

# Impact of Measuring Patient-Reported Outcomes in Dermatology Drug Development

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**Abstract** Although some symptoms of dermatologic diseases, such as pruritus and pain, can be subjectively assessed only by patients, the most commonly used end-points in dermatology drug research traditionally have been clinician-reported outcomes. Research has found that patient-reported outcomes (PROs) were included in only one-quarter of 125 trials conducted between 1994 and 2001. Our objective was to characterize the impact of PROs in dermatology drug development from the patient, prescriber, regulator, payer, and manufacturer perspectives using a case study approach. We conducted a structured literature review for pivotal clinical trials using PROs for six dermatologic products (MAS063DP, onabotulinum-toxinA, calcipotriene hydrate plus betamethasone dipropionate, pimecrolimus, tacrolimus, and ustekinumab). We also searched regulatory websites to identify product labeling and the UK National Institute for Health and Care Excellence website to identify submissions for the products of interest. A total of 32 articles illustrating the various perspectives were selected for inclusion. Clinical trials that include PROs allow patients to differentiate among treatments based on the experience of other patients participating in trials and enable prescribers to understand the benefit–risk profile of new treatments. The inclusion of PROs enables regulators to evaluate product benefits with a patient-centered perspective; five of the products of interest obtained eight total product labeling statements. PRO data

supported manufacturers' dissemination of product benefits in the form of publications and PRO labeling for the product. For payers, PRO data were used in an analysis of cost effectiveness of new treatments. Inclusion of PROs in dermatology drug development programs benefits patients, prescribers, regulators, manufacturers, and payers.

## Key Points for Decision Makers

Although many symptoms of dermatologic conditions can only be assessed by the patient, patient-reported outcomes are not commonly reported in dermatologic clinical trials.

Inclusion of patient-reported outcomes in clinical trials can allow patients and physicians to differentiate among dermatologic treatment options, enable regulators to evaluate new agents from a patient-centered perspective, and permit manufacturers to disseminate information regarding patient-reported benefits of new agents.

For payers, patient-reported outcomes data can be used in cost-effectiveness evaluations for new dermatologic treatments.

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## 1 Introduction

Dermatologic diseases (excluding melanoma) are among the top ten most prevalent of all diseases in the world, and dermatologic diseases combined are the fourth leading

cause of nonfatal disease burden at the global level [1]. Although dermatologic diseases are generally chronic and not life threatening, they account for a large burden on healthcare systems worldwide [1, 2]. In addition to the global impact of dermatologic skin diseases in terms of functional health loss and costs, the psychological burden of these diseases can be substantial for individual patients [1, 3]. The 2010 Global Burden of Disease study [2] found that skin conditions were among the leading causes of years lived with disability at the country level.

For most skin diseases, no satisfactory objective marker of disease activity is available. Consequently, many clinician-reported outcome scales have emerged that incorporate different aspects of disease that are combined in various ways into an overall score [4]. These scales may appear to be objective because they are recorded by a clinician or an observer rather than the participant, but few have been adequately validated, and many have not been validated at all [4].

Patients' assessments of efficacy of treatments are especially important in dermatology. Many symptoms of dermatologic diseases, such as pruritus, burning, and sleep disturbance, are difficult for physicians to assess objectively. Furthermore, some aspects of the value placed on various degrees of clinical improvement can be assessed only by study participants [4]. Nevertheless, a systematic literature review of randomized controlled dermatology-related clinical trials showed that patient-reported outcomes (PROs) were mentioned in some form in only 25.6 % of 125 trials conducted between 1994 and 2001 [4]. (It should be noted that this review was completed before the US FDA guidance on the use of PROs to support potential claims in product labeling was issued in 2009 [5]). One of the PRO measures used more recently in dermatology drug research is the Psoriasis Symptom Diary. This measure was included in two clinical trials of secukinumab to evaluate patient-reported improvement in the signs and symptoms of psoriasis. Importantly, during development of the Psoriasis Symptom Diary, qualitative interviews with patients with psoriasis revealed that plaque-related pain is a key symptom of psoriasis, among other previously recognized symptoms [6]. The Psoriasis Symptom Diary, the first psoriasis-related PRO measure to include pain, was then used to demonstrate clinically meaningful improvements in patient-reported itching, pain, and scaling with secukinumab relative to placebo in both the USA and Europe [7–9].

