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Treatment of early oligoarticular psoriatic arthritis with apremilast: primary outcomes at week 16 from the FOREMOST randomised controlled trial

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ABSTRACT

Objectives Oligoarticular psoriatic arthritis (PsA) is frequent but rarely studied. The objective was to assess the efficacy of apremilast in early oligoarticular PsA.

Methods FOREMOST (NCT03747939) was a phase 4 multicentre, randomised, double-blind, placebo-controlled trial. Patients had early (symptom duration ≤5 years) oligoarticular PsA (>1 but ≤4 swollen and >1 but ≤4 tender joints; 2–8 total active joints). Patients were randomised 2:1 to apremilast 30 mg two times per day or placebo for 24 weeks, with an early escape at week 16. The primary endpoint was the proportion of patients at week 16 who achieved minimal disease activity (MDA)-Joints (modification of MDA mandating ≤1 swollen joint and ≤1 tender joint) based on sentinel joints (those affected at baseline) with a combination of non-responder imputation and multiple imputations. Exploratory analysis assessed all joints.

Results Of 308 patients randomised (apremilast: n=203; placebo: n=105), mean (SD) PsA duration was 9.9 (10.2) months, mean (SD) age was 50.9 (12.5) years and 39.9% of patients were using a conventional synthetic disease-modifying antirheumatic drug. MDA-Joints (sentinel joints (primary endpoint) and all joints) were achieved by significantly more patients with apremilast (33.9% and 21.3%) vs placebo (16.0% and 7.9%) at week 16 (p=0.0008 and nominal p=0.0028, respectively). Greater improvements in patient-reported outcomes, clinical disease activity and skin involvement were also seen with apremilast versus placebo.

Conclusions FOREMOST is the first randomised controlled trial designed for early oligoarticular PsA and showed apremilast improves clinical and patient-reported outcomes. This trial may inform the optimal management of PsA in these patients.

Trial registration number NCT03747939.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Psoriatic arthritis (PsA) is frequently oligoarticular. Even with limited joint involvement, PsA can be associated with considerable disease burden and marked impact on quality of life.

⇒ There are limited data on drug effectiveness in oligoarticular PsA since most trials exclude patients with low counts of involved joints.

WHAT THIS STUDY ADDS

⇒ FOREMOST is the first trial targeting early oligoarticular PsA. This trial provides data on an under-represented group of patients. We found that even with limited joint involvement, the impact of PsA was high at baseline.

⇒ In this randomised controlled trial comparing apremilast and placebo, the primary outcome was met. Patients with oligoarticular PsA treated with apremilast showed improvements in clinical outcomes and patient-reported outcomes at week 16.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of FOREMOST suggest apremilast is effective for patients with early PsA and limited joint involvement.

INTRODUCTION

Psoriatic arthritis (PsA) is a heterogeneous inflammatory rheumatological disorder characterised by inflammatory arthritis which, based on the number of actively inflamed joints, can be divided into oligoarticular PsA and polyarticular PsA.[1] The oligoarticular phenotype has been frequently observed in different real-world cohorts, occurring in up to 50% of PsA patients.[2–5]

Despite fewer involved joints and generally lower rates of enthesitis and dactylitis,[3] oligoarticular PsA can significantly impact the quality of life.[3 4 6] Additionally, similar levels of pain and disease burden, including a high proportion of patients who found the state of their symptoms to be unacceptable, have been seen in oligoarticular PsA compared with polyarticular PsA.[4 7]

Both the European Alliance of Associations for Rheumatology (EULAR) recommendations and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis recommendations have put forward oligoarticular PsA as part of the research agenda, noting there are little data on the treatment of patients with oligoarthritis since published clinical trials have generally enrolled patients with at least three swollen joints and at least three tender

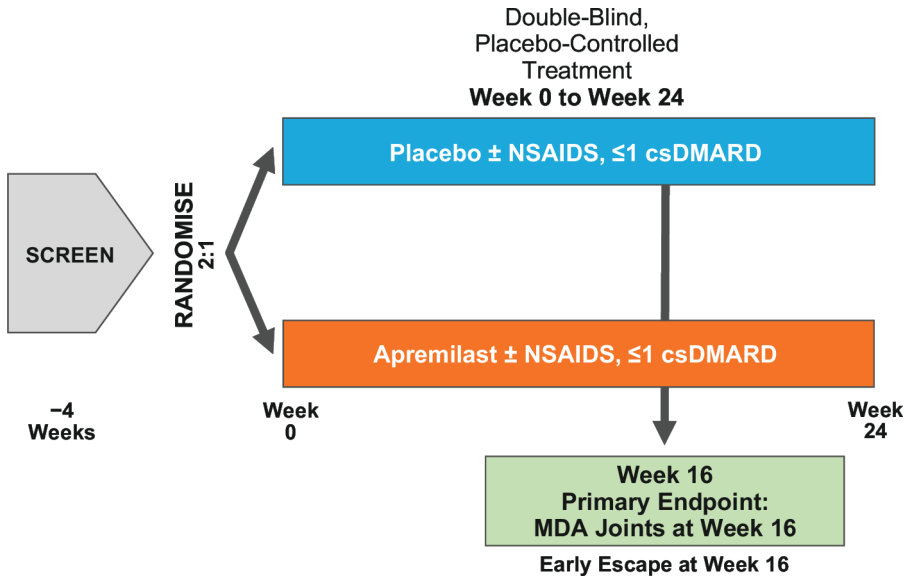

Figure 1 FOREMOST study design. csDMARD, conventional synthetic disease-modifying antirheumatic drug; MDA, minimal disease activity; NSAID, non-steroidal anti-inflammatory drug.

joints, with the actual mean active joint counts being much higher.[8–10] Knowledge regarding the efficacy of drugs in oligoarticular forms would be of great value to clinicians.

