Apremilast for oral ulcers associated with active Behçet's syndrome over 68 weeks: long-term results from a phase 3 randomised clinical trial

G. Hatemi[1], A. Mahr[2], M. Takeno[3], D.Y. Kim[4], D. Saadoun[5], H. Direskeneli[6], M. Melikoğlu[1], S. Cheng[7], S. McCue[7], M. Paris[7], M. Chen[7], Y. Yazici[8]

[1]Division of Rheumatology, Dept. of Internal Medicine and Behçet's Disease Research Centre, Istanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, and Behçet's Disease Research Centre, Istanbul, Turkey;
[2]Clinic for Rheumatology, Cantonal Hospital, St. Gallen, Switzerland;
[3]Dept. of Allergy and Rheumatology, Nippon Medical School, Musahi Kosugi Hospital, Kawasaki, Japan;
[4]Dept. of Dermatology, Yonsei University College of Medicine and Severance Hospital, Seoul, South Korea;
[5]Dept. of Internal Medicine and Clinical Immunology, Groupe Hospitalier Pitié Salpétrière, Paris, France;
[6]Division of Rheumatology, Marmara University School of Medicine, Istanbul, Turkey;
[7]Clinical Development, Amgen Inc., Thousand Oaks, CA, USA;
[8]Division of Rheumatology, New York University School of Medicine, NY, USA.

Gülen Hatemi, MD
Alfred Mahr, MD, MPH, PhD
Mitsuhiro Takeno, MD, PhD
Do Young Kim, MD, PhD
David Saadoun, MD, PhD
Haner Direskeneli, MD
Melike Melikoğlu, MD
Sue Cheng, MD, PhD
Shannon McCue, PhD
Maria Paris, MD
Mindy Chen, MS
Yusuf Yazici, MD

Please address correspondence to:
Gülen Hatemi,
Division of Rheumatology,
Department of Internal Medicine and Behçet's Disease Research Centre,
Istanbul University-Cerrahpaşa
34365 Istanbul, Turkey.
E-mail: gulenhatemi@yahoo.com

Received on May 27, 2021; accepted in revised form on September 9, 2021.

Clin Exp Rheumatol 2021; 39 (Suppl. 132): S80-S87.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2021.

Key words: Behçet's syndrome, long-term treatment, phosphodiesterase 4 inhibitor, quality of life, oral ulcers

Competing interests: page S87.

ABSTRACT

Objective. *This study assessed the efficacy and safety of apremilast for the oral ulcers associated with Behçet's syndrome (BS) up to 64 weeks.*

Methods. *The phase 3, double-blind, placebo-controlled RELIEF study randomised adult patients with active BS to placebo or apremilast 30 mg twice daily for 12 weeks, followed by an extension phase with all patients receiving apremilast through Week 64 and 4-week post-treatment follow-up (upon treatment discontinuation). The primary endpoint was area under the curve for the number of oral ulcers over 12 weeks (AUC_{Wk0-12}), reflecting the number of oral ulcers over time and accounting for their recurring-remitting course. Oral ulcer number, complete and partial responses, pain and disease activity and quality of life (QoL) were also assessed throughout the study.*

Results. *A total of 207 participants were randomised and received at least one dose of study medication; 178 entered the extension phase and 143 completed Week 64. AUC_{Wk0-12} was significantly lower with apremilast versus placebo ($p<0.0001$), and oral ulcers number, pain, complete/partial responses, disease activity and QoL with apremilast versus placebo showed improvements at Week 12, which were maintained through Week 64. The most common adverse events were diarrhoea, nausea, headache and upper respiratory tract infection; no new safety concerns were observed with longer-term apremilast exposure.*

Conclusion. *In patients with oral ulcers associated with BS, apremilast was efficacious and benefits were sustained up to 64 weeks with continued treatment. Apremilast was well tolerated, and safety was consistent with its known safety profile.*

Introduction

Behçet's syndrome (BS) is a multisystem, variable vessel vasculitis characterised by oral and genital ulcers, skin lesions, uveitis, arthritis, and vascular, neurologic, or gastrointestinal involvement (1-3). Oral ulcers are typically the first and most common manifestation of BS, follow a relapsing-remitting course, and may continue to recur for many years (1). The pain associated with recurring oral ulcers, along with resulting difficulties in eating or talking, may negatively impact patients' quality of life (QoL) (4, 5). Colchicine and topical agents are presently recommended as first-line therapy for the mucosal and skin lesions of BS (2). However, the efficacy of colchicine for oral ulcers appears limited, and topical corticosteroids may have a significant side effect profile, especially for longer-term use in patients with frequent recurrences (3, 6, 7). Thus, an unmet need remains for more effective and safe long-term systemic treatment options for BS with convenient long-term dosing (8, 9).

Apremilast is an oral phosphodiesterase 4 inhibitor which prevents degradation of cyclic adenosine monophosphate and leads to decreased production of pro-inflammatory cytokines and increased levels of anti-inflammatory mediators (10). By regulating the downstream inflammatory signalling cascade in this way, apremilast has the potential for a wide range of anti-inflammatory effects. Apremilast is approved for use in adult patients with moderate to severe plaque psoriasis as well as adult patients with active psoriatic arthritis and has demonstrated a favourable risk-benefit profile up to 52 weeks (11-14). Apremilast is also approved for use in adult patients with oral ulcers associated with BS in the United States (15), Japan (16) and the European Union (17). A 24-week

phase 2 trial was conducted in patients in Turkey and the United States with BS and active oral ulcers and found apremilast treatment to be effective in reducing the number and pain of oral ulcers and overall disease activity while improving QoL (8). Results from the phase 3 RELIEF trial demonstrated the efficacy and safety of apremilast in the treatment of oral ulcers associated with BS through 28 weeks, including a 12-week, placebo-controlled phase, and have been reported previously (18). We now report the long-term results from RELIEF demonstrating the maintenance of efficacy and safety with apremilast for up to 64 weeks of treatment.