'Patient-reported outcome' is an umbrella term used to describe outcomes collected directly from the patient without interpretation by clinicians or others [5, 10, 11]. PRO data are commonly collected via standardized questionnaires designed to measure an explicit concept (con-

struct) such as symptoms, activity limitations, or health status/health-related quality of life (HRQOL). The questionnaires used to collect PROs may also be referred to as instruments, scales, diaries, or checklists; collectively, they are referred to as PRO measures [5]. The validity, reliability, and responsiveness of some PRO measures for dermatologic diseases, such as the Dermatology Life Quality Index, the Psoriasis Symptom Assessment, and two itch measures, have been demonstrated by Shikiar et al. [12].

The assessment of PROs in clinical trials allows drug manufacturers and regulators to understand the symptoms and the burden associated with a disease from the perspective of the patient. Manufacturers have viewed the benefit of including PROs in drug development largely in terms of their potential to secure product labeling in the USA or a summary of product characteristics (SmPC) claim in Europe, or to support value propositions for reimbursement. Regulators and payers are only two of the key stakeholders who influence market access to new drugs; both clinicians and patients also play a key role in influencing the availability and use of pharmaceutical products.

Since the publication of the FDA PRO guidance [5], discussion about PROs and product labeling has received considerable attention both within the literature and at industry or professional meetings [13]. The FDA is now urging sponsors to routinely include PRO measures in all aspects of drug development. Its Patient-Focused Drug Development Initiative is a commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to more systematically gather and report patients' perspectives on their condition and available therapies to treat their condition [14]. In addition, the FDA publication of the pilot Clinical Outcome Assessment Compendium is part of the agency's efforts to foster patient-focused drug development [15]. Unlike the FDA, the European Medicines Agency (EMA), has not issued formal guidelines specific to PROs but has instead published a reflection paper to provide broad recommendations on HRQOL evaluation in the context of clinical trials [16].

Mild dermatologic conditions are typically treated with topical agents. For instance, approximately 80 % of patients with psoriasis have a mild to moderate form of disease that can be safely and effectively treated with a topical agent [17]. Moderate to severe or treatment-refractory dermatologic conditions traditionally have been treated with systemic agents such as acitretin, cyclosporine, and methotrexate. The relatively recent introduction of biological therapies for patients with moderate to severe dermatologic diseases has offered clinicians and patients additional treatment choices. The increasing use of biological therapies

has improved outcomes in dermatology but has also increased the cost of treatment [18]. Given the high cost of new therapies for dermatologic diseases, these drugs face reimbursement challenges from payers, who must balance treatment benefit and cost. Accordingly, there is a call to define ‘meaningful clinical benefits’ and ‘value’ for newer therapies. Treatment value can be determined, in part, when patients participating in clinical trials provide information about how they feel and function.

The purpose of this study was to use a case study approach to characterize the impact of PROs in the development of dermatological products from five key perspectives: those of patients, prescribers, regulators, manufacturers, and payers.

## 2 Methods

Products were selected as case studies if they had been recently approved (2000–2011) for atopic dermatitis, psoriasis, or hyperhidrosis and PROs were collected in the relevant confirmatory studies. Although not an exhaustive list of products during this time period, the products selected were anticipated to help illustrate the impact of PROs in dermatological drug development from each of the different perspectives. The products chosen were MAS063DP, onabotulinumtoxinA, calcipotriene hydrate plus betamethasone dipropionate, pimecrolimus, tacrolimus, and ustekinumab. Since the process followed was to identify relevant cases, we did not record the reasons for exclusion of other products.

