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Orismilast in moderate-to-severe psoriasis: Efficacy and safety from a 16-week, randomized, double-blinded, placebo-controlled, dose-finding, and phase 2b trial (IASOS)

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Background: Orismilast is a novel oral phosphodiesterase-4 (PDE4) B/D inhibitor being investigated as a potential treatment for moderate-to-severe psoriasis.

Objective: To evaluate efficacy and safety of orismilast modified-release formulation in moderate-to-severe psoriasis.

Methods: This multicenter, randomized (1:1:1:1 to 20, 30, 40 mg orismilast or placebo, twice daily), double-blinded, placebo-controlled, parallel-group, phase 2b, 16-week, dose-ranging study evaluated orismilast in adults with moderate-to-severe plaque psoriasis (NCT05190419). Efficacy end points were analyzed using multiple imputation.

Results: Of 202 randomized patients, baseline characteristics were balanced across arms, except greater severe disease proportions for orismilast vs placebo. Orismilast showed significant improvements in the primary end point, percentage change in Psoriasis Area and Severity Index (PASI), from baseline to week 16 (orismilast −52.6% to −63.7% and placebo, −17.3%; all P <.001). Greater proportions receiving orismilast achieved PASI75 (39.5%-49.0%; P <.05) and PASI90 (22.0%-28.3%; P <.05 for 20 and 40 mg) vs placebo (PASI75, 16.5% and PASI90, 8.3%) at week 16. Safety findings were as expected with PDE4 inhibition; dose-dependent tolerability effects observed.

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Limitations: Small sample size, disease severity imbalance between groups, limited duration and diversity in study population.

Conclusion: Orismilast demonstrated greater efficacy vs placebo and a safety profile in line with PDE4 inhibition. (J Am Acad Dermatol 2024;90:494-503.)

Key words: oral administration; PDE4 inhibitors; PDE4B; PDE4D; psoriasis; treatment efficacy.

INTRODUCTION

Psoriasis is a multisystemic chronic inflammatory disorder associated with comorbidities, including psoriatic arthritis, depression, atherosclerotic cardiovascular disease, obesity, metabolic syndrome, and certain malignancies.[1-5] Despite a growing number of available systemic treatments for moderate-to-severe psoriasis, significant undertreatment and persistent unmet therapeutic needs exist.[6-10] Although efficacious, injectable biologic therapies remain limited by patient preferences for oral medications, cost, and access barriers.[10-13] Conventional systemic therapies demonstrate high rates of treatment discontinuation because of lack of efficacy, adverse events, tolerability, and burden of monitoring.[6,10-12,14] Oral medications inhibiting the Janus kinase/tyrosine kinase-2 pathway have demonstrated efficacy in patients with moderate-to-severe psoriasis; safety concerns may impact wider application.[15] Collectively, this supports the need for more efficacious oral treatments with acceptable safety profiles and greater ease of initiation/monitoring.

Phosphodiesterase-4 (PDE4) enzymes, with subtypes regulating inflammatory pathways, are involved in the pathogenesis of psoriasis.[5,16] Orismilast belongs to an emerging class of PDE4 inhibitors demonstrating enhanced selectivity for PDE4B and PDE4D subtypes, the 2 primary subtypes involved in inflammation.[16] The specific targeting of these subtypes may have the potential to provide higher levels of efficacy compared with pan-PDE4 inhibitors, such as apremilast.[5,16-18] Orismilast demonstrated enhanced inhibition potency over apremilast for PDE4 subtypes in *in vitro* biochemical assays (2- to 40-fold) and more potent inhibition of proinflammatory tumor necrosis factor-α release in *ex vivo* assays (5- to 14-fold).[16]

CAPSULE SUMMARY

- Efficacious oral therapies with good safety and tolerability profiles are needed for patients with moderate-to-severe psoriasis.
- Orismilast, a potent oral phosphodiesterase-4 B/D inhibitor, significantly reduced Psoriasis Area and Severity Index compared with placebo and demonstrated a safety and tolerability profile expected with phosphodiesterase-4 inhibition

A randomized phase 2a trial with orismilast immediate release tablets in adults with moderate-to-severe psoriasis significantly improved the mean Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index at week 16 vs placebo.[2] Orismilast modified-release was developed to improve gastrointestinal (GI)-related tolerability issues with orismilast immediate release, while maintaining comparable pharmacokinetic properties and efficacy.[2] Here, we present efficacy and safety from a randomized phase 2b dose-ranging study of orismilast modified-release in moderate-to-severe psoriasis.