Patients and methods

Participants

Eligible patients were aged 18 years or older, were diagnosed with BS as defined in the International Study Group criteria (19), and had oral ulcers at least three times in the year before randomisation despite previous treatment with at least one non-biologic therapy. Patients were required to have active oral ulcers, defined as at least two oral ulcers at screening and either at least two oral ulcers at randomisation (occurring ≥14 days after screening) or at least three oral ulcers at randomisation (occurring between 1 and 42 days after screening). Eligible participants were considered by the investigator to be candidates for systemic oral ulcer therapy.

Patients were excluded if they had active major organ involvement related to BS which required the use of immunosuppressives during the previous 12 months, with the exception of mild uveitis treated topically. Use of previous biologic therapies was allowed for manifestations of BS other than oral ulcers. Although corticosteroids, colchicine, and immunosuppressants were not allowed during the placebo-controlled phase, topical corticosteroids and colchicine could be used during the extension phase for patients meeting non-response criteria.

Study design

RELIEF was a randomised, double-blind, placebo-controlled, phase 3 trial conducted at 53 sites in 10 countries across Asia, Europe, North America, Israel, Lebanon, and Turkey (www.ClinicalTrials.gov, NCT02307513). Participants were enrolled by investigators and randomised (1:1) to receive either placebo or apremilast 30 mg twice daily via a centralised interactive response technology. Randomisation was stratified by gender, history of uveitis, and region (Japan or other). Participants, investigators, study assessors, and study sponsor were masked to the treatment assignment.

The trial included a screening phase, a 12-week placebo-controlled phase, a 52-week extension phase in which patients in the apremilast group remained on apremilast treatment (apremilast/apremilast group) and patients in the placebo group were switched to apremilast (placebo/apremilast group), and a 4-week observational follow-up phase following discontinuation of apremilast at or before Week 64. Details of the study design have been previously reported (18). At treatment initiation, the apremilast dose was titrated during the first week (full titration schedule provided in prescribing information (15)) to reduce the occurrence of gastrointestinal adverse events.

Ethics approval

The RELIEF final study protocol and informed consent form were approved by an independent ethics committee or relevant institutional review board (IRB) at all participating sites (main IRB, Shulman Associates IRB, Inc., IRB #201406183), and written informed consent was obtained from all participants. RELIEF was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation E6 guidelines on Good Clinical Practice.

Efficacy outcomes

The primary efficacy endpoint was the area under the curve for the total number of oral ulcers over 12 weeks ($AUC_{Wk0\text{-}12}$), which represents the number of oral ulcers over time and thus accounts for the relapsing-remitting course of oral ulcers in patients with BS. Additional secondary and exploratory endpoints assessed through Week 64 included the number of oral ulcers, change from baseline in oral ulcer pain as assessed by a 100-mm visual analogue scale (VAS), and the proportions of patients achieving complete resolution of oral ulcers (*i.e.* oral ulcer-free) or partial response (defined as ≥50% reduction from baseline in the number of oral ulcers). Endpoints assessed at Week 12 and Week 64 included changes from baseline in patients' overall disease activity and QoL as assessed using the patient-reported BS Activity Score (BSAS; score range, 0-100), Behçet's Disease Current Activity Form (BDCAF) with its components (Behçet's Disease Current Activity Index [BDCAI] [score range, 0-12], Patient's Perception of Disease Activity [scale, 1–7], and Clinician's Overall Perception of Disease Activity [scale, 1–7]) and Behçet's Disease Quality of Life (BDQoL) (score range, 0–30). For the BSAS, BDCAF components and BDQoL, higher scores indicate more active disease or greater impairment in QoL; for each of these measures, negative changes from baseline indicate improvement.

Patient-reported new, recurrent, or worsening manifestations of BS were assessed at each visit and compared with baseline, including activity related to skin lesions, arthritis, and uveitis as well as gastrointestinal, central nervous system, or vascular symptoms.

Safety and tolerability were assessed at each visit and are presented for the placebo-controlled period and the apremilast-exposure period. The apremilast-exposure period encompassed all apremilast-exposure data from the first dose of apremilast, irrespective of when the apremilast exposure started (Week 0 or Week 12).

Statistical analyses

Statistical analyses for the placebo-controlled period have been previously reported (18). In this report, efficacy data were analysed descriptively by time point using all available data with no imputation for missing data. Safety data were analysed among the safety population, which included all randomised patients who received ≥1 dose of study medication. Data were analysed for (1)

