ORIGINAL ARTICLE

Trial of Apremilast for Oral Ulcers in Behçet's Syndrome

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ABSTRACT

BACKGROUND

The small-molecule phosphodiesterase 4 inhibitor apremilast modulates cytokines that are up-regulated in Behçet's syndrome. In a phase 2 trial involving patients with Behçet's syndrome, apremilast reduced the incidence and severity of oral ulcers. Data on the efficacy and safety of apremilast in patients with Behçet's syndrome who had active oral ulcers and had not previously received biologic agents are limited.

METHODS

In a phase 3 trial, we randomly assigned, in a 1:1 ratio, patients who had Behçet's syndrome with active oral ulcers but no major organ involvement to receive either apremilast at a dose of 30 mg or placebo, administered orally, twice daily for 12 weeks, followed by a 52-week extension phase. The primary end point was the area under the curve (AUC) for the total number of oral ulcers during the 12-week placebo-controlled period (with lower values indicating fewer ulcers). There were 13 secondary end points, including complete response of oral ulcers, change from baseline in pain associated with oral ulcers, disease activity, and change from baseline in the Behçet's Disease Quality of Life score (range, 0 to 30, with higher scores indicating greater impairment in quality of life). Safety was also assessed.

RESULTS

A total of 207 patients underwent randomization (104 patients to the apremilast group and 103 to the placebo group). The AUC for the number of oral ulcers was 129.5 for apremilast, as compared with 222.1 for placebo (least-squares mean difference, −92.6; 95% confidence interval [CI], −130.6 to −54.6; P<0.001). The change from baseline in the Behçet's Disease Quality of Life score was −4.3 points in the apremilast group, as compared with −1.2 points in the placebo group (least-squares mean difference, −3.1 points; 95% CI, −4.9 to −1.3). Adverse events with apremilast included diarrhea, nausea, and headache.

CONCLUSIONS

In patients with oral ulcers associated with Behçet's syndrome, apremilast resulted in a greater reduction in the number of oral ulcers than placebo but was associated with adverse events, including diarrhea, nausea, and headache. (Funded by Celgene; ClinicalTrials.gov number, NCT02307513.)

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Behçet's syndrome is a multisystem vasculitis that causes oral and genital ulcers, papulopustular and nodular lesions, arthritis, uveitis, arterial aneurysms, and arterial and venous thrombosis and may involve the central nervous system and gastrointestinal tract. Recurrent relapsing and remitting oral ulcers are often the first manifestations of Behçet's syndrome.[1] Oral ulcers cause pain; difficulty in eating, drinking, and talking; and decreased participation in routine daily activities and quality of life.[2] Although colchicine is recommended as first-line treatment for skin and mucosal involvement,[3] two of three small, randomized, controlled trials did not show efficacy of this drug for the treatment of oral ulcers.[4]

Apremilast, an orally available small-molecule phosphodiesterase 4 inhibitor,[5] prevents degradation of cyclic adenosine monophosphate, thereby decreasing the production of proinflammatory cytokines and increasing the production of anti-inflammatory mediators.[6] This potential for regulating the downstream inflammatory signaling cascade has led to its use in patients with psoriasis and psoriatic arthritis.[7,8] Apremilast may have therapeutic effects in patients with Behçet's syndrome by means of modulation of tumor necrosis factor α, interleukin-2, interleukin-8, interleukin-12, interleukin-17, and interferon-γ production,[5] all of which are up-regulated proinflammatory mediators in Behçet's syndrome.[9-16]

In a phase 2 trial, apremilast was effective in reducing the number of oral ulcers, the pain associated with oral ulcers, and overall disease activity.[17] In the current phase 3 trial, we evaluated the efficacy and safety of apremilast in a larger, geographically more diverse group of patients with Behçet's syndrome who had active oral ulcers that did not respond to previous treatment with at least one nonbiologic agent such as a topical glucocorticoid or systemic treatment.

METHODS

TRIAL DESIGN

This randomized, double-blind, placebo-controlled trial was conducted in 53 centers across 10 countries in Asia, Europe, North America, Israel, Lebanon, and Turkey. After a screening phase that lasted up to 6 weeks, patients were randomly assigned in a 1:1 ratio to receive apremilast (at a dose of 30 mg twice daily) or placebo for 12 weeks. Randomization was stratified according to sex, history of uveitis, and geographic region (Japan vs. other). At week 12, all patients were offered the opportunity to enter the extension phase and receive apremilast until week 64, followed by 4-week observational follow-up (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Efficacy results for the 12-week placebo-controlled period and the extension phase through week 28 were based on a modified intention-to-treat plan. Safety data are presented for the 12-week placebo-controlled period and for the accrued apremilast-exposure period, which included data from patients who switched from placebo to apremilast.

