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A Phase III Randomized Study of Apremilast, an Oral Phosphodiesterase 4 Inhibitor, for Active Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To evaluate the efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with active ankylosing spondylitis (AS).

Methods. This phase III, multicenter, double-blind, placebo-controlled study (ClinicalTrials.gov: NCT01583374) randomized patients with active AS (1:1:1) to placebo, apremilast 20 mg twice daily, or apremilast 30 mg twice daily for 24 weeks, followed by a long-term extension phase (up to 5 yrs). The primary endpoint was Assessment of the Spondyloarthritis international Society 20 (ASAS20) response at Week 16. The effect of treatment on radiographic outcomes after 104 weeks was assessed using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).

Results. In total, 490 patients with active AS were randomized in the study (placebo: n = 164; apremilast 20 mg twice daily: n = 163; apremilast 30 mg twice daily: n = 163). The primary endpoint of ASAS20 response at Week 16 was not met (placebo: 37%; apremilast 20 mg twice daily: 35%; apremilast 30 mg twice daily: 33%; $P = 0.44$ vs placebo). At Week 104, mean (SD) changes from baseline in mSASSS were 0.83 (3.6), 0.98 (2.2), and 0.57 (1.9) in patients initially randomized to placebo, apremilast 20 mg twice daily, and apremilast 30 mg twice daily, respectively. The most frequently reported adverse events through Week 104 were diarrhea, nasopharyngitis, upper respiratory infection, and nausea.

Conclusion. No clinical benefit was observed with apremilast treatment in patients with active AS. The safety and tolerability of apremilast were consistent with its known profile.

Key Indexing Terms: ankylosing spondylitis, apremilast, autoimmune diseases, biologic therapy, clinical trials

Ankylosing spondylitis (AS), which is characterized by back pain and sacroiliitis, can result in bone formation and spinal vertebrae fusion.[1,2] Nonsteroidal antiinflammatory drugs (NSAIDs) are recommended as first-line treatment for AS. Conventional disease-modifying antirheumatic drugs (cDMARDs) have not been effective in axial disease.[3] Biologic DMARDs (bDMARDs) are recommended when disease activity is persistently high despite adequate NSAID or cDMARD trials. Current practice starts with a tumor necrosis factor (TNF) inhibitor.[4,5]

Apremilast is an oral phosphodiesterase 4 (PDE4) inhibitor available for treating adult patients with plaque psoriasis, active psoriatic arthritis, or active Behçet syndrome.[6] PDE4 inhibition elevates intracellular cyclic adenosine monophosphate (cAMP) levels, which in turn downregulate inflammatory responses by modulating expression of TNF-α, interleukin (IL)-23, IL-17, and other proinflammatory cytokines.[7,8] Apremilast has been associated with increases in antiinflammatory mediators, including IL-10 and IL-1 receptor antagonists.[8,9]

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In a phase II study of 36 patients, apremilast 30 mg twice daily was associated with improvements in AS symptoms over 12 weeks, although patients did not appear to reach maximum clinical response at Week 12.[10] This phase III, randomized, double-blind study evaluated apremilast efficacy and safety in patients with documented AS. It included a 24-week, placebo-controlled period with long-term extension up to 5 years. These are the first results reported through 2 years.

METHODS

Study design. AS-001 (ClinicalTrials.gov: NCT01583374) included a 6-week screening period and 24-week, randomized, double-blind, placebo-controlled period with long-term extension up to 5 years. The study was conducted between May 2012 and October 2018 at 88 sites in North America, Europe, Australia, South Africa, and Russia. Patients were randomized (1:1:1) to placebo, apremilast 20 mg twice daily, or apremilast 30 mg twice daily for 24 weeks, stratified by C-reactive protein (CRP) concentration at screening (normal: ≤ 1.5 mg/dL; elevated: > 1.5 mg/dL) and baseline Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[11] score (< 6.0 and ≥ 6.0). A 7-day stepwise treatment titration schedule was implemented to decrease dose-related gastrointestinal effects associated with this drug class. At Week 16, patients receiving placebo or apremilast 20 mg without ≥ 20% or ≥ 1 unit improvement from baseline in at least 2 of the 4 domains of the Assessment of Spondyloarthritis international Society 20 (ASAS20)[12] response criteria were switched to apremilast 30 mg in a blinded manner; patients initially receiving apremilast 30 mg continued on that treatment.

At Week 24, patients could enter a long-term extension phase up to an additional 4.5 years (236 weeks). All remaining placebo patients were switched to apremilast 30 mg.

This study was conducted in accordance with the International Council on Harmonisation guidelines and Declaration of Helsinki's general ethical principles and received approval from institutional review boards (IRBs) or independent ethics committees at each study site (main IRB approval number 12/WM/0215). Informed written consent was obtained from patients before any study-related procedure. Detailed information related to IRBs can be found in the Supplementary Material (available with the online version of this article).

Patients. Eligible patients were aged ≥ 18 years with AS fulfilling modified New York criteria (radiographic criterion by a central reader; at least 1 clinical criterion).[13] Patients had active axial disease symptoms at screening and baseline (randomization), determined by BASDAI numerical rating scale (NRS) scores ≥ 4 and total back pain NRS scores ≥ 4.

