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Orismilast, a phosphodiesterase 4B/D inhibitor, in moderate-to-severe atopic dermatitis: efficacy and safety from a multicentre randomized placebo-controlled phase IIb dose-ranging study (ADESOS)

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Abstract

Background Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by eczematous skin lesions and pruritus. There is an unmet need for effective first-line systemic treatments with good safety profiles, particularly oral medications. Orismilast is a novel first-in-class oral phosphodiesterase 4 (PDE4) B/D inhibitor under investigation for the treatment of moderate-to-severe AD.

Objectives To evaluate the optimal dose, efficacy and safety of twice-daily orismilast in patients with moderate-to-severe AD.

Methods This 16-week, multicentre randomized placebo-controlled phase IIb dose-ranging study (NCT05469464) included patients from 48 centres in Europe and the USA. Adults with moderate-to-severe AD were given (1 : 1 : 1 : 1) orismilast 20 mg, 30 mg or 40 mg, or placebo, twice daily. The primary endpoint was percentage change in Eczema Area and Severity Index (EASI); the secondary endpoints (all at week 16) included achievement of a score of clear (0) or almost clear (1) with ≥2-point improvement on the Investigator Global Assessment (IGA 0/1); achievement of a Peak Pruritus Numerical Rating Scale (PP-NRS) reduction of ≥4 points; and achievement of a reduction in EASI of 75%, 90% and 100% from baseline.

Results Overall, 233 patients were randomly assigned to orismilast 20 mg ($n=58$), 30 mg ($n=61$), 40 mg ($n=59$) or placebo ($n=55$). At week 16, reductions in EASI (percentage points) from baseline to week 16 were seen across orismilast groups and placebo ($P>0.05$ for orismilast vs. placebo). Significantly more patients achieved IGA 0/1 with a ≥2-point improvement with orismilast 20 mg and 40 mg compared with placebo ($P<0.05$). Significantly greater proportions of patients achieving a ≥4-point reduction in PP-NRS were demonstrated with orismilast at week 2. The safety profile was consistent with that of the PDE4 class, with no major safety concerns reported.

Conclusions These data support the clinical relevance of selective PDE4B/D inhibition with orismilast, potentially offering a convenient, novel oral therapy for the treatment of AD.

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Lay summary

Atopic dermatitis ('AD' for short) is also known as eczema. It is a common condition that causes red, itchy and inflamed skin. It also affects a person's immune system.

We aimed to find the best dose of a new medication called 'orismilast'. We also wanted to check how well it works and how safe it is for adults with moderate-to-severe AD. For 16 weeks, people with AD were randomly given either 20, 30 or 40 milligrams of orismilast twice a day, or a placebo (a pill with no active medication). We measured how well the treatment worked by looking at the number of people whose skin cleared up or almost cleared up and how much itching was reduced. We used a measurement tool called the 'EASI' to monitor improvements. We also looked for side effects to check the medication's safety.

By week 16, more people who took 20 or 40 milligram doses of orismilast had clearer skin than those taking the placebo. People who took orismilast also reported less itching as early as week 2. Improvements in EASI score were seen across all the groups, including those taking placebo. The side effects were similar to those seen with other similar medications.

Studies that divide patients into smaller groups to test different doses can lead to variation. This must be considered when assessing how well different doses of a medication work and which doses should be taken into the next trials. We suggest that orismilast could be a promising new treatment for people with AD.

What is already known about this topic?

- Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by eczematous skin lesions and pruritus.
- Phosphodiesterase 4 inhibitors (PDE4i) are an established class of drug for the treatment of chronic inflammatory diseases, with an acceptable safety profile.
- Oral orismilast is a novel first-in-class PDE4i that potently inhibits the two primary PDE4 subtypes (B and D) involved in inflammation.
- Orismilast demonstrated efficacy in moderate-to-severe psoriasis and in hidradenitis suppurativa.

What does this study add?

- This phase IIb dose-ranging study (ADESOS) is the first to assess the efficacy and safety of oral orismilast, a PDE4B/D inhibitor, in moderate-to-severe AD.
- Orismilast was efficacious in improving multiple aspects of AD, including achievement of a score of clear (0) or almost clear (1) on the Investigator Global Assessment, and a rapid onset of itch reduction.
- The safety profile was consistent with that expected for the PDE4 class.

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease characterized by eczematous skin lesions and pruritus.[1] AD is associated with multiple comorbidities, such as asthma, depression and obesity,[2,3] and adversely affects patients' quality of life (QoL).[1] Until the approval of the first biologic (dupilumab), broad-acting immunosuppressants, such as systemic corticosteroids, were the only systemic treatments available for moderate-to-severe AD.[1] Biologics and immunomodulating therapies [e.g. Janus kinase inhibitors (JAKi)] are approved for the treatment of moderate-to-severe AD.[4] Despite the availability of these treatments, many patients with moderate-to-severe AD have inadequate disease control,[4] JAKi come with boxed warnings and there remains an unmet medical need for effective oral therapies with acceptable safety profiles.[5,6]

For more than 10 years, topical and oral phosphodiesterase 4 (PDE4) inhibitors (PDE4i) have been used for the treatment of chronic inflammatory diseases.[5,7,8] They benefit from a lack of routine monitoring requirements and a well-established, acceptable safety profile.[5] For example, topical crisaborole is approved for the treatment of AD from 3 months of age, and oral apremilast is approved for psoriasis of all severities and requires no laboratory monitoring.[7,8] Apremilast was evaluated in moderate-to-severe AD but showed limited efficacy and an unfavourable benefit-to-risk profile at the higher 40-mg dose.[9] Orismilast is a novel PDE4i that potently inhibits the two primary PDE4 subtypes (B and D) involved in inflammation.[10] Preclinical assays with human peripheral blood mononuclear cells demonstrated reduced production of cytokines related to T helper (Th)1, Th2 and Th17, and interleukin (IL)-4 and IL-13 inhibition.[10] In addition, PDE4 inhibition may improve skin barrier dysfunction in AD through upregulation of *FLG* expression in human keratinocytes.[11] The efficacy and safety of orismilast has previously been demonstrated in psoriasis and hidradenitis suppurativa (HS).[12,13] Therefore, orismilast could become a first-in-class oral AD treatment without boxed warnings. Here, the efficacy and safety of twice-daily oral orismilast was evaluated in a phase IIb dose-ranging study (ADESOS) in patients with moderate-to-severe AD, with the aim of identifying the best dose for use in the pivotal phase III programmes.

Materials and methods

Study design

This multicentre randomized double-blind placebo-controlled parallel-group phase IIb dose-ranging study (ADESOS) was

undertaken at 48 centres in Europe (Germany, Hungary and Poland) and the USA (NCT05469464).