To reduce the possibility of gastrointestinal adverse events, the dose of apremilast was increased gradually during the first week (Table 3 in the protocol, available at NEJM.org). After the dose adjustment, all patients received the full dose of 30 mg of apremilast orally twice daily.

The sponsor (Celgene) and three of the authors designed the trial. The sponsor provided the trial drug and placebo, performed the statistical analyses, and paid for professional writing assistance. Confidentiality agreements were in place between the sponsor and the authors. All the authors vouch for the fidelity of the trial to the protocol, the accuracy and completeness of the data, and the accurate reporting of adverse events. The initial draft of the manuscript was written by the first author.

The trial was approved by the institutional review board or ethics committee at each investigational site before the initiation of the trial and was performed in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent.

TRIAL PARTICIPANTS

Eligible patients were 18 years of age or older, had received a diagnosis of Behçet's syndrome according to International Study Group criteria,[18] and had active oral ulcers that had occurred at least three times in the previous 12-month period (including the screening visit) despite the previous use of at least one nonbiologic medication, such as (but not limited to) topical or systemic

glucocorticoids, nonsteroidal antiinflammatory drugs, colchicine, immunosuppressants, or thalidomide. Active oral ulcers were defined as two or more oral ulcers at the screening visit and two or more oral ulcers at randomization, when randomization occurred at least 14 days after screening, or two or more oral ulcers at the screening visit and three or more oral ulcers at randomization, when randomization occurred at any time between 1 and 42 days after screening.

Patients were excluded if they had Behçet's syndrome–related active major organ involvement that had led to systemic treatment, such as uveitis (except for mild uveitis treated with topical agents) or vascular or central nervous system involvement during the 12 months before trial entry, had previously used biologic agents for oral ulcers, or had any clinically significant medical condition (infection, cancer, laboratory abnormality, or psychiatric illness) that would prevent them from participating. Patients with Behçet's syndrome–related arthritis or skin manifestations could participate.

END POINTS

The primary efficacy end point was the area under the curve (AUC) for the total number of oral ulcers during the 12-week placebo-controlled period. This measure reflects the number of oral ulcers over time and accounts for the remitting and relapsing course of oral ulcers in Behçet's syndrome. Oral ulcers were assessed by the investigator at weeks 0, 1, 2, 4, 6, 8, 10, and 12 during the placebo-controlled period. The number of oral ulcers that was counted for the analysis of the primary end point included current and recurrent ulcers at each time point; a single oral ulcer could be recounted multiple times if it persisted or recurred at subsequent visits. The primary efficacy end point was also analyzed in prespecified subgroups defined according to baseline demographic and disease characteristics.

There were 13 secondary efficacy end points: the change from baseline in pain associated with oral ulcers (on a 100-mm visual-analogue scale, with higher scores indicating more pain); the change from baseline in the patient-reported Behçet's Syndrome Activity Scale score (scores range from 0 to 100, with higher scores indicating more disease activity); the Behçet's Disease Current Activity Form, which comprised three components (the Behçet's Disease Current Activity Index [on a scale from 0 to 12, with higher scores indicating more activity], the patient's perception of disease activity [on a scale from 1 to 7, with higher scores indicating more activity], and the physician's overall perception of disease activity [on a scale from 1 to 7, with higher scores indicating more activity]); the percentage of patients free from oral ulcers by week 6 who remained oral ulcer–free for at least 6 weeks; the time to resolution of oral ulcers (complete response); the percentage of patients free from oral ulcers at week 12; the change from baseline in the Behçet's Disease Quality of Life score (scores range 0 to 30, with higher scores indicating greater impairment in quality of life); the percentage of patients with genital ulcers at baseline who were ulcer-free at week 12; the percentage of patients with no oral ulcers after a complete response; the time to recurrence of oral ulcers after loss of complete response; the number of oral ulcers after loss of complete response; the change from baseline in the physician's global assessment of skin lesions (scores for acne-like, folliculitis, and erythema nodosum lesions range from 0 to 3, with higher scores indicating more lesions) in patients who had skin lesions at baseline (Table S1); and the change from baseline in pain associated with genital ulcers in patients who had genital ulcers at baseline.

To ensure no worsening of new, recurrent, or other manifestations of Behçet's syndrome, patients reported activity related to skin lesions, arthritis, and uveitis as well as gastrointestinal, central nervous system, and vascular symptoms at each visit; these were compared with baseline reports of symptoms. Patients had ophthalmologic examinations at baseline and at week 12.

At each trial visit, all medications and therapies (e.g., prescription and over-the-counter drugs and herbal supplements), including the dose, unit, frequency, route of administration, and start and stop dates, were recorded. Glucocorticoid eyedrops and oral and topical analgesic agents (withheld 24 hours before trial visits) were allowed throughout the trial. The use of colchicine, glucocorticoids, immunosuppressants, and biologic agents was not permitted during the placebo-controlled period (i.e., through visit 9).