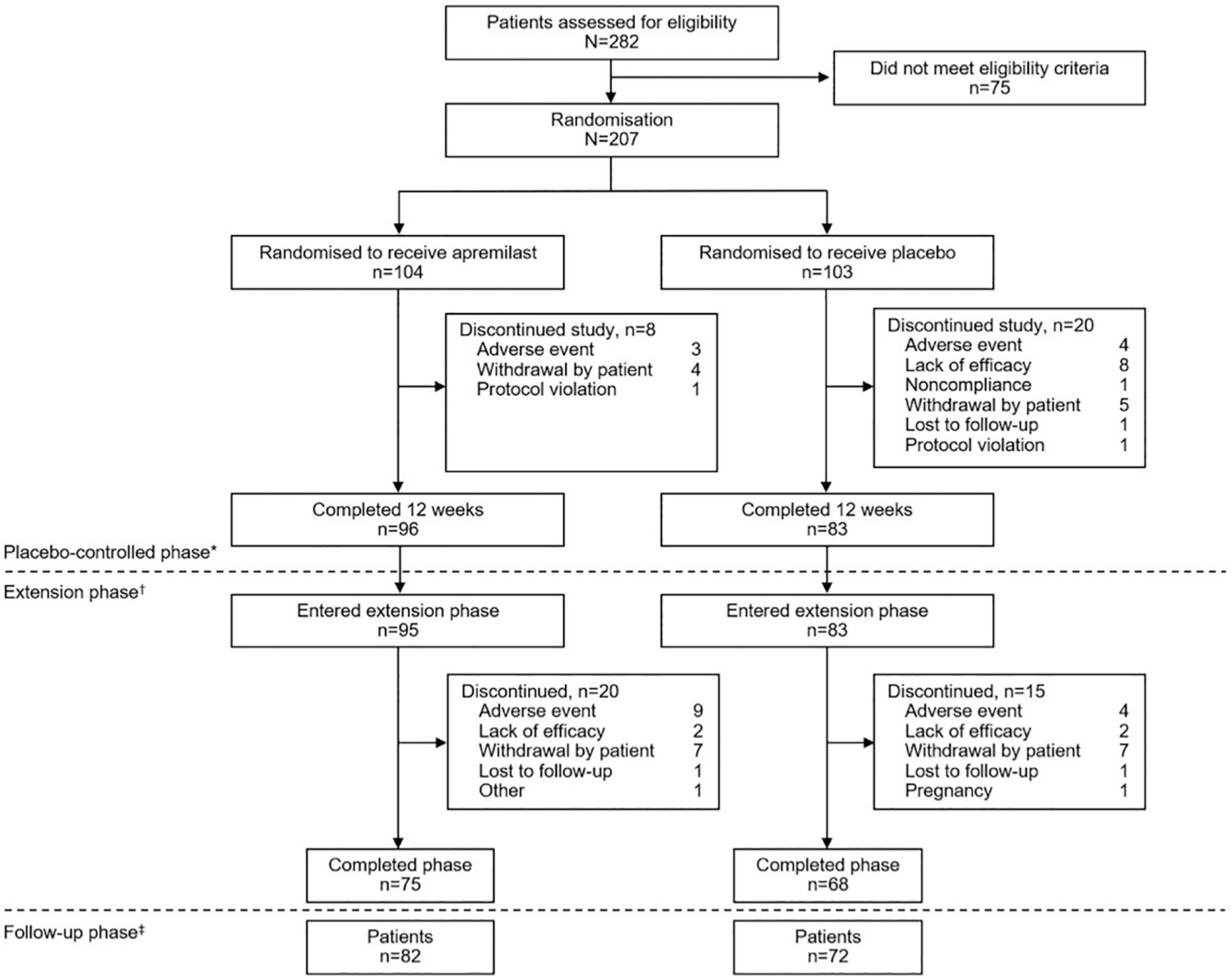


Fig. 1. Flow of participants in a randomised clinical study of apremilast *vs*. placebo for the oral ulcers associated with Behçet's syndrome.
*The placebo-controlled phase encompassed data from Week 0 to Week 12.
†The extension phase encompassed data for Week 12 to Week 64.
‡All patients who completed the extension phase, as well as all patients who discontinued for any reason, were eligible to enter the 4-week post-treatment observational follow-up phase. From: Hatemi G, Mahr A, Ishigatsubo Y *et al*.: Trial of apremilast for oral ulcers in Behçet's syndrome. *N Engl J Med 2019;* 381: 1922. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

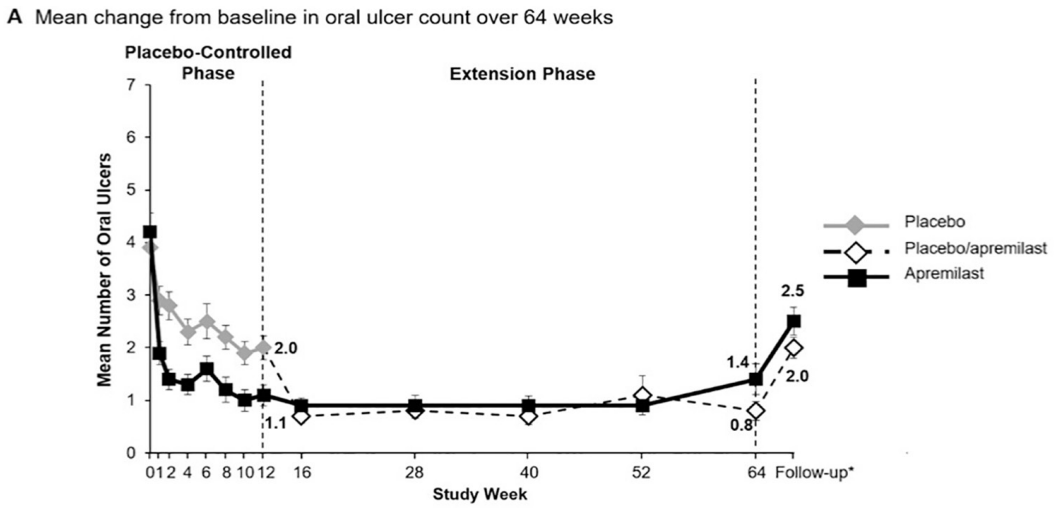
the placebo-controlled period, which included data through Week 12, and (2) the apremilast-exposure period, which included data for all patients who received at least one dose of apremilast regardless of when apremilast was initiated. Safety outcomes were summarised descriptively.