Apremilast is an oral phosphodiesterase 4 inhibitor approved for the treatment of active PsA.[11] The efficacy and safety of apremilast were demonstrated in patients with long-standing PsA in the phase 3 Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) clinical trial programme.[12–15] In the PALACE studies, mean swollen joint count (SJC) was approximately 10 and mean tender joint count (TJC) was approximately 20. The efficacy of apremilast in early oligoarticular PsA has not yet been evaluated.

The objective of the FOREMOST randomised controlled trial was to assess the efficacy of apremilast versus placebo for the treatment of early oligoarticular PsA. Here, we report the primary results of this trial.

METHODS

Study design

FOREMOST (ClinicalTrials.gov identifier: NCT03747939) was a phase 4 international, multicentre, randomised, double-blind, placebo-controlled, parallel-group study conducted from December 2018 to December 2022 in 80 sites in 10 countries. Patients were randomised 2:1 to receive either apremilast 30 mg two times per day or placebo. The study consisted of a 4-week screening period, followed by a 24-week double-blind, placebo-controlled phase (figure 1). Starting at week 16, patients who showed no improvement in SJC (assessed using sentinel joints) were eligible for early escape whereby patients initially randomised to placebo were switched to apremilast 30 mg two times per day and those initially randomised to apremilast continued to receive apremilast 30 mg two times per day. After week 24, all patients had the option to enter an active treatment extension phase in which all patients received apremilast through week 48.

PATIENTS

Patients had PsA according to the Classification Criteria for Psoriatic Arthritis. As we aimed to include oligoarticular PsA, joint involvement was limited to >1 but ≤4 swollen and >1 but ≤4 tender joints, of 66/68 SJC/TJC. Overall, patients could have 2–8 total active joints, considering there was no formal consensus on the definition of oligoarticular disease when the study was designed. Disease duration was originally required to be ≤2 years but was revised to ≤5 years after symptom onset in a protocol amendment dated July 2021 to reach a sufficient sample size. Patients taking a conventional synthetic disease-modifying antirheumatic drug (csDMARD) (either methotrexate or sulfasalazine) to treat PsA at baseline could continue treatment provided the treatment was taken at a stable dose for ≥3 months prior to baseline and patients remained at a stable dose (≤25 mg/week for methotrexate and ≤3 g/day for sulfasalazine) during the first 24 weeks of the study. Patients taking non-steroidal anti-inflammatory drugs (NSAIDs) at baseline were required to be on a stable dose for ≥2 weeks before baseline to be enrolled in the study and were required to remain on this dose through week 24. Stable low doses of glucocorticoids (prednisone ≤10 mg/day or equivalent) were allowed. Patients were excluded if they had received prior treatment with >2 csDMARDs, a Janus kinase inhibitor or a biological DMARD.

Assessments

The primary endpoint was the proportion of patients who achieved minimal disease activity (MDA)-Joints at week 16, based on sentinel joints (those affected at baseline). This outcome is a modified MDA[16] that requires the achievement of both SJC≤1 and TJC≤1 plus achieving ≥3 of the following remaining MDA criteria: psoriasis body surface area (BSA) ≤3%, patient pain Visual Analogue Scale (VAS) ≤15 mm on a 100 mm scale, Patient Global Assessment of Disease Activity (PtGA) ≤20 mm on a 100 mm scale, physical function Health Assessment Questionnaire Disability Index (HAQ-DI) ≤0.5 and enthesitis count ≤1 based on the Leeds Enthesitis Index (LEI).[16] This was selected as the primary endpoint to allow for the capture of different dimensions of PsA with a particular focus on improvement in the number of active joints.

Secondary endpoints assessed at week 16 included the proportion of patients achieving Clinical Disease Activity in Psoriatic Arthritis (cDAPSA) remission (≤4) or low disease activity (LDA, >4 to ≤13); SJC≤1, TJC≤1, or PtGA≤20 (based on the MDA

Table 1 Baseline demographics and disease characteristics

	Placebo (n=105)	Apremilast (n=203)	Total (N=308)
Age, mean (SD), years	50.2 (13.0)	51.3 (12.3)	50.9 (12.5)
Women, n (%)	51 (48.6)	118 (58.1)	169 (54.9)
Race, white, n (%)	99 (94.3)	192 (94.6)	291 (94.5)
PsA duration, mean (SD), months	10.0 (10.6)	9.8 (10.0)	9.9 (10.2)
Median (Q1, Q3)	6.0 (3.6, 12.7)	6.1 (3.7, 11.2)	6.0 (3.7, 11.7)
SJC (0–66), mean (SD)	2.6 (0.7)	2.7 (0.7)	2.6 (0.7)
Median (Q1, Q3)	2.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)
SJC category, n (%)			
2	57 (54.3)	93 (45.8)	150 (48.7)
3	38 (36.2)	79 (38.9)	117 (38.0)
4	10 (9.5)	31 (15.3)	41 (13.3)
TJC (0–68), mean (SD)	3.2 (0.8)	3.2 (0.8)	3.2 (0.8)
Median (Q1, Q3)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)
TJC category, n (%)			
2	23 (21.9)	41 (20.2)	64 (20.8)
3	38 (36.2)	77 (37.9)	115 (37.3)
4	44 (41.9)	85 (41.9)	129 (41.9)
Active joint involvement*, n (%)			
Small only	51 (48.6)	104 (51.2)	155 (50.3)
Large only	7 (6.7)	19 (9.4)	26 (8.4)
Small and large	47 (44.8)	80 (39.4)	127 (41.2)
PhGA (0–100 mm VAS), mean (SD)	43.2 (19.2)	42.2 (18.6)	42.6 (18.8)
PtGA (0–100 mm VAS), mean (SD)	50.5 (20.7)	51.6 (22.0)	51.3 (21.5)
Patient's assessment of pain (0–100 mm VAS), mean (SD)	51.1 (22.7)	52.3 (22.0)	51.9 (22.2)
cDAPSA (0–154), mean (SD)	15.9 (4.5)	16.3 (4.3)	16.2 (4.4)
PASDAS (0–10), mean (SD)	4.9 (1.0)	4.9 (1.1)	4.9 (1.1)
BSA, mean (SD), %	6.3 (10.9)	6.9 (12.3)	6.7 (11.8)
BSA>3%, n (%)	42 (40.0)	78 (38.4)	120 (39.0)
HAQ-DI (0–3), mean (SD)	1.1 (0.6)	1.0 (0.6)	1.0 (0.6)
LEI (0–6), mean (SD)†	2.6 (1.6)	2.4 (1.5)	2.5 (1.5)
LEI>0, n (%)	38 (36.2)	70 (34.5)	108 (35.1)
SPARCC Index (0–16), mean (SD)†	4.3 (3.9)	3.9 (3.5)	4.0 (3.6)
Physician's assessment of nail psoriasis (0–100 mm VAS), mean (SD)‡	28.9 (26.3)	30.8 (25.9)	30.2 (26.0)
PsAID-12 (0–10), mean (SD)	4.8 (2.2)	4.7 (2.0)	4.7 (2.1)
Prior csDMARD, n (%)	69 (65.7)	135 (66.5)	204 (66.2)
Concomitant csDMARD, n (%)	41 (39.0)	82 (40.4)	123 (39.9)
Methotrexate	34 (32.4)	73 (36.0)	107 (34.7)
Sulfasalazine	7 (6.7)	9 (4.4)	16 (5.2)

