




ORIGINAL ARTICLE

Characteristics and outcomes of patients treated with apremilast in the real world: results from the APPRECIATE study

M. Augustin,^{1,*}  C.E. Kley, C. Conrad,³ P.G. Sator,⁴ M. Stähle,⁵ K. Eyerich,⁶ M.A. Radtke,⁷ C. Bundy,⁸ L. Mellars,⁹ C. Greggio,¹⁰ M. Cordey,¹¹ V. Koscielny,¹⁰ C.E.M. Griffiths²

¹Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

²The Dermatology Centre, The University of Manchester, NIHR Manchester Biomedical Research Centre, Manchester, UK

³Service of Dermatology and Venereology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

⁴Department of Dermatology, Hietzing Hospital, Vienna, Austria

⁵Unit of Dermatology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

⁶Department of Dermatology and Allergy, Technical University of Munich, Munich, Germany

⁷Dermatologikum Hamburg, Hamburg, Germany

⁸College of Biomedical and Health Sciences Cardiff University, Cardiff, UK

⁹Celgene Corporation, Summit, NJ, USA

¹⁰Celgene International, Boudry, Switzerland

¹¹Amgen Europe GmbH, Rotkreuz, Switzerland

*Correspondence: M. Augustin. E-mail: m.augustin@uke.de

Abstract

Background APPRECIATE is a multinational, observational, retrospective, cross-sectional study in patients treated for psoriasis with apremilast, an oral phosphodiesterase 4 inhibitor.

Objectives To describe the characteristics of patients with psoriasis treated with apremilast in the clinical setting, to evaluate real-world outcomes of psoriasis treatment with apremilast and to better understand the perspectives of patients and physicians on treatment outcomes.

Methods In six European countries, patients with chronic plaque psoriasis treated in clinical practice who could be contacted 6 (\pm 1) months after apremilast initiation were enrolled. Patient characteristics, Dermatology Life Quality Index (DLQI) and Psoriasis Area and Severity Index (PASI) were obtained from medical records when available. Outcomes were evaluated using patient/physician questionnaires.

Results In 480 patients at treatment initiation, mean [median; 95% confidence interval (CI)] PASI and DLQI scores were 12.5 (10.7; 11.6–13.4) and 13.4 (13.0; 11.4–14.2), respectively. At 6 (\pm 1) months, 72.3% of patients ($n = 347$) continued apremilast treatment [discontinuations: lack of efficacy (13.5%), safety (11.7%), other (2.5%)]. In patients continuing treatment, 48.6% achieved a \geq 75% reduction in PASI score; mean (95% CI) DLQI score was 5.7 (4.5–6.9), and mean (SD) Patient Benefit Index score was 2.8 (1.2). Physicians perceived clinical improvement in 75.6% of patients. Physicians' perspective on overall success of apremilast in meeting expectations correlated with patients' perception of treatment benefit ($r = 0.691$). Most commonly reported adverse events ($>5\%$ of patients) were diarrhoea, nausea and headache.

Conclusions Patients in APPRECIATE reported high disease burden despite more moderate skin involvement than those who enrolled in clinical trials of apremilast. Findings from APPRECIATE demonstrate the real-world value of apremilast for psoriasis treatment, as 7 of 10 patients continued therapy and showed notable improvement in disease severity and quality of life 6 (\pm 1) months after apremilast initiation.

Received: 4 November 2019; Accepted: 25 February 2020

Conflicts of interest

MA is a consultant and/or paid speaker for AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene Corporation, Centocor, Eli Lilly, GSK, Janssen-Cilag, LEO Pharma, Medac, Merck, MSD, Novartis, Pfizer, UCB and XenoPort. MAR is an invited lecturer and involved in clinical studies and health services studies with Celgene Corporation and acts as a

Clinical Trial Registry Number: NCT02740218.

consultant and/or paid speaker for AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene Corporation, Centocor, Eli Lilly, GSK, Janssen-Cilag, LEO Pharma, Medac, Merck, MSD, Novartis, Pfizer, UCB and Xenoport. KE is an advisory board member and received honoraria from AbbVie, Amgen, Berlin-Chemie, Celgene Corporation, Hexal, Janssen and Novartis. CC is a scientific advisor and/or clinical study investigator for AbbVie, Actelion, Amgen, Celgene Corporation, Janssen, LEO Pharma, Lilly, MSD, Novartis and Pfizer. CEK is an investigator and advisory board member and was provided research grants from Amgen, Celgene Corporation, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer and UCB. PGS is a member of research grants, acted as lecturer and/or consultant, and provided travel grants from AbbVie, Actelion, Amgen, Celgene Corporation, Janssen, LEO Pharma, Lilly, Maruho, Merck Sharp & Dohme, Novartis, Pfizer and UC. MS is an advisory board member, consultant and/or speaker for AbbVie, Amgen, Celgene Corporation, Eli Lilly, Janssen-Cilag, LEO Pharma, Novartis, Pfizer, UCB and Wyeth. CB is an advisory board member, speaker and/or consultant for AbbVie, Bayer, Celgene Corporation, Janssen, Lilly, Novartis, Pfizer and UCB. LM, CG and VK were employed at the time of study conduct by Celgene Corporation. MC is employed by Amgen Inc. and was employed by Celgene Corporation at the time of study conduct. CEMG is an advisory board member, speaker and/or consultant for AbbVie, Amgen, Biogen, Boehringer Ingelheim, Bristol-Meyers Squibb, Celgene Corporation, Galderma, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Sandoz and UCB.

Funding sources

This research was sponsored by Celgene Corporation (Summit, NJ, USA). CEMG is a National Institute for Health Research (NIHR) Senior Investigator and is funded in part by the NIHR Manchester Biomedical Research Centre.

Introduction

Psoriasis, a long-term immune-mediated inflammatory disease,¹ is associated with several comorbidities, including psoriatic arthritis (PsA) and cardiometabolic disorders.^{2–5} In addition to its clinical burden, psoriasis has significant psychosocial impact.⁶ In large surveys of patients with psoriasis, respondents have reported that psoriasis can affect emotional state, interfere with daily life⁷ and have a negative impact on work, relationships and sleep.⁸

The impact of psoriasis on a patient's daily life may not always correlate directly with commonly used clinical measures of disease severity.^{6,9,10} Current psoriasis treatment algorithms and guidelines rely primarily on a clinician's assessment of disease severity, such as body surface area (BSA) and Psoriasis Area and Severity Index (PASI) and secondarily on patient-reported quality of life (QOL) including the Dermatology Life Quality Index (DLQI).¹¹ Standard severity measures do not encompass all factors that influence the disease burden.^{10,12} Additional factors, including involvement of highly visible or bothersome areas (e.g. scalp, nails, genitals, palms and/or soles) or symptoms (e.g. itching), significantly impair QOL and impact patient-perceived severity.^{13–16} Failure to assess all factors of disease involvement and associated symptoms may result in disparate physician and patient treatment goals.^{17,18} Moderate-to-severe psoriasis has been inadequately treated,¹⁹ and a European consensus statement was developed to identify and provide treatment guidelines for these patients.²⁰

Apremilast is an oral phosphodiesterase 4 inhibitor first approved in Europe for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis and PsA in 2015.^{21,22} In phase 3 and 4 placebo-controlled clinical studies,

apremilast demonstrated efficacy and safety in patients with moderate-to-severe psoriasis previously treated with systemic therapy (ESTEEM 1 and 2),^{21,23} in biologic-naïve patients with moderate-to-severe psoriasis (LIBERATE),²⁴ and in systemic- and biologic-naïve patients with moderate psoriasis (UNVEIL).²⁵ There is a need to investigate the use and effectiveness of apremilast in real-world settings.