Comedications were allowed if the corticosteroid (≤ 10 mg/day or prednisone equivalent at stable dose for ≥ 28 days) or cDMARD (methotrexate ≤ 25 mg/week, sulfasalazine (SSZ) ≤ 3 g/day, hydroxychloroquine ≤ 400 mg/day, or chloroquine ≤ 250 mg/day for ≥ 16 weeks) dose was stable at randomization and maintained through the 24-week placebo-controlled period. NSAIDs and/or cyclooxygenase-2 inhibitors, acetaminophen/paracetamol (≤ 2600 mg/day), and opioid analgesics (≤ 30 mg oral morphine or equivalent/day) were allowed.

Key exclusion criteria were prior treatment with bDMARD for AS; any alkylating agents or total lymphoid irradiation; intraarticular or parenteral corticosteroid 6 weeks before randomization; autoimmune disease or inflammatory joint disease diagnosis other than AS; uncontrolled, severe psoriasis (body surface area involvement > 10%); and active inflammatory bowel disease, uncontrolled uveitis, or any poorly controlled disease. Patients with history of suicide attempt before randomization or major psychiatric illness requiring hospitalization within 3 years were excluded.

The study protocol, amendments, and informed consent form (ICF) were approved by the IRB at each investigational site or by a central review board, which included public and patient representation. The ICF provided patients with information about the study and expected visits; patients signed the ICF at screening and were expected to have a randomization visit, scheduled on-study visits, and poststudy follow-up visit. Patients were randomized if the investigator confirmed they had active AS and met inclusion/exclusion criteria after the 6-week screening phase. Patients were asked about any treatment-emergent adverse events (TEAEs) and completed health assessment questionnaires throughout the study. Safety and efficacy monitoring were performed by an independent, external data monitoring committee.

Clinical outcomes measures. The primary endpoint was the proportion of patients achieving an ASAS20 response at Week 16, defined as improvement from baseline of ≥ 20% and ≥ 1 unit in at least 3 of the 4 ASAS20 domains on a scale of 0–10 units and no worsening from baseline of ≥ 20% and ≥ 1 unit in the remaining ASAS20 domain.

Secondary endpoints included ASAS20 response at Week 24 and changes from baseline scores at Week 24 in total BASDAI, Bath Ankylosing Spondylitis Functional Index[14] (BASFI; 0–10 range, higher score indicates reduced function), Ankylosing Spondylitis Quality of Life questionnaire (ASQoL; 0–18 range, higher scores indicate worse QoL), 36-item Short-Form Health Survey version 2 physical component summary (SF-36v2 PCS; 0–100 range for individual domain scores, with normative physical composite summary score of 50 and SD of 10; higher scores indicate better health), and total Bath Ankylosing Spondylitis Metrology Index (BASMI)-Linear (0–10 range; higher scores indicate more severe spinal mobility limitation). Exploratory endpoints included proportion of patients achieving an ASAS40, ASAS 5/6 (≥ 20% improvement in 5 of the 6 domains), ASAS partial remission (≤ 2 on 0–10 unit NRS in 4 domains of ASAS response criteria), Ankylosing Spondylitis Disease Activity Score[15] (ASDAS; higher scores indicate greater disease activity), Maastricht Ankylosing Spondylitis Enthesitis Score[16] (MASES; ≥ 20% improvement in scores), and mean change in CRP levels among all patients and in those with baseline CRP > 1.5 mg/dL.

Imaging outcomes. Radiographic analyses were based on changes from baseline in modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)[17] at Week 104 for all patients with radiographic data at this time point. Lateral-view radiographs of cervical and lumbar spines were obtained at baseline and after 2 years in all patients. Radiographs were mixed and scored by 2 trained, independent readers blinded to timepoints, study, and treatment using mSASSS; average scores from 2 readers were reported. Magnetic resonance imaging (MRI) of the entire spine and sacroiliac joints was conducted at Weeks 16, 52, and 104 in a subset of patients (those participating in the MRI substudy who had a baseline MRI) using the Berlin method of Ankylosing Spondylitis spine MRI score for activity[18] (Berlin-modified ASspiMRI-a) and Spondyloarthritis Research Consortium of Canada[19] (SPARCC) criteria for the sacroiliac joint (data only shown for Week 104). For the MRI substudy, assessments were conducted at selected sites with adequate MRI capabilities; patients signed a separate ICF. At least 2 trained independent central reviewers evaluated each case (double review) in a blinded fashion. If adjudication was required, a third reviewer completed an independent assessment. Total SPARCC scores (total possible score: 72) and total Berlin-modified ASspiMRI-a scores (total possible score: 69) were calculated for each time point.

Comparison to OASIS. Given the lack of control for radiographic assessments over 2 years, a posthoc analysis utilized the Outcome Assessments in Ankylosing Spondylitis International Study (OASIS) database to further assess radiographic progression with a historical control group. OASIS is a large prevalence cohort with AS from rheumatology centers in Belgium, France, and the Netherlands who received best standard of care initiated in 1996, before bDMARDs were available.[20] Baseline and 2-year radiographs from OASIS (N = 186) have been used as comparators to assess radiographic progression with TNF inhibitors.[20,21,22] Radiographic results from patients in this study with baseline and Week 104 spinal radiographic images (n = 286) were compared with data from the full OASIS cohort and

from a matched subset of patients meeting key active AS eligibility criteria (baseline BASDAI ≥ 4, total back pain ≥ 4). In a second reading, all radiographs were mixed with films from OASIS as a control cohort and read in a similar manner as described.