Participants

Key inclusion criteria were age ≥18 years; bodyweight > 40 kg; diagnosis of AD for ≥ 1 year before screening (Hanifin and Rajka criteria)[14] and moderate-to-severe AD [affected body surface area (BSA) ≥ 10%, Investigator Global Assessment (IGA) for Atopic Dermatitis (IGA-AD) grade ≥ 3 and Eczema Area and Severity Index (EASI) score ≥ 16] at screening and baseline; and a history of inadequate response to topical medications. Key exclusion criteria included treatment-resistant AD (≥ 2 treatment failures due to inadequate efficacy within 2 years of treatment with a biologic or JAKi, or phototherapy); unstable AD with acute deterioration requiring rescue treatment for AD within 4 weeks of screening or expected to require rescue treatment within 2 weeks after randomization; a chronic/recurrent gastrointestinal condition such as inflammatory bowel disease; suicidal ideation or behaviour; current major depression that would preclude the patient from adhering to the protocol or put the patient at risk; and previous treatment with apremilast or other systemic PDE4i. Concomitant medications, supplements or procedures within 6 months before baseline or received during the study were recorded, and emollients could be used at the patient's discretion as concomitant treatment. A full list of inclusion and exclusion criteria can be found in Appendix S1 (see Supporting Information) and disallowed concomitant medications in Table S1 (see Supporting Information).

Randomization, masking and procedures

Following screening within 28 days before baseline, participant randomization (using an Interactive Web Response System) was stratified by study site. All participants, investigators, care providers and outcomes assessors were masked to treatment assignment. Patients were randomized 1 : 1 : 1 : 1 to orismilast 20 mg, 30 mg or 40 mg, or placebo twice daily for 16 weeks, plus a 4-week follow-up (Figure S1; see Supporting Information). Tablets were to be taken morning and evening [every 12 h (approximately), with ≥ 6 h between doses]. The dose titration schedule is provided in Table S2 (see Supporting Information) and study visits in Appendix S1.

Outcomes

The primary endpoint was percentage change in EASI from baseline; secondary efficacy endpoints were achievement (at week 16) of a score of clear (0) or almost clear (1) on the IGA (IGA 0/1) and ≥ 2 point improvement in IGA-AD; a reduction in Peak Pruritus Numerical Rating Scale (PP-NRS) of ≥ 4 points; and achievement of a 75%, 90% and 100% reduction in EASI from baseline (EASI 75, EASI 90 and EASI 100, respectively). Other efficacy endpoints included change from baseline to week 16 in affected BSA; Dermatology Life Quality Index (DLQI); Patient-Oriented Eczema Measure (POEM); Sleep Disturbance Numerical Rating Scale (SD-NRS) and Skin Pain NRS (SP-NRS) scores; Hospital Anxiety and Depression Scale (HADS); and Patient Global Impression of Change score (PGIC) (also at weeks 1 and 2 for SD-NRS and SP-NRS).

To evaluate key biomarkers of AD,[15] 20 consecutive samples of stratum corneum were collected from lesional and nonlesional skin at baseline, and from lesional skin at week 16, using tape stripping (D squame® 3.8 cm; CuDerm, Walsall, UK). The biomarker population is a subset of the intention-to-treat (ITT) population, with comparable population size to EASI at baseline (Table S3; see Supporting Information). Protein extracted from the first 10 tape strips were quantified using Olink® technology (https://olink.com/).

Safety assessments, coded according to Medical Dictionary for Regulatory Activities classification,[16] included occurrence, severity and toxicity grade of treatment-emergent adverse events (TEAEs) reported over the 16-week treatment and 4-week follow-up periods. Changes from baseline in HADS and Columbia-Suicide Severity Rating Scale score were assessed at all visits except week 1. Adverse event (AE) severity was graded according to National Cancer Institute Common Terminology Criteria for AEs (CTCAE) version 5.0 (Table S4; see Supporting Information).[17] AEs of special interest (AESIs) were also evaluated (Appendix S1). Definition of the AESI of diarrhoea was CTCAE grade ≥ 2 (i.e. increase of 4–6 stools daily over baseline) or a moderate increase in ostomy output vs. baseline or limiting instrumental activities of daily living.

Statistical analysis

A sample size of at least 210 patients was planned to ensure a power of ≥ 80% and identify a 25% difference in EASI from baseline to week 16 between orismilast and placebo, assuming an SD of 43% and allowing for discontinuations. The full analysis set followed the ITT principle, included all randomized patients who received ≥ 1 study drug dose and was used for all efficacy and safety analyses.

Binary efficacy endpoints – achievement of an IGA 0/1 and ≥ 2-point improvement in IGA-AD, ≥ 4-point improvement in PP-NRS (integer scale 0–10), and EASI 50, EASI 75 and EASI 90 – were analysed using the Mantel–Haenszel test, comparing each active treatment group with placebo. Percentage change in EASI from baseline was analysed with ANCOVA, with treatment group as factor and baseline EASI as covariate. BSA, DLQI, POEM, SD-NRS, SP-NRS and PGIC scores were analysed using a mixed model for repeated measures (MMRM) similarly to percentage change in EASI. MMRM was used as a supportive analysis for continuous endpoints, with treatment group, visit and treatment-by-visit interaction as factors, and baseline EASI-by-visit interaction as a covariate. The treatment difference and least squares means are presented with the SE. Statistical testing of hypotheses were performed on a 5% nominal level without multiplicity adjustments, as per the statistical analysis plan and exploratory nature of the trial. Other efficacy endpoints were summarized descriptively in the ITT population. Tape-strip protein levels were log2 transformed and a linear mixed-effect model fitted to the data, using the time–lesion (e.g. week-16 lesional) interaction as fixed effects and a random effect for each patient. Log2-fold changes vs. baseline were calculated for each protein and *P*-values corrected for multiple comparisons [false discovery rate (FDR)] using

the Benjamini–Hochberg method.[18] Levels of thymus and activation-regulated chemokine (TARC) in the orismilast groups were additionally analysed in a stratified manner by IGA response (IGA 0/1 and ≥ 2 point improvement at week 16) using Student *t*-test statistical testing. AEs are summarized by number of events, system organ class, preferred term, severity and relationship to the study drug. Missing data and data treated as missing owing to intercurrent events (use of rescue medication or treatment discontinuation) for the primary and key secondary endpoints were handled using multiple imputation and imputed assuming the same distribution as observed values within the treatment group. As supportive analyses for key secondary endpoints, missing data were handled as nonresponse imputation (NRI).

Post hoc analyses

Post hoc analyses were conducted after analysis of the results. Post hoc analyses were of the percentage of patients achieving the following at week 16: (i) EASI 75 and EASI 90 in those with severe disease at baseline (EASI > 21), in those with moderate disease (EASI ≤ 21) and in the overall population; and (ii) EASI 75 and a ≥ 4-point improvement in PP-NRS in those with severe disease at baseline (EASI > 21 and PP-NRS > 7). Post hoc analyses were done using the same statistical model as in the predefined analyses but with a different analysis set or with a modified endpoint.