The Apremilast Clinical Treatment Experience in Psoriasis (APPRECIATE; NCT02740218) study, a multinational, observational, retrospective, cross-sectional study, was designed to describe the characteristics of patients with psoriasis treated with apremilast in the clinical setting, and to better understand treatment needs and outcomes from the perspectives of both the physician and the patient.^{26–28} To complement chart reviews and validated patient-reported outcomes tools, questionnaires were designed by expert consensus to capture perceived effectiveness, convenience and global satisfaction beyond standard disease assessment tools. This manuscript presents the results from the six participating European countries.

Materials and methods

Setting

This study was designed to capture outcome data 6 months after the initiation of apremilast treatment (Fig. 1). A 6-month time point was chosen because the greatest improvement during pivotal clinical trials was observed within the first 24 weeks of treatment.^{21,23–25} The analysis included patients and their physicians from 87 sites in six European countries (Austria, Germany, Ireland, Sweden, Switzerland and the United Kingdom). Sites were

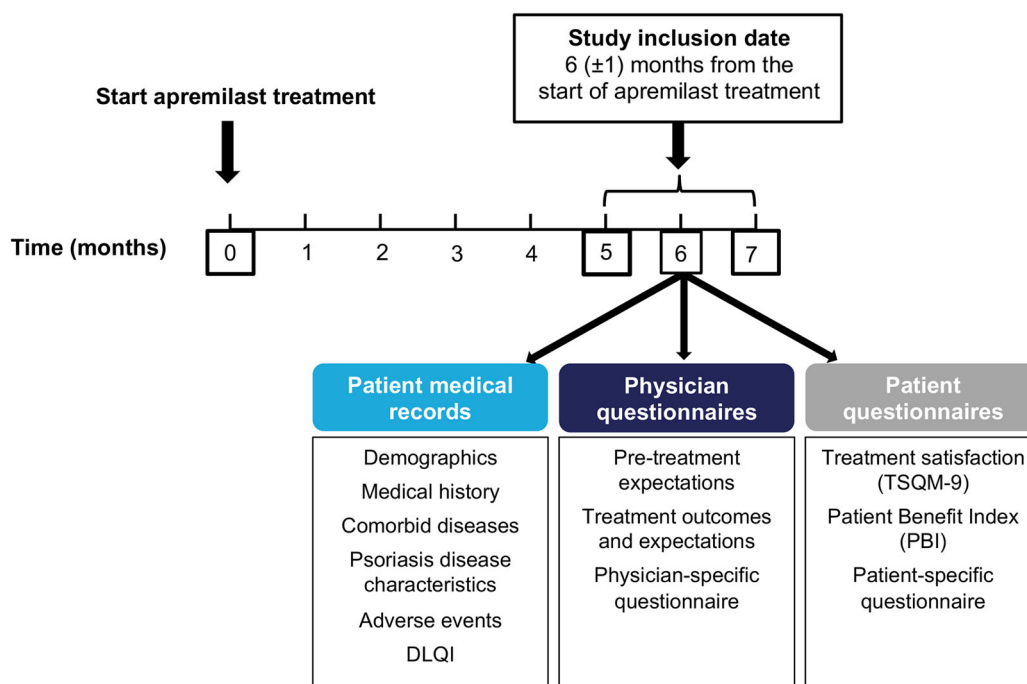


Figure 1 Study design. DLQI, Dermatology Life Quality Index; TSQM-9, 9-item Treatment Satisfaction Questionnaire for Medication.

selected based on their psoriasis management expertise, their access to apremilast through local reimbursement or access options and their research and governance capacity. Sites were representative of urban and rural areas, and hospital, clinic and private-practice settings. For sites that were considered for feasibility but not included ($N = 297$), reasons for non-selection ($n = 165$), non-participation ($n = 14$) and withdrawal ($n = 11$) are described in the supplementary appendix (Figure S1, Supporting Information). Patients were enrolled between May 2016 and July 2018 based on sequential opening of study sites in participating countries.

Participants

Patients were aged 18 years or older with physician-diagnosed chronic plaque psoriasis treated according to routine clinical practice, who could be contacted 6 (± 1) months after apremilast initiation. Patients were enrolled regardless of whether they were continuing apremilast treatment. Per protocol, patients were recruited consecutively at each site, and physicians were asked to log non-enrolled patients to keep track of their apremilast treatment status. All assessments were performed during routine clinical visits. Patients who were participating in another clinical trial were excluded from the study. The study was approved by the relevant ethics committees (Table S1, Supporting Information), and informed consent was obtained before any data collection occurred. The research was conducted according to the principles expressed in the Declaration of Helsinki.

Study medication

Apremilast treatment was initiated within the approved European Union (EU) label indication as per routine clinical practice; study inclusion was not a factor in clinical decision-making. Reimbursement criteria were largely similar across countries, although in the United Kingdom and Ireland apremilast was prescribed as part of an early patient access programme.

Data collection

Data were collected from three sources: medical records, physicians and patients.

Medical records provided data on patient demographics, disease characteristics, apremilast status 6 (± 1) months after its initiation and adverse events (AEs). Disease characteristics included disease severity (PASI and psoriasis-involved BSA), presence of specific manifestations and symptoms of psoriasis (scalp, nails, palmoplantar, genital, non-genital inverse, pruritus, fatigue, palmoplantar pustulosis and PsA), a skin-related QOL measure (DLQI) and prior phototherapy or systemic psoriasis treatments. Disease severity scores were collected at follow-up for patients remaining on apremilast therapy, and AEs were captured retrospectively. All data from medical records were entered into a password-protected, web-based electronic data capture (EDC) system by the physician.

Study-specific questionnaires were developed for both physicians and patients based on expert consensus. These questionnaires assessed the needs and goals of patients in relation to their

psoriasis treatment, as well as the ability of apremilast to meet patients' expectations and physicians' expectations on effectiveness and overall treatment success.

For each enrolled patient, the treating physician completed the study-specific physician questionnaire using the EDC system. This questionnaire collected information on the reasons for apremilast use, treatment effects on symptoms, treatment tolerability, effectiveness of apremilast on individual psoriasis symptoms (when data were available), fulfilment of expectations per symptom present at treatment initiation and overall success.

Patients were asked to complete three questionnaires 6 (\pm 1) months after apremilast initiation: the study-specific questionnaire and two other validated questionnaires [the Patient Benefit Index (PBI) for skin diseases and the 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9), details of which have been previously reported].^{29,30} The PBI consists of two questionnaires: the Patient Needs Questionnaire (PNQ), typically administered before initiating a therapy to assess treatment goals, and the Patient Benefit Questionnaire (PBQ), typically administered at follow-up to assess the extent to which treatment goals have been met.³¹ In APPRECIATE, owing to the retrospective nature of data collection, both the PNQ and PBQ were administered 6 (\pm 1) months after treatment initiation. The questionnaires were completed by patients on paper and then entered into the EDC system by the clinical research organization (Kantar Health GmbH, Munich, Germany).

The study-specific patient questionnaire collected patient demographics, socioeconomics, lifestyle factors, beliefs and expectations plus experience of taking apremilast. Completed patient questionnaires were reviewed for any AEs related to their apremilast treatment.