METHODS

Study design

This was a multicenter, randomized, double-blinded, placebo-controlled, parallel-group, phase 2b, dose-ranging study assessing oral orismilast modified-release in adults with moderate-to-severe plaque psoriasis (NCT05190419; Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/dkbxwxmtfv). Following a screening visit ≤28 days before baseline, patients were centrally assigned to study treatment using an Interactive Web Response System, with randomization stratified by study site. Patients were assigned 1:1:1:1 to 20, 30, 40 mg orismilast or placebo, twice daily for 16 weeks, with a 4-week follow-up. Patients, study site personnel, investigators, and the sponsor were treatment blinded. Active and placebo tablets were packaged in the same type of blister and had the same size, form, weight, and color. There was a dose titration period of ≤14 days for the orismilast arms (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/dkbxwxmtfv). Patients were seen onsite day 1 and weeks 4, 8, 12, and 16 (end-of-treatment visit), and 20 (follow-up

Abbreviations used:

AE: adverse event
GI: gastrointestinal
IGA: Investigator Global Assessment
MI: multiple imputation
NRI: nonresponse imputation
PASI: Psoriasis Area and Severity Index
PDE4: phosphodiesterase-4

visit after treatment completion/discontinuation); telephone visits were conducted at weeks 1 and 2. Protocol version 1.0 (October 2, 2020) was amended July 14, 2021 and May 20, 2022, to versions 2.0 and 3.0 (used for study duration), respectively.

Patient population

Adults (≥18 years) were enrolled at 31 centers in Germany, Poland, United Kingdom and the United States. Key inclusion criteria included body weight >40 kg; diagnosis of chronic, stable plaque psoriasis ≥2 months before screening; if diagnosed with psoriatic arthritis, the condition had to be stable with no treatment adaptation needed in the short-term; moderate-to-severe plaque psoriasis defined by PASI ≥12, body surface area ≥10%, and Investigator Global Assessment (IGA) score of ≥3 (using a scale of 0-4) at screening and baseline; considered a candidate for systemic treatment or phototherapy.

Key exclusion criteria included therapy-resistant psoriasis (≥2 biologic treatment failures [inadequate efficacy] within 5 years administered in adequate dose and duration according to the label or local/national guidelines); current diagnosis of predominant guttate, erythrodermic, exfoliative, pustular, or drug-induced psoriasis, or other skin conditions that might confound psoriasis vulgaris evaluation, as judged by the investigator; active infection requiring treatment with systemic antibiotics ≤4 weeks of the screening visit; recurrent medical conditions associated with serious GI diseases, including inflammatory bowel disease; significant medical or psychiatric conditions; therapies or systemic treatments described in the protocol as disallowed that do not comply with the indicated washout interval; and previous treatment with orismilast or failure of treatment with apremilast or other systemic PDE4 inhibitor.

This study was conducted in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, Declaration of Helsinki, and with approval of National Independent Ethics Committees.[19,20]

Objectives and outcomes

The primary efficacy end point was percentage change in PASI from baseline to week 16. Secondary efficacy end points were achievement of a 75% reduction in PASI (PASI75), a score of clear (0) or almost clear (1) skin and ≥2-point improvement in IGA (IGA 0/1) at week 16.

Other secondary efficacy end points were: percentage change from baseline in PASI; achievement of PASI50, PASI75, or PASI90; achievement of IGA 0/1 and ≥2-point improvement in IGA; change from baseline in total Psoriatic Symptom Scale score, in each individual item of the Psoriatic Symptom Scale and in the affected body surface area (all at weeks 4, 8, 12, and 20); change from baseline in Dermatology Life Quality Index at weeks 16 and 20; psoriasis which rebound by week 20 (PASI ≥125% of baseline or new generalized pustular, erythrodermic or more inflammatory psoriasis).

Exploratory end points included changes from baseline to week 16 in Physician Global Assessment of Fingernail Psoriasis; scalp-specific IGA in patients with baseline score of ≤2 (mild scalp psoriasis); and cardiovascular risk factors. Pharmacokinetic and pharmacodynamic data were collected. Although not predefined, data for achievement of PASI100 at week 16 were analyzed.

Safety outcomes assessed included: occurrence, severity, and seriousness of treatment-emergent adverse events (AEs) reported over the 16-week treatment and 4-week follow-up periods; changes from baseline in physical examination, vital sign measurements, electrocardiogram, laboratory values, and body weight. AE severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0[21] as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4), or death (grade 5) (Supplementary Table II, available via Mendeley at https://data.mendeley.com/datasets/dkbxwxmtfv). AEs of special interest were also evaluated.