FAS.
*Active joints are defined as swollen and/or tender joints. Large joints included shoulder, elbow, hip, knee and ankle. The remaining joints were considered small.
†In patients with pre-existing enthesopathy.
‡In patients with baseline nail VAS>0.
BSA, body surface area; cDAPSA, Clinical Disease Activity Index for Psoriatic Arthritis; csDMARD, conventional synthetic disease-modifying antirheumatic drug; FAS, full analysis set; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; LEI, Leeds Enthesitis Index; PASDAS, Psoriatic Arthritis Disease Activity Score; PhGA, Physician's Global Assessment of disease activity; PsA, psoriatic arthritis; PsAID-12, Psoriatic Arthritis Impact of Disease 12-item; PtGA, Patient Global Assessment of disease activity; SJC, swollen joint count; SPARCC, Spondyloarthritis Research Consortium of Canada; TJC, tender joint count; VAS, Visual Analogue Scale.

criteria); patient assessment of pain ≤15 (based on the MDA criteria); change from baseline in the Psoriatic Arthritis Impact of Disease (PsAID-12), a self-administered questionnaire that measures the impact of PsA from the perspective of the patient and Psoriatic Arthritis Disease Activity Score (PASDAS) good or moderate response. For assessments involving joint counts, primary and secondary analyses were based on sentinel joints. Exploratory analyses were performed for all joints (including those that were unaffected at baseline) to fully assess the impact of apremilast on disease activity. Treatment-emergent adverse events (TEAEs) were assessed throughout the study. Exploratory endpoints assessed at week 16 included PsAID-12 score ≤4 (considered a patient-acceptable symptom state[17]), change from baseline in physician's assessment by VAS of nail psoriasis, and the proportion of patients with skin clearance defined by BSA of 0. SJC and TJC over time, the proportion of patients whose total joint involvement increased from ≤4 at baseline to >4 over time, the proportion of patients achieving MDA and the proportion of patients achieving MDA-Joints among those with ≤4 active joints at baseline were assessed as post hoc analyses.

Statistical analysis

It was estimated that 285 patients would be needed to provide 80% power to detect a 15% absolute difference in the proportion of patients who achieved MDA-Joints with apremilast versus placebo using a χ^2 test with a two-sided significance level of 0.05.

Efficacy analyses used the full analysis set (FAS), which consisted of all randomised patients. The safety population consisted of all patients who received at least one dose of study medication. A sequential test procedure (in the order of the list of endpoints above) was applied to the primary and seven secondary efficacy endpoints to preserve the family-wise type I error rate. The primary endpoint and binary secondary endpoints were assessed using a Cochran-Mantel-Haenszel test controlling for concomitant use of glucocorticoids at baseline (yes or no) and use of a csDMARD (csDMARD naive, csDMARD use before baseline or csDMARD use before and concomitant at baseline). For binary response parameters, the missing data were imputed using non-responder imputation for patients who discontinued the study prior to week 16 due to adverse events or lack of efficacy, and multiple imputations (MI) for the remaining missing values at week 16. The number of responders was rounded based on the value given by MI. For the continuous secondary endpoint, a mixed-effect model for repeated measures (MMRM) was used that included change from baseline as the dependent variable and treatment group, time, treatment-by-time interaction, use of glucocorticoids and use of a csDMARD (as above) as factors, and baseline value as a covariate. Treatment differences in the least squares (LS) mean, the associated SEs and two-sided p values were obtained from the MMRM model.

RESULTS

Baseline characteristics and patient disposition

Of 308 patients randomised (apremilast: n=203; placebo: n=105), mean PsA duration was 9.9 (SD: 10.2) months, mean age was 50.9 (SD: 12.5) years and 39.9% (123/308) of patients were using a csDMARD, mostly methotrexate (107/123) (table 1). Mean (SD) SJC was 2.6 (0.7), and TJC was 3.2 (0.8), and these were similar between treatment groups; however, a slight imbalance was observed in median (Q1, Q3) SJC (apremilast: 3.0 (2.0, 3.0); placebo: 2.0 (2.0, 3.0)) due to a greater proportion of placebo patients with an SJC of 2 (apremilast: 45.8%; placebo: 54.3%). Small joints were most commonly affected. Close to 90% of study patients had ≤4 active joints at baseline (apremilast: n=176 (86.7%); placebo: n=92 (87.6%)).