Statistical analysis

This study is primarily descriptive; no a priori hypotheses were identified. Patient demographics, disease characteristics, treatment outcomes and AEs were summarized for all patients enrolled using descriptive statistics; 95% confidence intervals (CIs) were calculated. Missing values were not imputed. Results were stratified by apremilast therapy status: ongoing versus discontinued. Correlations between outcome measures were calculated.

Results

Patient population characteristics

There were 605 patients contacted about participating in the APPRECIATE study; 484/605 were enrolled. There were 4/484 patients who were excluded from the analysis because they were later determined to be in violation of eligibility criteria. Reasons for non-enrolment and violation are reported in Table S2, Supporting Information.

The current analysis includes the 480 eligible patients (Germany, $n = 124$; United Kingdom, $n = 111$; Switzerland, $n = 83$; Sweden, $n = 75$; Austria, $n = 72$; and Ireland, $n = 15$) with a diagnosis of chronic plaque psoriasis who had received apremilast for the primary indication of plaque psoriasis. Of these patients, 462 (96.3%) completed questionnaires. Patient demographics and psoriasis characteristics of enrolled patients at treatment initiation are summarized in Table 1. Most patients (430; 89.6%) had received at least one prior systemic psoriasis treatment, and 66

Table 1 Patient demographics and disease characteristics at study initiation

Patient demographics	Patients (N = 480)
Age, years	
Median (range)	53.0 (18.0–89.0)
Mean (SD)	51.3 (15.2)
Gender, n (%)	
Male	258 (53.8)
Female	222 (46.3)
Ethnicity and race, n (%)	
White	371 (77.3)
South Asian	19 (4.0)
Asian (Chinese or other)	4 (0.8)
Black African	1 (0.2)
Other	22 (4.6)
BMI, kg/m² (n = 196)	
Median (range)	27.3 (17.0–53.0)
Mean (SD)	28.2 (6.3)
Disease characteristics	
Time since diagnosis, years (n = 475)	
Median (range)	15 (0–71)
Mean (SD)	18.6 (14.3)
PASI (n = 350)	
Median (range)	10.7 (0.2–60.1)
Mean (SD)	12.5 (8.4)
PASI <10, n (%)	131 (37.4)
PASI \geq 10, n (%)	219 (62.6)
BSA, % (n = 141)	
Median (range)	16 (0–90)
Mean (SD)	25.4 (23.5)
DLQI (n = 205)	
Median (range)	13 (0–30)
Mean (SD)	13.4 (7.5)
Comorbid conditions reported in >5% of patients, n (%)	
PsA	124 (25.8)
Metabolic syndrome	70 (14.6)
Hypertension	57 (11.9)
Obesity	37 (7.7)
Depression	31 (6.5)
Specific manifestations of psoriasis	
Pruritus, n (%)	325 (67.7)
Genital, n (%)	97 (20.2)
Non-genital, inverse, n (%)	73 (15.2)

Table 1 Continued

Patient demographics	Patients (N = 480)
Palmoplantar pustulosis	16 (3.3)
Highly visible locations, n (%)	388 (80.8)
Scalp	325 (67.7)
Nail	182 (37.9)
Palmoplantar	114 (23.8)
Prior systemic psoriasis treatment	
Phototherapy, †n (%)	270 (56.3)
Conventional systemic therapy, ‡n (%)	328 (68.3)
Biologic therapy, §n (%)	72 (15.0)
Concomitant medications for psoriasis reported for >2 patients	
UVA/UVB	28 (5.8)
Glucocorticoids	10 (2.1)
NbUVB	8 (1.7)
Psoralen + UVA	7 (1.5)
Methotrexate	5 (1.0)

BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; SD, standard deviation.

†Phototherapy included UVA/UVB (114; 23.8%); nbUVB (99; 20.6%); and psoralen + UVA (78; 16.3%).

‡Conventional systemic therapy included methotrexate (211; 44.0%); fumaric acid esters (95; 19.8%); acitretin (59; 12.3%); ciclosporin (52; 10.8%); retinoids (31; 6.5%); glucocorticoids (20; 4.2%); leflunomide (7; 1.5%); and sulfasalazine (3; 0.6%).

§Biologic therapy included adalimumab (42; 8.8%); etanercept (27; 5.6%); ustekinumab (20; 4.2%); secukinumab (15; 3.1%); infliximab (9; 1.9%); efalizumab (3; 0.6%); and ixekizumab (2; 0.4%).

(13.8%) were receiving concomitant medication at treatment initiation (Table 1). The reasons cited for discontinuing previous treatments were lack of efficacy (347; 72.3%), AEs (198; 41.3%), too burdensome (42; 8.8%) and cost (4; 0.8%). The most common reasons for considering apremilast included ease of use (272; 56.7%), ineffective prior treatments (263; 54.8%), fewer side-effects compared with other treatments (254; 52.9%) and anticipated efficacy (241; 50.2%). Approximately half (237; 49.4%) of all patients believed the decision to initiate apremilast was primarily a joint decision with their healthcare provider, whereas 191 (39.8%) thought the physician was the primary decision-maker and 23 (4.8%) that the decision had been primarily theirs.

At treatment initiation, mean (median; 95% CI) PASI and BSA scores were 12.5 (10.7; 11.6–13.4; $n = 350$) and 25.4% (16.0%; 21.5–29.3%; $n = 141$), respectively. There was a small, positive correlation between PASI and DLQI ($r = 0.29$; $P < 0.0001$; $n = 191$; Figure S2, Supporting Information). Although 37.4% of patients had a PASI score <10 at treatment initiation, the mean (median; 95% CI) DLQI score was 13.4 (13.0; 12.4–14.4; $n = 205$), indicating a very large impact of disease on QOL.

Apremilast treatment

After 6 (± 1) months, 72.3% of patients ($n = 347$) continued apremilast treatment, with a mean duration of 6.0 months

(Table 2) at the time of the follow-up assessment. The proportion of patients who continued apremilast treatment for 6 (± 1) months was similar for those who were contacted but did not enrol in the study (70.2%, 85/121). Enrolled patients who discontinued apremilast had a mean of 3.6 months (110.3 days) of treatment.

Among patients continuing apremilast with disease scores available at treatment initiation and at follow-up, an overall 55.5% improvement in PASI from treatment initiation was reported. Mean (95% CI) PASI at follow-up was 4.6 (3.9–5.2; Table 3). A $\geq 50\%$ reduction in PASI (PASI-50 response) was achieved by 68.9% (166/241) of patients, and a $\geq 75\%$ reduction in PASI (PASI-75 response) was achieved by 48.6% (117/241) of patients. Mean (95% CI) DLQI score at follow-up was 5.7 (4.5–6.9; $n = 111$) compared with 12.8 (11.4–14.2; $n = 111$) at treatment initiation (Table 3; Figure S3, Supporting Information). The extent of improvement in DLQI was largely comparable across subgroups of patients with specific manifestations of psoriasis (Fig. 2). More than half (56.0%) of the patients with DLQI score ≥ 5 at treatment initiation who were continuing treatment achieved both PASI-50 response and a ≥ 5 -point improvement in DLQI. In patients with DLQI score ≥ 4 at treatment initiation, 66.0% (64/97) achieved an improvement at follow-up of ≥ 4 points (the recommended minimal clinically important difference for DLQI treatment response).