Safety assessments. Safety endpoints included TEAEs, discontinuations due to TEAEs, and clinically significant changes in physical examination, vital signs, or laboratory findings.

Statistical analyses. A sample size of 456 patients (152 patients/treatment group) was calculated to have 90% power to detect an absolute treatment difference of 17.5% between placebo (25.0%) and apremilast (combined; 42.5%) for the proportion of patients achieving ASAS20 responses. The safety population (safety analyses) and modified intention-to-treat (mITT) population (efficacy analyses) included all patients who were randomized and received at least 1 dose of study drug.

Proportions of patients achieving an ASAS20 response at Week 16 (primary endpoint) between the apremilast 30 mg and placebo groups were compared using the Cochran-Mantel-Haenszel test, adjusting for the strata of high-sensitivity CRP concentration from screening (≤ 1.5/> 1.5 mg/dL) and baseline BASDAI score (< 6.0/≥ 6.0). Patients prematurely discontinuing study drug due to lack of efficacy before the Week 16 evaluation were considered ASAS20 nonresponders. For any missing data in ≥ 1 ASAS domains, ASAS20 response was derived using the last-observed value(s) for the missing domain(s) at Week 16. For secondary Week 24 response endpoints, the same approach of defining nonresponders applied in the primary endpoint was used for patients meeting early escape criteria at Week 16. For continuous endpoints with missing values, last observation carried forward methodology was used for missing values; for patients who escaped early at Week 16, baseline values were used for imputing missing values at Week 16 or 24. Statistical tests were conducted between groups for predefined primary and secondary endpoints in a hierarchical manner. A gatekeeping procedure using serial testing was applied to adjust for multiplicity. Efficacy endpoints beyond Week 24 were summarized using descriptive statistics. Based on data as observed, categorical data were summarized using frequency counts; continuous data were summarized by change from baseline. Two-sided 95% CIs were provided as appropriate.

Change from baseline in mSASSS at Week 104 was calculated for the placebo, apremilast 20 mg, and apremilast 30 mg groups (per randomization). Comparisons to the complete OASIS dataset (full cohort) and OASIS-matched cohort were conducted at the $\alpha = 0.050$ (2-sided) level. An analysis of covariance model was used, including van der Waerden normal scores of change from baseline in mSASSS with the response variable with group/cohort as a factor and van der Waerden normal scores of the baseline value as a covariate. Change from baseline in mSASSS to Week 104 was summarized for the apremilast and OASIS populations. Radiographic progression was defined as change in mSASSS > 0 in the AS-001 Week 104 analysis and change in mSASSS ≥ 1 in the OASIS analysis.

RESULTS

Patients. In total, 490 patients were randomized initially to placebo (n = 164), apremilast 20 mg (n = 163), or apremilast 30 mg (n = 163), of whom 58%, 66%, and 66% completed Week 104, respectively. Patient disposition at Weeks 16, 24, 52, and 104, and reasons for discontinuation are shown in Figure 1. At Week 16, a total of 149 patients met early escape criteria (apremilast 20 mg/30 mg: n = 49 [30%]; apremilast 30 mg/30 mg: n = 49 [30%]; placebo/apremilast 30 mg: n = 51 [31%]). Baseline patient demographics and clinical characteristics represented a typical AS population with active disease and were generally comparable across treatment groups (Table 1). Mean (median) duration of AS (since diagnosis) was 10.6 (7.2) years, with 38.4% of patients having a > 10-year duration of AS before study entry. Mean BASDAI score was 6.4, indicating active disease, and mean BASMI-Linear score was 4.47, indicating moderate to severe limitation. Overall, 71% of patients had prior treatment with at least 1 conventional AS therapy, such as corticosteroids, NSAIDs, or DMARDs (Table 1); 28% were taking at least 1 DMARD at baseline, with most receiving SSZ.

Efficacy. The primary endpoint of ASAS20 at Week 16 was not met. At Week 16, similar ASAS20 responses were achieved: 37% (60/164) of patients receiving placebo, 35% (57/163) receiving apremilast 20 mg, and 33% (53/163) receiving apremilast 30 mg (mITT population, $P = 0.44$; Table 2).

ASAS20 response rates were generally similar at Week 24: 32% (52/164) with placebo, 36% (59/163) with apremilast 20 mg, and 34% (55/163) with apremilast 30 mg. ASAS40 response rates (exploratory endpoint) were achieved by 18% of patients receiving placebo, 20% receiving apremilast 20 mg, and 15% receiving apremilast 30 mg. Additional secondary endpoints for disease activity and self-reported health-related outcomes at Week 24 are summarized (Table 2). Compared with placebo, no significant differences were observed with apremilast 30 mg in change from baseline in BASDAI, BASFI, ASQoL, SF-36v2 PCS, BASMI-Linear scores, or ASDAS. Proportions of patients achieving an ASAS 5/6 response, ASAS partial remission, and ≥ 20% improvement in enthesitis by MASES were similar among placebo and apremilast treatment groups. No significant change in CRP was observed with apremilast vs placebo in all patients or in patients with baseline CRP > 1.5 mg/dL.

Week 104 ASAS20 response rates for patients remaining in the study were generally comparable across groups: 69.5% (66/95), 57.8% (63/109), and 53.3% (57/107) for those initially randomized to placebo, apremilast 20 mg, and apremilast 30 mg, respectively.

