related numeric decreases in median platelet count were observed in patients in both abrocitinib groups, with a nadir observed at week 4, and a return toward baseline values thereafter (appendix p 28). Most patients in all treatment groups maintained platelet counts within the normal range (appendix p 28). One patient in the 200 mg abrocitinib group had a decreased platelet count on day 30 of the study, which was deemed to be non-serious; the patient discontinued treatment because of this adverse event on day 55. The patient's platelet count returned to normal 5 days after treatment discontinuation. No patients had significant changes in haemoglobin, neutrophil, or lymphocyte counts. All other observed changes in clinical laboratory values, ECG measurements, and vital signs were not deemed to be clinically significant.

Discussion

The results of this phase 3 monotherapy trial showed that adolescent and adult patients given abrocitinib 200 mg or 100 mg once daily for 12 weeks had significant improvement in the signs and symptoms of atopic dermatitis when compared with placebo. Clinically meaningful Investigator Global Assessment and EASI-75 responses were observed in the abrocitinib groups as early as week 2 of treatment and continued to increase until week 12. Sensitivity analysis using the per-protocol analysis set and a tipping point analysis yielded similar results: Investigator Global Assessment and EASI-75 response rates were higher among the two abrocitinib groups than the placebo group, when stratified by age and disease severity. A significant, rapid (ie, within 2 days) reduction in pruritus severity and other atopic dermatitis symptoms was also observed between treatment initiation and week 12. Patients in the abrocitinib groups had improvements in patient-reported quality of life compared with placebo, and both abrocitinib doses had a favourable benefit–risk profile. The CIs for the primary analysis of differences in Investigator Global Assessment and EASI-75 response rates versus placebo for the 100 mg and 200 mg abrocitinib groups did not overlap, indicating that the 200 mg dose could potentially be more effective in patients with moderate-to-severe atopic dermatitis. However, the study was not designed or powered to compare the abrocitinib 200 mg and 100 mg doses with one another.

The results of this phase 3 study are consistent with the results of a previous phase 2b study of abrocitinib in adults with moderate-to-severe atopic dermatitis.[19] However, the phase 2b study did not include patients aged younger than 18 years. This phase 3 study included adolescent patients, although they only comprised 20% of the study population. The preliminary efficacy results in adolescent and adult patients suggest that the applicability of abrocitinib treatment might be extended to adolescents. The treatment differences observed between both abrocitinib groups and the placebo group for the coprimary endpoints were observed by week 2 and did not seem to have plateaued by the end of the treatment period of this study, although it is unknown whether more prolonged treatment would have resulted in additional responders.

In this 12-week study of patients with moderate-to-severe atopic dermatitis, both doses of abrocitinib seemed to have a positive benefit–risk profile compared with placebo. The incidence of serious adverse events was low (<4%) in both abrocitinib groups and seemed to be comparable to placebo, with most events not deemed to be treatment-related. The number of patients who discontinued treatment due to treatment-related adverse events was low in both abrocitinib groups compared with the placebo group. JAK inhibition can potentially increase the risk of infections due to the involvement of JAKs in signalling pathways that regulate host defence and immune response.[28] However, the incidence of serious infections and herpes virus infections was low. Additionally, no cases of malignancy were reported in this study. Future trials with a longer duration are required to provide information about the risk of malignancy. Depending on selectivity, JAK inhibition can potentially result in changes in blood cell counts, which are considered to be related to JAK2 effects on haematopoiesis. However, in this study of a selective JAK1 inhibitor, no significant changes in haemoglobin, neutrophils, or lymphocyte counts were observed. However, we did observe a slight reduction in platelet count that retuned towards baseline levels after the nadir at week 4. A similar effect on platelet count was observed with abrocitinib treatment in the phase 2b study.[19] The mechanism that led to changes in platelet count is unclear but could be a pharmacological effect of the drug that could potentially be mediated by the inhibition of JAK1 and downstream inhibition of thrombopoietin production.[29] No cases of venous thromboembolism or major adverse cardiovascular events were reported, which have been associated with some JAK inhibitors. This 12-week study did not address long-term safety.

Comparisons of efficacy and safety results of this phase 3 study with studies of other treatments for atopic dermatitis are complicated by differences in administration route, treatment period, efficacy endpoints, and patient inclusion criteria. However, the efficacy of abrocitinib seems to be at least comparable to dupilumab in a broadly similar patient population. Considering that response to abrocitinib treatment had not plateaued by week 12 of the study, comparisons with the 16-week SOLO studies[30] might underestimate the full effect of abrocitinib.

Additionally, previous dupilumab monotherapy studies have not included adolescents.

Abrocitinib is a small molecule, thus obviating issues potentially arising from subcutaneous injection such as injection-site reactions and minimising the possibility of development of anti-drug antibodies compared with biologic treatments. Additionally, abrocitinib can be used by patients who are unwilling to receive injections, such as paediatric patients, and might have a potential use in patients that only require seasonal or episodic treatment or a more flexible dosing regimen adapted to individual signs and symptoms. Conjunctivitis is a side-effect that has been observed in up to 28% of patients in previous dupilumab trials;[31] however, in our study, 3% of participants in the abrocitinib treatment groups reported conjunctivitis.

