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ORIGINAL RESEARCH

Impact of apremilast on quality of life in Behçet's syndrome: analysis of the phase 3 RELIEF study

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ABSTRACT

Objective To assess apremilast's impact on patient quality of life (QoL) in active Behçet's syndrome and correlations between improvement in patients' QoL and efficacy measures in the phase 3 RELIEF study.

Methods QoL measures included Behçet's Disease QoL (BDQoL), 36-Item Short-Form Health Survey V.2 (SF-36v2) Physical/Mental Component Summary (PCS/MCS) and eight subscale scores, focusing on Physical Functioning (PF). Pearson's correlation coefficients assessed relationships between efficacy endpoints (oral ulcer count, oral ulcer pain, Behçet's Syndrome Activity Scale (BSAS), Behçet's Disease Current Activity Form (BDCAF)) and QoL endpoints for apremilast at Week 12.

Results Apremilast (n=104) demonstrated significantly greater improvements versus placebo (n=103) in SF-36v2 PCS (3.1 vs 0.9), MCS (4.6 vs −0.7) and PF (2.9 vs 0.14), respectively (all $p<0.05$). Mild correlations were observed in improvements of SF-36v2 measures (PCS, MCS, PF) with oral ulcer count (r=−0.11, PCS), and change in oral ulcer pain from baseline (r=−0.28, PCS; r=−0.10, PF) and BSAS (r=−0.38, PCS; r=−0.20, PF; r=−0.16, MCS). Correlations among BDCAF and SF-36v2 components and BDQoL were variable. BDQoL showed mild/moderate correlations with SF-36v2 components (r=−0.18, PCS; r=−0.13, PF; r=−0.45, MCS).

Conclusions Apremilast was associated with significant improvements in QoL measures of SF-36v2 PCS, MCS and PF and BDQoL in patients with Behçet's syndrome. Correlations of improvement among QoL endpoints support the beneficial clinical effects of apremilast in Behçet's syndrome.

Trial registration number NCT02307513.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Behçet's syndrome is a chronic, multisystem inflammatory disorder which may impair quality of life.
⇒ Apremilast is an oral phosphodiesterase 4 inhibitor approved in the USA, Japan, Israel, Switzerland, Canada and the European Union for the treatment of oral ulcers associated with Behçet's disease.

WHAT THIS STUDY ADDS

⇒ This study is the first to confirm that the clinical benefits of apremilast in reducing the number and pain of oral ulcers correlated with patient-reported improvements in quality of life.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Apremilast is the only agent with proven efficacy in improving the quality of life of patients with Behçet's syndrome.
⇒ This study provides further support for the use of apremilast in the treatment of Behçet's syndrome.

INTRODUCTION

Behçet's syndrome is a chronic, multisystem variable vessel vasculitis that impacts the skin, mucosa, joints, eyes, arteries, veins, nervous system and gastrointestinal system.[1–5] Oral ulcers are usually the first and most frequent symptom, and are considered to be the cardinal and defining feature of Behçet's syndrome.[4 6] Painful, recurrent and disabling oral ulcers negatively impact patients' quality of life (QoL).[1 4 7 8] QoL impairment in patients with Behçet's syndrome has been confirmed in studies using different QoL instruments, including the Behçet's Disease Quality of Life (BDQoL) and the Short-Form Health Survey V.2 (SF-36v2).[9–13] A previous study had shown that patients with Behçet's syndrome report greater impairment in QoL than with several other chronic diseases, including long-standing and severe arthritis and inflammatory bowel diseases.[14]

Colchicine is currently recommended as first-line treatment for the mucocutaneous lesions of Behçet's syndrome.[5] When lesions recur despite colchicine treatment, immunomodulatory or immunosuppressive therapy is recommended.[5 15] However, these drugs are characterised by high interindividual and intraindividual variability of efficacy and safety with a narrow therapeutic index.[5 16] This

highlights the need for more effective and well-tolerated treatment options for the management of patients with Behçet's syndrome.