A structured search was conducted in 2014 in PubMed for the six products of interest. Limits included studies published between 2004 and 2 July 2014; English language only; humans only; and no comments, letters, editorials, preclinical studies, or phase I clinical trials. A total of 436 abstracts were reviewed by a single reviewer. Of these, 63 were selected for full-text review (MAS063DP for atopic dermatitis,  $n = 2$  articles; onabotulinumtoxinA for hyperhidrosis,  $n = 9$ ; calcipotriol plus betamethasone dipropionate gel for scalp psoriasis,  $n = 5$ ; pimecrolimus for atopic dermatitis,  $n = 13$ ; tacrolimus for atopic dermatitis,  $n = 15$ ; and ustekinumab for psoriasis,  $n = 19$ ). A total of 32 articles were selected for inclusion in the study.

Regulatory (FDA and EMA) websites were also searched for the US approval year and for any documentation of PRO labeling within the US product package inserts and EU SmPCs, respectively. The website of the UK National Institute for Health and Care Excellence (NICE) was also searched for the use of PRO data in health technology assessment submissions for the products of interest.

## 3 Results

The following sections describe the impact of PROs in dermatology drug development for key stakeholders.

### 3.1 Impact on Patients and Prescribers

Patients’ involvement in their care is receiving greater emphasis. Patients already decide when to seek medical advice, whether to accept that advice, and ultimately whether to comply with prescribed medications or present a case for an alternative medication. Inclusion of PROs in clinical trials ensures that the full benefit of a treatment from the patient perspective has been demonstrated, including improvement in symptoms, HRQOL, and treatment satisfaction. Results from clinical trials that have included PROs enable patients to differentiate between treatments based on the experience of their peers who took part in the trials. The primary downside to collecting PROs in clinical trials is additional burden on the patient in completing the questionnaires.

Clinician-reported outcome scales have long been employed in drug development and clinical practice. However, there can be discrepancies between patient and clinician views of treatment effectiveness. Clinicians often report fewer problems than patients and may underestimate the severity of the problems or overestimate treatment improvement. For example, for rheumatoid arthritis, clinicians consistently rate pain levels as lower and health status as higher than patients rate their disease status on these scales [19]. Similarly, it has been shown that physicians underestimate the incidence, severity, or distress of symptoms experienced by patients with cancer [20]. A study evaluating objective and self-assessed severity measures in patients with acne, psoriasis, or atopic eczema found only very modest agreement between clinician-assessed disease severity and patients’ self-assessed disease severity [21].

Furthermore, Fortune et al. [22] evaluated quality of life (QOL) in psoriasis and found that clinical severity and duration of psoriasis were not related to QOL impairment, whereas the anatomical location (or social visibility) of psoriasis was associated with patient self-reports of poor physical and mental health. Patient perspectives on these experiences would not have been evident via traditional clinician-reported dermatologic outcomes.

The inclusion of PROs in comparative trials allows prescribers to better understand patients’ symptom experience and satisfaction with treatment. This understanding allows clinicians to make informed treatment decisions based on evidence provided by physicians and patients who

took part in clinical trials, further enabling clinicians to provide improved quality care and encourage compliance.

In a non-interventional prospective trial conducted in Germany, 579 patients with psoriasis were treated with a once-daily fixed combination of calcipotriol 50 µg/g plus betamethasone gel 0.5 mg/g for 4 weeks, and calcipotriol/betamethasone gel was compared with prior therapy [23]. PROs were assessed using the Dermatology Life Quality Index (DLQI) to evaluate dermatology-specific QOL, the Psoriasis Disability Index (PDI) to evaluate patient burden, the Patient Global Assessment of disease severity (PGA) (range of 0–5) to evaluate psoriasis severity, and questions about how easy the new medication was to use. The DLQI total score improved significantly from baseline to week 4 (8.7–3.2 points, respectively;  $p < 0.0001$ ). Additionally, the impact of the fixed combination on patient burden was decreased compared with prior therapy as assessed by the PDI: whereas 32, 49, and 60 % of patients, respectively, reported that their prior treatment had a negative impact on domains relating to frequency of changing clothes, frequency of bathing, and household untidiness, only 5, 32, and 19 % of patients, respectively, reported that the fixed combination had a negative impact on these domains. For disease severity as judged by the patients, 83.6 % had moderate, severe, or very severe psoriasis at baseline; at the end of the study, only 25.5 % were in these categories. Overall, 85.7 % of patients were ‘very satisfied’ or ‘satisfied’ with the efficacy of calcipotriol/betamethasone gel, whereas only 27.6 % of the patients were ‘very satisfied’ or ‘satisfied’ with prior topical treatment. The assessment of tolerability as ‘very satisfied’ was 75.4 % for calcipotriol/betamethasone gel and 29.5 % for prior treatment. Regarding the convenience of use of calcipotriol/betamethasone gel therapy, 66.1 % of the patients were ‘very satisfied,’ in comparison with 11.6 % of the patients with prior treatment. The application of the study medicine was 30 % less time consuming. The authors concluded this study substantiated a significant improvement in HRQOL for patients being treatment with the fixed combination. Patients benefited from the convenience and time-saving features of the fixed combination compared with prior therapy [23].