Results

Patient disposition and baseline characteristics

Between 11 July 2022 and 29 September 2023, 355 people were screened; 233 were randomized to placebo ($n=55$), or orismilast 20 mg ($n=58$), 30 mg ($n=61$) or 40 mg ($n=59$) twice daily. In all, 151 completed week 16 (Figure 1), prior to a 4-week follow-up. Of 71 discontinuations in the orismilast groups, 35 were due to AEs; of 13 discontinuations in the placebo group, 5 were due to withdrawal of consent (Figure 1). The 30-mg orismilast group had higher total discontinuations and the 20-mg group the lowest due to AEs. Few patients reported using disallowed topical concomitant corticosteroid medication during the study (placebo, $n=3$; orismilast 20 mg, $n=2$; 30 mg, $n=1$; 40 mg $n=2$). Baseline demographics and characteristics were generally balanced between patients in the placebo and orismilast groups (Table 1). At baseline, mean (SD) EASI score was 22.7 (7.4), 45.1% had an EASI score of > 21 [severe (placebo, 40.0%; orismilast 20 mg, 50.0%; orismilast 30 mg, 45.9%; orismilast 40 mg, 44.1%)]; 85.4% of patients had an IGA score of 3 [moderate (placebo, 83.6%; orismilast 20 mg, 84.5%; orismilast 30 mg, 80.3%; orismilast 40 mg, 93.2%)] and 14.6% had an IGA score of 4 [severe (placebo, 16.4%; orismilast 20 mg, 15.5%; orismilast 30 mg, 19.7%; orismilast 40 mg, 6.8%)] (Table 1).

Efficacy

At week 16, reductions in EASI (percentage point) were seen across all orismilast groups from baseline, as well as in the placebo group ($P \geq 0.05$; Figure 2c); changes were statistically significant with orismilast 30 mg at week 2 and 40 mg at weeks 2 and 8 ($P < 0.05$) vs. placebo (Figure 2c). Significantly greater proportions of patients achieved IGA 0/1 with a ≥ 2-point improvement at week 16 (multiple imputation) with orismilast 20 mg and 40 mg vs. placebo [orismilast 20 mg, 26.3%; orismilast 30 mg, 24.3%; orismilast 40 mg, 30.9% ($P < 0.05$ for 20-mg and 40-mg doses; $P \geq 0.05$ for 30-mg dose); Figure 2a]. These findings were similar using NRI, but with a significant improvement reported for orismilast 40 mg only ($P < 0.05$; Figure 2a). Numerically more patients receiving orismilast achieved ≥ 4-point improvements in PP-NRS at week 16 ($P \geq 0.05$; Figure 2b); significant improvements were seen at week 1 with orismilast 30 mg and 40 mg ($P < 0.05$) and at week 2 for orismilast 20 mg, 30 mg and 40 mg ($P < 0.05$; Figure 2b). At week 16, the proportions of patients who achieved EASI 75 and EASI 90 were similar across all groups, including the placebo group ($P \geq 0.05$; Figure 2d). Significantly more patients achieved EASI 100 with orismilast 20 mg and 30 mg compared with placebo at week 16 [orismilast 20 mg, 7.0% ($P < 0.05$); orismilast 30 mg, 8.4% ($P < 0.05$); orismilast 40 mg, 5.3% ($P \geq 0.05$); placebo, 0%; Figure 2d].

Overall, numerical improvements were seen in BSA, DLQI, POEM, SD-NRS, SP-NRS and HADS across all groups from baseline to week 16 (Table S5; see Supporting Information). The proportions of patients who achieved ≥ 4-point improvement in SP-NRS were significantly greater with orismilast 20 mg and 30 mg compared with placebo at week 1 ($P < 0.05$) and orismilast 30 mg at week 2 [$P < 0.05$; Figure S2 (see Supporting Information)]. Improvements in PGIC were significant for patients in all orismilast groups at week 16 ($P < 0.05$; Table S5), with more orismilast-treated patients reporting their AD as 'very much improved' (Figure 2f).

Tape strip assessments

Significant decreases in TARC levels at week 16 were seen across all orismilast groups compared with the placebo group [FDR < 0.05; Figure 3a, Figure S3 (see Supporting Information)], for orismilast IGA 0/1 responders compared with nonresponders ($P < 0.05$; Figure 3b), and orismilast IGA 0/1 responders and nonresponders compared with placebo. Key proteins related to Th2 cells (e.g. TARC and IL-4 receptor), Th17 cells (e.g. IL-17A, IL-17C and CCL20) and general inflammation (e.g. IL-18 and IL-19) were also significantly decreased in the orismilast groups (FDR < 0.05; Figure S3).

Post hoc analyses

To understand the unanticipated large placebo response for EASI results and the impact of more patients with an EASI score ≤ 21 (moderate AD) at baseline, we conducted post hoc analyses. We found that more participants receiving orismilast 20 mg and 40 mg achieved EASI 75 or EASI 90 at week 16 in the group with severe AD (baseline EASI score > 21) than those in the group with moderate AD (EASI score ≤ 21; Figure 4). Furthermore, fewer participants receiving placebo achieved EASI 75 or EASI 90 at week 16 in the severe AD group than those in the moderate AD or overall population groups (Figure 4). In an analysis of an