Rescue therapy with colchicine and topical glucocorticoids was permitted during the extension phase in patients who did not have at least a partial response, which was defined as a reduction from baseline of at least 50% in the number of oral ulcers. Adherence to the trial regimen was calculated as 100 times the total number of tablets taken (the total number of tablets dispensed minus the total number of tablets returned) divided by the intended total number of tablets taken over the same period.

STATISTICAL ANALYSIS

We calculated that a sample of 204 patients (102 in each treatment group) would provide the trial with 90% power, at a two-sided significance level of 0.05, to detect a treatment difference of 66 in the AUC of oral ulcer counts through week 12. The sample-size estimation was based on the results of the phase 2 trial. Efficacy and safety were assessed in the modified intention-to-treat population, which included all the patients who underwent randomization and received at least one dose of apremilast or placebo. Statistical tests were conducted between apremilast and placebo for the prespecified primary and secondary end points in a hierarchical manner. A serial gatekeeping procedure was used for the primary and secondary end points, which were tested in the order specified above to account for multiple testing. The analysis was stopped if the between-group difference for an end point in the hierarchy was not significant at a two-sided alpha of 0.05.

The method of counting total oral ulcers in the AUC analysis is described above. The linear trapezoidal method was used to determine the AUC for each time interval; the AUC for the 12-week period was the sum of the AUCs in each time interval. For the Behçet's Disease Current Activity Form outcome measure, each of the three individual components was analyzed. All three components were required to have a P value of less than 0.05 in order to be considered significant and to advance hierarchical testing. The primary efficacy end point, the AUC for the total number of oral ulcers during the 12-week placebo-controlled period, was assessed with the use of an analysis of covariance model with AUC as the response variable; treatment, sex, and geographic region as factors; and the number of oral ulcers at baseline as a covariate. The AUC analysis accounted for missing data for oral ulcer counts by the multiple imputation method, as stated in the statistical analysis plan (available with the protocol). Multiple sensitivity analyses were performed to support the multiple imputation analysis for the primary end point (Table S2).

For secondary end points, the Cochran–Mantel–Haenszel test, controlling for stratification factors, was used for discrete variables. Analysis of covariance, with the use of a model similar to that described for the primary end point, was used for continuous variables. Missing data in the analyses of binary secondary end points were imputed under the assumption that the patient did not have a response. The original statistical analysis plan used the last-observation-carried-forward approach to handle missing data for continuous secondary end points; a post hoc analysis, reported here, used multiple imputation and a mixed-effects model with repeated measures. Descriptive statistics were provided to summarize safety end points.

RESULTS

PATIENTS

From December 2014 through May 2017, a total of 207 patients were randomly assigned to receive apremilast (104 patients) or placebo (103). All the patients received at least one dose of apremilast or placebo, and the analysis therefore equated to an intention-to-treat analysis. (Concomitant medications that were received during the placebo-controlled period are listed in Table S3.) Adherence to the trial regimen was 94% in the apremilast group and 95% in the placebo group. A total of 96 patients (92%) receiving apremilast and 83 (81%) receiving placebo completed the 12-week placebo-controlled period; all but 1 patient in the apremilast group from the placebo-controlled period entered the extension phase. Figure 1 shows the assignment of the patients to the trial groups as well as the reasons for discontinuation.

The baseline demographic and disease characteristics of the patients, as well as their history of Behçet's syndrome manifestations and previous medications, were similar in the two trial groups (Table 1). Patients had a history of skin lesions (in 99%; 56% of the patients had active skin lesions at baseline), genital ulcers