Physician satisfaction with apremilast treatment

Physicians reported clinical improvement in overall clearance of plaque psoriasis in 75.6% (363/480) of patients. Specific manifestations including scalp, nail and palmoplantar involvement were improved in 71.1% (231/325), 67.6% (123/182) and 75.4% (86/114) of patients, respectively (Fig. 3a). Physicians also reported clinical improvement of key clinical symptoms such as pruritus (75.4%; 245/325) and fatigue (57.3%; 86/150) and noted an improvement in overall well-being (69.0%; 331/480) and 'achieving a normal everyday life' (64.6%; 310/480) for the majority of enrolled patients. As expected, improvement ratings were increased in patients who continued apremilast (Fig. 3b).

Table 2 Duration of treatment with apremilast

Group (N = 480)	n (%)	Duration of treatment (days)			
		Mean	SD	Median	Range
Ongoing treatment	347 (72.3)	183.5	26.6	183.0	64–350
Discontinued treatment†	133 (27.7)	110.3	56.6	119.0	5–212
Lack of efficacy	65 (13.5)	137.4	40.9	138.0	49–212
Safety/tolerability	56 (11.7)	77.0	57.1	56.0	5–202
Other	9 (1.9)	110.6	41.3	114.5	58–161
Unknown	3 (0.6)	159.0	39.2	146.0	128–203

SD, standard deviation.

†Patients who discontinued treatment within 5–7 months after starting apremilast. Duration of treatment data was missing for 5 patients who discontinued treatment.

Table 3 Clinical assessments at treatment initiation and follow-up†

Assessment at initiation and follow-up	<i>n</i>	Mean	95% CI	SD	Median	Range (min–max)	
PASI	Treatment initiation	241	13.1	12.0–14.2	8.7	11.0	0.4–48.0
	Follow-up	241	4.6	3.9–5.2	5.0	3.0	0–28.0
BSA (%)	Treatment initiation	87	28.3	23.2–33.4	23.8	20.0	1.0–80.0
	Follow-up	87	10.9	8.1–13.7	13.3	5.0	0–60.0
DLQI	Treatment initiation	111	12.8	11.4–14.2	7.3	12.0	0–29.0
	Follow-up	111	5.7	4.5–6.9	6.2	4.0	0–27.0

BSA, body surface area; CI, confidence index; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; SD, standard deviation.

†Patients with assessment at both treatment initiation and follow-up.

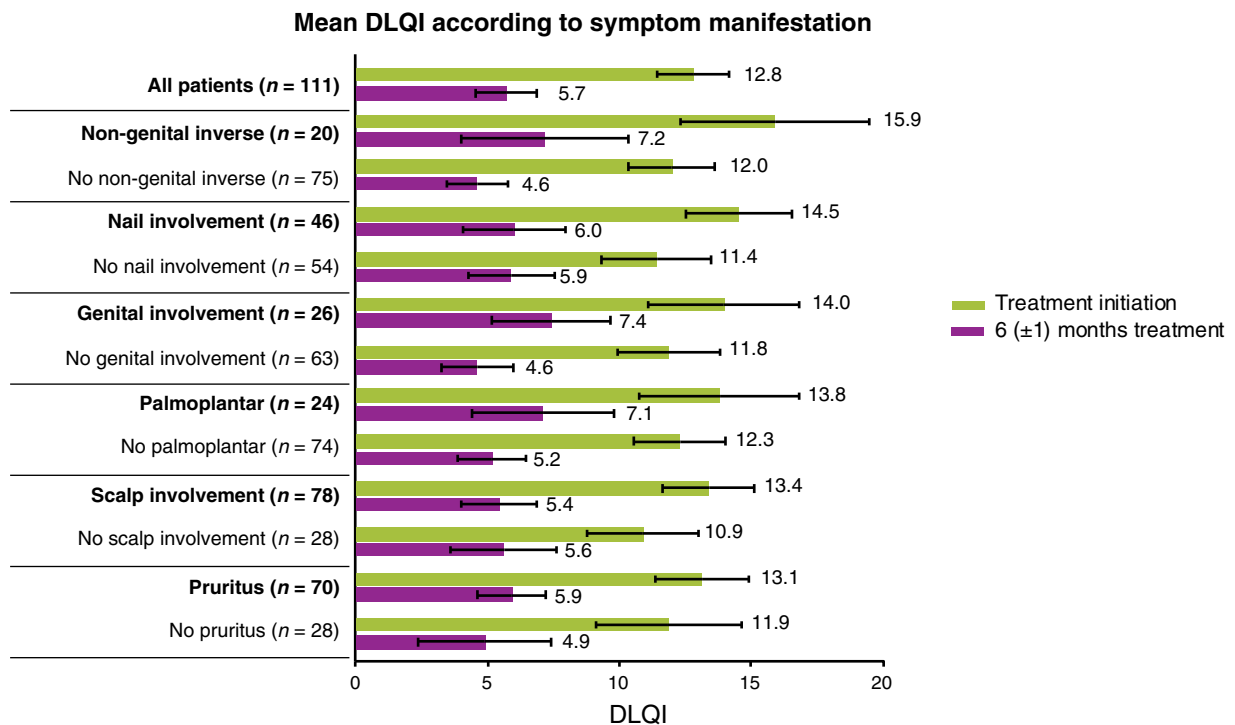


Figure 2 Mean Dermatology Life Quality Index (DLQI) score at treatment initiation and follow-up by specific manifestations of psoriasis. Data are for patients with assessments at treatment initiation and at 6 (±1) months (follow-up) who were continuing apremilast treatment. Error bars show 95% confidence intervals.

Physicians believed that more than half (53.8%; 258/480) of patients achieved or exceeded their treatment expectations with apremilast (Fig. 3c).

Patient needs and satisfaction with apremilast treatment

Overall, the mean (SD) PBI score was 2.4 (1.4), and a PBI of ≥ 1 , which is considered to represent clinically meaningful benefit,²⁹ was achieved by 78.7% of patients (Fig. 4a).

In patients who continued apremilast, mean (SD) PBI score was 2.8 (1.2), and a PBI score ≥ 1 was achieved by

90.9% of patients (Fig. 4a). Based on the TSQM-9, patient ratings of treatment effectiveness, convenience and global satisfaction were >65 among patients who continued apremilast (Fig. 4b).

Alignment of physicians' expectations and patients' expectations of treatment effects

Patients and physicians expressed similar levels of satisfaction regarding onset and duration of treatment response to apremilast, the impact of treatment on specific manifestations of