Apremilast is a non-biological oral phosphodiesterase 4 inhibitor recently approved in the USA, Japan, Israel, Switzerland, Canada and the European Union for the treatment of oral ulcers associated with Behçet's syndrome.[17–19] The efficacy of apremilast in reducing the number and pain of oral ulcers in patients with Behçet's syndrome has been demonstrated in a phase 2 clinical study (BCT-001)[15] and more recently in a larger, multinational phase 3 study (BCT-002, RELIEF).[20] Long-term, sustained improvements in individual QoL and disease activity outcomes (Behçet's Syndrome Activity Scale (BSAS), Behçet's Disease Current Activity Form (BDCAF) components and BDQoL) with apremilast treatment have also been demonstrated.[21]

Herein, we focus on the impact of apremilast on QoL through BDQoL and SF-36v2 assessments in patients with Behçet's syndrome treated with apremilast 30 mg two times per day or placebo for 12 weeks from the RELIEF study. Correlations between these measures and the number of oral ulcers, change in oral ulcer pain, BSAS and BDCAF components were evaluated. Although modest correlations between QoL and disease activity outcome measures have been reported in Behçet's syndrome previously,[10 22–26] this subanalysis is aimed to provide additional comprehensive information from the RELIEF study, the only randomised phase 3 clinical trial that evaluated QoL in Behçet's syndrome.

METHODS

Study design and treatments

The RELIEF study design has been previously published.[20] Briefly, the phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group study randomised eligible patients with active Behçet's disease (1:1) to apremilast 30 mg two times per day or placebo for 12 weeks, after a 6-week screening phase. Randomisation was stratified by sex, history of uveitis and region (Japan and other). The 12-week placebo-controlled period was followed by a 52-week active treatment phase in which all patients received apremilast 30 mg two times per day. Patients who completed the active treatment phase or discontinued from the study at any time point for any reason entered into a 4-week post-treatment observational follow-up phase.

Patient and public involvement

RELIEF study enrolment began in December 2014 at the assigned investigational sites. The study protocol, amendment and informed consent forms (ICFs) were approved by the Institutional Review Board at each investigational site or by a central review board which included public and patient representation. Patients were required to sign the ICF before screening. Patients were invited to participate in the treatment phase if the investigator confirmed they had active Behçet's syndrome and met the study entry requirements (inclusion and exclusion criteria) during the 6-week screening phase. Eligible patients were expected to have a randomisation visit, scheduled on-study visits and a post-study follow-up visit. The ICF provided patients with information about the study and expected visits; patients were asked about any adverse effects and completed health assessment questionnaires throughout the duration of the study. The outcome measures for the study were drawn from drug development guidelines established by the US Food and Drug Administration. All the mandatory domains for mucocutaneous involvement in the Core Domain Set for Behçet's syndrome endorsed by OMERACT, which was developed and voted on by patient participation, were assessed.[27] Safety and efficacy monitoring in both studies were also performed by an independent, external data monitoring committee (DMC) as outlined in the DMC charter. At the time results of this study were made available to the public, investigators were provided with a summary of the results, which was written for the lay person. Investigators were responsible for sharing these results with the patient and/or their caregiver as agreed by the patient.

Study participants

Patients eligible to participate had to be ≥18 years of age with a confirmed diagnosis of Behçet's syndrome according to International Study Group criteria.[7] Patients must have had oral ulcers which occurred ≥3 times in the previous 12-month period, at screening and at randomisation despite prior treatment with at least one non-biological therapy such as topical corticosteroids or systemic treatment. Patients were required to have active oral ulcers, defined as ≥2 oral ulcers at screening and ≥2 oral ulcers at randomisation (occurring ≥14 days after screening) or ≥3 oral ulcers at randomisation (occurring between 1 and 42 days after screening). Additional key inclusion and exclusion criteria have been previously described.[20]

QoL and disease activity assessments

QoL was assessed through change from baseline in SF-36v2 domains and Physical and Mental Component Summary (PCS and MCS) scores and BDQoL. SF-36v2 is a generic QoL index, whereas BDQoL is a disease-specific instrument developed and validated for Behçet's syndrome.[28 29] Correlations were also conducted at Week 12 among selected key efficacy endpoints of the number of oral ulcers and changes from baseline in oral ulcer pain (100 mm Visual Analogue Scale (VAS)), overall disease activity measures (BSAS, BDCAI), BDQoL and SF-36v2 PCS, Physical Functioning (PF) and MCS scores.