Ortonne et al. [24] conducted an 8-week randomized investigator-blinded study in 17 centers in five countries (Belgium, Canada, Denmark, France, and Sweden) comparing the once-daily, two-compound scalp formulation calcipotriol 50 µg/g, betamethasone 0.5 mg/g with twice-daily calcipotriol (50 µg/g). PROs were assessed using the Physical Component Summary and Mental Component Summary scores from the Short-Form 36-Item Health Survey (SF-36) and three scale scores (symptoms, emotions, and functioning) and a total score from the Skindex-16. Treatment with the two-compound scalp formulation

( $n = 207$ ) resulted in significant improvements from baseline on the SF-36 Physical Component Summary at week 8 ( $p = 0.005$ ). For the Skindex-16 total score, there was statistically significant treatment difference in favor of the two-compound scalp formulation over the calcipotriol scalp solution at weeks 2 and 4 ( $p < 0.001$ ) and at week 8 ( $p = 0.008$ ). Analysis of the individual scale scores of the Skindex-16 also showed significant treatment differences in favor of the two-compound scalp formulation over the calcipotriol scalp solution (symptoms at weeks 2 and 4 [ $p < 0.001$ ] and week 8 [ $p = 0.004$ ]; emotions at weeks 2 and 4 [ $p < 0.001$ ] and week 8 [ $p = 0.005$ ]; and functioning at week 4 [ $p = 0.032$ ]). Based on these results, the authors concluded that the two-compound formulation was superior to calcipotriol scalp solution in improving HRQOL in patients with scalp psoriasis.

Staab et al. [25] conducted a 20-week randomized controlled study in Germany in pediatric patients aged 3–23 months comparing pimecrolimus with vehicle. PROs were assessed using the QOL in Parents of Children with Atopic Dermatitis (PQOL-AD) questionnaire, which includes five subscales (psychosomatic well-being; effects on social life; confidence in medical treatment; emotional coping; and acceptance of the disease) assessing the impact of caring for a child with atopic dermatitis on the caregiver’s life. The differences showing the largest magnitude of change between the pimecrolimus and vehicle groups were observed for psychosomatic well-being, emotional coping, and acceptance of disease in favor of pimecrolimus. In this study, the rate of improvement in terms of pruritus and patients’ sleep loss, as assessed by the caregivers, was rapid. Statistically significant differences between the pimecrolimus and vehicle groups, in the percentage of patients with at least a 50 % improvement from baseline, were observed as early as day 2 for pruritus and day 3 for sleep loss. The full effects of treatment were predominantly achieved within 1 week and sustained for the study duration. The authors concluded that, consistent with other studies, this trial showed only weak correlations between clinical parameters and QOL. This finding suggested that patients’ clinical scores do not sufficiently describe the improvement in parents’ QOL, and the measurement of QOL is an important complementary assessment to the clinical evaluation.

### 3.2 Impact on Regulators and Manufacturers

For regulators, the inclusion of PROs in clinical trials as well as in US product labeling and European SmPCs allows for a robust and holistic evaluation of the product benefits, taking into account data from patients in addition to data from physicians and laboratory values. Similarly, for manufacturers, PRO data generate product labeling,

which enable manufacturers to communicate product benefits directly to patients and support publications that allow for extensive public dissemination of product benefits. Some downsides for manufacturers regarding collection of PRO data include the cost of research to select the right instrument as well as costs for implementation and analysis [26]. The largest cost is incurred if a new instrument needs to be developed.