Imaging assessment. The radiographic subset included 92 patients initially receiving placebo, 104 receiving apremilast 20 mg, and 101 receiving apremilast 30 mg. Baseline demographics and clinical characteristics of patients with radiographic data were similar to the overall study population. Mean baseline mSASSS was slightly higher in the apremilast 30 mg group vs the group initially randomized to placebo (baseline mSASSS: 12.83, 15.69, and 15.16 for placebo, 20 mg, and 30 mg, respectively). At Week 104, mean (SD) changes from baseline in mSASSS were 0.83 (3.6), 0.98 (2.2), and 0.57 (1.9) in patients initially randomized to placebo, apremilast 20 mg, and apremilast 30 mg, respectively (Table 3). Cumulative probability of changes in mSASSS from baseline to Week 104 showed 71% of patients receiving placebo, 67% receiving apremilast 20 mg, and 75% receiving apremilast 30 mg did not have radiographic progression (Table 3; Supplementary Figure 1, available with the online version of this article).

Mean (SD) MRI Berlin-modified ASspiMRI-a scores at baseline were 4.6 (7.0), 4.0 (5.7), and 4.1 (4.5) in the placebo (n = 22), apremilast 20 mg (n = 14), and apremilast 30 mg (n = 18) groups, respectively. At Week 104, mean (SD) change from baseline in MRI Berlin-modified ASspiMRI-a scores were −0.6 (3.7), −2.0 (3.2), and −1.2 (1.7), respectively. Mean (SD) MRI

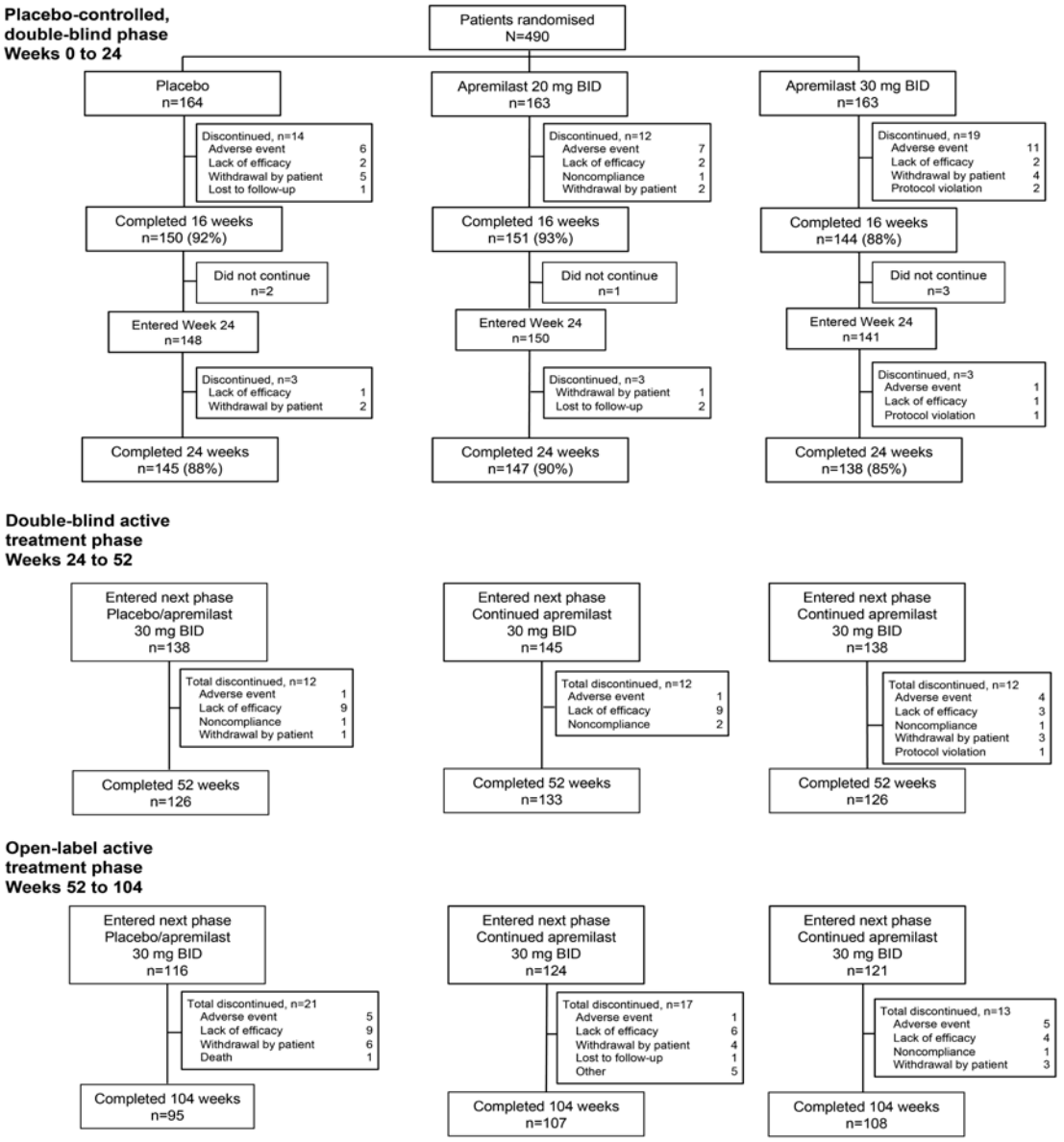

Figure 1. Patient disposition through Week 104.