BSAS and BDCAF are validated instruments for the assessment of overall disease activity in Behçet's syndrome.[30 31] BSAS was completed by the patient on a secure, validated, hand-held device. BSAS is a patient-reported outcome (PRO) measure that comprises 10 items with a total score range between 0 and 100; a lower

total score indicates less disease activity and a higher total score indicates more disease activity. The BDCAF questionnaire was administered to the patient by the investigator, who completed the form on a secure, validated hand-held device. BDCAF includes three components, the Behçet's Disease Current Activity Index (BDCAI), the Patient's Perception of Disease Activity and the Clinician's Overall Perception of Disease Activity. In BDCAI, active disease manifestations over the previous 4 weeks are quantified on a 12-point scale, with a higher score indicating higher level of activity.

BDQoL and SF-36v2 are self-administered forms completed by patients on a secure, validated, hand-held device. BDQoL comprises 30 items which measure disease-related restrictions on patients' activities and emotional responses to these restrictions. Each item is scored 0 or 1 with a total scoring range of 0–30; a lower score indicates better QoL. SF-36v2 measures concepts which are not specific to any age, disease or treatment group, thereby allowing comparison of the relative burden of different diseases and the relative benefit of different treatments. This general health status instrument consists of eight scales: PF, Role Limitations–Physical, Vitality, General Health Perceptions, Bodily Pain, Social Functioning, Role Limitations–Emotional and Mental Health. Scale scores range from 0 to 100, with higher scores indicating better health. Two overall summary scores for SF-36v2 were the PCS score and the MCS score. All scale scores and PCS and MCS scores were norm based and transformed to have a mean of 50 and SD of 10, with higher scores indicating better health.

Statistical analysis and correlations

Comparisons between treatments at Week 12 were performed for a modified intent-to-treat population, which was defined as all patients who were randomised and received at least one dose of study medication. QoL measures were evaluated using an analysis of covariance model, with treatment, sex and region as a factor and value at baseline as a covariate. Missing values were imputed using the last-observation-carried-forward approach. Efficacy results were considered statistically significant after adjustment for multiplicity; all tests were two-sided (α=0.05).

The relationship between the disease severity and QoL as well as disease-related QoL and overall health-related QoL was evaluated. The strength of the correlations of the number of oral ulcers at Week 12 and the change from baseline in the pain associated with oral ulcers, BSAS and BDCAF components at Week 12 with SF-36v2 PCS, PF and MCS scores as well as BDQoL were assessed in the apremilast group based on Pearson's correlation coefficients and associated p values. We applied the commonly used rule to determine the strength of correlation between the variables based on the Pearson correlation coefficient: correlation coefficient values greater than 0.7 or less than −0.7 indicate a strong correlation, values between 0.4 and 0.7 or −0.4 and −0.7 indicate a moderate correlation, values less than 0.4 or greater than −0.4 are considered a mild correlation, and a correlation coefficient value close to 0.0 shows no linear relationship between the movement of the two variables.

RESULTS

Patients

A total of 207 patients were randomised to apremilast 30 mg two times per day (n=104) or placebo (n=103); of these, 179 (86.5%) completed the 12-week placebo-controlled phase (apremilast: 96 (92.3%); placebo: 83 (80.6%)). Baseline patient demographics and disease characteristics were generally similar between the apremilast and placebo groups.[20] Patients randomised to the apremilast and placebo groups had similar oral ulcer counts (4.2 and 3.9, respectively) and mean oral ulcer pain VAS scores (61.2 and 60.8, respectively). Mean BSAS (42.8 and 44.3), SF-36v2 PCS (41.3 and 39.8), MCS (41.3 and 42.3), PF (43.4 and 42.6) and BDQoL (10.2 and 11.2) were similar between the apremilast and placebo groups.

Patients' QoL

Significantly greater improvements from baseline were observed with apremilast in SF-36v2 PCS (p=0.0204), MCS (p<0.0001) and SF-36v2 PF subscale scores (p=0.0060) compared with placebo (figure 1). Mean scores for all eight SF-36v2 subscales showed improvement from baseline to Week 12 with apremilast (figure 2). Across the SF-36v2 subscale scores, 10%–25% more patients receiving apremilast versus placebo experienced an improvement of at least 2.5 points (minimal clinically important difference[32 33]) at Week 12 (figure 3). Some of the scores on the SF-36v2 measures and subscales were similar at baseline and Week 12 in the placebo group, indicating no improvement in these patients. The positive impact of apremilast on QoL was supported by significant improvement in BDQoL score with apremilast versus placebo at Week 12 (−3.5 vs −0.5; p=0.0003).