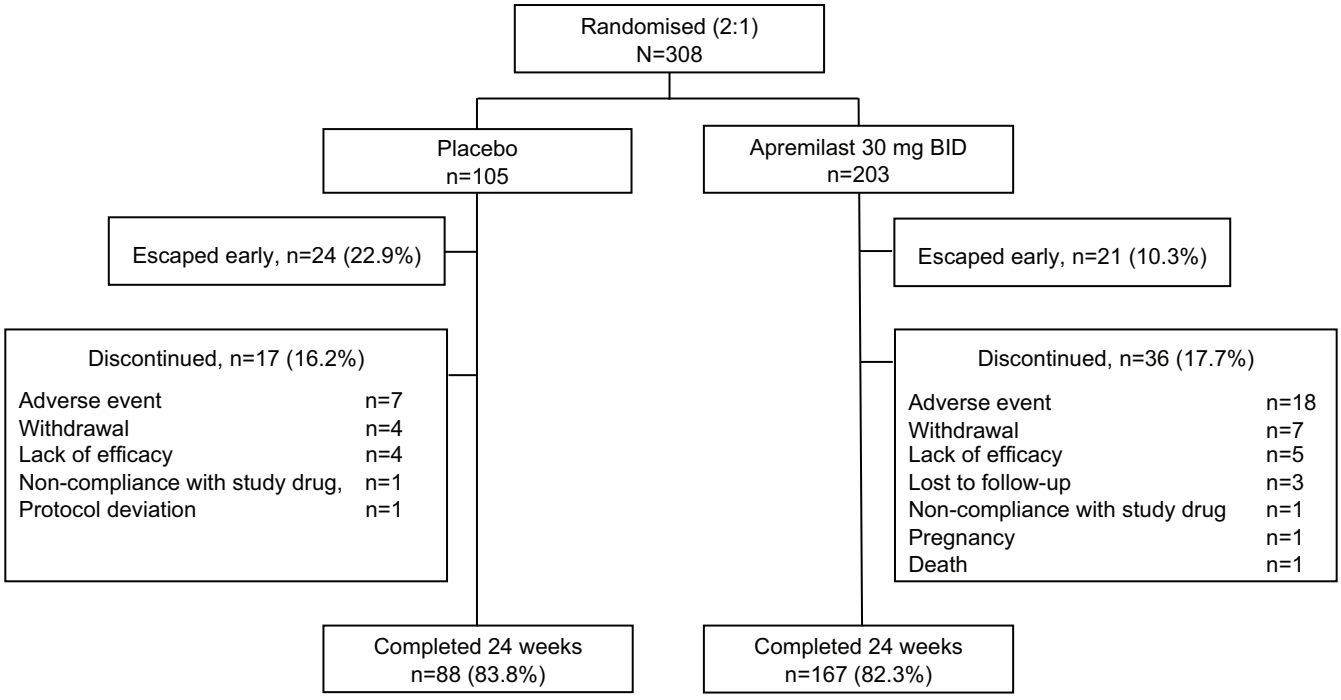

Figure 2 Patient disposition through week 24 in the FOREMOST trial. FAS. All 45 patients who escaped early completed 24 weeks. FAS, full analysis set.

21 (10.3%) apremilast-treated patients and 24 (22.9%) placebo-treated patients underwent early escape (figure 2). A total of 255 (82.8%) patients completed the 24-week placebo-controlled phase (apremilast: n=167 (82.3%); placebo: n=88 (83.8%)) and 53 (17.2%) discontinued the study (apremilast: n=36 (17.7%); placebo: n=17 (16.2%)) (figure 2).

Primary endpoint

The primary endpoint was met: MDA-Joints response based on sentinel joints was achieved by significantly more patients with apremilast (69/203, 33.9%) vs placebo (17/105, 16.0%) at week 16 (treatment difference (95% CI) 18.5% (8.9% to 28.1%), p=0.0008) (figure 3A).

Secondary endpoints

At week 16, a significantly greater proportion of patients treated with apremilast achieved cDAPSA remission or LDA versus placebo (70.2% vs 51.8%; p=0.0017) (table 2). Proportions of patients achieving SJC≤1 based on sentinel joints at week 16 were higher with apremilast versus placebo, although not statistically significant (74.0% vs 69.0%; p=0.35). More patients treated with apremilast achieved TJC≤1 at week 16 than placebo