Statistical analysis

The sample size of ~50 patients per group was based on the assumption that the percentage change from baseline in PASI would be −32.2% and −50.9% for placebo and each orismilast group, respectively, with a standard deviation of 33%.[22,23] A 2-sided 2-sample *t* test with 50 patients per treatment arm achieved a power of 80% at the significance level of 5%. The intention-to-treat population (primary analysis population for efficacy end points) and the safety population consisted of all randomized patients receiving at least 1 study drug dose. The per

protocol population included all intention-to-treat patients without major protocol deviations.

Missing data for the primary analysis of primary and secondary binary end points was handled using multiple imputation (MI), assuming Missing At Random within arms. As a supportive analysis, missing data for secondary binary end points was treated as nonresponse imputation (NRI). The primary end point was analyzed using analysis of covariance, with treatment group as factor and baseline PASI as covariate. Least-square means and 95% confidence interval of the difference between each active treatment and placebo was calculated. Mixed model for repeated measures was used as a supportive analysis and for other continuous secondary end points. No adjustment for multiplicity was made and the 0.05 level of significance was used to claim efficacy vs placebo. Secondary binary end points (IGA 0/1, PASI50, PASI75, and PASI90) were analyzed using the Mantel-Haenszel test, comparing each active treatment group to placebo in the intention-to-treat population. Analysis of PASI100 also used MI.

RESULTS

Patient disposition and baseline characteristics

Between December 30, 2021, and December 20, 2022, 202 patients were randomized, with 62.4% completing treatment (Supplementary Fig 2 and Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/dkbxwxmtfv). Baseline characteristics and previous psoriasis treatments are displayed in Table I. Baseline characteristics were generally balanced between placebo and orismilast twice daily groups. However, there were differences in PASI>20 (placebo, 33.3%; orismilast 20 mg, 45.8%; orismilast 30 mg, 36.0%; and orismilast 40 mg, 52.8%), severe IGA (placebo, 21.6%; orismilast 20 mg, 35.4%; orismilast 30 mg, 30.0%; and orismilast 40 mg, 41.5%) and number of participants with psoriatic arthritis (placebo, 2.0%; orismilast 20 mg, 4.2%; orismilast 30 mg, 10.0%; and orismilast 40 mg, 11.3%).

Primary efficacy end point

Orismilast showed a statistically significant improvement (P <.001) in percentage PASI reduction from baseline to week 16 for all doses (−17.3% for placebo vs −52.6%, −61.2% and −63.7% for 20, 30, and 40 mg orismilast, respectively; Table II and Fig 1, *A*). Improvements were significant from the first measurement at week 4 (−14.4% for placebo vs −35.4%, −38.4% and −38.7% for 20, 30, and 40 mg orismilast, respectively) (Supplementary Fig 3, available via Mendeley at https://data.mendeley.com/datasets/dkbxwxmtfv).

Secondary efficacy end points

Orismilast vs placebo showed greater proportions achieving PASI75 (orismilast 20 mg, 39.5%; 30 mg, 49.0%; 40 mg, 46.4%; and placebo, 16.5%; all P <.05; Fig 1, *B*) and PASI90 (orismilast 20 mg, 24.1%; 30 mg, 22.0%; 40 mg, 28.3%; and placebo, 8.3%; P <.05 for 20 and 40 mg doses; Fig 1, *B*) from baseline to week 16 with MI. Findings using NRI were generally similar to those with MI, except for PASI75 responder rates after week 8, which were higher and more sustained with the 30 mg vs 40 mg dose (Supplementary Fig 4, available via Mendeley at https://data.mendeley.com/datasets/dkbxwxmtfv). PASI100 was also achieved in some patients at week 16 (orismilast 20 mg, 8.7%; 30 mg, 8.9%; 40 mg, 4.3%; and placebo, 2.2%) using MI. A significantly greater proportion achieved IGA 0/1 with orismilast 20 and 30 mg vs placebo (orismilast 20 mg, 26.2%; 30 mg, 24.5%; 40 mg, 20.6%; and placebo, 6.9%; 20 and 30 mg, P <.05) using MI and with orismilast 20 mg using NRI (Table II). Other efficacy outcomes for orismilast vs placebo at week 16, and cases of psoriasis rebound at week 20, are shown in Table II.