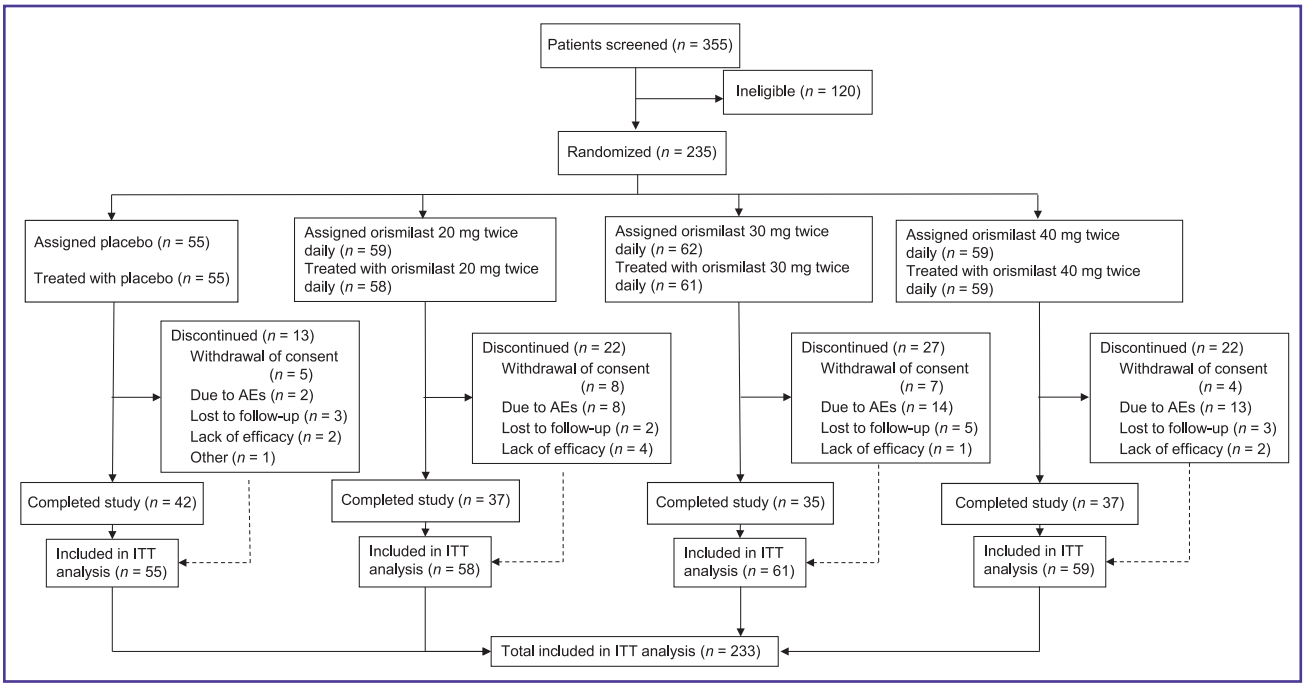

Figure 1 Trial profile. AE, adverse event; ITT, intention-to-treat.

additional severe AD group (baseline EASI score > 21 and PP-NRS > 7), more patients receiving orismilast 20 mg and 40 mg achieved EASI 75 and ≥ 4-point reduction in PP-NRS than those taking placebo (placebo, 9%; orismilast 20 mg, 42%; orismilast 30 mg, 13%; orismilast 40 mg, 33%).

Safety

No new safety signals were identified with orismilast compared with those previously known for the PDE4 class.[19] The most common TEAEs, reported in ≥ 10% patients in

Table 1 Baseline demographics and clinical characteristics of the participants included in the study

		Orismilast (twice daily)			
	Placebo (*n* = 55)	**20 mg (*n* = 58)**	**30 mg (*n* = 61)**	**40 mg (*n* = 59)**	**Total (*n* = 233)**
Age (years), mean (SD)	40.9 (16.9)	40.2 (14.3)	39.1 (13.3)	42.5 (15.7)	40.6 (15.0)
Sex					
Female	27 (49.1)	37 (63.8)	27 (44.3)	28 (47.5)	119 (51.1)
Male	28 (50.9)	21 (36.2)	34 (55.7)	31 (52.5)	114 (48.9)
Race					
Asian	2 (3.6)	2 (3.4)	5 (8.2)	4 (6.8)	13 (5.6)
Black or African American	9 (16.4)	9 (15.5)	11 (18.0)	15 (25.4)	44 (18.9)
White	41 (74.5)	43 (74.1)	42 (68.9)	37 (62.7)	163 (70.0)
Other[a]	2 (3.6)	2 (3.4)	1 (1.6)	0	5 (2.1)
Not reported	1 (1.8)	2 (3.4)	2 (3.3)	3 (5.1)	8 (3.4)
Weight (kg), mean (SD)	80.9 (21.3)	80.5 (17.1)	80.7 (19.5)	86.6 (23.4)	82.2 (20.5)
Disease duration (years), mean (SD)	17.6 (14.2)	19.6 (12.8)	19.9 (14.9)	20.4 (14.4)	19.4 (14.1)
EASI, mean (SD)	22.5 (7.2)	23.3 (8.2)	23.3 (7.9)	21.6 (6.1)	22.7 (7.4)
EASI > 21 (severe)	22 (40.0)	29 (50.0)	28 (45.9)	26 (44.1)	105 (45.1)
IGA					
3 (moderate)	46 (83.6)	49 (84.5)	49 (80.3)	55 (93.2)	199 (85.4)
4 (severe)	9 (16.4)	9 (15.5)	12 (19.7)	4 (6.8)	34 (14.6)
BSA (m^2), mean (SD)	34.1 (18.7)	32.9 (17.5)	29.5 (16.5)	28.3 (14.4)	31.1 (16.9)
SD-NRS, mean (SD)	5.4 (2.7)	5.9 (2.5)	5.7 (2.6)	5.7 (2.9)	5.7 (2.6)
SP-NRS, mean (SD)	5.7 (3.0)	5.6 (2.8)	5.7 (2.3)	5.2 (2.8)	5.5 (2.7)
PP-NRS, mean (SD)	7.5 (1.7)	7.3 (2.3)	7.3 (1.8)	7.3 (1.9)	7.4 (1.9)
DLQI, mean (SD)	14.1 (7.1)	13.7 (7.5)	13.6 (7.0)	13.5 (6.8)	13.7 (7.0)
POEM, mean (SD)	19.1 (5.9)	18.1 (6.1)	19.0 (5.6)	19.2 (5.7)	18.8 (5.8)

All data presented are for the intention-to-treat population. Data are presented as *n* (%) unless otherwise stated. BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; POEM, Patient-Orientated Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; SD-NRS, Sleep Disturbance Numerical Rating Scale; SP-NRS, Skin Pain Numerical Rating Scale. [a]The 'Other' group included patients identifying as mixed race, South American or East Indian.