Correlation of efficacy measures of disease symptom and activity with patients' QoL

Mild correlations were observed between the number of oral ulcers and the improvement in SF-36v2 PCS in patients treated with apremilast at Week 12 (table 1). Similarly, change in oral ulcer pain at Week 12 was mildly correlated with the change from baseline in SF-36v2 PCS as well as PF (table 1). Change from baseline in BSAS was mildly correlated with SF-36v2 PCS, PF and MCS. Variable correlations were observed between the BDCAF components of BDCAI and Physician's and Patient's Perception of Disease Activity with SF-36v2 component scores and physical function domain (table 1). Mild correlations were observed between the change in BDQoL and changes from baseline in oral ulcer pain, BSAS and the Physician's and Patient's Perception of Disease Activity components of the BDCAF (table 1). Change from baseline in BDQoL showed a moderate and significant

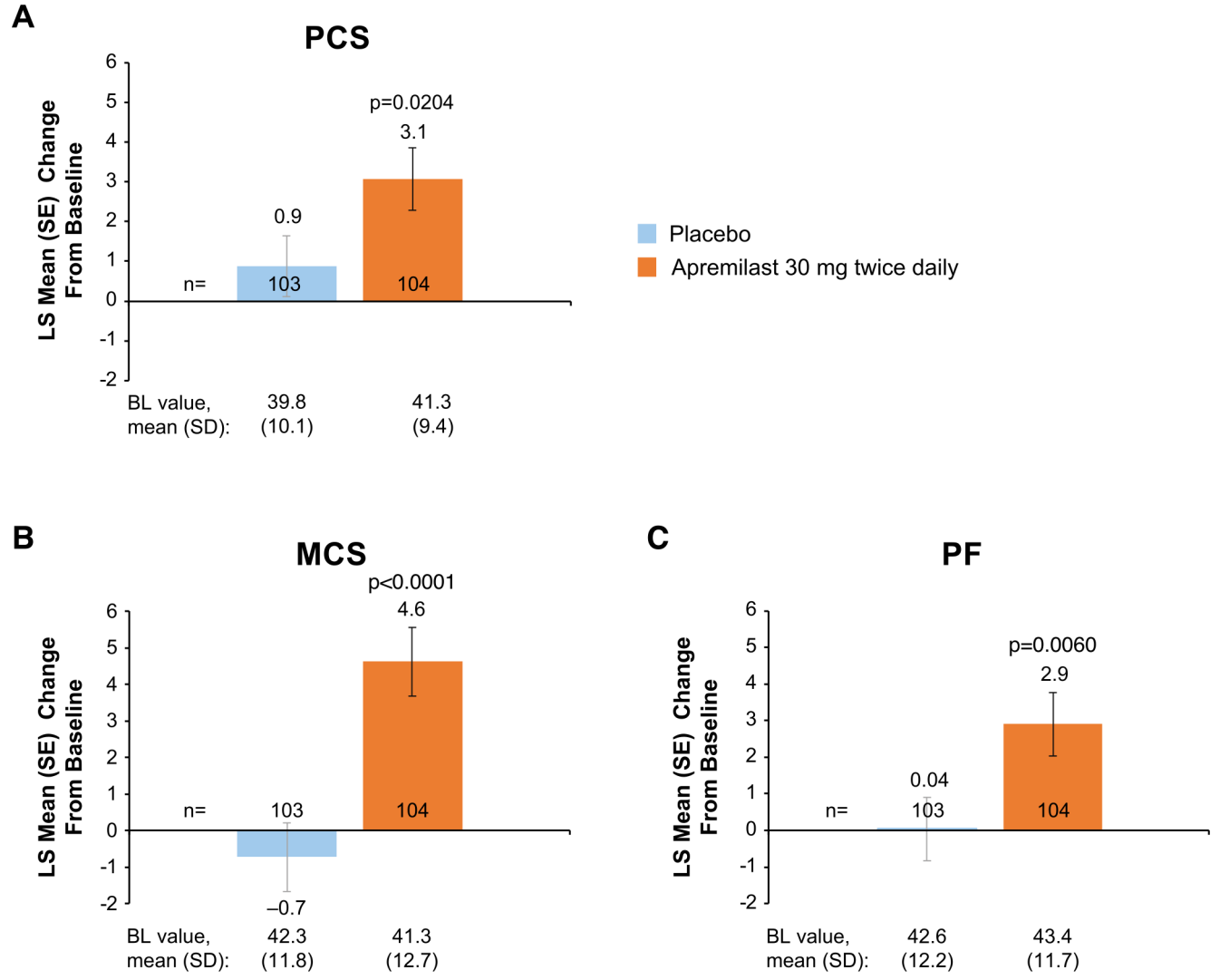


Figure 1 Improvement in SF-36v2 (A) PCS, (B) MCS and (C) PF subscale scores at Week 12 (modified intent-to-treat population). Scores range from 0 to 100. Higher scores indicate better functioning; positive changes from baseline represent improvement. Missing values were assessed using last-observation-carried-forward analysis. BL, baseline; LS, least squares; MCS, Mental Component Summary; PCS, Physical Component Summary; PF, Physical Functioning; SF-36v2, 36-Item Short-Form Health Survey V.2.