All but one of the six products reviewed in our study included PROs in the US product labeling and the European SmPC (Table 1). For the FDA, PRO labeling statements were obtained for MAS063DP, onabotulinumtoxinA, pimecrolimus, tacrolimus, and ustekinumab. For the EMA, PRO SmPC claims were obtained for onabotulinumtoxinA, pimecrolimus, tacrolimus, and ustekinumab. Specifically, symptom improvement (e.g., itching, burning, pain) for MAS063DP (FDA), pimecrolimus (FDA and EMA), and tacrolimus (FDA and EMA); reductions of interference with daily activities (FDA and EMA), and satisfaction with treatment (EMA) for onabotulinumtoxinA; and global subject assessment of pruritus severity for pimecrolimus (FDA and EMA). Several labeling statements/SmPC claims related to QOL were obtained for ustekinumab, based on the Health Assessment Questionnaire-Disability Index (HAQ-DI) (FDA), the DLQI (EMA), the SF-36 (EMA), and the Hospital Anxiety and Depression Scale (HADS) (EMA). Finally, an SmPC claim for improvement in work limitations ( $n = 1$ ) was obtained for ustekinumab (EMA).

### 3.3 Impact on Payers

For payers, PRO data may facilitate economic evaluations of products. In our study, utility values based on PROs were used in cost-effectiveness evaluations for two products (and three indications) of the six products of interest. These evaluations were identified via the NICE website.

A Markov simulation model was constructed to estimate whether tacrolimus ointment for regular treatment of moderate-to-severe atopic dermatitis would be a cost-effective treatment alternative for patients with moderate-to-severe atopic dermatitis in comparison with standard treatment in Sweden [27]. Patients were asked to rate their QOL/health status at present and during their most severe symptoms using a visual analog scale (VAS). An ordinary least-squares regression model was used to estimate a relationship between disease severity index and VAS score. Based on this model, treatment with tacrolimus ointment was considered cost effective and yielded considerable potential gains in QOL in patients with severe and moderate atopic dermatitis. These findings emphasize the importance of considering QOL in addition to disease severity when an atopic dermatitis treatment is chosen.

Wollenberg et al. [28] conducted an economic evaluation of maintenance treatment with tacrolimus 0.1 % ointment compared with standard use in adults with moderate to severe atopic dermatitis. Based on SF-36 data collected every 2 months, utility values (from 0 = death to 1 = perfect health) were calculated by using the mapping algorithm by Brazier et al. [29]. The improvements in health status were statistically significant in the maintenance-use group but not in the standard-use group. Based on the number of disease exacerbations, utility data, and the prospectively collected resource utilization data, the authors concluded that maintenance treatment with 0.1 % tacrolimus ointment was more effective and led to cost savings and improved HRQOL compared with standard use, especially in patients with severe atopic dermatitis.

Finally, to assess the cost utility of pimecrolimus as a treatment for mild and moderate atopic dermatitis when compared with conventional treatments, a Markov state transition model was developed from the perspective of the UK National Health Service [30]. Utility values for childhood eczema were taken from a previous study [31] and adapted for an adult population using standard-gamble methodology. Baseline cost-utility outputs from the model showed that, in all tested scenarios, treatment with a topical corticosteroid dominated pimecrolimus (i.e., was both cheaper and more effective). Exceptions were likely to be in cases where topical corticosteroids were ineffective, unacceptable because of adverse events, or unacceptable to the patient.

## 4 Discussion

In contrast with symptoms that necessarily require subjective input (e.g., pain), many dermatologic signs can be assessed visually, and measures of treatment response in dermatology traditionally have been evaluated by clinicians. Unfortunately, this approach has limited patient input on meaningful treatment outcomes in dermatology. Although clinicians' opinions might be a primary driver of decision making in some therapeutic areas (e.g., those relating to behavioral disorders or circulatory diseases), patients' views of their symptoms and how they may affect their lives are key in treatment decisions in dermatology. Moreover, a patient with a dermatologic disease affecting only a small body surface area may experience a considerable negative impact on HRQOL, whereas a patient with a similar condition affecting a large area could experience only a minimal burden. For example, a population-based survey of patients with psoriasis found that most patients (59 %) had little or no involvement (i.e., body surface area affected by psoriasis), but that more than 20 % indicated a substantial dissatisfaction with their treatment [32]. Only