In terms of changes in metabolic or cardiovascular risk factors, those receiving orismilast showed dose-dependent reductions in body weight (Supplementary Table IV, available via Mendeley at https://data.mendeley.com/datasets/dkbxwxmtfv). Hip circumference reductions were seen across all doses; systolic and diastolic blood pressure remained stable during the trial. Reductions in C-reactive protein were seen with orismilast 30 and 40 mg vs placebo (Supplementary Table IV, available via Mendeley at https://data.mendeley.com/datasets/dkbxwxmtfv).

Subgroup analyses

When exploring efficacy in subgroups by severity at baseline (defined by baseline IGA), greater proportions achieved PASI75, PASI90, and IGA0/1 at week 16 with orismilast 20 and 30 mg in the moderate group than placebo, using MI. Among those with severe disease, a larger response was observed with 30 and 20 mg for PASI75, but not PASI90 and IGA 0/1, at week 16 vs placebo (Supplementary Table V, available via Mendeley at https://data.mendeley.com/datasets/dkbxwxmtfv). In the <100 kg body weight group, orismilast 20 and 30 mg appeared to provide generally similar improvements vs placebo, while results from the ≥100 kg group indicated numerically higher response rates with orismilast 30 mg than 20 mg

Table I. Baseline demographics and clinical characteristics (intention-to-treat population)

Baseline demographics and clinical characteristics	Placebo (*n* = 51)	Orismilast			Total (*N* = 202)
		20 mg TWICE A DAY (*n* = 48)	30 mg TWICE A DAY (*n* = 50)	40 mg TWICE A DAY (*n* = 53)	
Age, median y (Q1-Q3)	42.0 (37.0-54.0)	42.5 (35.5-56.0)	47.0 (37.0-58.0)	44.0 (31.0-54.0)	43.5 (35.0-56.0)
Sex, *n* (%)					
Male	39 (76.5)	31 (64.6)	39 (78.0)	38 (71.7)	147 (72.8)
Female	12 (23.5)	17 (35.4)	11 (22.0)	15 (28.3)	55 (27.2)
Race, *n* (%)					
White	44 (86.3)	43 (89.6)	46 (92.0)	47 (88.7)	180 (89.1)
Other	2 (3.9)	0	0	1 (1.9)	3 (1.5)
Not reported	5 (9.8)	5 (10.4)	4 (8.0)	5 (9.4)	19 (9.4)
Weight, median kg (Q1-Q3)	86.30 (79.0-107.0)	89.85 (76.15-108.50)	90.40 (79.80-102.60)	89.00 (78.70-102.00)	89.65 (78.40-105.00)
PASI, median (Q1-Q3)	17.40 (13.40-21.60)	19.25 (13.85-23.35)	16.85 (14.90-23.00)	20.80 (14.80-24.40)	18.40 (14.20-23.40)
PASI >20, *n* (%)	17 (33.3)	22 (45.8)	18 (36.0)	28 (52.8)	85 (42.1)
IGA, *n* (%)					
Moderate	40 (78.4)	31 (64.6)	35 (70.0)	31 (58.5)	137 (67.8)
Severe	11 (21.6)	17 (35.4)	15 (30.0)	22 (41.5)	65 (32.2)
BSA, median (Q1-Q3)	20.00 (14.00-29.00)	26.00 (15.00-37.50)	21.00 (15.00-34.00)	22.50 (15.00-35.00)	22.25 (15.00-34.00)
Disease duration, median y (Q1-Q3)	18.0 (10.0-27.0)	23.0 (9.0-32.0)	16.5 (9.0-26.0)	17.0 (10.0-29.0)	17.0 (10.0-29.0)
DLQI, median (Q1-Q3)	13.0 (8.00-18.00)	12.0 (8.50-18.00)	13.0 (7.00-20.00)	15.0 (10.00-20.00)	13.0 (8.00-19.00)
Psoriatic arthritis, *n* (%)	1 (2.0)	2 (4.2)	5 (10.0)	6 (11.3)	14 (6.9)
Psoriasis Symptom Scale, median (Q1-Q3)	8.0 (6.0-11.0)	9.0 (7.0-12.0)	8.5 (7.0-11.0)	9.0 (8.0-11.0)	9.0 (7.0-11.0)
PGA-F, median (Q1-Q3)	1.0 (0-2.0)	1.0 (0-2.0)	1.0 (0-2.0)	1.0 (0-2.0)	1.0 (0-2.0)
ss-IGA, median (Q1-Q3)	3.0 (2.0-3.0)	3.0 (2.0-3.0)	3.0 (2.0-3.0)	3.0 (2.0-3.0)	3.0 (2.0-3.0)
Previous psoriasis treatment, *n* (%)	40 (78.4)	40 (83.3)	39 (78.0)	40 (75.5)	159 (78.7)
Conventional systemics or biologics	21 (41.2)	19 (39.6)	20 (40.0)	21 (39.6)	81 (40.1)
Conventional systemics	12 (23.5)	14 (29.2)	9 (18.0)	13 (24.5)	48 (23.8)
Biologics	12 (23.5)	10 (20.8)	15 (30.0)	11 (20.8)	48 (23.8)