Results

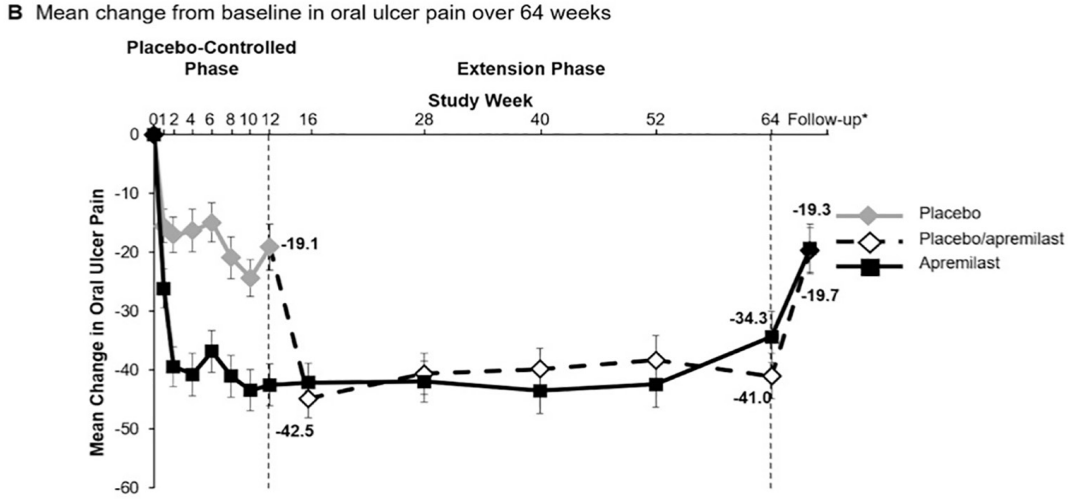
A total of 207 patients were randomised and included in the analysis. Patients initially assigned to receive placebo or apremilast were comparable in terms of baseline demographics and disease characteristics (8). At baseline, prior use of colchicine and topical corticosteroid use was similar between the placebo and apremilast groups. During the extension phase, 8.4% (7/83) of patients in the placebo/apremilast group and 8.7% (9/104) in the apremilast/apremilast group used colchicine and 10.8% (9/83) and 14.4% (15/104), respectively, used topical corticosteroids. In total, 96 (92.3%) patients in the apremilast group and 83 (80.6%) in the placebo group completed the 12-week placebo-controlled phase (Fig. 1). Except for one patient assigned to apremilast, all patients entered the extension phase. A total of 143 patients completed Week 64 (75 initially assigned to apremilast and 68 who switched from placebo to apremilast at Week 12). The most common reasons for discontinuation during the extension phase were patient withdrawal and adverse events.

Efficacy

The $AUC_{Wk0\text{-}12}$ for the number of oral ulcers (primary endpoint) was significantly lower in the apremilast group than in the placebo group, with a least-squares mean (SE) of 129.5 (15.9) and 222.1 (15.9), respectively (treatment difference [95% confidence interval], -92.6 [-130.6, -54.6]; $p<0.0001$) (18). This is equivalent to a daily average number of oral ulcers of 1.54 in the apremilast group and 2.64 in the place-



Week	0	1	2	4	6	8	10	12	16	28	40	52	64	Follow-up*
Placebo, n	103	98	97	93	91	86	83	82†						
Placebo/apremilast, n									83	78	73	70	67	82
Apremilast, n	104	101	101	101	98	94	94	97	95	92	85	79	75	85



Week	0	1	2	4	6	8	10	12	16	28	40	52	64	Follow-up*
Placebo, n	102	95	96	91	90	85	82	81†						
Placebo/apremilast, n									82	77	73	70	68	81
Apremilast, n	103	95	97	99	97	92	93	95	94	91	84	78	75	84

Fig. 2. Effect of apremilast *vs*. placebo on oral ulcer count and pain by time point over 64 weeks.
A: Mean change in the number of oral ulcers in the intent-to-treat population (data as observed).
B: Mean change in the pain of oral ulcers, assessed using a 100-mm visual analogue scale, in the intent-to-treat population (data as observed). Error bars represent standard error.
*Patients entered a 4-week post-treatment observational follow-up phase following discontinuation of apremilast at or before Week 64.
†One patient did not have a valid oral ulcer assessment at the Week 12 visit.

bo group (daily difference of 1.10 oral ulcers and a 42% reduction).

The least-squares mean number of oral ulcers was consistently lower with apremilast *versus* placebo at every visit, starting from Week 1 through Week 12. Among patients originally assigned to apremilast, improvements in the mean number of oral ulcers were maintained through Week 64 (Fig. 2A). Among patients originally randomised to placebo who switched to apremilast at Week 12, the improvements (reductions) in the mean number of oral ulcers observed in patients remaining in the study were comparable to those in patients originally randomised to apremilast; improvements were maintained with continued apremilast treatment for up to 64 weeks. After discontinuing apremilast treatment at or before Week 64, patients in the 4-week observational follow-up phase experienced a return of oral ulcer symptoms. The mean (SD) number of oral ulcers increased from 0.8 (1.5) in the placebo/apremilast group and 1.4 (2.6) in the apremilast/apremilast group at Week 64 to 2.0 (1.8) and 2.5 (2.5), respectively, 4 weeks following discontinuation of apremilast (Fig. 2A).

In parallel with oral ulcer number reductions, greater least-squares mean reductions from baseline in oral ulcer pain VAS were observed over 12 weeks with apremilast *versus* placebo. Among patients originally randomised to placebo who switched to apremilast at Week 12, the improvements (decreases) in oral ulcer pain observed in patients remaining in the study were comparable to those in patients originally randomised to apremilast; improvements were main-

Table I. Safety profile during the placebo-controlled and apremilast-exposure periods.

	Placebo-controlled period*				Apremilast-exposure period†			
	Placebo (Weeks 0 to 12)		Apremilast (Weeks 0 to 12)		Placebo/apremilast (Week 12 up to Week 68)		Apremilast/apremilast (Week 0 up to Week 68)	
	n (%)	EAIR‡/100 patient-years	n (%)	EAIR‡/100 patient-years	n (%)	EAIR‡/100 patient-years	n (%)	EAIR‡/100 patient-years
Sample size	103			104	83		104	
Patients with ≥1 AE	74 (71.8)	813.1	82 (78.8)	1039.6	70 (84.3)	322.6	90 (86.5)	452.7
TEAE in ≥5% of apremilast patients								
Diarrhoea	21 (20.4)	115.4	43 (41.3)	297.1	24 (28.9)	44.5	50 (48.1)	82.0
Nausea	11 (10.7)	56.5	20 (19.2)	102.4	12 (14.5)	17.9	24 (23.1)	28.4
Headache	11 (10.7)	55.6	15 (14.4)	72.2	15 (18.1)	23.6	23 (22.1)	26.2
URTI	5 (4.9)	24.6	12 (11.5)	55.0	7 (8.4)	10.2	19 (18.3)	20.1
Upper abdominal pain	2 (1.9)	9.6	9 (8.7)	41.6	7 (8.4)	10.4	13 (12.5)	13.3
Vomiting	2 (1.9)	9.6	9 (8.7)	41.7	5 (6.0)	7.1	9 (8.7)	9.1
Back pain	6 (5.8)	30.1	8 (7.7)	36.2	6 (7.2)	8.7	10 (9.6)	10.2
Viral URTI	5 (4.9)	24.0	7 (6.7)	31.6	8 (9.6)	11.3	12 (11.5)	12.3
Insomnia	2 (1.9)	9.7	1 (0.5)	4.4	7 (8.4)	10.2	5 (4.8)	4.8
Abdominal pain	3 (2.9)	14.6	4 (3.8)	17.9	6 (7.2)	8.9	6 (5.8)	5.8
Patients with ≥1 severe TEAE	6 (5.8)	29.3	6 (5.8)	27.0	4 (4.8)	5.6	17 (16.3)	17.3
Patients with ≥1 serious TEAE	4 (3.9)	19.4	3 (2.3)	13.2	7 (8.4)	9.9	10 (9.6)	9.6
Patients with ≥1 AE leading to discontinuation	5 (4.9)	23.8	3 (2.3)	13.0	3 (3.6)	4.1	12 (11.5)	11.3
Death	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0