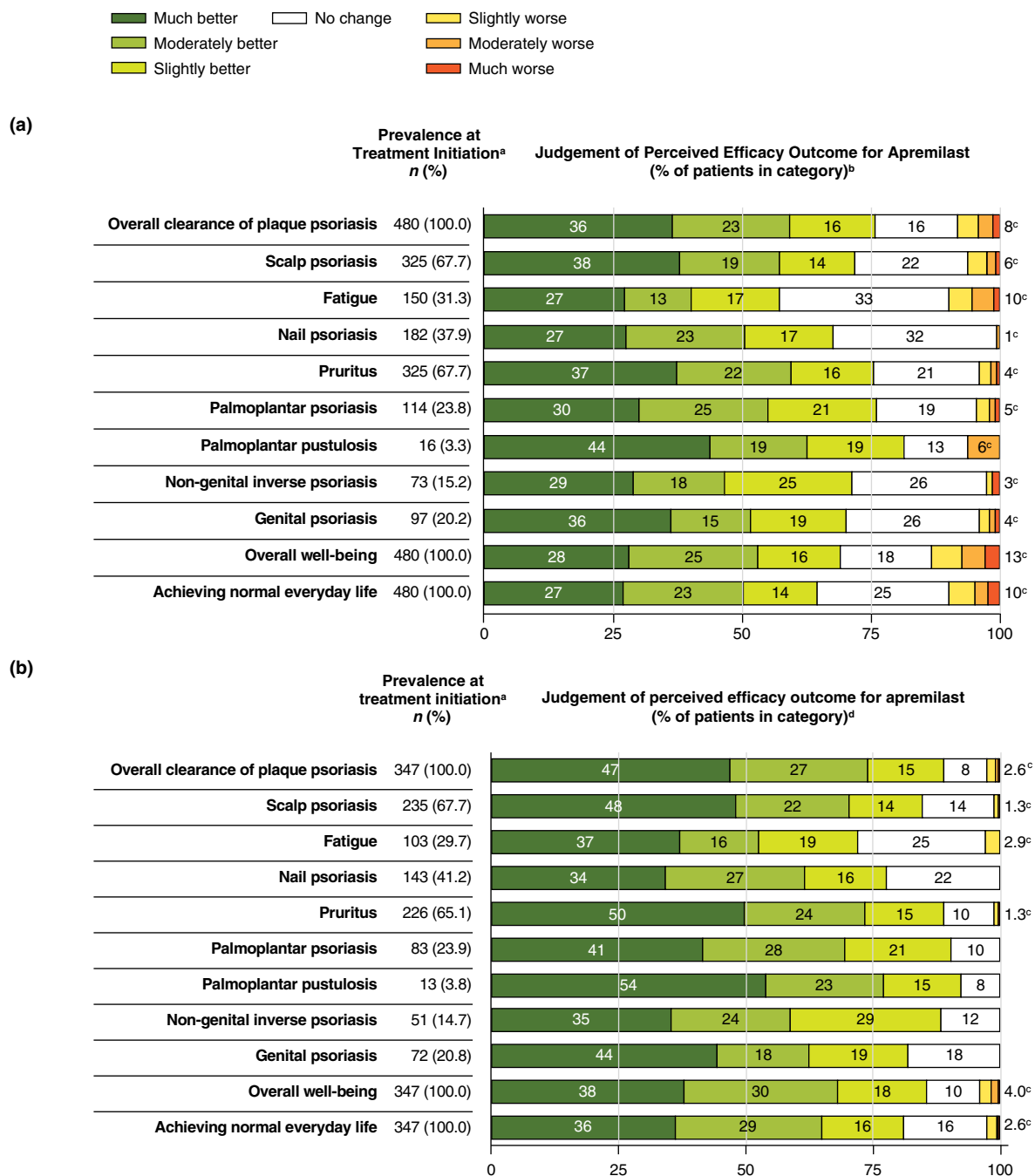


Figure 3 Physician judgement of perceived effectiveness outcomes for apremilast on psoriasis manifestations for all patients (a) and for patients continuing apremilast treatment at 6 (±1) months (b), and physician perceptions of overall success with apremilast treatment (c). ^aIncludes patients with missing data (n = 2 for overall, n = 4 for scalp, n = 1 for palmoplantar). ^bChart data are for patients with clinical signs and symptoms pre-apremilast initiation (patients with missing data are not shown). ^cSum of much, moderately and slightly worse values. ^dIncludes patients with missing data (n = 1 for overall, n = 2 for scalp, n = 1 for palmoplantar).

psoriasis, reductions in itching and joint pain and improvement in mood and overall well-being (Fig. 5). Physicians' assessments of the overall success of apremilast in meeting expectations

(Fig. 3c) and patients' perception of benefit from therapy (Fig. 4a) were positively correlated (Fig. 6). Strong agreement was observed between physicians reporting that their

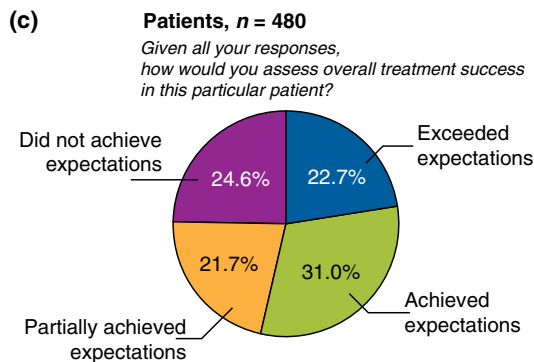


Figure 3 Continued

expectations were achieved or exceeded and patients achieving high benefit (PBI ≥ 3 ; Fig. 6).

Tolerability and safety

In total, 216 patients experienced at least one AE (Table 4); the most commonly reported AEs [occurring in ≥ 5 (1%) patients] were diarrhoea, nausea and headache. Likewise, the AEs most frequently leading to treatment discontinuation were diarrhoea (3.3%), nausea (3.3%) and headache (1.9%). Three patients experienced serious AEs that were not suspected to be related to apremilast (colon cancer, pancreatic carcinoma and myocardial infarction; $n = 1$ for each). Four patients had serious AEs that were suspected by the treating physician to be related to treatment (gastritis, Guillain–Barré syndrome and dyspnoea, $n = 1$ for each; events of migraine, nightmare and night sweats were all

reported in one patient). The relationship of the case of Guillain–Barré syndrome to apremilast treatment was based on the timing of apremilast initiation and onset of symptoms; however, prior respiratory infection may have been a confounding factor.

A total of 23.3% (112/480) of patients reported weight loss. Mean (SD) weight loss was -6.2 (9.5) kg in patients who reported weight loss and -1.0 (3.4) kg in all patients with weight data ($n = 195$).

Discussion

Randomized clinical trials provide standardized and well-defined measures of treatment efficacy in a specific patient population; however, their outcomes may lack generalizability to the diversity and complexity of real-world clinical practice. Both the physician's and the patient's judgements of an individual patient's needs and clinical outcomes influence everyday treatment decisions. The APPRECIATE study provided insight into the treatment decisions that physicians and patients face in daily life. A PASI score was recorded in 73% of patients at treatment initiation, with scores <10 in approximately a third of these patients. Importantly, the median DLQI score of >10 (mean, 13.4) indicates a very large impact of disease on QOL at treatment initiation for most patients. This is in keeping with previous findings that many patients treated with apremilast in clinical practice have more moderate skin involvement than those participating in clinical trials, yet still perceive a high burden of psoriasis on their QOL.^{21,23,25,32–37} Of note, several European registries reported a greater mean PASI score in patients initiated on biologic therapy, suggesting that in clinical practice, where permissible geographically according to