SPARCC scores at baseline were 4.4 (9.7), 6.0 (10.3), and 5.7 (9.4) in the placebo (n = 30), apremilast 20 mg (n = 24), and apremilast 30 mg (n = 23) groups, respectively. At Week 104, mean (SD) change from baseline in MRI SPARCC scores were −1.7 (5.7), −1.9 (5.5), and −2.1 (6.4), respectively (data not shown).

Comparison to OASIS. Compared with the OASIS-matched group, apremilast cohorts had higher body weight, shorter AS disease duration, and higher DMARD usage. Baseline disease activity measures were slightly greater in the apremilast cohorts than the OASIS-matched cohort. Mean [SD] baseline mSASSS for the OASIS-matched and AS-001 cohorts were not similar (7.4 [10.8] and 12.3 [17.9], respectively). Baseline characteristics of the OASIS-matched and AS-001 cohorts are shown in Supplementary Table 1 (available with the online version of this article). The OASIS-matched cohort had milder disease at baseline than AS-001 patients. Patients in AS-001 had a greater change in mSASSS from baseline and a lower proportion of patients without radiographic progression over 2 years (70.4% vs 82.1% [OASIS matched] and 76.4% [OASIS overall]; second reading of films; Table 4).

Safety. At Week 24, at least 1 TEAE was observed in half of patients receiving placebo (82/164; 50%), apremilast 20 mg (89/163; 55%), and apremilast 30 mg (85/163; 52%). Rates of serious TEAEs (SAEs) were 0.6% with placebo (n = 1), 1.8% with apremilast 20 mg (n = 3), and 3.7% with apremilast 30 mg (n = 6). SAEs included malignant melanoma (placebo); uveitis, alcoholic liver disease, urinary calculus, and renal colic (apremilast 20 mg); and AS exacerbation, chest pain, depression, vertigo, sick sinus syndrome, abdominal hernia, upper abdominal pain, and postoperative cardiac function disturbance (apremilast 30 mg). Rates of TEAEs leading to discontinuation were < 10%

Table 1. Baseline demographics and clinical characteristics (mITT population[a]).

	Placebo, n = 164	Apremilast 20 mg Twice Daily, n = 163	Apremilast 30 mg Twice Daily, n = 163
Age, yrs, mean (SD)	44.0 (12.9)	45.2 (11.9)	44.8 (11.8)
Female, n (%)	40 (24.4)	42 (25.8)	56 (34.4)
Race, n (%)			
White	158 (96.3)	154 (94.5)	158 (96.9)
Asian	2 (1.2)	2 (1.2)	0 (0.0)
Black	1 (0.6)	2 (1.2)	2 (1.2)
Pacific Islander	1 (0.6)	0 (0.0)	0 (0.0)
Other	1 (0.6)	2 (1.2)	3 (1.8)
Missing	1 (0.6)	3 (1.8)	0 (0.0)
Region, n (%)			
North America	26 (15.9)	26 (16.0)	24 (14.7)
Europe	114 (69.5)	115 (70.6)	125 (76.7)
Rest of world	24 (14.6)	22 (13.5)	14 (8.6)
Weight, kg, mean (SD)	80.3 (17.7)	79.4 (15.3)	79.8 (17.2)
BMI, kg/m^2, mean (SD)	26.9 (5.4)	27.0 (4.5)	27.0 (4.8)
AS duration since diagnosis[b], yrs, mean (SD)	10.4 (10.4)	11.1 (11.3)	10.3 (9.9)
CRP category at screening, n (%)			
Normal (≤ 1.5 mg/dL)	118 (72.0)	117 (71.8)	118 (72.4)
Elevated (> 1.5 mg/dL)	46 (28.0)	46 (28.2)	45 (27.6)
Positive HLA-B27, n (%)	140 (85.4)	136 (83.4)	131 (80.4)
Prior conventional therapy use[c], n (%)	114 (69.5)	118 (72.4)	118 (72.4)
Prior DMARD use, n (%)	49 (29.9)	47 (28.8)	61 (37.4)
MTX (mean dose: 14.6 mg/wk)	15 (9.1)	17 (10.4)	13 (8.0)
SSZ (mean dose: 1.9 g/day)	39 (23.8)	32 (19.6)	46 (28.2)
HCQ (mean dose: 200 mg/day)	0 (0.0)	1 (0.6)	1 (0.6)
Other (not specified)	0 (0.0)	0 (0.0)	3 (1.8)
Glucocorticoid (mean dose: 5.5 mg/day), n (%)			
With baseline DMARD use	8 (4.9)	4 (2.5)	6 (3.7)
Without baseline DMARD use	1 (0.6)	1 (0.6)	5 (3.1)
NSAID use, n (%)	145 (88.4)	128 (78.5)	133 (81.6)
Narcotic and/or analgesic use[d], n (%)	11 (6.7)	20 (12.3)	18 (11.0)
PtGA (0–10, NRS), mean (SD)	7.2 (1.7)	7.0 (1.8)	6.9 (1.7)
Total back pain (0–10, NRS), mean (SD)	7.2 (1.5)	7.1 (1.5)	6.9 (1.7)
ASDAS, mean (SD)	3.7 (0.8)	3.6 (0.9)	3.6 (0.8)
BASFI score (0–10, NRS), mean (SD)	5.8 (2.2)	5.8 (2.1)	5.7 (2.1)
BASDAI score (0–10, NRS), mean (SD)	6.5 (1.3)	6.5 (1.4)	6.4 (1.4)
BASMI score (0–10, NRS), mean (SD)	4.4 (1.6)	4.6 (1.7)	4.4 (1.7)
ASQoL score (0–18), mean (SD)	9.1 (4.6)	8.4 (4.5)	8.6 (4.9)
SF-36v2 PCS, mean (SD)	32.6 (7.8)	31.9 (8.6)	32.2 (8.8)
SF-36v2 MCS, mean (SD)	46.9 (10.4)	49.5 (8.9)	47.5 (9.5)