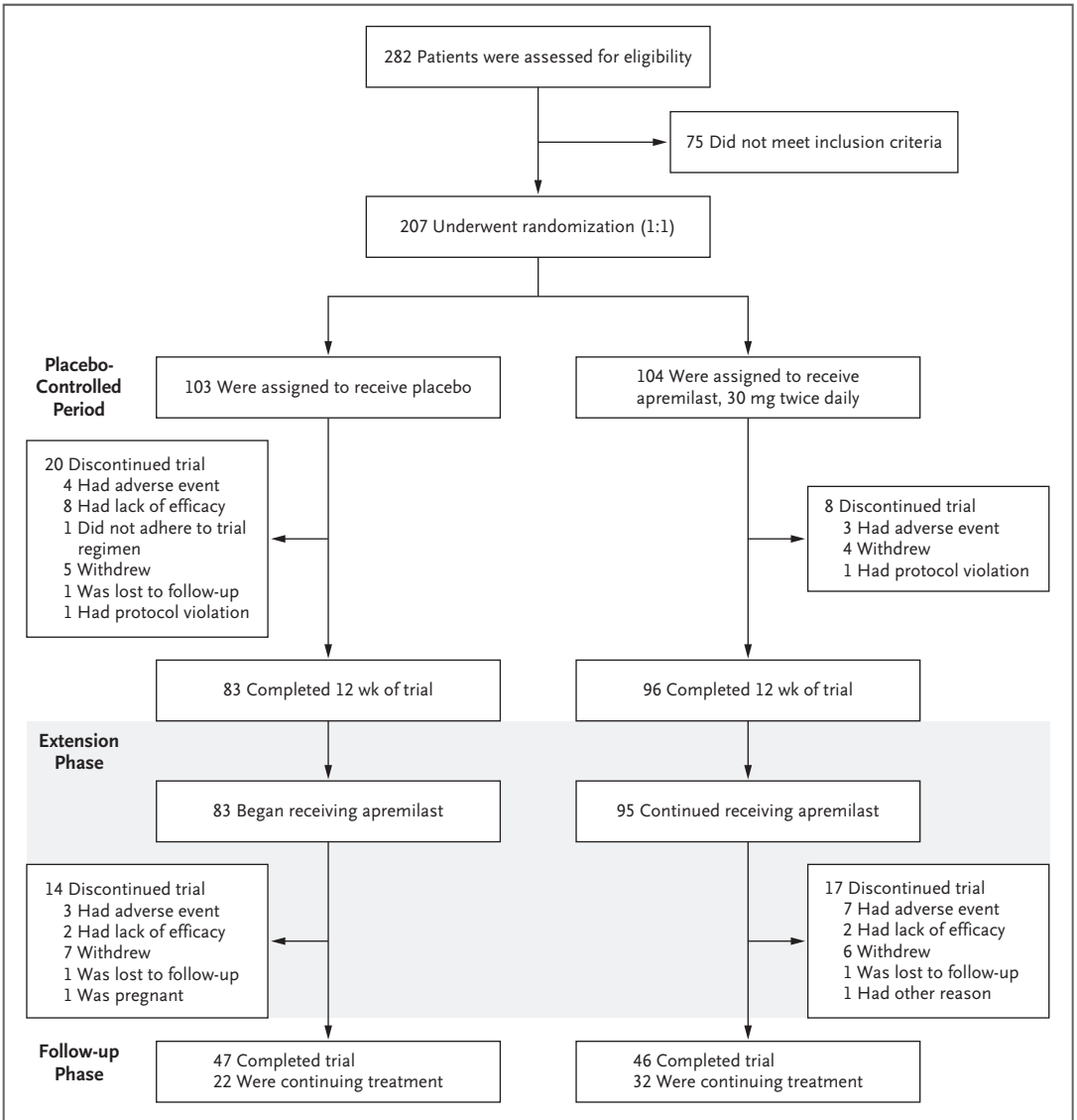


Figure 1. Randomization, Treatment, and Follow-up.

The placebo-controlled period encompassed data from week 0 (baseline) to week 12. The extension phase encompassed data from week 12 to week 64. All the patients who completed the extension phase, as well as all the patients who discontinued for any reason, were eligible to enter the 4-week post-treatment observational follow-up phase. The apremilast-exposure period encompassed all apremilast-exposure data from receipt of the first dose of apremilast, regardless of when the apremilast exposure started (at week 0 or week 12), and included 4 weeks of follow-up. All but one patient from the placebo-controlled period (who was in the apremilast group) entered the extension phase.

(90%), musculoskeletal manifestations (72%), uveitis (17%), and involvement of the central nervous system (10%), gastrointestinal system (9%), and vascular system (1%). A total of 10 patients in each group had a history of anterior uveitis; 3 patients receiving apremilast and 4 receiving placebo had a history of posterior uveitis. None of the patients had active uveitis at baseline, as judged on ophthalmologic examination.

EFFICACY THROUGH WEEK 12

The primary end point of the AUC of the total mean (±SE) number of ulcers during the 12-week placebo-controlled period was 129.5±15.9 in the

Table 1. Baseline Demographic and Clinical Characteristics of the Patients, Including Previous Medications.*