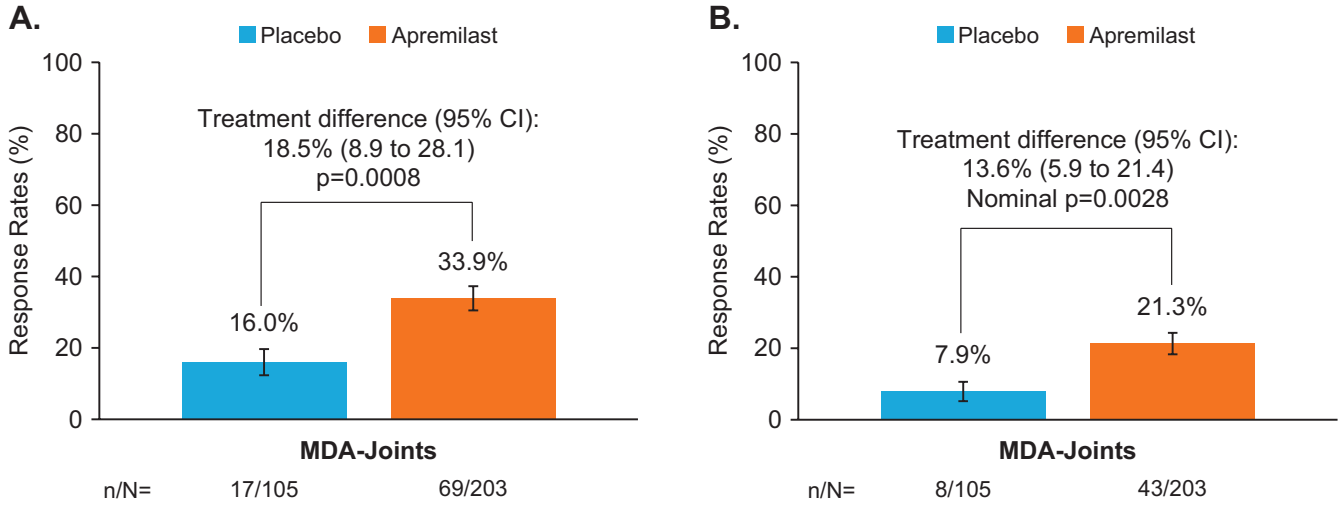

Figure 3 MDA-joints response at week 16. (A) Based on sentinel joints. (B) Based on all joints. FAS. Error bars represent SE. The number of responders was rounded based on the value given by multiple imputations. MDA-joints is a composite of TJC≤1 and SJC≤1 plus achievement of three of the following: BSA≤3%, patient pain VAS≤15, PtGA≤20, HAQ-DI≤0.5 and LEI≤1. BSA, body surface area; CI, confidence interval; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; LEI, Leeds Enthesitis Index; MDA, minimal disease activity; PtGA, Patient Global Assessment of disease activity; SE, standard error; SJC, swollen joint count; TJC, tender joint count; VAS, Visual Analogue Scale.

Table 2 Outcomes at week 16 comparing apremilast and placebo

	Sentinel* joints			All joints		
	Placebo (n=105)	Apremilast (n=203)	Difference (95% CI)	Placebo (n=105)	Apremilast (n=203)	Difference (95% CI)
cDAPSA REM/LDA, n (%)	54 (51.8)	143 (70.2)	18.6% (7.0 to 30.2) p=0.0017	40 (38.0)	122 (60.3)	22.5% (10.7 to 34.3) p=0.0004†
SJC≤1, n (%)	72 (69.0)	150 (74.0)	5.1 (–5.8 to 16.0) p=0.3539	43 (41.5)	117 (57.9)	16.4 (4.7 to 28.0) p=0.0068†
TJC≤1, n (%)	47 (44.4)	134 (66.2)	22.1 (10.4 to 33.7) p=0.0003†	17 (16.7)	77 (38.0)	21.4 (11.6 to 31.2) p=0.0002†
PtGA VAS≤20, n (%)	–	–	–	20 (19.1)	62 (30.4)	11.8% (1.7 to 22.0) p=0.0286†
Patient pain VAS≤15, n (%)	–	–	–	14 (13.1)	60 (29.4)	16.3% (6.9 to 25.8) p=0.0022†
PsAID-12, LS mean (SE) change from baseline	–	–	–	–0.4 (0.2)	–1.5 (0.2)	–1.0 (–1.5 to –0.6) p<0.0001†
PASDAS good/moderate response, n (%)	45 (42.7)	122 (59.9)	17.7% (5.7 to 29.7) p=0.0043†	42 (39.8)	120 (59.3)	20.0% (8.1 to 32.0) p=0.0014†

FAS. The number of responders was rounded based on the value given by multiple imputations.
*Sentinel joints are defined as joints affected at baseline.
†Nominal p value.
cDAPSA, Clinical Disease Activity in Psoriatic Arthritis; CI, confidence interval; csDMARD, conventional synthetic disease-modifying antirheumatic drug; FAS, full analysis set; LDA, low disease activity; LS, least squares; MDA, minimal disease activity; PASDAS, PsA Disease Activity Score; PsAID-12, Psoriatic Arthritis Impact of Disease; PtGA, Patient Global Assessment of disease activity; REM, remission; SE, standard error; SJC, swollen joint count; TJC, tender joint count; VAS, Visual Analogue Scale.

(based on sentinel joints, 66.2% vs 44.4%; nominal p=0.0003) (table 2).

Improvements in patient-reported outcomes were more frequent with apremilast; achievement of PtGA≤20 was greater with apremilast versus placebo at week 16 (30.4% vs 19.1%), as was the achievement of low pain levels (29.4% vs 13.1%) and decreases in PsAID-12 (–1.5 vs –0.4) (table 2). Greater proportions of patients achieved a good or moderate response in PASDAS score with apremilast versus placebo (59.9% vs 42.7%) at week 16 (table 2).

All joints analysis

When outcomes were evaluated based on all joints, MDA-Joints response at week 16 was seen in 21.3% vs 7.9% for apremilast versus placebo (treatment difference (95% CI) 13.6% (5.9% to 21.4%); nominal p=0.0028) (figure 3B). More patients treated with apremilast achieved SJC≤1 (57.9% vs 41.5%; nominal p=0.0068) and TJC≤1 (38.0% vs 16.7%; nominal p=0.0002) at week 16 than placebo (table 2). At week 16, a significantly greater proportion of patients treated with apremilast achieved cDAPSA remission or LDA versus placebo (60.3% vs 38.0%; nominal p=0.0004) (table 2). However, 28.6% of placebo-treated patients and 22.2% of apremilast-treated patients had LDA at baseline. Among those not already in LDA or remission at baseline (apremilast: n=153; placebo: n=75), 54.4% of patients treated with apremilast achieved remission or LDA at week 16 vs 30.1% of patients who received placebo (online supplemental figure 1). PASDAS response rates at week 16 were consistently higher with apremilast versus placebo when evaluated by all joints impacted (table 2).