[a] The n reflects the number of modified intention-to-treat patients; actual number of patients available for each parameter may vary. [b] Low back pain and stiffness duration. [c] Includes corticosteroids, DMARDs, and NSAIDs. [d] Baseline medications used ≤ 28 days on/before the first dose of investigational drug; use of permitted medications must have continued concomitantly per protocol. AS: ankylosing spondylitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life questionnaire; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BMI: body mass index; CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drug; HCQ: hydroxychloroquine; MCS: mental component summary; mITT: modified intention to treat; MTX: methotrexate; NRS: numerical rating scale; NSAID: nonsteroidal antiinflammatory drug; PCS: physical component summary; PtGA: patient global assessment of disease activity; SF-36v2: 36-item Short Form Health Survey version 2; SSZ: sulfasalazine.

in all treatment groups (placebo: 4%; apremilast 20 mg: 6%; apremilast 30 mg: 7%). At Week 24, the most common TEAEs observed in any treatment group (placebo, apremilast 20 mg, and apremilast 30 mg) were diarrhea (3%, 12%, and 9%, respectively), headache (5%, 6%, and 10%, respectively), and nausea (4%, 6%, and 9%, respectively; Table 5).

At Week 104, at least 1 TEAE was observed in 104 (64%) patients receiving apremilast 20 mg, 42 (58%) receiving apremilast 20 mg/30 mg, and in 219 (72%) receiving apremilast 30 mg. Rates of SAEs were 6% in the apremilast 20 mg group (n = 10), 6% in the apremilast 20/30 mg group (n = 4), and 9% in the apremilast 30 mg group (n = 28). Rates of TEAEs

Table 2. Summary of primary, secondary, and exploratory efficacy endpoints (mITT population[a]).

Endpoint	Placebo, n = 164	Apremilast, mg: 20 mg Twice Daily, n = 163	Apremilast, mg: 30 mg Twice Daily, n = 163	Difference for Apremilast 30 mg vs Placebo (95% CI)	*P* for Apremilast 30 mg vs Placebo
Primary endpoint (Week 16)					
ASAS20 response, n (%)	60 (37)	57 (35)	53 (33)	−4.1 (−14.3, 6.2)	0.44
Secondary endpoints (Week 24)					
ASAS20 response, n (%)	52 (32)	59 (36)	55 (34)	2.0 (−8.1, 12.2)	0.70
Change from baseline in BASFI (0–10), LSM (SE)	−0.94 (0.14), (n = 164)	−1.11 (0.14), (n = 162)	−0.99 (0.14), (n = 160)	−0.05 (−0.41, 0.32)	0.80
Change from baseline in BASDAI (0–10), LSM (SE)	−1.21 (0.14), (n = 164)	−1.30 (0.14), (n = 162)	−1.18 (0.14), (n = 160)	0.03 (−0.33, 0.40)	0.86
Change from baseline in ASQoL (0–18), LSM (SE)	−1.77 (0.28), (n = 160)	−1.50 (0.28), (n = 161)	−1.52 (0.28), (n = 156)	0.25 (−0.49, 0.99)	0.51
Change from baseline in SF-36v2 PCS, LSM (SE)	3.50 (0.55), (n = 160)	3.46 (0.55), (n = 161)	3.79 (0.56), (n = 155)	0.29 (−1.18, 1.76)	0.70
Change from baseline in SF-36v2 MCS, LSM (SE)	1.93 (0.55), (n = 160)	1.09 (0.55), (n = 161)	1.07 (0.55), (n = 155)	−0.87 (−2.33, 0.59)	0.24
Change from baseline in BASMI-Linear, LSM (SE)	−0.19 (0.04), (n = 163)	−0.16 (0.04), (n = 162)	−0.13 (0.04), (n = 158)	0.06 (−0.06, 0.17)	0.33
Exploratory endpoints (Week 24)					
Proportion of patients achieving ASAS40 response, n (%)[b]	30 (18.3)	32 (19.6)	24 (14.7)	−3.6 (−11.5, 4.3)	0.39
ASAS5/6 response, n (%)	27 (17)	25 (15)	26 (16)	−0.5 (−8.4, 7.3)	0.90
ASAS partial response, n (%)	7 (4)	10 (6)	7 (4)	0 (−4.3, 4.4)	0.99
Change from baseline in ASDAS, LSM (SE)	−0.39 (0.06)	−0.47 (0.06)	−0.42 (0.06)	−0.03 (−0.19, −0.12)	0.71
≥ 20% Improvement in enthesitis by MASES, n/N (%)	52/117 (44)	46/113 (41)	42/101 (42)	−3.0 (−16.1, 10.1)	0.66
Mean (SE) change from baseline in CRP (mg/dL) in all patients	0.06 (0.09), (n = 164)	0.00 (0.09), (n = 163)	0.00 (0.09), (n = 163)	−0.07 (−0.31, 0.18)	0.60
Mean (SE) change from baseline in CRP in patients with baseline CRP > 1.5 mg/dL	0.08 (0.23), (n = 46)	−0.48 (0.23), (n = 46)	−0.01 (0.23), (n = 45)	−0.09 (−0.74, 0.56)	0.79