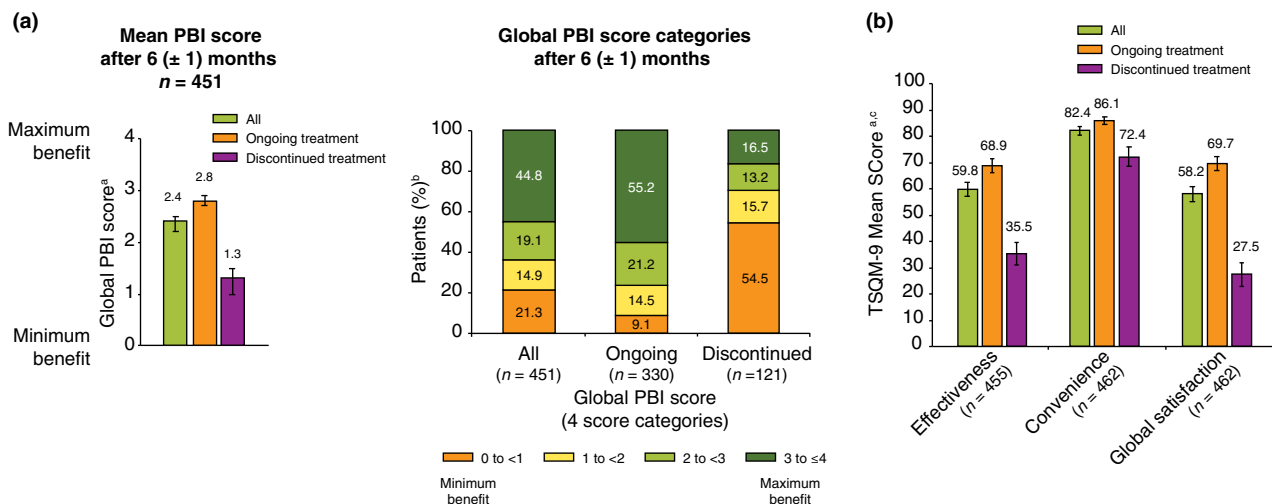


Figure 4 Patient Benefit Index (PBI) for patients ongoing or discontinuing treatment at 6 (± 1) months (a) and 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9) patient ratings of medication satisfaction for patients ongoing or discontinuing treatment at 6 (± 1) months (b). ^aError bars show 95% confidence intervals. ^bData for all, ongoing and discontinued groups are based on non-missing values. ^c100 means greatest effectiveness, convenience and global satisfaction. Check attachments - replace (LZ)

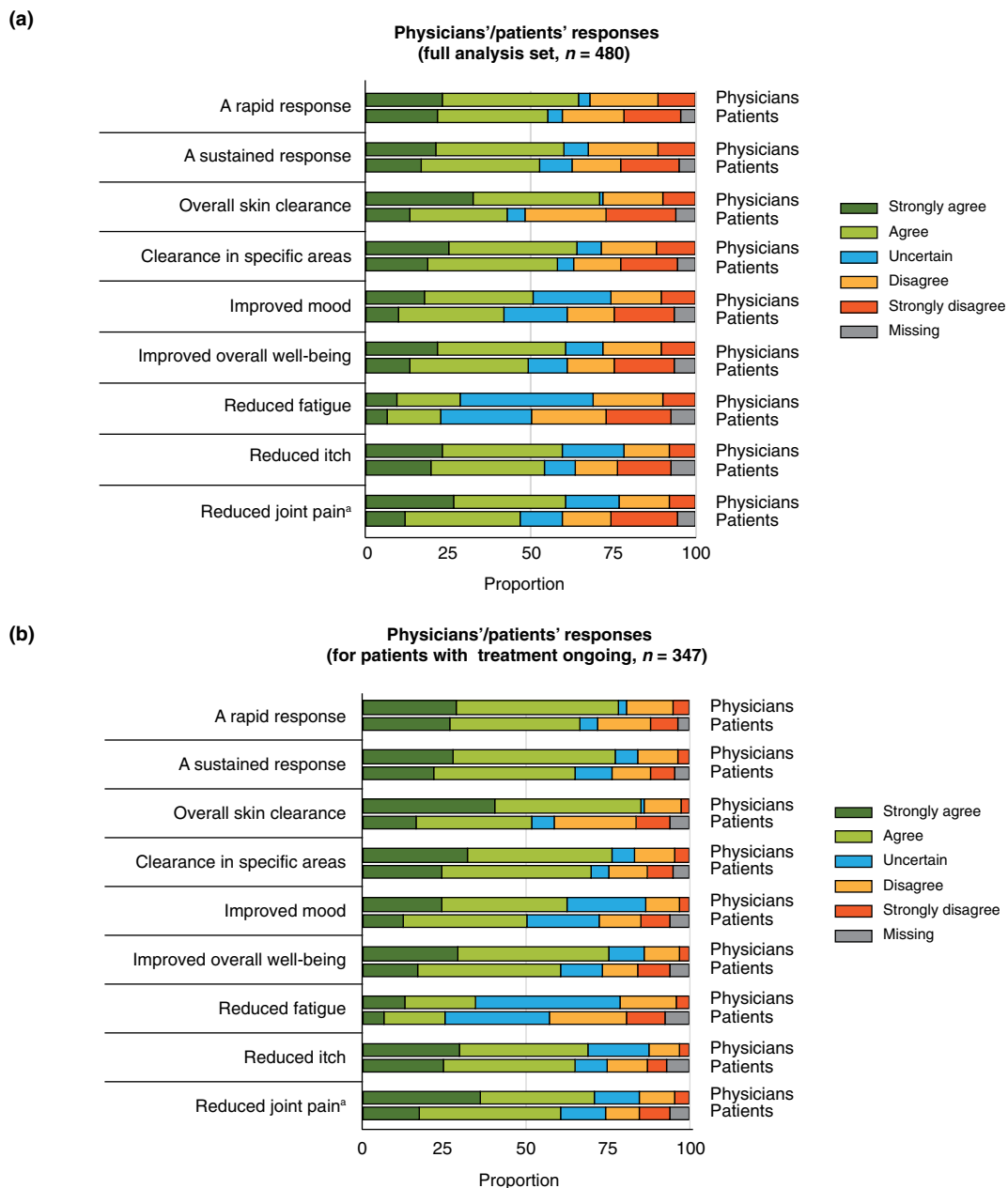


Figure 5 Physician and patient questionnaire responses regarding the effect of treatment on symptoms for the full analysis set (a) and for patients with ongoing treatment at 6 (±1) months (b). Physicians completed a separate questionnaire for each patient. Question to physician: ‘In what way do you think apremilast has helped this patient’s psoriasis specifically?’ Question to patient: ‘In what way do you think apremilast has helped your psoriasis specifically?’ ^aData only for patients with the presence of psoriatic arthritis at treatment initiation (full analysis set, n = 124; ongoing treatment set, n = 86).

guidelines, apremilast is used in patients with more moderate skin involvement and may therefore fill a key treatment need for this patient population.^{32,38–43} Importantly, at treatment initiation in APPRECIATE, PASI had a low correlation with

DLQI, indicating that the level of skin involvement is not the only factor that patients take into account when assessing the severity and impact of their disease. Recent studies have highlighted the difficulty of defining psoriasis severity⁴⁴ and the

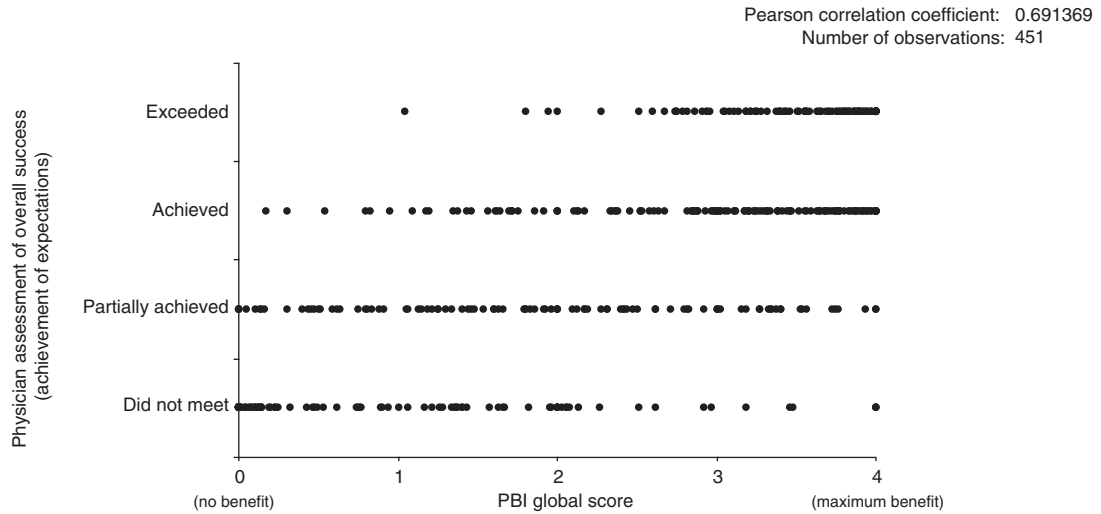


Figure 6 Scatter plot of physician assessment of overall treatment success to global Patient Benefit Index (PBI). $n = 451$. Missing data excluded.