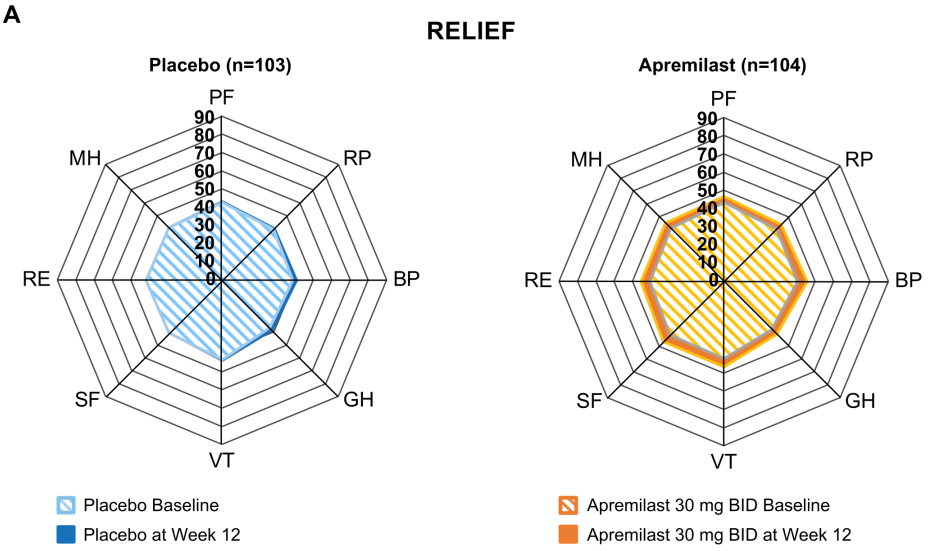
correlation with SF-36v2 MCS and mild correlations with PCS and PF (table 1).

DISCUSSION

In the phase 3 RELIEF study, apremilast treatment was associated with significant improvements in Behçet's syndrome-related QoL. Significant improvement in overall health-related QoL, assessed using the SF-36v2, was observed in MCS, PCS and the physical function domain. In addition, clinically meaningful improvement in subscale scores with apremilast compared with placebo were observed. Patients treated with apremilast in the placebo-controlled period reported physical health disabilities at baseline as severe as patients with fibromyalgia (SF-36v2 PCS score of 41.3 vs 38.6[34]), mental health disabilities as severe as patients with rheumatoid arthritis (SF-36 MCS score of 41.3 vs 39.4–40.2[34 35]) and severity of impaired physical function similar to that reported in patients with peripheral psoriatic arthritis (SF-36v2 PF value of 43.4 vs 43.5[35]), signifying reduced QoL. Following treatment with apremilast, health and function, as measured by SF-36v2 PCS (mean 44.8), MCS (mean 46.1) and PF (mean 46.5) scores, improved toward values observed in a US general population of healthy people (SF-36v2 PCS (49.2), MCS (53.8), PF (50.1)).[36] Changes from baseline to Week 12 exceeded the estimated minimal clinically important difference threshold of 2.5,[32 33] thus supporting the clinical meaningfulness of the improvement in the signs and symptoms of Behçet's syndrome.