*The placebo-controlled period encompassed data Week 0 to Week 12.
†The apremilast-exposure period encompassed all apremilast-exposure data from the first dose of apremilast, irrespective of when the apremilast exposure started (at Week 0 or Week 12) and includes 4 weeks of follow-up.
‡EAIR/100 patient-years is defined as 100 times the number of patients (n) reporting the event divided by patients' total exposure, up to the first event start date for patients reporting the event, in years.
AE: adverse event; EAIR: exposure-adjusted incidence rate; TEAE: treatment-emergent adverse event; URTI: upper respiratory tract infection.

tained with continued apremilast treatment for up to 64 weeks (Fig. 2). Reductions from baseline on the oral ulcer pain VAS at Week 64 (mean [SD], -41.0 [32.0] in the placebo/apremilast group, -34.3 [37.5] in the apremilast/apremilast group) were not fully maintained at 4 weeks following treatment discontinuation (-19.7 [35.3] in the placebo/apremilast group, -19.3 [37.3] in the apremilast/apremilast group) (Fig. 2B).

Greater proportions of patients receiving apremilast achieved complete or partial response of oral ulcers at Week 12 compared with patients receiving placebo, and rates of complete and partial response of oral ulcers were maintained at 64 weeks with continued apremilast treatment (complete response: 53.3% [40/75]; partial response: 76.0% [57/75]; Fig. 3). Comparable, sustained results were observed in the placebo/apremilast group at Week 64 (complete response: 64.2% [43/67]; partial response: 83.6% [56/67]; Fig. 3). The proportion of patients with complete or partial response declined within 4 weeks following treatment discontinuation (Fig. 3).

Improvements in overall disease activity and patients' QoL, as measured using the BSAS, BDCAF (including the BDCAI, Patient's Perception of Disease Activity score, and Clinician's Overall Perception of Disease Activity score), and BDQoL were observed in patients treated with apremilast *versus* placebo at Week 12 (Fig. 4A-E). These improvements were maintained with continued treatment at Week 64 for patients initially assigned to apremilast. Comparable effects were observed for patients switching from placebo to apremilast at Week 12 (Fig. 4A-E). Disease activity and QoL improvements were lost or reduced within 4 weeks after discontinuing apremilast treatment.

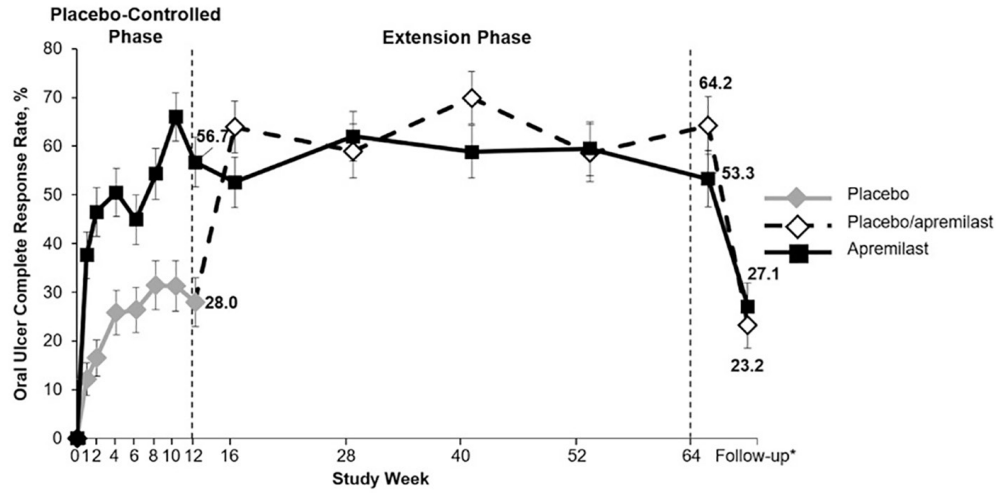
Safety

During the placebo-controlled period, no evidence of worsening uveitis or other new organ involvement or relapse of major organ involvement (including gastrointestinal involvement) was observed with apremilast.

During the apremilast-exposure period, one patient in the apremilast/apremilast treatment group experienced serious adverse events of ischaemic myositis (myositis) and arterial thrombosis, which were both severe. The patient had swelling of her left arm, and magnetic resonance imaging demonstrated regional increased water content, suggesting ischaemic myositis, which was interpreted as due to a small muscular artery thrombosis. Doppler ultrasonography showed the large vessels were intact. The swelling resolved in 3 days. The investigator considered these events were not related to apremilast, but most likely because of the underlying BS. No evidence of worsening other major organ involvement was observed. During the apremilast-exposure period, no events of new or worsening uveitis were reported in patients originally randomised to apremilast 30 mg twice daily; one new event of anterior uveitis (iridocyclitis) was reported at Week 64 in a patient originally randomised to placebo 1 day after the last dose of apremilast. Ophthalmological examinations did not reveal any abnormal findings.