Exploratory endpoints

At week 16, there was a difference in the proportion of patients achieving response in non-musculoskeletal manifestations. More patients achieved skin clearance at week 16 with apremilast versus placebo (31.2% vs 16.9%; nominal p=0.0073) (online supplemental figure 2A). Improvement from baseline in nail VAS was significantly greater with apremilast (LS mean change −13.9) than placebo (−6.8) at week 16 (nominal p=0.0094) (online supplemental figure 2B).

Post hoc analysis

Among patients with baseline PsAID-12>4, more patients achieved a PsAID-12 score≤4 (considered a patient-acceptable symptom state) with apremilast (50.7%) vs placebo (23.1%; nominal p=0.0005) at week 16 (online supplemental figure 3). Decreases in the mean number of swollen and tender joints were seen over time with apremilast treatment, with noticeable differences observed with apremilast versus placebo when evaluated by all joints at week 16 (online supplemental figure 4).

An analysis was conducted to assess the achievement of each domain of MDA other than SJC and TJC in patients who did not meet response criteria for that domain at baseline (online supplemental figure 5). Of patients with BSA>3% at baseline, more achieved BSA≤3% with apremilast versus placebo at week 16 (52.2% vs 25.1%; nominal p=0.0043). Of patients with a patient assessment of pain score >15 at baseline, patient assessment of pain ≤15 was reached by more patients with apremilast versus placebo at week 16 (27.1% vs 9.9%; nominal p=0.0012). Of patients with PtGA>20 at baseline, more achieved PtGA≤20 at week 16 with apremilast versus placebo (28.5% vs 13.0%; nominal p=0.0044). Of patients with HAQ-DI>0.5 at baseline,

more achieved HAQ-DI≤0.5 at week 16 with apremilast versus placebo (32.4% vs 19.0%; nominal p=0.0302). In the small number of patients with LEI>1 at baseline (placebo: n=27, apremilast: n=41), numerically greater proportions achieved LEI≤1 at week 16 with apremilast versus placebo, although this was not significant (53.1% vs 41.0%; nominal p=0.3815).

The proportion of patients achieving MDA at week 16 was consistent with rates of MDA-Joints. A higher proportion of patients receiving apremilast (30.7%) achieved MDA (all joints) than patients receiving placebo (15.1%; nominal p=0.0026) (figure 4).

In light of the more stringent definition of oligoarthritis as ≤4 active joints,[8] we assessed outcomes in a subgroup of the FOREMOST population that met this definition (n=268/308, 87.0%). Clinical characteristics were similar between patients with ≤4 active joints at baseline and patients with >4 active joints (online supplemental table 2). MDA-Joints response rates (based on sentinel or all joints) were similar in this population compared with the overall study population (online supplemental figure 6).

More patients in the placebo group progressed from a baseline total active joint count ≤4 to a total active joint count >4 at week 16 than patients in the apremilast group, with separation between the two groups observed at the week 12 study visit (data are as observed; figure 5).

Safety

TEAEs were reported in 59.3% of patients taking apremilast and 47.1% of patients taking placebo (table 3). The most frequently reported (≥5% of patients in either group) adverse events were diarrhoea (apremilast: 23.0%; placebo: 10.6%), nausea (apremilast: 10.8%; placebo: 3.8%) and headache (apremilast: 7.8%; placebo: 2.9%). The incidence of severe TEAEs was similar with apremilast (3.9% of patients) and placebo (3.8% of patients). The incidence of serious TEAEs was similar with apremilast (4.4% of patients) and placebo (5.8% of patients). The proportions of patients with TEAEs leading to drug interruption were 7.8% with apremilast and 2.9% with placebo. TEAEs leading to drug withdrawal occurred in 10.3% of apremilast patients and 6.7% of placebo patients. The most common TEAEs (occurring in >2 patients) leading to withdrawal were diarrhoea (apremilast: 2.5%; placebo: 1.0%), nausea (apremilast: 2.9%; placebo: 0.0%) and fatigue (apremilast: 1.5%; placebo: 0.0%). Two deaths were reported during the study in the apremilast group and none in the placebo group. One patient died of sudden cardiac death 2 months after initiation of apremilast. The other patient died of anoxic brain injury following a planned routine abdominal herniorrhaphy, 88 days after the last dose of apremilast. Both deaths were assessed by the study investigators as not related to the study drug. These two deaths were not adjudicated.

DISCUSSION

Clinical trial data to support treatment guidelines for oligoarticular PsA are currently limited. FOREMOST is, to our knowledge, the first large, randomised, placebo-controlled trial only enrolling patients with oligoarticular PsA and provides valuable information on how patients with early disease and limited joint involvement respond to apremilast treatment.

The FOREMOST study enrolled patients with PsA with limited joint involvement and early disease, despite prior treatment with NSAIDs or ≤2 csDMARDs. At baseline, the vast majority of patients had ≤4 active joints and mean disease duration was 10 months. More patients achieved the primary endpoint (MDA-Joints) with apremilast versus placebo when evaluated by sentinel joints, with a treatment difference of 18.5%. When evaluated by all joints, the rate of MDA-Joints was 21.3% with apremilast, with a consistent treatment benefit versus placebo. Apremilast-treated patients showed a higher level of benefit in the different dimensions of the MDA score, an overall higher level of disease activity control as measured by cDAPSA and PASDAS, and better patient-reported outcomes. TEAEs were consistent with the known apremilast safety profile and no new safety signals were observed.[12–15] Although there were two deaths in the apremilast group during this study, they were not suspected to be related