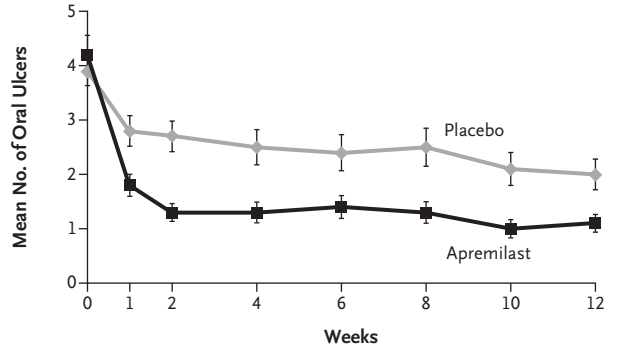
Characteristic	Placebo Group (N=103)	Apremilast Group (N=104)	Total (N=207)
Age — yr	40.6±12.7	39.4±12.1	40.0±12.4
Female sex — no. (%)	63 (61)	64 (62)	127 (61)
Geographic region — no. (%)			
Asia	29 (28)	32 (31)	61 (29)
Europe	27 (26)	25 (24)	52 (25)
North America	11 (11)	14 (13)	25 (12)
Other†	36 (35)	33 (32)	69 (33)
Duration of Behçet's syndrome — yr	6.9±8.0	6.7±7.4	6.8±7.7
No. of oral ulcers	3.9±2.7	4.2±3.7	4.1±3.2
Oral ulcer pain‡	60.8±26.9	61.2±27.6	61.0±27.2
Behçet's Disease Current Activity Index score§	3.6±1.7	3.7±1.6	3.7±1.6
Behçet's Syndrome Activity Scale score¶	44.3±16.9	42.8±16.2	43.5±16.5
Behçet's Disease Quality of Life score‖	11.2±8.2	10.2±8.2	10.7±8.2
Previous medications — no. (%)**			
Immunosuppressive agent	14 (14)	14 (13)	28 (14)
Colchicine	57 (55)	52 (50)	109 (53)
Glucocorticoid	15 (15)	17 (16)	32 (15)
Topical glucocorticoid	16 (16)	13 (12)	29 (14)
Biologic agent	3 (3)	2 (2)	5 (2)

* Plus–minus values are means ±SD. There were no significant differences in the patients' characteristics between the two groups at baseline. Percentages may not total 100 because of rounding.
† Other trial sites were located in Israel (four sites), Lebanon (two), and Turkey (five).
‡ Pain associated with oral ulcers was assessed with the use of a 100-mm visual-analogue scale, with higher scores indicating more pain.
§ Scores on the Behçet's Disease Current Activity Index range from 0 to 12, with higher scores indicating more activity.
¶ Scores on the Behçet's Syndrome Activity Scale range from 0 to 100, with higher scores indicating more disease activity.
‖ Behçet's Disease Quality of Life scores range from 0 to 30, with higher scores indicating greater impairment in quality of life.
** Previous medications were defined as those used within 30 days before screening, except for biologic agents, which were reported regardless of when they had been used previously.

apremilast group, as compared with 222.1±15.9 in the placebo group (least-squares mean difference, –92.6; 95% confidence interval [CI], –130.6 to –54.6; P<0.001). The mean counts of oral ulcers at the trial visits are shown in Figure 2.

At week 12, the mean reduction from baseline in the pain associated with oral ulcers as assessed on a 100-mm visual-analogue scale was –42.7 in the apremilast group, as compared with –18.7 in the placebo group (least-squares mean difference, –24.1; 95% CI, –32.4 to –15.7). In a prespecified exploratory analysis, the reduction in oral ulcer pain paralleled the reduction in the number of oral ulcers from week 1 to week 12 (Fig. S2).

The results regarding the primary and secondary end points are presented in Table 2 in their prespecified sequence of analysis without P values for secondary end points because of post hoc imputation for missing data. At week 12, the mean change from baseline in the Behçet's Syndrome Activity Scale score was –19.8 points in the apremilast group and –8.8 points in the placebo group (least-squares mean difference, –11.0 points; 95% CI, –15.6 to –6.4). The change from baseline in the mean (±SE) scores



No. of Patients (LS mean)								
Placebo	103 (3.9)	103 (2.8)	103 (2.7)	103 (2.5)	103 (2.4)	103 (2.5)	103 (2.1)	103 (2.0)
Apremilast	104 (4.2)	104 (1.8)	104 (1.3)	104 (1.3)	104 (1.4)	104 (1.3)	104 (1.0)	104 (1.1)

Figure 2. Number of Oral Ulcers According to Time Point over the 12-Week Placebo-Controlled Period (Modified Intention-to-Treat Population).

The modified intention-to-treat population included all the patients who underwent randomization and received at least one dose of apremilast or placebo. The I bars indicate the standard error. The least-squares (LS) mean numbers of oral ulcers in each group at the specified time points are also shown.

for the individual components of the Behçet's Disease Current Activity Form was –1.1±0.2 points in the apremilast group and –0.6±0.2 points in the placebo group (least-squares mean difference, –0.5 points; 95% CI, –1.0 to 0.0) for the Behçet's Disease Current Activity Index; –1.8±0.2 and –1.2±0.2 points, respectively (least-squares mean difference, –0.6 points; 95% CI, –1.0 to –0.2), for the patient's perception of disease activity; and –1.7±0.2 and –1.1±0.2 points, respectively (least-squares mean difference, –0.7 points; 95% CI, –1.0 to –0.3), for the physician's overall perception of disease activity.