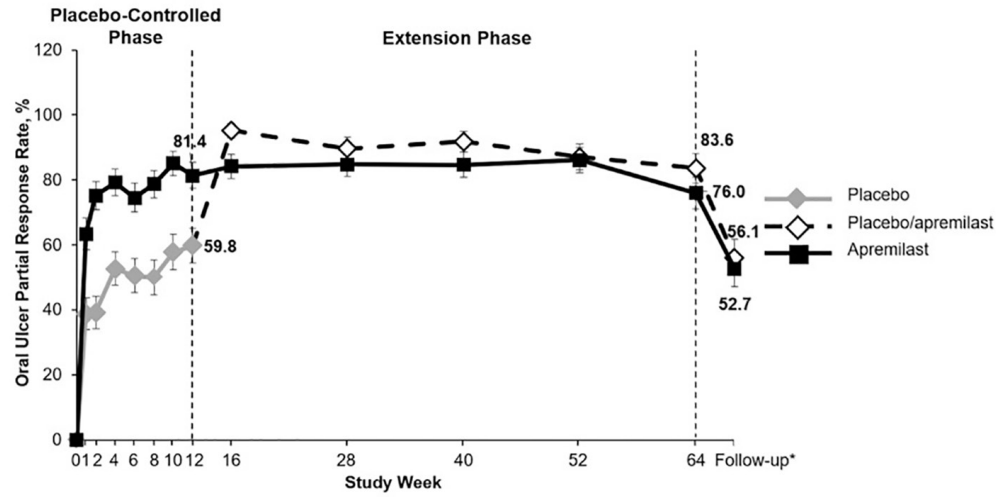
This study provides safety data for a

A Proportions of patients achieving complete resolution of oral ulcers over 64 weeks



Week	0	1	2	4	6	8	10	12	16	28	40	52	64	Follow-up*
Placebo, n	103	98	97	93	91	86	83	82						
Placebo/apremilast, n									83	78	73	70	67	82
Apremilast, n	104	101	101	101	98	94	94	97	95	92	85	79	75	85

B Proportions of patients achieving partial resolution of oral ulcers over 64 weeks



Week	0	1	2	4	6	8	10	12	16	28	40	52	64	Follow-up*
Placebo, n	103	98	97	93	91	86	83	82						
Placebo/apremilast, n									83	78	73	70	67	82
Apremilast, n	104	101	101	101	98	94	94	97	95	92	85	79	75	85

Fig. 3. Effect of apremilast *vs*. placebo on complete and partial resolution of oral ulcers by time point over 64 weeks in:
A: The proportions of patients who achieved complete resolution of oral ulcers over 64 weeks in the intent-to-treat population (data as observed);
B: The proportions of patients who achieved complete resolution of oral ulcers over 64 weeks in the intent-to-treat population (data as observed).
*Patients entered a 4-week post-treatment observational follow-up phase following discontinuation of apremilast at or before Week 64. Partial response was defined as the proportion of patients with ≥50% reduction in the number of oral ulcers from baseline. Error bars represent standard error.

total of 187 patients exposed to apremilast, including those who switched from placebo. As was observed during the placebo-controlled period, the proportion of patients with at least one adverse event through Week 64 was comparable for patients who continued apremilast treatment *versus* those who switched from placebo to apremilast (86.5% *vs*. 84.3%) (Table I). The most common adverse events during the apremilast-exposure periods were diarrhoea, nausea, headache, upper respiratory tract infection, and viral upper respiratory tract infection, similar to the placebo-controlled period. No new safety concerns were identified with apremilast treatment during longer-term exposure (through Week 64). Through Week 64, serious adverse events were reported for 17 (9.1%) patients during apremilast exposure, with each serious adverse event reported by one patient each. Serious adverse events reported only during the apremilast-exposure period were worsening BS, endometrial cancer, herpes zoster, infectious colitis, vaginal stricture, and vestibular neuronitis in the placebo/apremilast group and appendicitis, arterial thrombosis (considered by investigator to be related to underlying BS), breast cancer, bronchitis, joint dislocation, lymph node tuberculosis, migraine, myositis (considered by investigator to be related to underlying BS), acute pancreatitis, road traffic accident, and tibia fracture in the apremilast/apremilast group. Of these, herpes zoster, endometrial cancer, and lymph node tuberculosis were considered related to treatment. No deaths were reported during the trial. Exposure-adjusted incidence rates of serious