[a] Baseline observation carried forward for early escape or discontinuation due to lack of efficacy; last observation carried forward for other early discontinuation. [b] ASAS40 response criteria: included patient global Assessment of disease activity(0–10 units), total back pain, function (BASFI score), and inflammation (mean of BASDAI Questions #5 and #6 for morning stiffness), where 3 of 4 domains improved by ≥ 40% and ≥ 2 units on scale of 0–10 and no worsening in remaining domain. ASAS: Assessment of the Spondyloarthritis international Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life questionnaire; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI-Linear: Bath Ankylosing Spondylitis Metrology Index-Linear; CRP: C-reactive protein; LSM: least squares mean; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; MCS: mental component summary; mITT: modified intention to treat; PCS: physical component summary; SE: standard error; SF-36v2: 36-item Short Form Health Survey version 2.

leading to discontinuation were ≤ 10% in all treatment groups (apremilast 20 mg: 10%; apremilast 20/30 mg: 1%; apremilast 30 mg: 10%). Two deaths occurred during the study, including thrombotic cerebral infarction (n = 1; apremilast 20/30 mg) and cardiopulmonary arrest (n = 1; apremilast 30 mg). At Week 104, the most common TEAEs observed in any treatment group (apremilast 20 mg, apremilast 20/30 mg, and apremilast 30 mg) were diarrhea (15%, 4%, and 11%, respectively), nasopharyngitis (13%, 11%, and 15%, respectively), upper respiratory infection (8%, 7%, and 7%, respectively) and nausea (7%, 7%, and 8%, respectively; Table 5). Thirty-four patients (6.9%) had a medical history of uveitis. Among all patients, 17 (3.6%) reported uveitis during the apremilast-exposure period. Two patients (1 each in the apremilast 20 mg and 30 mg groups) had an SAE of uveitis; both had a history of uveitis.

DISCUSSION

This phase III study of patients with AS could not establish a treatment benefit for apremilast. The proportions of patients who achieved an ASAS20 response at Weeks 16 (primary endpoint) and 24 with apremilast and placebo were similar, indicating no improvement in signs or symptoms of AS. No significant differences were observed at Week 24 in other measures of disease activity, including changes from baseline in BASDAI, BASFI, BASMI-Linear, or ASDAS scores or CRP levels. In addition, no improvement was observed in health-related quality of life measures (ASQoL and SF-36v2 PCS). No differences were observed among treatment groups in MRI Berlin-modified ASspiMRI-a or MRI SPARCC scores at Week 104 vs baseline scores.

During the study, clinical safety and efficacy results were presented and provided at investigators' meetings to allow

Table 3. Change from baseline in radiographic mSASSS and proportion of patients with no radiographic progression at Week 104 (original reading of films).

	Placebo/Apremilast 30 mg Twice Daily, n = 92	Apremilast 20/20 mg and 20/30 mg Twice Daily, n = 104	Apremilast 30 mg/ 30 mg Twice Daily, n = 101	All, n = 297
Baseline mSASSS, mean (SD)	12.83 (18.63)	15.69 (19.65)	15.16 (20.75)	14.62 (19.70)
Change from baseline at Week 104, mean (SD)[a]	0.83 (3.57)	0.98 (2.18)	0.57 (1.86)	0.79 (2.60)
Proportion of patients with no radiographic progression[b], n (%)	65 (70.7)	70 (67.3)	76 (75.2)	211 (71.0)

[a] As observed. [b] Radiographic progression was defined as a change in mSASSS > 0. CRP: C-reactive protein; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score.

Table 4. Comparison of change from baseline in radiographic mSASSS at Week 104: AS-001 vs OASIS data (second reading of films).

	AS-001 Apremilast 30 mg Twice Daily Population, n = 98	OASIS-Matched Population, n = 56	OASIS Overall Population, n = 178
Baseline mSASSS, mean (SD)	12.3 (17.9)	7.4 (10.8)	7.9 (12.6)
mSASSS to Week 104, mean change from baseline (SD)	0.87 (2.5)	0.55 (3.2)	0.63 (2.5)
Patients without radiographic progression[a], %	70.4	82.1	76.4

[a] Radiographic progression was defined as a change in mSASSS ≥ 1 for this analysis. mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; OASIS: Outcome Assessments in Ankylosing Spondylitis International Study.