The percentage of patients who were free from oral ulcers by week 6 and who remained ulcer-free at each visit for at least 6 more weeks was 30% in the apremilast group (31 of 104 patients) and 5% in the placebo group (5 of 103 patients) (difference, 25 percentage points; 95% CI, 16 to 35). The median time to oral ulcer resolution was 2.1 weeks in the apremilast group and 8.1 weeks in the placebo group (hazard ratio for complete resolution of oral ulcers, 2.4; 95% CI, 1.7 to 3.4). The percentage of patients who were free from oral ulcers at week 12 was 53% in the apremilast group (55 patients) and 22% in the placebo group (23 patients) (adjusted difference, 31 percentage points; 95% CI, 18 to 43). The change in quality of life, as assessed by the Behçet's Disease Quality of Life score, was –4.3 points in the apremilast group and –1.2 points in the placebo group (least-squares mean difference, –3.1 points; 95% CI, –4.9 to –1.3).

A total of 17 patients in each group had genital ulcers at baseline. The percentage of patients who were free from genital ulcers at week 12 was 71% in the apremilast group (12 patients) and 41% in the placebo group (7 patients); the between-group difference was not significant. Because the hierarchical analysis failed at this end point, formal statistical testing stopped, and no inferences can be made for subsequent end points (Table 2).

In prespecified analyses, the AUC for the total number of oral ulcers during the 12-week placebo-controlled period in the subgroups defined according to disease duration, number of oral ulcers at baseline, geographic region, and previous use of colchicine and glucocorticoids was assessed (Fig. S3). The percentage of patients with at least a partial response at week 12 was 76% (79 patients) in the apremilast group and 48% (49 patients) in the placebo group. (Sensitivity analyses are presented in Tables S2 and S4.)

A total of 164 patients completed week 28 of the trial. The prespecified analyses of the number of oral ulcers and the pain associated with oral ulcers at week 28 are shown in Figure S4A and S4B, respectively.

The percentage of patients with at least one new, recurrent, or worsening manifestation of Behçet's syndrome other than oral or genital ulcers was assessed in a prespecified exploratory analysis. There was no evidence of worsening uveitis or other adverse event in a major organ with apremilast (including gastrointestinal signs or symptoms). On the basis of ophthalmologic examination, two patients in the placebo group had uveitis flares during the placebo-controlled period; one had anterior uveitis, and the other had panuveitis. Both patients had a history of uveitis that had not been active at the time of enrollment. No patients receiving apremilast had active uveitis. Except for these uveitis flares, no other patients had new or worsening major organ involvement related to Behçet's syndrome during the placebo-controlled period. There were no new or worsening major organ disorders through week 28.

Table 2. Primary and Key Secondary Efficacy End Points at Week 12 during the Placebo-Controlled Period.*

End Point	Placebo Group (N=103)	Apremilast Group (N=104)	Estimated Treatment Difference (95% CI)†
AUC for total no. of oral ulcers from baseline through wk 12‡	222.1±15.9	129.5±15.9	−92.6 (−130.6 to −54.6)
Change from baseline in pain associated with oral ulcers, as measured by VAS, at wk 12§	−18.7±3.3	−42.7±3.1	−24.1 (−32.4 to −15.7)
Change from baseline in Behçet's Syndrome Activity Scale score at wk 12‡	−8.8±2.0	−19.8±1.8	−11.0 (−15.6 to −6.4)
Behçet's Disease Current Activity Form components‡¶			
Change from baseline in Behçet's Disease Current Activity Index score at wk 12	−0.6±0.2	−1.1±0.2	−0.5 (−1.0 to 0.0)
Change from baseline in patient's perception of disease activity at wk 12	−1.2±0.2	−1.8±0.2	−0.6 (−1.0 to −0.2)
Change from baseline in physician's overall perception of disease activity at wk 12	−1.1±0.2	−1.7±0.2	−0.7 (−1.0 to −0.3)
Complete response for oral ulcers (oral ulcer–free) by wk 6 after start of administration and oral ulcer–free for ≥6 wk more during 12-wk placebo-controlled period — % of patients‖	5	30	25 (16 to 35)
Median time to complete response for oral ulcers during placebo-controlled period (95% CI) — wk	8.1 (4.7 to NR)	2.1 (2.0 to 4.0)	2.4 (1.7 to 3.4)**
Complete response for oral ulcers at wk 12 — % of patients‖	22	53	31 (18 to 43)
Change from baseline in Behçet's Disease Quality of Life score at wk 12‡	−1.2±0.8	−4.3±0.8	−3.1 (−4.9 to −1.3)
Complete response for genital ulcers at wk 12 among patients who had genital ulcers at baseline — % of patients‖††‡‡	41	71	28 (−4 to 60)
No oral ulcers after complete response during placebo-controlled period — % of patients‖	13	31	18 (4 to 31)
Median time to recurrence, defined as oral ulcers after loss of complete response during placebo-controlled period (95% CI) — wk	2.3 (2.1 to 4.1)	4.6 (3.1 to 6.1)	0.6 (0.4 to 0.9)
No. of oral ulcers after loss of complete response during placebo-controlled period	1.5±0.2	1.1±0.2	−0.4 (−0.9 to 0.0)
Change from baseline in static physician's global assessment of skin lesions total score (acne-like lesions, folliculitis, and erythema nodosum) at wk 12 in patients who had Behçet's skin lesions at baseline‡§§	−0.9±0.2	−0.9±0.2	0.0 (−0.4 to 0.4)
Change from baseline in pain associated with genital ulcers, as measured by VAS at wk 12, among patients who had genital ulcers at baseline§‡‡	−42.8±10.0	−48.4±8.8	−5.6 (−25.7 to 14.4)