Table 4 Overview of apremilast safety

Adverse events (AE), n (%)	All patients ($N = 480$)
Patients with any AE	216 (45.0)
Patients with serious AE	7 (1.5)
Patients with AE leading to drug withdrawal	51 (10.6)
AE occurring in $\geq 1\%$ of patients	
Diarrhoea	90 (18.8)
Nausea	69 (14.4)
Headache	42 (8.8)
Fatigue	13 (2.7)
Weight decrease [†]	13 (2.7)
Arthralgia	7 (1.5)
Upper abdominal pain	7 (1.5)
Vomiting	7 (1.5)
Abdominal discomfort	6 (1.3)
Flatulence	6 (1.3)
Insomnia	6 (1.3)
Migraine	6 (1.3)
Dizziness	5 (1.0)
Dyspepsia	5 (1.0)
Depression	5 (1.0)

AE, adverse event.

[†]Medical records show mean weight loss: -1.5 kg (females, $n = 94$) and -0.6 kg (males, $n = 101$).

underestimation bias of the DLQI for patients with a high disease burden.⁴⁵ For most enrolled patients, factors contributing to the reported high burden of disease may include long-standing disease duration, prior systemic therapy failure, comorbidities, pruritus and involvement of visible or high-

impact, bothersome locations such as the scalp, nails, genitals and/or palmoplantar regions.

Although clinical assessment tools including the PASI are commonly used to evaluate and study disease severity and treatment efficacy, it is notable that only 107 of the 480 enrolled patients (22.3%) in our study had documented PASI and DLQI scores at treatment initiation and follow-up, indicating that these tools are not used consistently in everyday practice to make treatment decisions. This emphasizes the need to improve the assessment of patients' needs and treatment effectiveness beyond traditional measures and to use patient-reported outcomes that consider the impact on all aspects of patients' daily lives. The PBI for skin diseases captures patients' treatment needs as well as their perception of how well those needs are met by a given therapy.²⁹ In the current analysis, patients who remained on apremilast therapy had improvements in PASI, BSA and DLQI, and also self-reported benefits via the PBI and TSQM-9. Furthermore, when comparing with patients who discontinued, those who remained on therapy had higher scores on the TSQM-9 subscales of effectiveness and satisfaction, but not convenience, suggesting that convenience was not the main driver for persistence in this study. Overall, physicians and patients reported similar satisfaction with apremilast treatment, including quick onset of action, duration of treatment response, the impact of treatment on specific manifestations and symptoms of psoriasis (e.g. pruritus), and improvement in mood and overall well-being. Treatment satisfaction with apremilast in APPRECIATE was consistent with the results of the UNVEIL study, in which patients reported satisfaction with the effectiveness, safety and convenience of apremilast.²⁵

Real-world studies allow for the assessment of treatments in broad, diverse patient samples more representative of patients seen in clinical practice. In addition, they allow observation of the impact of disease and its treatment beyond standard clinical outcomes and within the context of true treatment patterns. However, real-world clinical practice studies are limited by their lack of a control group and reliance on the availability of assessments. The effectiveness, tolerability and safety observed in our study were consistent with findings in clinical trials of apremilast^{21,23,24}; however, our analyses were limited by the inconsistent use of assessment tools at follow-up visits. The study also has the limitations inherent to retrospective analyses. Recall bias cannot be ruled out, although the 6-month follow-up period was chosen to minimize the recall bias of retrospectively administered questionnaires while allowing sufficient time for treatment effects to emerge. There was also a potential for patient selection bias because patients with positive treatment experience may have been more inclined to be contacted and available for enrolment.

Conclusions

Real-world studies can extend the existing knowledge of the utility of new treatments by focusing on the acceptability and everyday use of these treatments. The APPRECIATE study importantly identified that, in clinical practice, patients who initiated apremilast had more moderate skin involvement than those who were enrolled in clinical trials of apremilast. Despite more moderate psoriasis severity, most patients reported an impact of psoriasis on their QOL at apremilast initiation that was reflective of high disease burden. Taken together, findings suggest that patients consider factors other than extent of skin involvement when assessing the impact of psoriasis on QOL.

The results of this study highlight the need for a more comprehensive definition of psoriasis severity, which looks beyond traditional skin-centric measures of PASI and DLQI to more patient-centric measures, allowing for a more personalized approach to evaluating the burden of psoriasis on patients' lives and impact of treatment. Efforts are underway to study the impact of apremilast on QOL, efficacy and safety in people with specific manifestations of plaque psoriasis and impaired QOL.

Acknowledgements

We would like to acknowledge all investigators, coordinators and study site personnel, as well as the patients for their participation in this study. Medical writing support was provided by OPEN Health Medical Communications. Logistical support was provided by Kantar GmbH, Munich, Germany.

References

- Parisi R, Symmons DP, Griffiths CE *et al*. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol* 2013; **133**: 377–385.
- Neimann AL, Shin DB, Wang X *et al*. Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol* 2006; **55**: 829–835.
- Kimball AB, Gladman D, Gelfand JM *et al*. National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening. *J Am Acad Dermatol* 2008; **58**: 1031–1042.
- Strober B, Karki C, Mason M *et al*. Characterization of disease burden, comorbidities, and treatment use in a large, US-based cohort: results from the Corrona Psoriasis Registry. *J Am Acad Dermatol* 2018; **78**: 323–332.
- Baliwag J, Barnes DH, Johnston A. Cytokines in psoriasis. *Cytokine* 2015; **73**: 342–350.
- Feldman SR, Goffe B, Rice G *et al*. The challenge of managing psoriasis: unmet medical needs and stakeholder perspectives. *Am Health Drug Benefits* 2016; **9**: 504–513.
- Armstrong AW, Schupp C, Wu J *et al*. Quality of life and work productivity impairment among psoriasis patients: findings from the National Psoriasis Foundation survey data 2003–2011. *PLoS ONE* 2012; **7**: e52935.
- Armstrong A, Jarvis S, Boehncke WH *et al*. Patient perceptions of clear/almost clear skin in moderate-to-severe plaque psoriasis: results of the Clear About Psoriasis worldwide survey. *J Eur Acad Dermatol Venereol* 2018; **32**: 2200–2207.
- Lebwohl MG, Bachelez H, Barker J *et al*. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J Am Acad Dermatol* 2014; **70**: 871–881.
- Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. *Ann Rheum Dis* 2005; **64**(Suppl 2): ii18–ii23; discussion ii4–5.
- Menter A, Gottlieb A, Feldman SR *et al*. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol* 2008; **58**: 826–850.
- Armstrong AW, Robertson AD, Wu J *et al*. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003–2011. *JAMA Dermatol* 2013; **149**: 1180–1185.
- Balp MM, Khalil S, Tian H *et al*. Burden of chronic urticaria relative to psoriasis in five European countries. *J Eur Acad Dermatol Venereol* 2018; **32**: 282–290.
- Amatya B, Wennersten G, Nordlind K. Patients' perspective of pruritus in chronic plaque psoriasis: a questionnaire-based study. *J Eur Acad Dermatol Venereol* 2008; **22**: 822–826.
- Amatya B, Nordlind K. Focus groups in Swedish psoriatic patients with pruritus. *J Dermatol* 2008; **35**: 1–5.
- Globe D, Bayliss MS, Harrison DJ. The impact of itch symptoms in psoriasis: results from physician interviews and patient focus groups. *Health Qual Life Outcomes* 2009; **7**: 62.
- Armstrong AW, Siegel MP, Bagel J *et al*. From the Medical Board of the National Psoriasis Foundation: treatment targets for plaque psoriasis. *J Am Acad Dermatol* 2017; **76**: 290–298.
- Griffiths CEM, Augustin M, Naldi L *et al*. Patient-dermatologist agreement in psoriasis severity, symptoms and satisfaction: results from a real-world multinational survey. *J Eur Acad Dermatol Venereol* 2018; **32**: 1523–1529.
- van deKerkhof PCM, Reich K, Kavanaugh A *et al*. Physician perspectives in the management of psoriasis and psoriatic arthritis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis survey. *J Eur Acad Dermatol Venereol* 2015; **29**: 2002–2010.
- Mrowietz U, Kragballe K, Reich K *et al*. Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res* 2011; **303**: 1–10.
- Papp K, Reich K, Leonardi CL *et al*. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (Efficacy and

- Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM 1]). *J Am Acad Dermatol* 2015; **73**: 37–49.
- 22 Otezla [summary of product characteristics]. Amgen Europe B.V., Breda, The Netherlands, 2020.
 - 23 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**: 1387–1399.
 - 24 Reich K, Gooderham M, Green L *et al.* The efficacy and safety of apremilast, etanercept, and placebo, in patients with moderate to severe plaque psoriasis: 52-week results from a phase 3b, randomized, placebo-controlled trial (LIBERATE). *J Eur Acad Dermatol Venereol* 2017; **31**: 507–517.
 - 25 Stein Gold L, Bagel J, Lebwohl M *et al.* Efficacy and safety of apremilast in systemic- and biologic-naïve patients with moderate plaque psoriasis: 52-week results of UNVEIL. *J Drugs Dermatol* 2018; **17**: 221–228.
 - 26 Augustin M, Radtke MA, Eyerich K *et al.* First patient-reported insights from a multinational, retrospective, cross-sectional study of real-world experience of psoriasis patients treated with apremilast in clinical dermatology practice (APPRECIATE) [abstract]. *Acta Derm Venereol* 2018; **98**: 13.
 - 27 Shams K, Laws P, Chen KS *et al.* Patient-reported insights from the APPRECIATE study: real-world experience of psoriasis patients treated with apremilast in the United Kingdom and Ireland [abstract]. *Br J Dermatol* 2018; **179**: 29–30.
 - 28 Yeo L, Shams K, Laws P. Quality of life and patient satisfaction in an apremilast-treated psoriasis population: analysis of 126 patients from the APPRECIATE study in the United Kingdom and Ireland. Presented at: *Annual Meeting of the Scottish Dermatological Society*. Glasgow, UK, 2018.
 - 29 Feuerhahn J, Blome C, Radtke M *et al.* Validation of the patient benefit index for the assessment of patient-relevant benefit in the treatment of psoriasis. *Arch Dermatol Res* 2012; **304**: 433–441.
 - 30 Atkinson MJ, Kumar R, Cappelleri JC *et al.* Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. *Value Health* 2005; **8** (Suppl 1): S9–S24.
 - 31 Augustin M, Radtke MA, Zschocke I *et al.* The patient benefit index: a novel approach in patient-defined outcomes measurement for skin diseases. *Arch Dermatol Res* 2009; **301**: 561–571.
 - 32 Kleyn E, Radtke M, Bundy C *et al.* Real-world experience with apremilast in patients with psoriasis: interim analysis of 104 patients from the APPRECIATE study [abstract]. Presented at: *Psoriasis: From Gene to Clinic International Congress*. London, UK, 2017.
 - 33 Armstrong A, Levi E. Real-world clinical experience with apremilast in a large US retrospective cohort study of patients with moderate to severe plaque psoriasis. *J Drugs Dermatol* 2017; **16**: 1240–1245.
 - 34 Vujic I, Herman R, Sanlorenzo M *et al.* Apremilast in psoriasis – a prospective real-world study. *J Eur Acad Dermatol Venereol* 2018; **32**: 254–259.
 - 35 Ighani A, Georgakopoulos JR, Walsh S *et al.* A comparison of apremilast monotherapy and combination therapy for plaque psoriasis in clinical practice: a Canadian multicenter retrospective study. *J Am Acad Dermatol* 2018; **78**: 623–626.
 - 36 Mayba JN, Gooderham MJ. Real-world experience with apremilast in treating psoriasis. *J Cutan Med Surg* 2017; **21**: 145–151.
 - 37 Papadavid E, Rompoti N, Theodoropoulos K *et al.* Real-world data on the efficacy and safety of apremilast in patients with moderate-to-severe plaque psoriasis. *J Eur Acad Dermatol Venereol* 2018; **23**: 1173–1179.
 - 38 Kojanova M, Fialova J, Cetkovska P *et al.* Characteristics and risk profile of psoriasis patients included in the Czech national registry BIOREP and a comparison with other registries. *Int J Dermatol* 2017; **56**: 428–434.
 - 39 Gniadecki R, Bang B, Bryld LE *et al.* Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. *Br J Dermatol* 2015; **172**: 244–252.
 - 40 Carretero G, Ferrandiz C, Dauden E *et al.* Risk of adverse events in psoriasis patients receiving classic systemic drugs and biologics in a 5-year observational study of clinical practice: 2008–2013 results of the Biobadaderm registry. *J Eur Acad Dermatol Venereol* 2015; **29**: 156–163.
 - 41 Iskandar IY, Ashcroft DM, Warren RB *et al.* Demographics and disease characteristics of patients with psoriasis enrolled in the British Association of Dermatologists Biologic Interventions Register. *Br J Dermatol* 2015; **173**: 510–518.
 - 42 Reich K, Mrowietz U, Radtke MA *et al.* Drug safety of systemic treatments for psoriasis: results from The German Psoriasis Registry PsoBest. *Arch Dermatol Res* 2015; **307**: 875–883.
 - 43 Augustin M, Spehr C, Radtke MA *et al.* German psoriasis registry PsoBest: objectives, methodology and baseline data. *J Dtsch Dermatol Ges* 2014; **12**: 48–57.
 - 44 Augustin M, Langenbruch A, Gutknecht M *et al.* Definition of psoriasis severity in routine clinical care: current guidelines fail to capture the complexity of long-term psoriasis management. *Br J Dermatol* 2018; **179**: 1385–1391.
 - 45 Langenbruch A, Radtke MA, Gutknecht M *et al.* Does the Dermatology Life Quality Index (DLQI) underestimate the disease-specific burden of psoriasis patients? *J Eur Acad Dermatol Venereol* 2019; **33**: 123–127.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. List of approving central ethics committees

Table S2. Reasons for ineligibility and non-enrolment

Figure S1. Study site disposition

Figure S2. Correlation between Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) at treatment initiation by treatment status at 6 (\pm 1) months (follow-up)

Figure S3. Dermatology Life Quality Index (DLQI) at treatment initiation and follow-up