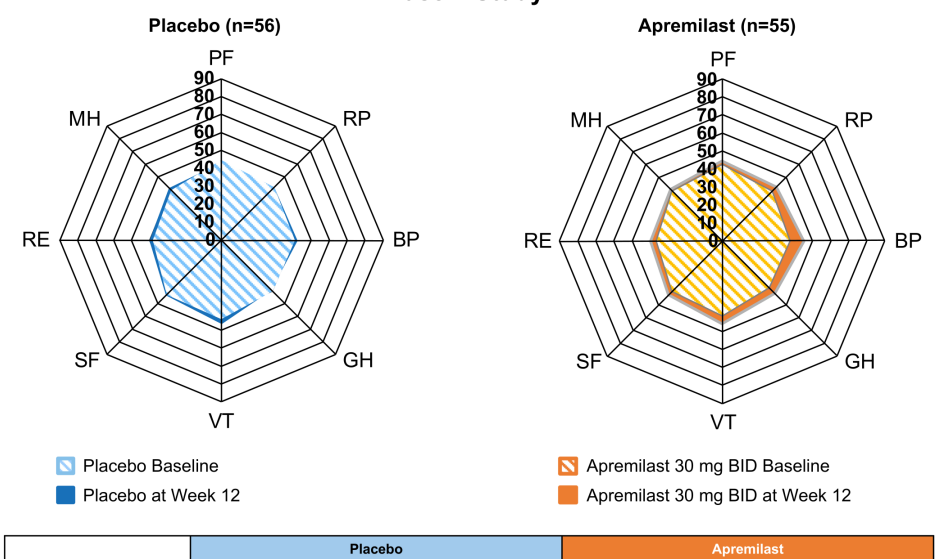
RELIEF and the previously reported BCT-001 study[15] are the only randomised clinical trials to evaluate the efficacy of a drug on QoL among patients with Behçet's syndrome to date. The current analysis from RELIEF extends these results, confirming that the clinical benefit of apremilast in reducing the number of oral ulcers was correlated with SF-36v2 PCS and pain of oral ulcers was

A



	Placebo		Apremilast	
	Baseline	Week 12	Baseline	Week 12
PF	42.6	43.1	43.4	46.5
RP	39.7	40.2	40.9	44.3
BP	38.8	40.8	40.3	45.7
GH	36.7	38.5	37.1	40.7
VT	43.3	43.9	42.2	46.9
SF	41.0	40.8	41.6	46.8
RE	41.6	40.8	40.4	45.5
MH	41.0	40.9	41.2	45.1

B



	Placebo		Apremilast	
	Baseline	Week 12	Baseline	Week 12
PF	44.5	42.3	42.5	44.4
RP	41.6	40.9	39.1	42.3
BP	40.8	41.4	37.4	45.2
GH	40.3	38.7	36.7	41.1
VT	44.0	45.6	41.6	45.6
SF	43.0	42.7	39.4	42.3
RE	78.4	81.2	74.7	82.3
MH	39.7	40.2	39.4	40.4

Figure 2 SF-36v2 subscale scores at baseline and improvement at Week 12 (modified intent-to-treat population). Scores range from 0 to 100. Higher scores indicate better functioning; positive changes from baseline represent improvement. Missing values were assessed using last-observation-carried-forward analysis. BID, twice per day; BP, Bodily Pain; GH, General Health; MH, Mental Health; PF, Physical Functioning; RE, Role/Emotional; RP, Role/Physical; SF, Social Functioning; SF-36v2, 36-Item Short-Form Health Survey V.2; VT, Vitality.