* Plus–minus values are least-squares means ±SE. Medians with two-sided 95% confidence intervals are based on Kaplan–Meier estimates. The fixed-sequence testing procedure was applied to adjust for multiplicity. Formal statistical testing was performed, in a prespecified sequence, as presented in the table, until one of the end points in the hierarchy failed to be significant at an alpha level of 0.05. AUC denotes area under the curve, NR not reached, and VAS visual-analogue scale.

† Differences for continuous end points are shown as least-squares means, and differences for categorical end points are shown in percentage points. Hazard ratios are shown for time to response or recurrence end points.

‡ Data are from a multiple imputation analysis.

§ The analysis was conducted with the use of a mixed-effects repeated-measures model.

¶ Each of the three individual components of the Behçet's Disease Current Activity Form was analyzed. All three components were required to have a significant P value ($P<0.05$) in order to be considered statistically significant and to advance the hierarchical testing. The patient's perception of disease activity and physician's overall perception of disease activity were each assessed on a scale from 1 to 7, with higher scores indicating more activity.

‖ Missing data were imputed as no response.

** The hazard ratio is for complete resolution of oral ulcers.

†† The hierarchical analysis failed at this end point, and no inferences can be made from this and subsequent end points.

‡‡ A total of 17 patients in each group had genital ulcers at baseline.

§§ A total of 59 patients in the placebo group and 58 in the apremilast group had skin lesions at baseline.

SAFETY

Safety data include 187 patients who had exposure to apremilast, including the patients who switched from placebo during the extension phase; 107 patients had exposure to apremilast for 1 year or longer. The percentage of patients with at least one adverse event during the placebo-controlled period was 79% in the apremilast group and 72% in the placebo group (Table 3). The most common adverse events were diarrhea, nausea, headache, upper respiratory tract infection, and viral upper respiratory tract infection, all of which occurred in a higher percentage of patients receiving apremilast than in those receiving placebo. Gastrointestinal adverse events began mostly within the first week of apremilast treatment and generally resolved within 15 days.

During the placebo-controlled period, serious adverse events were reported in three patients in the apremilast group and in four in the placebo group. Among these patients, two in the apremilast group (with migraine and soft-tissue injury, each in one patient) and three in the placebo group (one patient with infectious diarrhea and genital infection, one with fungal genital infection and erythema multiforme, and one with acute febrile neutrophilic dermatosis) had serious adverse events that were not related to Behçet's syndrome. Serious adverse events that were related to Behçet's syndrome were observed in one patient in each group. Worsening of Behçet's syndrome, genital or buccal ulcerations, and aphthae were reported in one patient in the apremilast group, which led to the discontinuation of apremilast, and oral ulcers and skin lesions were reported in one patient in the placebo group, which led to the discontinuation of placebo. There were no deaths reported during the entire trial (placebo-controlled period and extension phase).

Other adverse events leading to discontinuation during the placebo-controlled period occurred in two patients in the apremilast group and in four in the placebo group. In the apremilast group, one patient reported headache, nausea, and vomiting, and one reported upper abdominal pain. In the placebo group, one patient reported headache, lethargy, cough, and musculoskeletal chest pain, one reported diarrhea, one reported acute febrile neutrophilic dermatosis, and one reported pemphigus.

DISCUSSION

This trial showed a greater reduction in the number of oral ulcers in patients with Behçet's syndrome with apremilast than with placebo in a population that had not been exposed to biologic agents for the treatment of oral ulcers. A decrease in the number of oral ulcers and the pain associated with oral ulcers started as early as week 1. These results were consistent across subgroups analyzed according to baseline characteristics (disease duration, number of oral ulcers, geographic region, and history of use of colchicine and glucocorticoids). A total of 53% of the patients assigned to the apremilast group and 22% of those assigned to the placebo group were free from oral ulcers at week 12, and improvements were observed in overall disease activity and patient-reported outcomes. Decreases in the number of oral ulcers and the pain associated with oral ulcers were maintained through week 28 with continued treatment. Nausea, diarrhea, upper respiratory tract infection, headache, upper abdominal pain, and vomiting occurred in a higher percentage of patients receiving apremilast than of those receiving placebo.