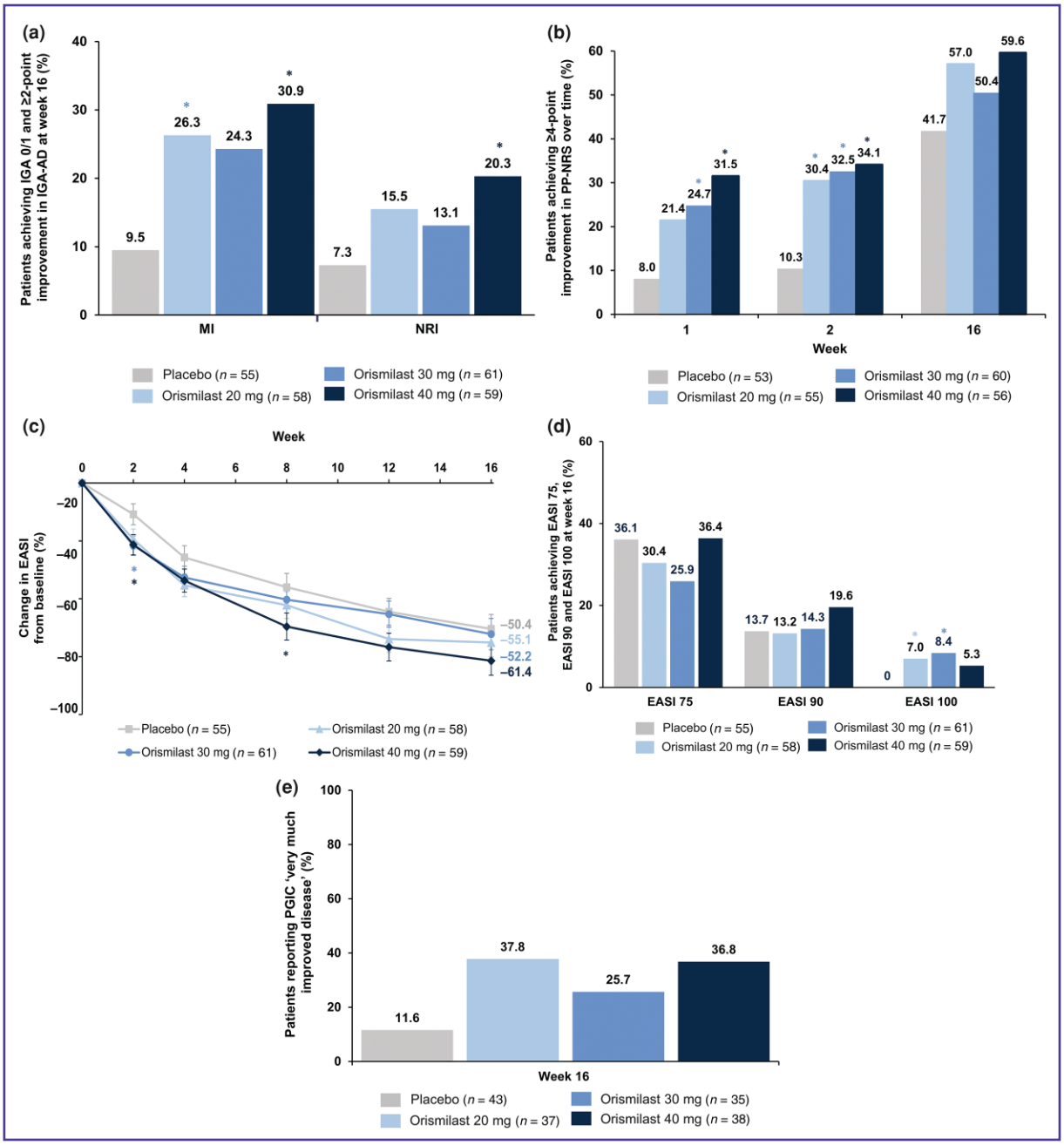

Figure 2 Proportions of patients achieving (a) an Investigator Global Assessment (IGA) score of 0/1 (clear/almost clear) and ≥2-point improvement in IGA for Atopic Dermatitis (AD) at week 16 [multiple imputation (MI) and nonresponse imputation]; and (b) a ≥4-point reduction in 'itch' Peak Pruritus Numerical Rating Scale (PP-NRS) at weeks 1, 2 and 16 (MI); (c) change in Eczema Area and Severity Index (percentage point) over time from baseline to week 16 (MI); (d) proportion of patients achieving 75%, 90% and 100% improvements in EASI (EASI 75, EASI 90 and EASI 100, respectively) at week 16 (MI); and (e) proportion of patients with a Patient Global Impression of Change (PGIC) response of 'very much improved disease' (observed) at week 16. All data presented are for the intention-to-treat population. Change in EASI from baseline is presented as least squares mean (LSM) (SE). Change from baseline was analysed using ANCOVA with treatment group as the factor and baseline EASI as the covariate. Change in PGIC from baseline is LSM (SE) and analysed using a mixed model for repeated measures with treatment group, visit and treatment-by-visit interaction as factors. If an EASI, IGA-AD or PP-NRS value was missing or treated as missing, it was imputed by MI. If an EASI, IGA-AD or 'itch' PP-NRS value was missing or treated as missing, the value was imputed by NRI. *$P<0.05$ for active comparator vs. placebo.

the total orismilast group, were nausea, diarrhoea, vomiting, headache and dizziness (Table 2). Serious AEs were reported in two patients in the orismilast 20-mg and 40-mg groups and none in the placebo group (Table 2); these were grade 3 pneumonia (orismilast 20 mg), unrelated to study medication, and grade 1 hypokalaemia and grade 2 vasovagal syndrome (orismilast 40 mg), probably related to the study medication. TEAEs were generally mild or moderate in severity and occurred within the first 4 weeks [Tables S6, S7; Figure S4 (see Supporting Information)]. The number of patients who experienced AEs, and the number of AEs experienced, were generally dose-dependent (Table 2).