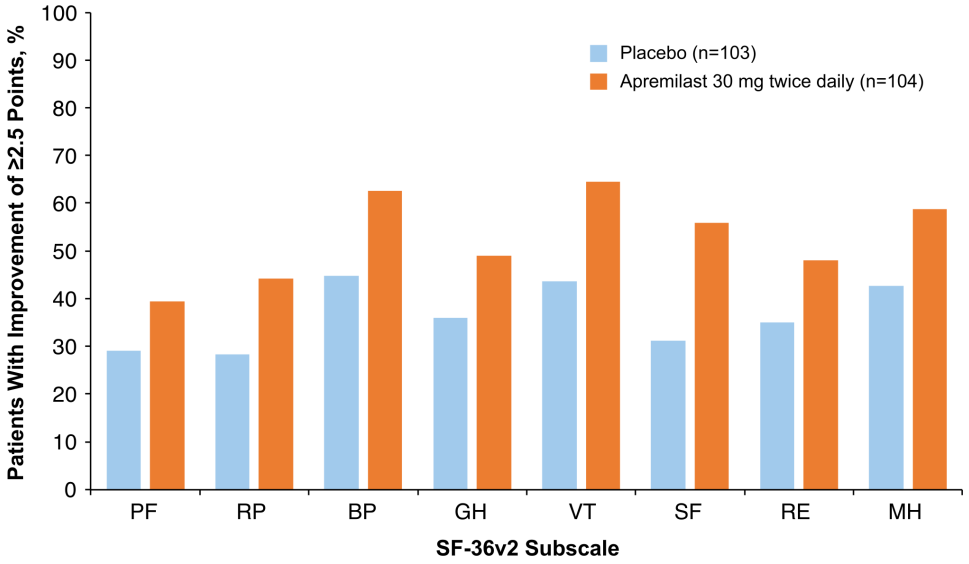


Figure 3 Percentages of patients with improvement of ≥2.5 points (MCID) at Week 12 for SF-36v2 subscale scores (modified intent-to-treat population). Missing values were assessed using last-observation-carried-forward analysis. BP, Bodily Pain; GH, General Health; MCID, minimal clinically important difference; MH, Mental Health; PF, Physical Functioning; RE, Role/Emotional; RP, Role/Physical; SF, Social Functioning; SF-36v2, 36-Item Short-Form Health Survey V.2; VT, Vitality.

mildly correlated with QoL measures of SF-36 PCS and PF along with BDQoL.

This is the first randomised, placebo-controlled study that analysed QoL measures recognising that the symptoms (oral ulcers and oral ulcer pain) of Behçet's syndrome have a negative impact on patients' QoL and QoL impairments related to disease severity.[4 8 10 11 13 37 38] The comprehensive assessment of Behçet's syndrome in RELIEF using a multidimensional approach, combining the use of generic-specific, disease-specific and symptom-specific PROs support the importance of patient-centric outcomes in studies.[39 40]

Table 1 Correlation of change from baseline in SF-36v2 PCS, PF and MCS and BDQoL with Behçet's Disease Activity, Week 12 (modified intent-to-treat population,)

	Apremilast 30 mg two times per day (n=104)			
Change from baseline at week 12	**PCS**	**PF**	**MCS**	**BDQoL**
OU count*	−0.11 p=0.2472	−0.07 p=0.4734	−0.02 p=0.8746	0.07 p=0.4656
Pain VAS	−0.28 p=0.0035	−0.10 p=0.3072	−0.09 p=0.3875	0.28 p=0.0036
BSAS	−0.38 p<0.0001	−0.20 p=0.0435	−0.16 p=0.0954	0.22 p=0.0237
BDCAF†				
BDCAI	−0.19 p=0.0505	0.01 p=0.9108	−0.06 p=0.5380	0.04 p=0.6680
Physician's perception	−0.10 p=0.3206	0.01 p=0.9021	−0.13 p=0.1734	0.20 p=0.0465
Patient's perception	−0.27 p=0.0060	−0.13 p=0.2031	−0.08 p=0.4283	0.23 p=0.0194
BDQoL	−0.18 p=0.0606	−0.13 p=0.1884	−0.45 p<0.0001	–

Pearson's correlations are presented. The stronger the correlation of the two variables, the closer the Pearson correlation coefficient to either +1 or −1 depending on whether the relationship is positive or negative, respectively. A correlation coefficient close to 0.0 shows no linear relationship between the movement of the two variables. We defined a strong correlation as >0.7 or <−0.7; a moderate correlation as 0.4 to 0.7 or −0.4 to −0.7; and a mild correlation as <0.4 or >−0.4.
*OU count at Week 12.
†BDCAI, Physician's Perception of Disease Activity and Patient's Perception of Disease Activity are three components of the BDCAF. For OU count, OU pain, BSAS, BDCAF and BDQoL, a negative change depicts improvement. For SF-36v2 outcomes positive changes depict improvement.
BDCAF, Behçet's Disease Current Activity Form; BDCAI, Behçet's Disease Current Activity Index; BDQoL, Behçet's Disease Quality of Life; BSAS, Behçet's Syndrome Activity Score; MCS, Mental Component Summary; OU, oral ulcer; PCS, Physical Component Summary; PF, Physical Functioning; SF-36v2, 36-Item Short-Form Health Survey V.2; VAS, Visual Analogue Scale.