A phase 2 trial of apremilast, which included patients with Behçet's syndrome from Turkey and the United States, showed results similar to those in the current trial.[17] The phase 2 trial enrolled a lower percentage of men than the current trial. The current trial included a larger number of patients representing 10 countries over three continents; more than one third of the patients were men. Unlike the phase 2 trial, the current trial included patients who had previously used at least one medication for oral ulcers. Because both trials excluded patients who had used biologic agents for the treatment of oral ulcers, no conclusion can be drawn regarding the efficacy of apremilast in patients previously treated with biologic therapy for oral ulcers. In addition, our trial had no active comparator, and therefore conclusions cannot be drawn regarding the relative efficacy of apremilast as compared with other agents, particularly thalidomide.

This trial was not designed to determine whether apremilast would improve mucocutaneous manifestations other than oral ulcers. Although 56% of patients had active skin lesions at baseline, the degree of skin disease was low and the measures of skin lesions used in the trial were

Table 3. Adverse Events Occurring in at Least 5% of the Patients during the 12-Week Placebo-Controlled Period and the Apremilast-Exposure Period.*

Adverse Event	Placebo-Controlled Period				Apremilast-Exposure Period			
	Placebo (N=103)		Apremilast (N=104)		Placebo to Apremilast (N=83)		Apremilast to Apremilast (N=104)	
	no. of patients (%)	*exposure-adjusted incidence rate per 100 patient-yr*	*no. of patients (%)*	*exposure-adjusted incidence rate per 100 patient-yr*	*no. of patients (%)*	*exposure-adjusted incidence rate per 100 patient-yr*	*no. of patients (%)*	*exposure-adjusted incidence rate per 100 patient-yr*
Any adverse event	74 (72)	813.1	82 (79)	1039.6	69 (83)	336.7	89 (86)	511.5
Events occurring in ≥5% of patients in apremilast group								
Diarrhea	21 (20)	115.4	43 (41)	297.1	24 (29)	49.7	48 (46)	89.7
Nausea	11 (11)	56.5	20 (19)	102.4	10 (12)	16.9	24 (23)	32.0
Headache	11 (11)	55.6	15 (14)	72.2	15 (18)	26.2	22 (21)	28.4
Upper respiratory tract infection	5 (5)	24.6	12 (12)	55.0	6 (7)	9.9	19 (18)	22.9
Upper abdominal pain	2 (2)	9.6	9 (9)	41.6	9 (11)	15.1	13 (12)	14.9
Vomiting	2 (2)	9.6	9 (9)	41.7	3 (4)	4.8	9 (9)	10.2
Back pain	6 (6)	30.1	8 (8)	36.2	6 (7)	9.8	10 (10)	11.5
Viral upper respiratory tract infection	5 (5)	24.0	7 (7)	31.6	8 (10)	12.8	11 (11)	12.8
Insomnia	NA	—	NA	—	7 (8)	11.6	5 (5)	5.4
Abdominal pain	NA	—	NA	—	5 (6)	8.4	5 (5)	5.5
Any severe adverse event	6 (6)	29.3	6 (6)	27.0	4 (5)	6.4	14 (13)	15.8
Any serious adverse event	4 (4)	19.4	3 (3)	13.2	6 (7)	9.6	10 (10)	10.9
Any adverse event leading to discontinuation	5 (5)	23.8	3 (3)	13.0	2 (2)	3.1	11 (11)	11.6

* Adverse events were assessed during the treatment periods. The placebo-controlled period encompassed data obtained from week 0 through week 12, and the apremilast-exposure period encompassed all apremilast-exposure data from receipt of the first dose of apremilast, regardless of when the apremilast exposure started (at week 0 or week 12), and included 4 weeks of follow-up (up to week 68). The exposure-adjusted incidence rate per 100 patient-years was defined as 100 times the number of patients who reported the event, divided by the patients' total exposure, up to the start date of the first event in patients reporting the event, in years. NA denotes not applicable.

not sensitive enough to detect changes in skin lesions. As reported by Kolios et al. in this issue of the *Journal*,[19] in a retrospective case series involving five patients with recurrent aphthous stomatitis that was refractory to conventional treatment, apremilast therapy (used off-label) resulted in a Physician Global Assessment (PGA) score of 0 (clear) or 1 (almost clear) in all the patients over a period of 2 to 6 weeks. A PGA score of 1 was maintained in four of the five patients at 24 months of continued treatment.

This trial showed the efficacy of apremilast as compared with placebo for the treatment of oral ulcers in patients with Behçet's syndrome. Trials using an active comparator and longer follow-up are required in order to determine whether the effect of apremilast would be sustained beyond the 28 weeks of the active treatment duration of this trial and safe over long periods of administration.

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