BSA, Body surface area; *DLQI*, Dermatology Life Quality Index; *IGA*, Investigator Global Assessment; *NRS*, numeric rating scale; *PASI*, Psoriasis Area and Severity Index; *PGA-F*, Nail Psoriasis Physician Global Assessment; *ss-IGA*, Scalp-Specific Investigator Global Assessment.

(Supplementary Table VI, available via Mendeley at https://data.mendeley.com/datasets/dkbxwxmtfv).

Safety

No new safety signals were identified with orismilast. The most common (≥5%) AEs were mainly GI events, headaches, and dizziness.[24] AEs were generally mild in severity (Supplementary Table VII, available via Mendeley at https://data.mendeley.com/datasets/dkbxwxmtfv), occurring within the first 4 weeks (Supplementary Table VIII, available via Mendeley at https://data.mendeley.com/datasets/dkbxwxmtfv). The proportion experiencing AEs, and number of AEs, were dose-dependent, increasing from 20 to 40 mg (Table III). The difference between 20 and 30 mg was driven by more grade 1 AEs (and GI AEs) and the difference between 30 and 40 mg was driven by more grade 2 AEs (and GI AEs) on 40 mg. Discontinuations were similar between placebo and orismilast 20 and 30 mg, but an increased dropout rate for the 40 mg dose was observed (Table III and Supplementary Fig 2, available via Mendeley at https://data.mendeley.com/datasets/dkbxwxmtfv), mainly due to diarrhea and nausea. Most discontinuations with orismilast were due to AEs, whereas discontinuations for placebo were due to lack of efficacy (Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/dkbxwxmtfv). The rate of infections was similar across groups (orismilast 20 mg, 16.7%; orismilast 30 mg, 22.0%; orismilast 40 mg, and 15.1%; and placebo, 17.6%).

Table II. Summary of key efficacy results at week 16

Efficacy results at week 16	Placebo (n = 51)	Orismilast 20 mg TWICE A DAY (n = 48)	Orismilast 30 mg TWICE A DAY (n = 50)	Orismilast 40 mg TWICE A DAY (n = 53)
Percent change in PASI from baseline				
MI, ITT	−17.3%	−52.6%*	−61.2%*	−63.7%*
MI, PP	−36.8%	−67.4%*	−77.2%*	−82.8%*
	NRI N//MI	NRI//MI	NRI//MI	NRI//MI
PASI50	25.5%//28.3%	47.9%//57.3%*	60.0%//71.5%*	47.2%//74.2%*
PASI75	15.7%//16.5%	35.4%*//39.5%*	44.0%*//49.0%*	32.1%//46.4%*
PASI90	7.8%//8.3%	22.9%*//24.1%*	20.0%//22.0%	22.6%*//28.3%*
IGA 0/1	5.9%//6.9%	22.9%*//26.2%*	18.0%//24.5%*	11.3%//20.6%
Patients experiencing rebound at week 20	11.8%	4.2%	10.0%	3.8%
Change from baseline in other secondary end points				
DLQI, least-square mean (SE)	−4.9 (1.02)	−8.8 (1.01)*	−7.7 (1.00)	−7.3 (1.14)
BSA, least-square mean (SE)	−6.9 (1.87)	−13.5 (1.86)*	−14.4 (1.85)*	−18.1 (2.02)*
Total PSS, least-square mean (SE)	−1.8 (0.54)	−5.0 (0.53)*	−4.2 (0.53)*	−3.8 (0.58)*
PGA-F, mean (SD)	−0.1 (0.95)	−0.4 (1.07)	−0.6 (1.14)	−0.9 (1.43)
ss-IGA among patients with baseline score ≥2, mean (SD)	−0.9 (1.16)	−1.7 (1.09)	−2.1 (1.08)	−1.8 (1.54)
Scalp itch NRS among patients with baseline score ≥4, mean (SD)	−2.1 (2.73)	−4.1 (3.67)	−3.1 (3.28)	−2.3 (3.11)

N numbers represent the overall population and may differ from these values depending on the assessment/analyses. Population analyzed is the ITT, unless otherwise specified.