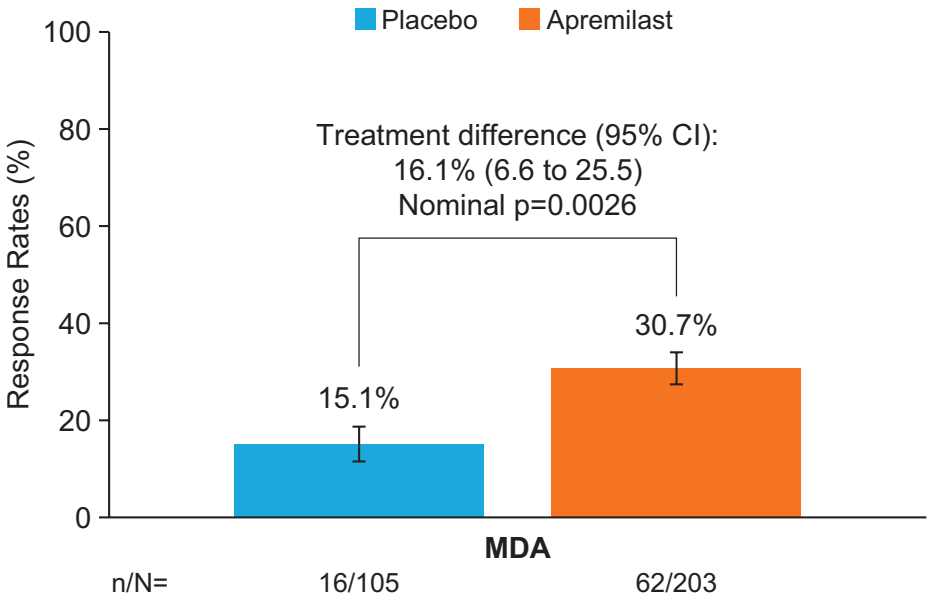

Figure 4 Proportion of patients achieving MDA at week 16. FAS. Based on all joints. Error bars represent SE. CI, confidence interval; FAS, full analysis set; MDA, minimal disease activity; SE, standard error.

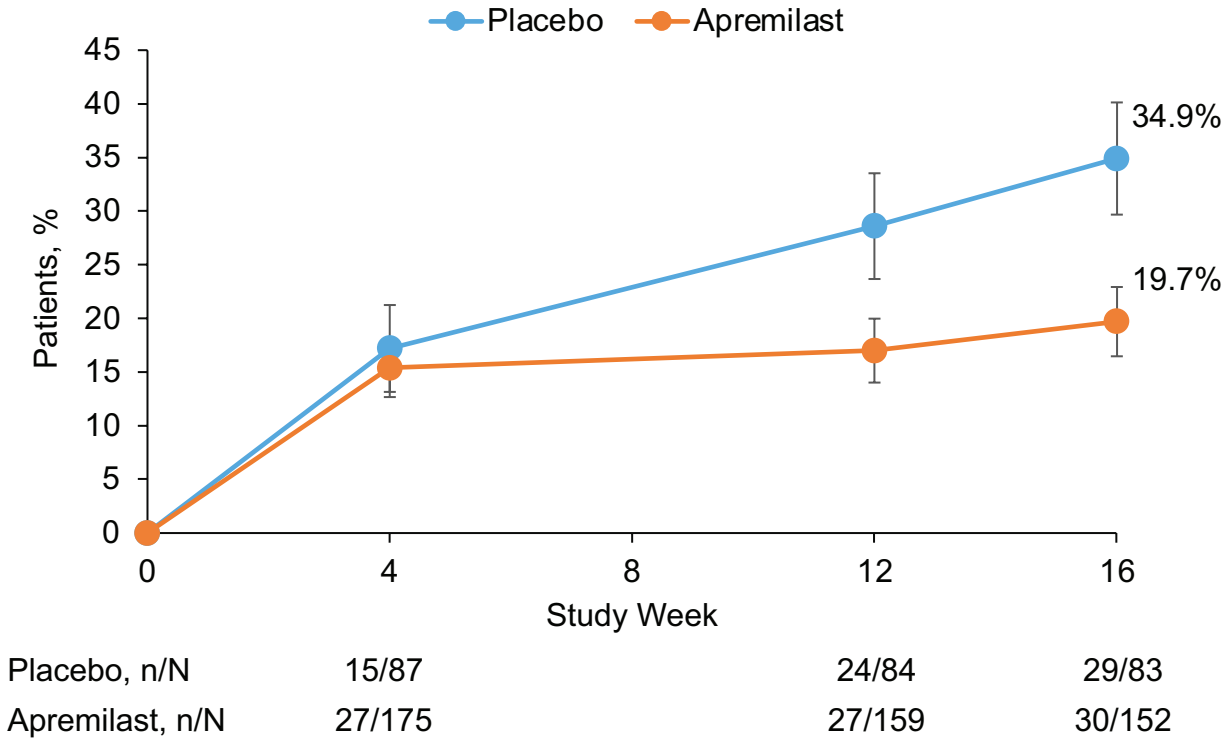

Figure 5 Proportion of patients who progressed to active joint count >4 among patients with ≤4 active joints at baseline. FAS with ≤4 active joints at baseline. Error bars represent SE based on all joints. Data are as observed. FAS, full analysis set; SE, standard error.

to apremilast treatment. According to a pooled analysis of 15 randomised, placebo-controlled trials of apremilast including 4763 patients, 9 treatment-emergent deaths were reported during apremilast exposure. Only one was suspected by the investigator to be related to apremilast.[18]

Separation between the placebo and apremilast groups was seen for both mean SJC and mean TJC over time. We also found that in the placebo arm, approximately 35% of patients with ≤4 active joints at baseline developed an active joint count >4 after 16 weeks. In contrast, 20% of patients with ≤4 active joints at baseline receiving apremilast developed a joint count >4 over 16 weeks. SJC≤1 was achieved by 69.0% of placebo patients at week 16 and was not significantly different from apremilast response rates (74.0%) when evaluated by sentinel joints. This may be due to the low median SJC at baseline (2.0 with placebo, 3.0 with apremilast). Due to limited knowledge of disease evolution in patients with early oligoarticular PsA, sentinel joints were considered in the study protocol when defining primary and other secondary endpoints. However, evaluation by all joints is clinically relevant as it considers the development of arthritis in new joints. When evaluating all joints, overall response rates were lower than those observed with sentinel joints but still significantly greater with apremilast than with placebo. These results may reflect a recently diagnosed population whose disease presentation is still evolving, as well as the waxing and waning course of the disease.