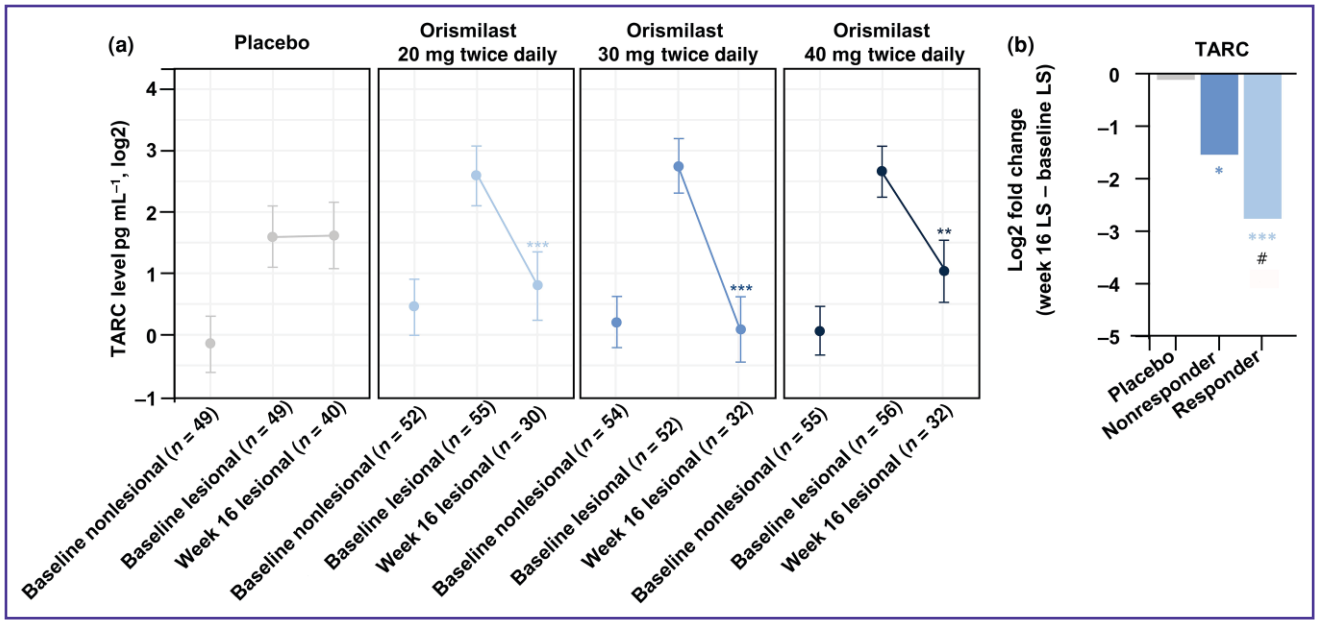

Figure 3 Thymus and activation-regulated chemokine (TARC) levels in the skin at baseline and change in lesional levels of TARC from baseline to week 16, and change in lesional TARC level stratified by Investigator Global Assessment response of 'clear' or 'almost clear' (IGA 0/1). (a) A linear mixed-effect model was fitted to the data to estimate TARC levels. Least square means (SE) are displayed. Adjusted *P*-values [false discovery rate (FDR)] are shown for baseline lesional vs. week 16 lesional skin (**FDR < 0.01, ***FDR < 0.001). (b) Comparison of log2-fold changes in TARC in IGA responders (n=28), IGA nonresponders (n=66) and placebo (n=40). Asterisks denote comparison with placebo and the hash sign denotes comparison between IGA nonresponders and responders. Statistical testing was done with a Student's *t*-test (*P<0.05, ***P<0.001; #P < 0.05). LS, lesional.

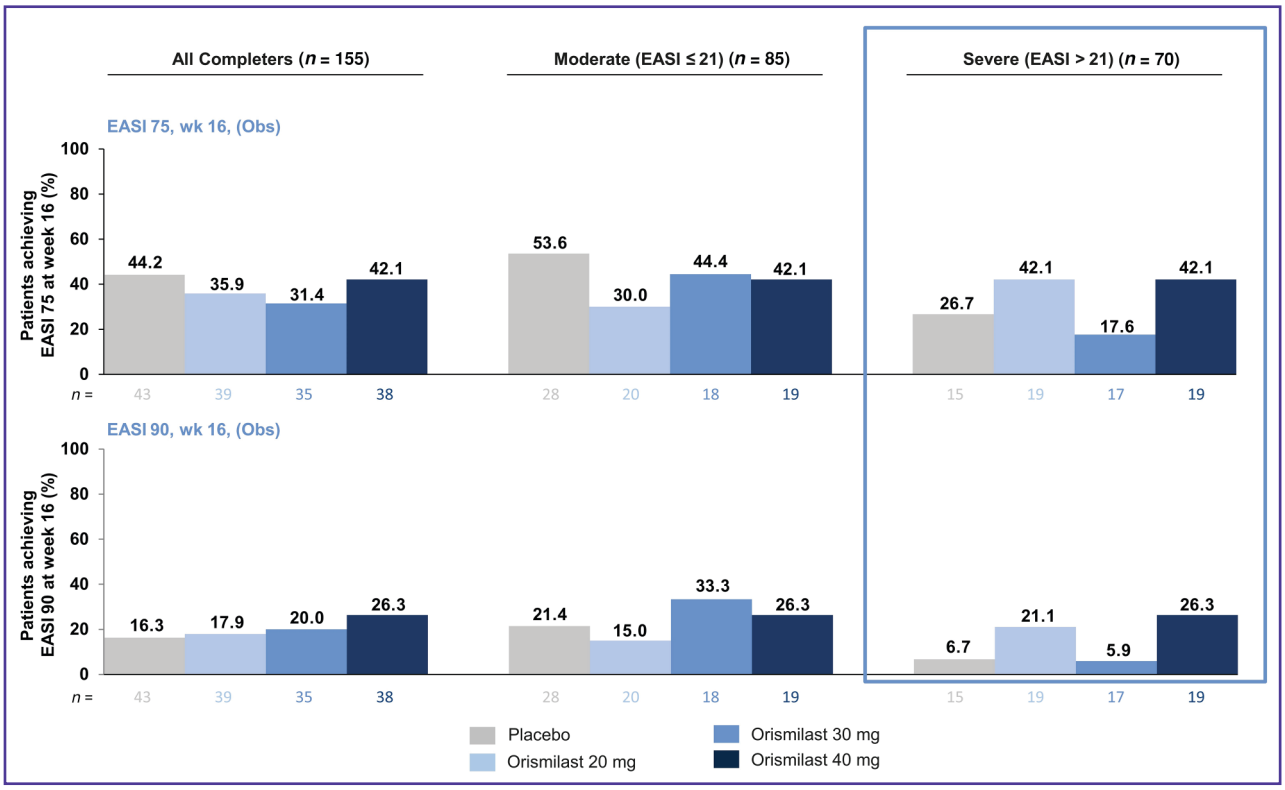

Figure 4 Percentage of patients achieving a 75% and 90% improvement in Eczema Area and Severity Index (EASI 75 and EASI 90, respectively) at week 16, stratified by baseline severity (observed). Percentages of patients achieving EASI 75 and EASI 90 are based on observed data and include all participants with nonmissing information. Obs, as observed; wk, week.

Table 2 Overall summary of treatment-emergent adverse events (TEAEs; safety population)