investigators to determine whether patients were obtaining sufficient clinical benefit to continue the study during the long-term extension phase. On initial radiological assessment at the first reading, apremilast showed modest improvement in radiographic progression over 2 years. Given that an initial signal of potential radiographic improvement was observed and the analysis had no comparator, a posthoc analysis was undertaken utilizing the OASIS database as a historical comparison group to further understand the possible modest radiographic effect observed with apremilast. After matching for disease activity, a second reading of apremilast radiographs was not consistent with the first reading and did not show a halt in radiographic progression vs standard of care. However, limitations should be noted with this comparison, as there were differences in the demographic, disease activity, and radiographic data between patients in the OASIS and AS-001 studies. Further, there were differences in the mSASSS between the radiographic re-reading and initial reading for the apremilast and OASIS cohorts. Therefore, effects on radiographic progression could not be accurately determined due to these discrepancies, but are unlikely due to lack of effect on clinical disease activity, and if present, suggest a modest effect between the original readings and re-readings. Although efficacy in AS treatment was not observed in this study, safety findings were consistent with previous clinical studies of apremilast and confirmed the acceptable safety and tolerability profile, with no new safety issues identified.[23,24,25,26,27,28]

It is known that PDE4 inhibition raises intracytoplasmic AMP, which has a number of subsequent effects.[9] These effects include enhanced production of antiinflammatory IL-10, as well as activation of protein kinase A, which in turn inhibits NFkB-mediated production of proinflammatory cytokines, including TNF, IL-17, IL-23, and interferon-γ. Overall, this pattern of cytokine modulation might be expected to be beneficial in the amelioration of symptoms and signs of AS. However, it is difficult to extrapolate from preclinical studies whether some of these mediators may be more dominantly affected than others and whether the effects may vary in different immune cell subtypes. A hypothetical speculation might be that the failure of apremilast to demonstrate efficacy in this study suggests a dominant effect of PDE4 inhibition on IL-23 in keeping with the failure of bDMARDs targeting p19 to show efficacy in such a disease phenotype.

In this phase III study, apremilast did not demonstrate a treatment benefit in patients with active AS. Safety and tolerability assessments were consistent with the known safety profile of apremilast in other patient populations, including psoriasis and psoriatic arthritis.

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DATA AVAILABILITY

Qualified researchers may request data from Amgen clinical studies. Complete details are available at http://www.amgen.com/datasharing.

Table 5. Overview of adverse events at Weeks 24 and 104 (safety population).

	Placebo, n = 164		Apremilast 20 mg Twice Daily, n = 163		Apremilast 30 mg Twice Daily, n = 163	
	n (%)	EAIR/100 PY	n (%)	EAIR/100 PY	n (%)	EAIR/100 PY
Week 24 (safety population)		63.3 PY		63.1 PY		67.5 PY
Any TEAE	82 (50)	184.5	89 (55)	223.2	85 (52)	193.6
Any serious TEAE	1 (1)	1.6	3 (2)	4.8	6 (4)	9.0
Any TEAE leading to discontinuation	6 (4)	9.5	9 (6)	14.4	12 (7)	17.9
Week 24 TEAEs in ≥ 5% in any group						
Headache	8 (5)	13.1	9 (6)	14.9	16 (10)	25.4
Nausea	6 (4)	9.6	10 (6)	16.8	14 (9)	22.4
Nasopharyngitis	6 (4)	9.8	9 (6)	14.7	7 (4)	10.6
Diarrhea	5 (3)	8.0	20 (12)	35.1	15 (9)	23.8
Upper abdominal pain	3 (2)	4.8	3 (2)	4.8	9 (6)	13.7

	Apremilast 20 mg Twice Daily[a], n = 163		Apremilast 20/30 mg Twice Daily[b] n = 72		Apremilast 30 mg Twice Daily[c], n = 305	
	n (%)	EAIR/100 PY	n (%)	EAIR/100 PY	n (%)	EAIR/100 PY
Week 104		181.2 PY		113.7 PY		492.8 PY
Any TEAE	104 (64)	131.6	42 (58)	76.0	219 (72)	97.1
Any serious TEAE	10 (6)	5.7	4 (6)	3.7	28 (9)	6.0
Any TEAE leading to discontinuation	16 (10)	8.9	1 (1)	0.9	31 (10)	6.4
Week 104: TEAEs in ≥ 5% in any group						
Diarrhea	25 (15)	16.5	3 (4)	2.7	34 (11)	7.6
Nasopharyngitis	21 (13)	13.3	8 (11)	7.6	46 (15)	10.4
Upper respiratory infection	13 (8)	7.7	5 (7)	4.6	22 (7)	4.8
Nausea	12 (7)	7.2	5 (7)	4.7	24 (8)	5.2
Headache	10 (6)	5.9	3 (4)	2.7	22 (7)	4.7
Bronchitis	6 (4)	3.4	5 (7)	4.6	8 (3)	1.7
Muscle spasm	5 (3)	2.8	4 (6)	3.7	2 (1)	0.4
Frequent bowel movements	2 (1)	1.1	4 (6)	3.7	3 (1)	0.6

[a] Includes patients randomized to apremilast 20 mg at baseline who continued on apremilast 20 mg. [b] Includes patients treated with apremilast 20 mg from Week 0 who escaped to apremilast 30 mg. [c] Includes patients who were treated with apremilast 30 mg from Week 0 and patients treated with placebo from Week 0 who transitioned to apremilast 30 mg; these patients' TEAEs that occurred under 30 mg treatment are counted. AE: adverse event; EAIR: exposure-adjusted incidence rate; PY: patient-years; TEAE: treatment-emergent adverse event.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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