Oligoarticular PsA is highly prevalent in clinical practice, present in up to 50% of patients in certain cohorts.[3 4] It is the most frequent clinical pattern reported in early disease, and it has been shown to be a less erosive form of PsA.[19 20] EULAR recommendations emphasise the value of earlier, more aggressive treatment in patients with oligoarthritis.[8] The FOREMOST study illustrates the risk of undertreatment for progression from oligoarticular to polyarticular disease, arguing for earlier and more proactive intervention for oligoarthritis and the value of apremilast in this approach.

The need for treatment optimisation in patients with oligoarticular PsA is supported by our observations of early oligoarticular disease in FOREMOST compared with those of the phase 3 PALACE trials, which required ≥3 swollen and ≥3 tender joints.[12 14 15] Mean TJC and SJC were much lower in FOREMOST (3.2 and 2.6, respectively) than in the PALACE trials (18.0–23.3 and 9.2–12.8, respectively).

Table 3 Summary of safety through week 24

	Placebo (n=104*)	Apremilast (n=204*)
Any TEAE, n (%)	49 (47.1)	121 (59.3)
Any drug-related TEAE, n (%)	20 (19.2)	67 (32.8)
Any severe TEAE, n (%)	4 (3.8)	8 (3.9)
Any serious TEAE, n (%)	6 (5.8)	9 (4.4)
TEAEs leading to drug withdrawal, n (%)	7 (6.7)	21 (10.3)
Deaths, n (%)	0 (0.0)	2 (1.0)†
TEAEs occurring in ≥5% of patients, n (%)		
Diarrhoea	11 (10.6)	47 (23.0)
Nausea	4 (3.8)	22 (10.8)
Headache	3 (2.9)	16 (7.8)

*Patients were included in the treatment group for the treatment they actually received. One patient randomised to the placebo group received apremilast and was included in the placebo group for the FAS and the apremilast group for the safety analysis set.
†Two deaths reported (sudden cardiac death and anoxic brain injury following a planned routine abdominal herniorrhaphy) in the apremilast group were not related to study drug as assessed by the investigator. Safety analysis set. Includes data through week 16/visit 5 for placebo-treated patients who escaped early and data up to week 24 for all other patients.
FAS, full analysis set; TEAE, treatment-emergent adverse event.

Despite this, baseline PtGA scores were similar between FOREMOST (51.3) and the PALACE trials (52.3–58.8).[12 14 15] However, the Physician's Global Assessment was lower in the FOREMOST population (42.6) than in PALACE 1–4 (51.7–56.1). Baseline HAQ-DI was similar between patients in FOREMOST (1.0) and in PALACE 1–4 (1.0–1.2).[12–15] These observations highlight the discordance between patient and physician assessments of disease, as well as how oligoarticular disease appears to have a similar impact on HAQ-DI as polyarticular PsA despite fewer joints involved. However, it should be considered that there may be an index event bias and patients with greater pain may be disproportionately driven to seek care, resulting in higher HAQ-DI scores. Thus, not all oligoarticular patients in clinical practice may have been captured in the FOREMOST study. A post hoc analysis evaluating secukinumab efficacy in patients with 1–4 swollen and 1–4 tender joints in a pooled analysis of 5 phase 3 trials found similar levels of disease burden and demonstrated potential for oligoarticular patients to benefit from systemic treatment, in line with results from FOREMOST.[21]

Due to the limited studies in patients with early oligoarticular PsA, the design of this study posed some challenges. At the time of protocol development, and to an extent at the time of this publication, there was no formal consensus on the definition of oligoarticular PsA. As a result, the study's inclusion criteria allowed for patients with up to eight inflamed joints (≤4 swollen and≤4 tender). Nonetheless, almost 90% of the patients in FOREMOST fit a more stringent definition of ≤4 actively inflamed joints.[8] Assessment of sentinel joints was chosen to follow joints initially impacted at baseline and evaluate differences at 16 weeks, as little information was available on the course of disease in patients with early oligoarticular PsA. In addition, an examination of all joints was performed to comprehensively assess disease status and identify any extension of arthritis involvement over the study period. Apremilast showed consistent benefit over placebo whether assessed by sentinel joints or all joints. FOREMOST enrolled patients with short disease duration and limited joint involvement. Certain dimensions of psoriatic disease might be underrepresented in the study population, and the full variety of disease severity in patients with oligoarticular PsA may not be captured in the study. Because this is the first global prospective study in oligoarticular PsA and the only to use MDA-Joints, comparisons to other studies are unavailable. Although the inclusion criterion was extended from 2 to 5 years' disease duration, mean disease duration was 10 months, median was 6 months and the third quartile was around 12 months, showing that most patients in FOREMOST had PsA of <1 year's duration. This is clinically relevant, as patients likely had lower chances of changing from an initial polyarticular phenotype to an oligoarticular one. Although this provides valuable data on how early disease responds to apremilast treatment, the results may not be applicable to patients with longstanding oligoarticular PsA who may have cycled through multiple conventional and biologic DMARD therapies.

In conclusion, FOREMOST is unique as a global randomised controlled trial exclusively studying early oligoarticular PsA. We report the primary results of FOREMOST and show better disease control was achieved with apremilast, with greater MDA-Joints response compared with placebo at 16 weeks. These findings show apremilast treatment of early oligoarticular PsA improved clinical and patient-reported outcomes. This study may inform the appropriate management of disease in these patients, but further studies are needed.

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Patient consent for publication Not applicable.

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consent before study-related procedures. Participants gave informed consent to participate in the study before taking part.

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