BSA, Affected body surface area; *DLQI*, Dermatology Life Quality Index; *IGA*, Investigator Global Assessment; *ITT*, intention-to-treat population; *MI*, multiple imputation; *NRS*, Numeric Rating Scale; *PASI*, Psoriasis Area and Severity Index; *PGA-F*, Physician's Global Assessment of Finger Nails; *PP*, per protocol population; *PSS*, Psoriasis Symptoms Scale; *SD*, standard deviation; *SE*, standard error; *ss-IGA*, Scalp-Specific Investigator Global Assessment.

*P <.05 vs placebo.

Rates of depression were low (placebo, 1 patient; and orismilast 30 mg, 1 patient). No suicidal ideation or malignancies were reported (Table III).

DISCUSSION

In this study, orismilast twice daily demonstrated significant efficacy vs placebo at week 16 in patients with moderate-to-severe plaque psoriasis for percentage change in PASI, and proportions achieving PASI75 and PASI90. The benefits in percentage change of PASI, were observed early, at 4 weeks. Orismilast, a PDE4B/D inhibitor, may have the potential to provide greater efficacy than previous pan-PDE4 inhibitors, indicated by *in vitro* and *ex vivo* study results.[16] This may, in part, explain the higher proportion achieving PASI90 (22.0%-28.3%) across orismilast arms using MI (placebo 8.3%, P <.05 for 20 and 40 mg vs placebo), which is numerically greater than apremilast (9.8% vs placebo 0.4%, using last observation carried forward methodology; P >.05) and roflumilast (13% vs placebo 0%, NRI analysis; P >.05) at weeks 16 and 12, respectively.[17,25] Similar results for orismilast were seen when employing NRI, reflecting the consistency of these findings. Comparison of data between trials should be interpreted with caution as differences in patient population, design, and discontinuation rates can influence results.

The AE profile of PDE4 inhibition has been studied extensively; no new safety signals were identified in this study. Dose-dependent diarrhea, nausea, and headache, occurring in ≥5%, were the main AEs. AEs were generally mild in severity, occurring within the first 4 weeks. A more detailed understanding of the orismilast safety profile in future trials would be beneficial, as this knowledge would aid clinicians in managing AEs and addressing patient expectations. Rates of depression were low;