It has been reported previously that BSAS had moderate correlation with BDCAF and is a reliable and valid patient-reported measure of disease activity.[26] Our data are the first to correlate investigator-assessed oral ulcer count and patient-reported improvements in the PCS score of the SF-36v2. We observed that there was mild correlation between improvements in oral ulcer pain and BSAS with SF-36v2 and BDQoL assessment results. Furthermore, improvements with apremilast treatment in BDQoL had mild or moderate correlation with MCS, PCS and PF scores of the SF-36v2, which were reflected in the results of PRO measures of Behçet's syndrome-related QoL and overall health-related well-being. One might have expected stronger correlations between the improvement in number and pain of oral ulcers and the improvement in QoL measures. However, it should be noted that data on other Behçet's syndrome manifestations, including genital ulcers, papulopustular lesions and nodular lesions, as well as arthritis, are limited, so the impact of these lesions on QoL was not analysed. In addition, it should be noted that results from RELIEF mainly focused on the patient population of Behçet's syndrome associated with oral ulcers, as the selection criteria excluded patients with Behçet's syndrome-related active major organ involvement. The present study was limited in duration with a 12-week placebo-controlled period. A separate publication reports long-term, sustained improvement in individual QoL and disease activity outcomes (BSAS, BDCAF components and BDQoL) with apremilast.[21]

Across the SF-36v2 subscale scores, up to 25% more patients receiving apremilast versus placebo experienced an improvement of at least 2.5 points; however, the minimal clinically important difference (MCID) cut-off used was based on studies in psoriasis and rheumatoid arthritis. Confirmation of this MCID cut-off in Behçet's syndrome is needed. Interestingly, the correlations between BDQoL and SF-36v2 components were also not strong. Findings from a previous study aiming to understand patients' experiences with Behçet's syndrome focusing on different disease manifestations had suggested that the current PRO measures were not capturing all aspects of the patients' perception of Behçet's syndrome.[38] Altogether, these findings suggest that there may be room for improvement regarding PRO measures for Behçet's syndrome.

In conclusion, apremilast was associated with significant improvements in QoL measures of SF-36v2 PCS, MCS and PF and BDQoL in patients with Behçet's syndrome. Overall, correlations of key efficacy endpoints, such as improvements in oral ulcer number, oral ulcer pain and disease activity with improvement in QoL in patients treated with apremilast were mild and heterogenous. BDQoL and SF-36v2 MCS were correlated moderately well, supporting consistent symptom improvement with apremilast in Behçet's syndrome.

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Contributors GH and SC contributed to the conception of the work, acquisition of data and the analysis and interpretation of the study results. AM, MT, D-YK, MM, SM, MP, MC and YY contributed to the acquisition of data, analysis and/or interpretation of the study results. GH is the guarantor for the overall content. All authors critically reviewed the manuscript and approved the final version.

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Competing interests GH has received grant/research support from Celgene, Amgen and Silk Road Therapeutics, and has served as a speaker for AbbVie, Boehringer Ingelheim, Novartis and UCB Pharma. AM has served as a consultant for Celgene and Amgen, a consultant and speaker for Chugai and a speaker for Roche. MT has served as a consultant for Celgene and Amgen, has received grant/research support from AbbVie, Asahi Kasei, Chugai, Eisai and Tanabe-Mitsubishi, and has served as a speaker for Astellas, Ayumi, Eli Lily, Jansen Pharma, Nippon Shinyaku, Novartis, Ono Pharmaceuticals and Takeda. D-YK has no conflicts to disclose. MM has no conflicts to disclose. SC, MP and MC are employees of and stockholders in Amgen. SM is a former employee of Celgene. YY has served as a consultant for Amgen, Bristol Myers Squibb, Celgene, Genentech and Sanofi.

Patient consent for publication Not applicable.

Ethics approval The studies were designed by the sponsor and authors and conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines, as described in International Conference on Harmonisation Guideline E6. The institutional review board or ethics committee at each participating site approved the protocol. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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

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