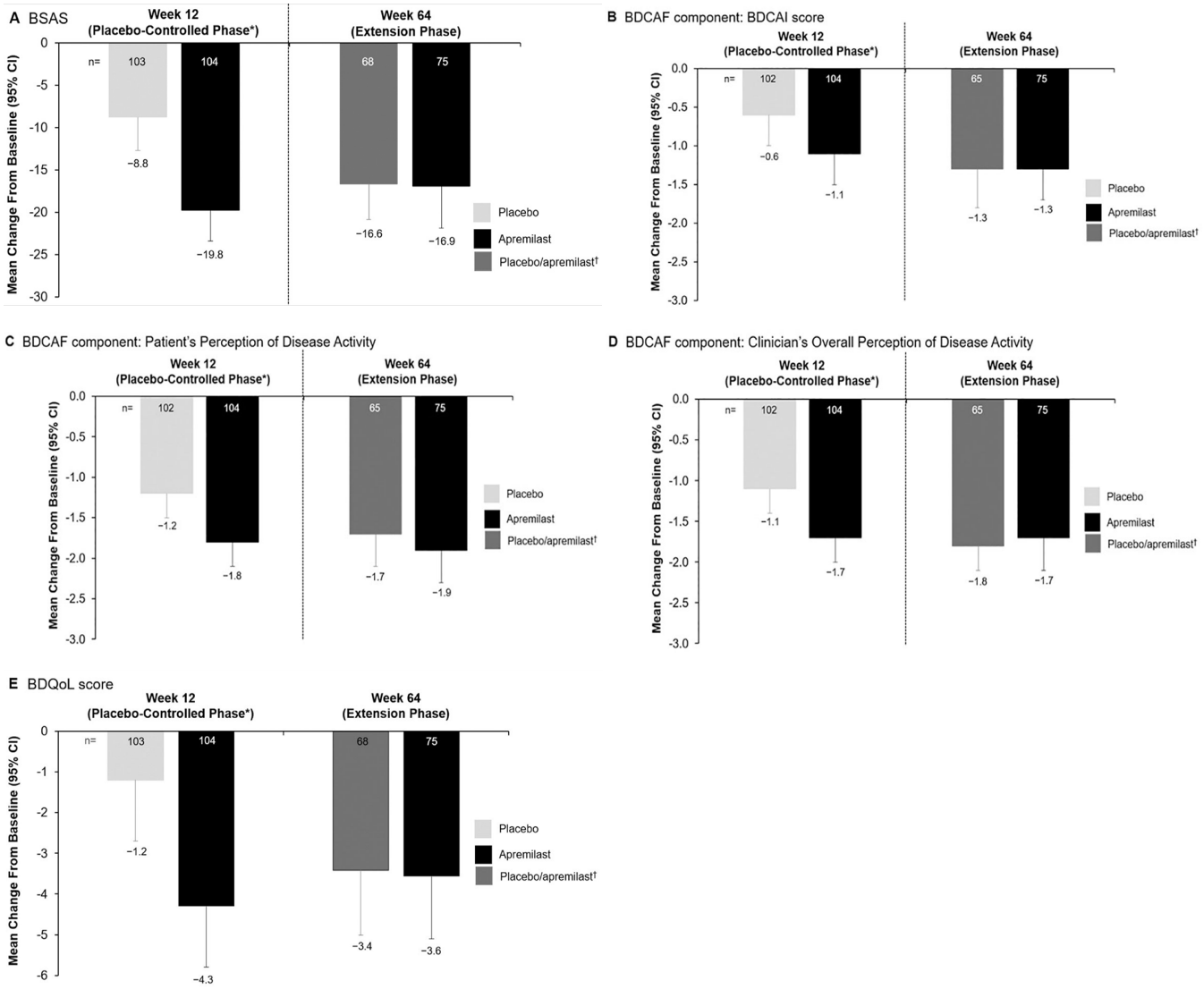


Fig. 4. Effect of apremilast *vs*. placebo on disease activity and quality-of-life measures at Weeks 12 and 64. Week 12 (placebo-controlled) analyses (least-squares mean change from baseline) are based on an analysis of covariance model using multiple imputation to handle missing data; Week 64 used data as observed.

A: Mean changes from baseline in the Behçet's Syndrome Activity Score (BSAS) in the intent-to-treat population.

B: Changes from baseline in the Behçet's Disease Current Activity Form (BDCAF) component, Behçet's Disease Current Activity Index (BDCAI), in the intent-to-treat population.

C: Changes from baseline in the BDCAF component, Patient's Perception of Disease Activity, in the intent-to-treat population. Patient's Perception of Disease Activity range, 1 to 7. Negative changes from baseline indicate improvement. Error bars represent 95% confidence interval.

D: Changes from baseline in the BDCAF component, Clinician's Overall Perception of Disease Activity, in the intent-to-treat population. Clinician's Overall Perception of Disease Activity range, 1 to 7. Negative changes from baseline indicate improvement. Error bars represent 95% confidence interval.

E: Changes from baseline in the Behçet's Disease Quality of Life (BDQoL) score in the intent-to-treat population. BSAS score range, 0 to 100. BDCAI score range, 0 to 12. BDQoL score range, 0 to 30. Higher scores indicate more disease activity or greater QoL impairment. Negative changes from baseline indicate improvement.

*Significant based on Week 12 treatment difference in least-squares mean for apremilast *vs*. placebo: BSAS, $p<0.0001$; BDCAI, $p=0.0367$; Patient's Perception of Disease Activity, $p<0.0077$; Clinician's Perception of Disease Activity, $p=0.0006$; and BDQoL, $p=0.0008$.

†Patients randomised to placebo switched to apremilast at Week 12. Error bars represent 95% confidence interval.

or severe adverse events and the most common adverse events reported with apremilast stayed the same or decreased during the apremilast-exposure period relative to the placebo-controlled period.

Discussion

RELIEF is notably the first large global clinical trial to evaluate the long-term efficacy and safety of a treatment for BS. This trial demonstrated the efficacy of apremilast in patients with active oral ulcers despite prior treatment with at least one non-biologic agent, suggesting a benefit for patients who are candidates for systemic therapy for the treatment of oral ulcers refractory to or intolerant of other treatments.

Findings from patients with at least 1 year of active apremilast treatment demonstrated the improvements in multiple measures of oral ulcers (number of oral ulcers, oral ulcer pain, oral ulcer complete response, and oral ulcer partial response) were maintained through Week 64. At the follow-up visit after 4 weeks without active treatment, worsening in

measures of oral ulcers was observed in both treatment groups. This observation is strongly suggestive of a treatment effect. Consistently, the improvements in overall BS activity and QoL were also maintained. Apremilast offers patients with oral ulcers associated with BS an effective therapy with the convenience of long-term dosing (8, 18, 20).

The safety profile for apremilast in this trial was consistent with the known safety profile of apremilast from clinical and real-world studies (8, 18, 20), and no new safety concerns were identified with apremilast treatment during longer-term exposure (up to 64 weeks). No evidence of new or worsening of organ involvement was observed outside of the reported single serious adverse event of swelling in the arm, which lasted 3 days.

Limitations of this study include that it had no active comparator and no control group after the 12-week double-blind placebo phase, limiting the ability to draw comparisons between apremilast and other long-term treatments. In addition, patients who had previously received biologics for oral ulcers were excluded; thus, no conclusions can be made regarding the efficacy of apremilast treatment for oral ulcers in biologic-experienced patients. Finally, as the trial was powered to assess AUC of oral ulcer counts through Week 12, effects of apremilast on manifestations other than oral ulcers (*e.g.* skin, joints, genital ulcers, uveitis) should be interpreted with caution.