		Orismilast (twice daily)			
	Placebo (*n* = 55)[a]	**20 mg (*n* = 58)[a]**	**30 mg (*n* = 61)[a]**	**40 mg (*n* = 59)[a]**	**Total (*n* = 178)[a]**
Any TEAEs	35 (63.6)	44 (75.9)	48 (78.7)	51 (86.4)	143 (80.3)
No. of events	62	135	160	175	470
Any related TEAEs	14 (25.5)	37 (63.8)	39 (63.9)	42 (71.2)	118 (66.3)
No. of events	22	97	119	129	345
SAEs	0	1 (1.7)	0	1 (1.7)	2 (1.1)
No. of events	0	1	0	2	3
Deaths	0	0	0	0	0
TEAEs occurring in ≥ 10% of patients in the orismilast total group[b]					
Gastrointestinal disorders	11 (20.0)	36 (62.1)	37 (60.7)	40 (67.8)	113 (63.5)
No. of events	14	67	85	88	240
Nausea	5 (9.1)	17 (29.3)	23 (37.7)	27 (45.8)	67 (37.6)
No. of events	7	24	29	31	84
Diarrhoea	3 (5.5)	19 (32.8)	24 (39.3)	20 (33.9)	63 (35.4)
No. of events	3	22	32	24	78
Vomiting	1 (1.8)	2 (3.4)	9 (14.8)	9 (15.3)	20 (11.2)
No. of events	1	3	13	10	26
Nervous system disorders	8 (14.5)	17 (29.3)	17 (27.9)	22 (37.3)	56 (31.5)
No. of events	9	25	25	26	76
Headache	5 (9.1)	12 (20.7)	11 (18.0)	17 (28.8)	40 (22.5)
No. of events	5	15	13	20	48
Dizziness	0	6 (10.3)	8 (13.1)	5 (8.5)	19 (10.7)
No. of events	0	7	10	5	22
TEAEs occurring in ≥ 10% of patients in any orismilast groups leading to study drug discontinuation[b]					
All TEAEs	2 (3.6)	8 (13.8)	16 (26.2)	14 (23.7)	38 (21.3)
No. of events	3	10	22	23	55
Nausea	0	2 (3.4)	7 (11.5)	6 (10.2)	15 (8.4)
No. of events	0	2	7	6	15
TEAEs by toxicity grade					
1	30 (54.5)	37 (63.8)	41 (67.2)	44 (74.6)	122 (68.5)
No. of events	49	90	101	135	326
2	9 (16.4)	19 (32.8)	26 (42.6)	20 (33.9)	65 (36.5)
No. of events	13	41	53	38	132
3	0	4 (6.9)	6 (9.8)	2 (3.4)	12 (6.7)
No. of events	0	4	6	2	12
4	0	0	0	0	0
No. of events	0	0	0	0	0
Key TEAEs					
Cardiac disorders	0	2 (3.4)	0	0	2 (1.1)
No. of events	0	4	0	0	4
Infections and infestations	10 (18.2)	7 (12.1)	8 (13.1)	9 (15.3)	24 (13.5)
No. of events	12	8	12	12	32
Herpes simplex	0	0	2 (3.3)	0	2 (1.1)
No. of events	0	0	2	0	2
Herpes zoster	0	1 (1.7)	0	0	1 (0.6)
No. of events	0	1	0	0	1
Skin and subcutaneous tissue disorders	4 (7.3)	4 (6.9)	2 (3.3)	3 (5.1)	9 (5.1)
No. of events	5	5	2	3	10
Psychiatric disorders	8 (14.5)	4 (6.9)	8 (13.1)	10 (16.9)	22 (12.4)
No. of events	10	4	12	14	30
Depression	3 (5.5)	1 (1.7)	4 (6.6)	3 (5.1)	8 (4.5)
No. of events	3	1	5	4	10
Suicidal ideation	0	0	0	0	0
No. of events	0	0	0	0	0

Data are presented as *n* (%) unless otherwise stated. Adverse events were coded using the Medical Dictionary for Regulatory Activities version 24.0.[16] [a]Numbers represent the total population for each treatment arm and may differ from these values depending on the assessment/analyses. [b]By preferred term. SAE, serious adverse event.

TEAE-related discontinuations were higher in the orismilast groups than with placebo (Table 2). Patients who reported key TEAEs were similar between the placebo and total orismilast group, except for slightly more infections and infestations in the placebo vs. orismilast groups [placebo 18.2%; orismilast 20 mg 12.1%; orismilast 30 mg 13.1%; orismilast 40 mg 15.3% (Table 2)]. Reported occurrences of depression were low [placebo group, 5.5% (*n* = 3/55); orismilast 20 mg, 1.7% (*n* = 1/58); orismilast 30 mg, 6.6% (n = 4/61); orismilast 40 mg, 5.1% (*n* = 3/59)]. There were no occurrences of suicidal behaviour and ideation (Table 2). Arthralgia and common AEs of interest, such as conjunctivitis, herpes simplex, herpes zoster and acne, were reported in < 1% of patients.

Discussion

This phase IIb study in patients with moderate-to-severe AD found nonsignificant improvements in EASI from baseline to week 16 (multiple imputation) for patients in the orismilast groups compared with those in the placebo group. A clear treatment effect of orismilast vs. placebo was demonstrated by the achievement of IGA 0/1 with ≥ 2-point improvement in IGA-AD and ≥ 4-point reduction in PP-NRS. Significant improvements in PP-NRS were seen early (weeks 1 and 2). The impact of these changes was reflected by significant improvements in PGIC.

Baseline EASI severity has diminished in recent AD trials. A review of clinical trials in AD found that decrease in baseline EASI severity is associated with higher EASI placebo responses.[20] This study found a similar trend. While EASI is a widely used tool, the degree of changes for less severe AD may be difficult to rate and hence not be fully captured.[2] In patients with severe AD at baseline (EASI score > 21),[21] the results were consistent with the other study endpoints, with both EASI 75 and EASI 90 showing clear separation for orismilast 20 mg and 40 mg vs. placebo.

The efficacy of orismilast was further supported by the significant reduction in lesional skin levels of TARC between baseline and week 16 in the orismilast groups compared with the placebo group. Accumulating evidence supports the amplification of cytokine pathways, including Th2, Th22, Th17 and Th1.[22] PDE4i, oral apremilast and topical crisaborole inhibit a range of inflammatory mediators, including tumour necrosis factor-α, IL-17A and IL-23.[22] Here, we have demonstrated that orismilast treatment resulted in reduced levels of biomarkers across the Th1, Th2 and Th17 immune axes, substantiating the broad anti-inflammatory effect induced by PDE4B/D inhibition. Furthermore, Th2 cytokines have been associated with decreased expression of genes such as *FLG*, which contributes to skin barrier defects and, as such, may be counteracted with PDE4 inhibition.[11,22]

The safety data from this study were in line with the previously demonstrated safety profile of orismilast and PDE4i, and there were no major safety concerns,[19] with low rates of depression and no suicidal ideation. Additionally, conjunctivitis and arthralgia, AEs associated with IL-13-targeting biologics,[4] were infrequently reported (one patient for each in the total orismilast group). While JAKi showed efficacy vs. IL-13-targeting biologics,[4] they were assigned multiple class-wide boxed warnings in psoriasis and AD by the U.S. FDA and require laboratory monitoring for hepatoxicity and hyperlipidaemia.[23,24] None of the JAKi-associated AEs were observed with orismilast in this study.

A patient survey found that the top treatment goal and primary reason for AD-related healthcare use for patients is improving itch.[6] Patients with itch-dominant AD have also reported greater impairment in their QoL compared with mild-to-moderate itch.[4] Therefore, the early improvements in itch seen here support the clinical value of orismilast.