This study was limited by the 12-week treatment period, which did not address the long-term efficacy and safety of abrocitinib. Additionally, this study did not compare the efficacy of abrocitinib versus the current standard of care in moderate-to-severe atopic dermatitis. Although concomitant topical therapies were not allowed in this study, abrocitinib could be used in combination with topical therapies in patients with moderate-to-severe atopic dermatitis in clinical practice, which was not addressed by this study. Several current and future phase 3 studies are designed to address these topics (NCT03627767, NCT03720470). Furthermore, the study was not designed to compare the 200 mg and 100 mg abrocitinib doses.

In conclusion, oral abrocitinib 100 mg or 200 mg monotherapy given once daily was effective and well tolerated in patients with moderate-to-severe atopic dermatitis with a favourable benefit-risk profile. Abrocitinib could present a promising novel oral systemic drug to treat moderate-to-severe atopic dermatitis not controlled by topical therapies in patients aged 12 years and older.

Contributors

ELS, RS, SF, AW, RA, MC, TB, JPT, GY, CFl, NM, CM, and CFe contributed to literature search, figures, data interpretation, and writing. PB contributed to study design, data analysis, figures, data interpretation, and writing. HV, RR, and ST contributed to study design, literature search, figures, data interpretation, and writing.

Declaration of interests

ELS is a consultant for Pfizer; reports personal fees from AbbVie, Celgene, Dermira Pharmaceuticals, Galderma, Genentech, Menlo Therapeutics, LEO Pharma, Sanofi Genzyme, Valeant Pharmaceutical, Dermavant, and Pierre Fabre Dermo Cosmetique; grants and personal fees from Anacor Pharma, Eli Lilly, GlaxoSmithKline, Pfizer, Regeneron Pharmaceuticals, and Novartis; and grants from MedImmune, Tioga Pharmaceuticals, and Vanda Pharmaceuticals. RS has been principal investigator in clinical trials, served on advisory boards, received personal fees or non-financial support from Pfizer, AbbVie, Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Botanix, Celgene, Coherus, Dermira, Eli Lilly, Galderma, Janssen, LEO Pharma, Principia, MedImmune, Merck, Novartis, Roche, Sanofi-Genzyme, Regeneron, UCB, and Valeant. AW has been an advisor, speaker, or investigator for Pfizer during the conduct of the study; and reports personal fees from AbbVie, Chugai, Galderma, Eli Lilly MedImmune, Novartis, Pfizer, Regeneron, and Sanofi-Aventis; and grants and personal fees from Leo Pharma, outside the submitted work. MC reports grants from Sheffield Teaching Hospitals, during the conduct of the study; grants and personal fees from Sanofi-Genzyme/Regeneron, Pfizer, Leo Pharma, L'Oreal, La Roche-Possay, Johnson & Johnson, Perrigo/ACO Nordic, and Hyphens Pharma; and grants from Galapagos, outside the submitted work. TB reports personal fees from Pfizer, during the conduct of the study; personal fees from Lilly, AbbVie, Sanofi, LEO, and Galapagos; and grants from Glenmark and Galderma, outside the submitted work. JPT reports personal fees from Pfizer; and is an advisor, investigator, and speaker for Pfizer, AbbVie, Eli Lilly, LEO Pharma, and Sanofi-Genzyme. GY reports grants, personal fees, and non-financial support from Pfizer during the conduct of the study; grants from Pfizer and LEO Pharma, Sun Pharmaceutical Industries; grants and personal fees from Sanofi-Regeneron, Menlo Therapeutics, and Kiniksa; personal fees and non-financial support from Galderma; and personal fees from Sienna Biopharmaceuticals, and Trevi Therapeutics, Bellus, Bayer, AbbVie, CeraVe, Novartis, Eli Lilly, and Ortho, outside the submitted work. CFl reports grants from the EU IMI BIOMAP consortium, the UK National Institute for Health Research for TREAT trial, and the British Skin Foundation for UK-Irish Atopic Eczema Systemic Therapy Register, outside the submitted work. CM reports grants from Pfizer, during the conduct of the study; grants and personal fees from Lilly Pharma, Sanofi-Regeneron, and AbbVie; and grants from Asana Bioscience and Glenmark, outside the submitted work. CFe, PB, ST, HV, and RR are employees and shareholders of Pfizer. SF and NM declare no competing interests.

Data sharing

On request, and subject to certain criteria, conditions and exceptions, Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices for indications that have been approved in the USA or Europe or in programmes that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data can be requested from Pfizer 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

For more on **Pfizer's criteria, conditions, and exceptions for sharing clinical trial data** see https://www.pfizer.com/science/clinical-trials/trial-data-and-results

Acknowledgments

Editorial and medical writing support under the guidance of authors was provided by Juan Sanchez-Cortes (ApotheCom, San Francisco, CA, USA), and was funded by Pfizer.

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