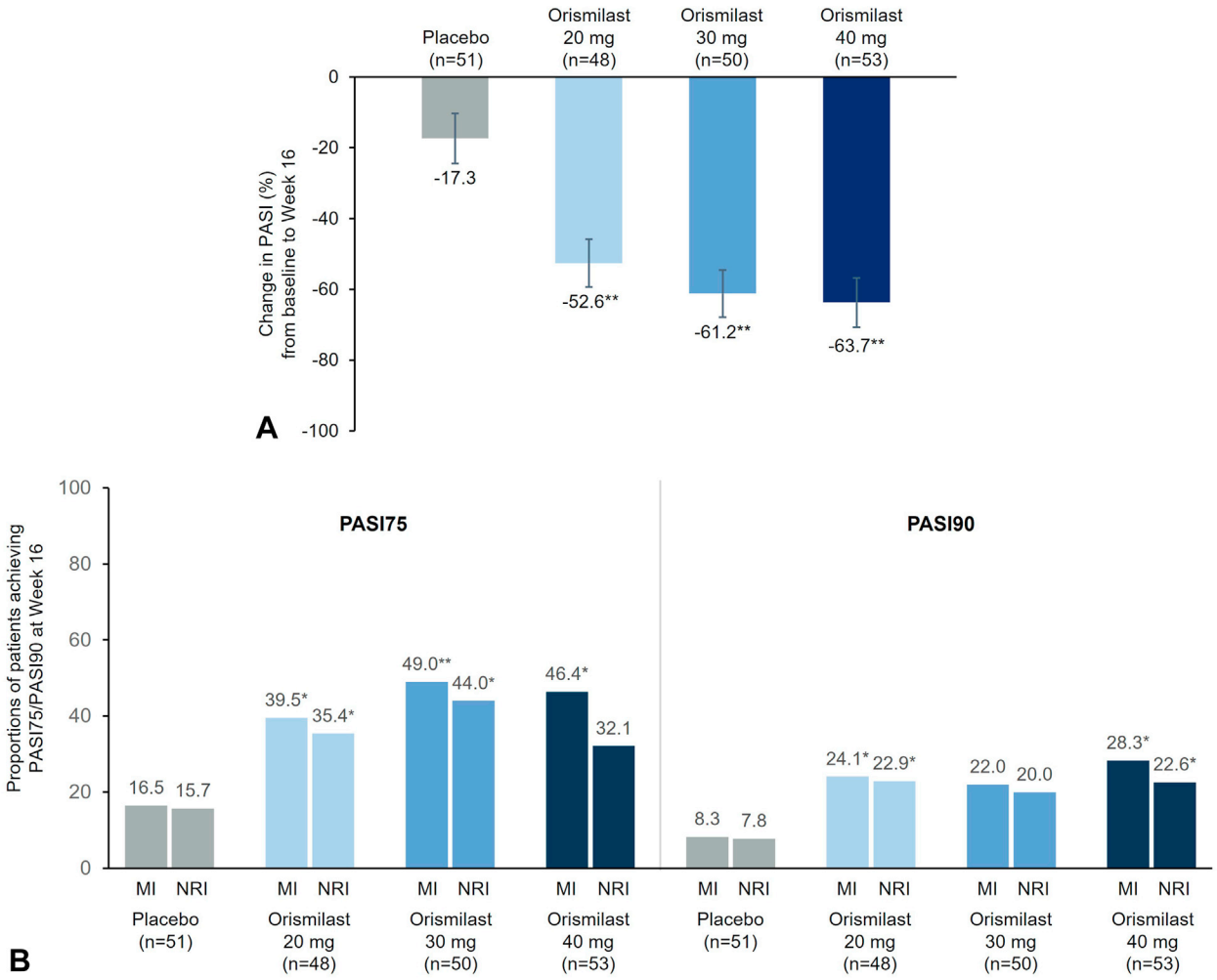

Fig 1. A, Percent change of PASI at week 16 with MI and **(B)** proportion of patients achieving PASI75 and PASI90 with MI and NRI. **P* <.05; ***P* <.001 for all doses vs placebo. *P* values were calculated using analysis of covariance with treatment group as a factor and baseline PASI as covariate. Panel **(A)** presents least squares means with standard error bars. MI: if a PASI score is missing, the value was imputed by MI. NRI: if a PASI score is missing, the value will be handled as nonresponse. MI, multiple imputation; NRI, nonresponse imputation; PASI, Psoriasis Area and Severity Index.

no suicidal ideation or malignancies were reported. No differences were observed across treatment groups in depression, suicidal ideation or infections.

It should be noted that discontinuation rates were higher than what was reported with apremilast[17] and highest for the 40 mg group, but similar for the placebo, 20, and 30 mg orismilast groups. The best risk-benefit profile was demonstrated for the 20 and 30 mg orismilast groups; within the 40 mg group dropout rates were driven mainly by diarrhea and nausea. Reduction in discontinuation rates in future studies would positively impact overall efficacy observed with orismilast across doses.

Notably, patients receiving orismilast also demonstrated weight loss (orismilast −2.6 to −3.1 kg; and placebo −0.2 kg), previously reported for apremilast.[26] These findings are potentially relevant, because patients with psoriasis are at greater risk of obesity and cardiovascular disease.[1,3,4] However, these data do not provide long-term efficacy or safety information and the study data were limited by the small and relatively homogenous population and short study duration.

Owing to the role of PDE4 B and D enzymes in regulating inflammatory pathways, orismilast and other selective PDE4B/D inhibitors may be broadly relevant for treatment of chronic inflammatory diseases, such as hidradenitis suppurativa, atopic dermatitis, and ulcerative colitis.[5,27,28] Orismilast is under investigation in people with hidradenitis

Table III. Overall summary of treatment-emergent adverse events (safety population)