Broad beneficial effects of orismilast have also been demonstrated in a phase II trial in patients with moderate-to-severe psoriasis, with significant improvements in Psoriasis Area and Severity Index from baseline to week 16 compared with placebo, and changes seen at the first week-4 measurement.[25] Orismilast has also shown promising early results in HS, with 67% of patients who completed a study reporting improvements in the HS clinical response with a 50% reduction in the abscesses and nodules count.[12] Collectively, the results from this phase IIb study in moderate-to-severe AD, and previous studies in psoriasis and HS, suggest that orismilast is an effective treatment with an acceptable safety profile in a number of inflammatory skin diseases. Future studies with larger patient numbers and – if possible – a population with more severe AD are needed to confirm and extend these findings. Based on our findings, the exposure provided by the orismilast 20-mg dose had the best benefit–risk profile for further development.

The limitations of this study include the short study duration and the small number of treated patients. Another potential limitation was the weekly on-site assessment of PP-NRS, whereas other trials used daily e-diary assessments averaged per week,[26] thus capturing fluctuations in AD. Additionally, baseline AD severity was lower than in other studies, limiting the number of patients in the analysis of efficacy in patients with severe AD. The study strengths include the sufficiently powered analysis, the range of doses of the investigational drug, and use of a placebo comparator and proteomic biomarkers.

In summary, treatment with orismilast resulted in significantly more patients achieving IGA 0/1 and a rapid onset of itch reduction compared with placebo. No new safety signals were identified, and the safety profile was aligned with the PDE4 class. The study was affected by high EASI placebo responses; however, in patients with severe AD, more patients receiving orismilast 20 mg and 40 mg achieved EASI 75 and EASI 90 than those receiving placebo, consistent with the IGA 0/1 results, patient-reported efficacy and biomarker results. These data confirm the clinical relevance of selective PDE4B/D inhibition with orismilast, potentially offering a convenient, novel oral therapy for the treatment of AD.

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Conflicts of interest

J.I.S. has received honoraria as a consultant and/or advisory board member for AbbVie, Alamar, Aldena, Amgen, AOBiome, Apollo, Arcutis, Arena, Asana, ASLAN, ATTOVIA, BioMX, Biosion, Bodewell, Boehringer Ingelheim, Bristol Myers Squibb, Cara, Castle Biosciences, Celgene, Connect Biopharma, CorEvitas, Dermavant, Eli Lilly, FIDE, Galderma, GlaxoSmithKline, Incyte, Inmagene, Invea, Kiniksa, LEO Pharma, Merck, My-Or Diagnostics, Nektar, Novartis,

Optum, Pfizer, RAPT, Recludix, Regeneron, Sandoz, Sanofi-Genzyme, Shaperon, TARGET-RWE, Teva, Union and UpToDate; has been a speaker for AbbVie, Eli Lilly, LEO Pharma, Pfizer, Regeneron and Sanofi-Genzyme; and has received institutional grants from Galderma, Incyte and Pfizer. L.F.E. declares institutional grants from AbbVie, Amgen, Arcutis, Castle Dermavant, Galderma, Pfizer, Regeneron and Sanofi-Genzyme; consulting fees to self or institution from AbbVie, Arcutis, ASLAN, Bristol Myers Squibb, ATTOVIA, Dermavant, Forte, Galderma, Incyte, Janssen, LEO Pharma, Eli Lilly, Novartis, Pfizer, Incyte, UNION therapeutics, Regeneron and Sanofi; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AbbVie, Arcutis, Galderma, LEO Pharma, OrthoDerm, Pfizer, Regeneron, Sanofi and Incyte; support for attending meetings and/or travel from Sanofi, Regeneron and Pfizer; leadership or a fiduciary role in other board, society, committee or advocacy group, paid or unpaid, as a Board of Directors member at Forte and the National Eczema Association Chair and Medical/Scientific Advisory Committee (unpaid); and stock or stock options as a Board of Directors member at Forte. A.B. has been a clinical study investigator for AbbVie, ACELYRIN, Allakos, Almirall, Alumis, Amgen, Arcutis, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Concert, Dermavant, DermBiont, Eli Lilly, Evelo, Evommune, Galderma, Incyte, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, Takeda, UCB Pharma and Ventyx; a scientific consultant for AbbVie, Abcentra, Aclaris, Affibody, Aligos, Almirall, Alumis, Amgen, AnaptysBio, Apogee, Arcutis, Arena, ASLAN, Athenex, Bluefin Biomedicine, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Celldex, Celltrion, CTI BioPharma, Dermavant, EcoR1, Eli Lilly, Escient, Evelo, Evommune, Forte, Galderma, HighlightII Pharma, Incyte, InnoventBio, Janssen, Landos, LEO Pharma, Lipidio, Microbion, Merck, Monte Rosa Therapeutics, Nektar, Novartis, Oruka, Overtone Therapeutics, Paragon, Pfizer, Q32 Bio, Rani, Rapt, Regeneron, Sanofi Genzyme, Spherix Global Insights, Sun Pharma, Takeda, TLL Pharmaceutical, TrialSpark, UCB Pharma, Union, Ventyx, Vibliome and Xencor; has been a speaker for Eli Lilly and UCB; and has stock or stock options in Lipidio and Oruka. A.D.I. has received consulting fees from AbbVie, Eli Lilly, Pfizer, Benevolent AI, Arena, Novartis, Regeneron, Sanofi and LEO Pharma; has been a speaker for Regeneron, Sanofi, AbbVie, Eli Lilly, LEO Pharma and Janssen Pharmaceuticals; has pending patents with Johnson & Johnson and Regeneron; has participated on a Data Safety Monitoring Board or Advisory Board for Novartis, OM Pharma and Moon Lake; has been president of the International Eczema Council (unpaid); and has been in receipt of equipment, materials, drugs, medical writing, gifts or other services from Regeneron, Sanofi, AbbVie, Almirall, Eli Lilly and Novartis. 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K.K. is an employee and stock and warrant holder of UNION therapeutics; declares involvement in multiple patents related to orismilast; and leadership or fiduciary roles in other board, society, committee or advocacy groups, paid or unpaid, including Chairman of the Danish Life Science Cluster – a nonprofit private public entity. E.L.S. declares institutional grants from AbbVie, Acrotech, Amgen, Arcutis, ASLAN, Castle, CorEvitas, Dermavant, Dermira, Incyte, Lilly, Kymab, Kyowa Kirin, National Jewish Health, LEO Pharma, Pfizer, Regeneron, Sanofi, Target and VeriSkin; consulting fees from AbbVie, Amgen, Arcutis, Areteia Therapeutics, Bristol Myers Squibb, CorEvitas, Corvus, Dermira, Eli Lilly, Evelo Biosciences, FIDE, Forte Bio RX,

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

This study was conducted in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use and the Declaration of Helsinki, and with the approval of national independent ethics committees. All patients provided written informed consent before any study-related activities were carried out and the study protocol was approved by the relevant local institutional review boards and independent ethics committees; a redacted protocol is included in Appendix S1.

Patient consent

Written patient consent for publication was obtained.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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