Taken together, these findings indicate apremilast was well tolerated and had a clinically beneficial effect in the reduction of oral ulcer symptoms and recurrence over the long term.

Data availability

Qualified researchers may request data from Amgen clinical studies.

Complete details are available at: http://www.amgen.com/datasharing.

Acknowledgements

We thank the participants and the RELIEF study investigators for their contributions to the study. The full list of study investigators can be found in the Supplementary material. The RELIEF study was sponsored by Celgene. Amgen Inc. acquired the worldwide rights to Otezla® (apremilast) on November 21, 2019. Sponsor authors contributed to the study design, data collection, data analysis, data interpretation, manuscript and publication decisions. Writing support was funded by Celgene and Amgen Inc. and provided by Kristin Carlin, BSPharm, MBA, of Peloton Advantage, LLC, an OPEN Health company, and Cathryn M. Carter, MS, employee of and stockholder in Amgen Inc.

Competing interests

G. Hatemi has received grant/research support from Celgene and has served as a speaker for AbbVie, Celgene, Novartis and UCB Pharma. A. Mahr has served as a consultant for Celgene, as a consultant and speaker for Chugai and as a speaker for Roche. M. Takeno has received consulting fees and a speaking fee from Amgen Inc., research grants and personal fees from AbbVie, Asahi Kasei, Chugai, Eisai, and Tanabe-Mitsubishi, and speaking fees from Astellas, Ayumi, Eli Lilly, Novartis, Ono Pharmaceuticals, and Takeda. D. Saadoun has received grant/research support from AbbVie and Roche and has served as a consultant for AbbVie, Celgene, Janssen, and Roche. H. Direskeneli has received grant/research support from Celgene and educational grants to attend meetings from Celgene and Amgen Inc. S. Cheng, M. Paris, and M. Chen are employees of Amgen Inc. S. McCue is a former employee of Celgene and Amgen Inc. Y. Yazici has served as a consultant for Bristol Myers Squibb, Celgene, Genentech, and Sanofi. The other co-authors have declared no competing interests.

References

1. YAZICI H, SEYAHI E, HATEMI G, YAZICI Y: Behçet's syndrome: a contemporary view. *Nat Rev Rheumatol* 2018; 14: 119.
2. HATEMI G, CHRISTENSEN R, BANG D *et al*.: 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann Rheum Dis* 2018; 77: 808-18.
3. HATEMI G, SEYAHI E, FRESKO I, TALARICO R, HAMURYUDAN V: One year in review 2020: Behçet's syndrome. *Clin Exp Rheumatol* 2020; 38 (Suppl. 127): S3-10.
4. HATEMI G, MEARA A, OZGULER Y *et al*.: Developing a core set of outcome measures for Behçet's disease: report from OMERACT 2016. *J Rheumatol* 2017; 44: 1750-3.
5. SENUSI AA, OLA D, MATHER J, MATHER J, FORTUNE F: Behçet's syndrome and health-related quality of life: influence of symptoms, lifestyle and employment status. *Clin Exp Rheumatol* 2017; 35 (Suppl. 108): S43-50.
6. LECCESE P, OZGULER Y, CHRISTENSEN R *et al*.: Management of skin, mucosa and joint involvement of Behçet's syndrome: a systematic review for update of the EULAR recommendations for the management of Behçet's syndrome. *Semin Arthritis Rheum* 2018; 48: 752-62.
7. GONZALEZ-MOLES MA: The use of topical corticoids in oral pathology. *Med Oral Patol Oral Cir Bucal* 2010; 15: e827-31.
8. HATEMI G, MELIKOGLU M, TUNC R *et al*.: Apremilast for Behçet's syndrome - a phase 2, placebo-controlled study. *N Engl J Med* 2015; 372: 1510-8.
9. TAYLOR J, GLENNY AM, WALSH T *et al*.: Interventions for the management of oral ulcers in Behçet's disease. Cochrane Database Syst Rev 2014; 2014: CD011018.
10. SCHAFER P: Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. *Biochem Pharmacol* 2012; 83: 1583-90.
11. PAUL C, CATHER J, GOODERHAM M *et al*.: Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe plaque psoriasis over 52 weeks: a phase III, randomized, controlled trial (ESTEEM 2). *Br J Dermatol* 2015; 173: 1387-99.
12. CUTOLO M, MYERSON GE, FLEISCHMANN R *et al*.: A phase III, randomized, controlled trial of apremilast in patients with psoriatic arthritis: results of the PALACE 2 trial. *J Rheumatol* 2016; 43: 1724-34.
13. KAVANAUGH A, MEASE PJ, GOMEZ-REINO JJ *et al*.: Longterm (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis. *J Rheumatol* 2015; 42: 479-88.
14. EDWARDS CJ, BLANCO FJ, CROWLEY J *et al*.: Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). *Ann Rheum Dis* 2016; 75: 1065-73.
15. Otezla [package insert]. Thousand Oaks, CA: Amgen Inc.; June 2020.
16. Otezla Japan [package insert]. Tokyo, Japan: Celgene; 2019.
17. EUROPEAN MEDICINES AGENCY: Otezla Summary of Opinion (post authorisation) Amsterdam, The Netherlands: European Medicines Agency; 2020. Available at: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-otezla-ii-29_en.pdf. Accessed April 9, 2021.
18. HATEMI G, MAHR A, ISHIGATSUBO Y *et al*.: Trial of apremilast for oral ulcers of Behçet's syndrome. *N Engl J Med* 2019; 381: 1918-28.
19. INTERNATIONAL STUDY GROUP FOR BEHÇET'S DISEASE: Criteria for diagnosis of Behçet's disease. *Lancet* 1990; 335: 1078-80.
20. ATIENZA-MATEO B, MARTÍN-VARILLAS JL, GRAÑA J *et al*.: Apremilast in refractory orogenital ulcers and other manifestations of Behçet's disease. A national multicentre study of 51 cases in clinical practice. *Clin Exp Rheumatol* 2020; 38 (Suppl. 127): S69-75.