TEAEs	Placebo (*n* = 51) *n* (%) [E]	Orismilast			
		20 mg TWICE A DAY (*n* = 48) *n* (%) [E]	30 mg TWICE A DAY (*n* = 50) *n* (%) [E]	40 mg TWICE A DAY (*n* = 53) *n* (%) [E]	Orismilast Total (*n* = 151) *n* (%) [E]
Any TEAEs	23 (45.1) [59]	37 (77.1) [106]	42 (84.0) [160]	50 (94.3) [205]	129 (85.4) [471]
Any related TEAEs	13 (25.5) [31]	29 (60.4) [70]	41 (82.0) [121]	46 (86.8) [168]	116 (76.8) [359]
SAEs	0	1 (2.1) [1]	1 (2.0) [1]	0	2 (1.3) [2]
Deaths	0	0	0	0	0
TEAE leading to study drug discontinuation	2 (3.9) [3]	10 (20.8) [14]	10 (20.0) [17]	21 (39.6) [38]	41 (27.2) [69]
TEAE by toxicity grade					
Grade 1	17 (33.3) [37]	25 (52.1) [58]	36 (72.0) [105]	40 (75.5) [143]	101 (66.9) [306]
Grade 2	10 (19.6) [18]	18 (37.5) [34]	19 (38.0) [40]	26 (49.1) [47]	63 (41.7) [121]
Grade 3	2 (3.9) [4]	7 (14.6) [13]	6 (12.0) [12]	7 (13.2) [13]	20 (13.2) [38]
Grade 4	0	1 (2.1) [1]	1 (2.0) [3]	1 (1.9) [2]	3 (2.0) [6]
AEs occurring in ≥5% of patients across all orismilast groups*					
GI disorders	7 (13.7) [11]	26 (54.2) [50]	35 (70.0) [76]	42 (79.2) [116]	103 (68.2) [242]
Diarrhea	2 (3.9) [2]	18 (37.5) [24]	24 (48.0) [35]	24 (45.3) [43]	66 (43.7) [102]
Nausea	2 (3.9) [2]	11 (22.9) [12]	19 (38.0) [23]	22 (41.5) [24]	52 (34.4) [59]
Vomiting	1 (2.0) [1]	3 (6.3) [3]	4 (8.0) [6]	7 (13.2) [19]	14 (9.3) [28]
Abdominal pain upper	0	1 (2.1) [2]	3 (6.0) [3]	6 (11.3) [9]	10 (6.6) [14]
Nervous system disorders	4 (7.8) [7]	10 (20.8) [14]	20 (40.0) [32]	20 (37.7) [31]	50 (33.1) [77]
Headache	3 (5.9) [6]	6 (12.5) [9]	13 (26.0) [16]	11 (20.8) [14]	30 (19.9) [39]
Dizziness	0	3 (6.3) [3]	7 (14.0) [8]	8 (15.1) [10]	18 (11.9) [21]
AEs of special interest					
Infections and infestations	9 (17.6) [9]	8 (16.7) [10]	11 (22.0) [13]	8 (15.1) [9]	27 (17.9) [32]
Psychiatric disorders	1 (2.0) [1]	1 (2.1) [1]	1 (2.0) [1]	3 (5.7) [4]	5 (3.3) [6]
Depression	1 (2.0) [1]	0	1 (2.0) [1]	0	1 (0.7) [1]
Suicidal ideation	0	0	0	0	0
Neoplasms benign, malignant and unspecified	0	0	0	0	0

Adverse events are coded using MedDRA version 24.0.[24]
AE, Adverse event; *E*, number of events; *GI*, gastrointestinal; *PT*, preferred term; *SAE*, serious adverse event; *SOC*, system organ class; *TEAE*, treatment-emergent adverse event.
*Presented data reflect AEs occurring in ≥5% of patients for PT data outputs.

suppurativa,[29] atopic dermatitis, and ulcerative colitis.

CONCLUSIONS

Orismilast, a PDE4B/D inhibitor, demonstrated superior efficacy compared with placebo in a 16-week, randomized, double-blinded, dose-finding, phase 2b trial in patients with moderate-to-severe psoriasis. Safety and tolerability were dose dependent and as expected for this drug class. These data support the potential of selective PDE4B/D inhibition as a promising therapeutic option in psoriasis and the further development of orismilast for the treatment of plaque psoriasis.

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Conflicts of interest

Dr Warren has received research grants from AbbVie, Almirall, Amgen, Celgene, Janssen, Lilly, Leo Pharma, Novartis, Pfizer, and UCB, and consulting fees from AbbVie, Almirall, Amgen, Arena, Astellas, Avillion, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, DiCE, GlaxoSmithKline, Janssen, Lilly, Leo Pharma, Novartis, Pfizer, Sanofi, Sun Pharma, UCB, and UNION therapeutics. Dr French has received consulting fees and/or honoraria from AbbVie, AC Immune, Almirall, Amgen, Biotest, Eli Lilly, Galderma, InflaRx, Janssen, Leo Pharma, Novartis, Regeneron, UCB, UNION therapeutics, and Vaderis Therapeutics, and has served as president of the International League of Dermatological Societies. Dr Blauvelt has received research grants from AbbVie,

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