**Table 1** Summary of patient-reported outcomes labeling and summary of product characteristics claims for select dermatologic drug products approved in the USA and EU by July 2014

Product country: generic name	Product labeling indication	US approval date/product PRO labeling	EU approval date/SmpPC PRO claim
USA and EU: MAS063DP (nonsteroidal cream) [38] Not found in Drugs@FDA or EMA databases Identified by manufacturer's website: <a href="http://www.flexus.com/Atopiclair/healthcarepros01.html">http://www.flexus.com/Atopiclair/healthcarepros01.html</a>	Manufacturer prescribing information, indications for use: To manage and relieve the itching, burning, and pain experienced with various types of dermatoses, including atopic dermatitis and allergic contact dermatitis. Atopiclair nonsteroidal cream helps to relieve dry, waxy skin by maintaining a moist skin environment, which is beneficial to the healing process	January 2011 FDA: Not applicable (510(k) clearance for medical devices); prescribing information includes PRO labeling for <b>itching, burning, and pain</b>	Not applicable
USA: OnabotulinumtoxinA [39] EMA: OnabotulinumtoxinA ( <i>Clostridium botulinum</i> type A neurotoxin complex) [40]	USA: Most recent (18 January 2013) product labeling indication: "Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients" "Important limitations: Treatment of hyperhidrosis in body areas other than axillary" EU: Persistent severe primary hyperhidrosis of the axillae, which interferes with the activities of daily living and is resistant to topical treatment	20 July 2004 approval for primary axillary hyperhidrosis Most recent (18 January 2013) product labeling Clinical Studies section: "HDSS is a 4-point scale with 1 = "underarm sweating is never noticeable and never interferes with my daily activities"; to 4 = "underarm sweating is intolerable and always interferes with my daily activities" "The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a > 50 % decrease from baseline in axillary sweat production was greater in both BOTOX® groups than in the placebo group ( $p < 0.001$ ), but was not significantly different between the 2 BOTOX® doses"	20 February 2003 CPMP positive opinion; final decision 25 June 2003: Annex II Scientific Conclusions on Benefit/Risk: "These clinical findings [reduction in mean sweat production], along with high levels of <b>patient satisfaction with treatment</b> , were consistently statistically superior to those seen with placebo" Annex III (SmpPC) indication: "persistent severe primary hyperhidrosis of the axillae, which <b>interferes with the activities of daily living</b> and is resistant to topical treatment" Pharmacological properties (Clinical Studies) section: no PROs
USA: Calcipotriol plus betamethasone dipropionate gel [41] EU: Calcipotriol/betamethasone [42]	USA: Topical treatment of plaque psoriasis of the scalp and body in patients 18 years and older EU: Topical treatment of scalp psoriasis in adults	Approved June 2006; no PRO labeling (July 2014)	Approved Q4 2008; SmpPC 21 July 2013; no PRO claims
USA: Pimecrolimus 1 % cream [43] EU: Pimecrolimus [44]	USA: Second-line therapy for the short-term and noncontinuous chronic treatment of mild-to-moderate atopic dermatitis in nonimmunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable EU: Treatment of patients aged 2 years and over with mild or moderate atopic dermatitis where treatment with topical corticosteroids is either inadvisable or not possible. This may include: Intolerance to topical corticosteroids Lack of effect of topical corticosteroids Use on the face and neck where prolonged intermittent treatment with topical corticosteroids may be inappropriate	Approved 2001; Clinical Studies section: "More ELIDEL subjects (57 %) had mild or no pruritus at 6 weeks compared to vehicle subjects (34 %). The improvement in pruritus occurred in conjunction with the improvement of the subjects' atopic dermatitis." Per the Medical Review section of the drug approval package: "Overall pruritus was assessed using a score ranging from 0–3. Pruritus was assessed by the primary caregiver, in discussion with the subject, and concerned the intensity of the overall itching/scratching during the 24 h prior to the visit"	Approved 29 May 2006; SmpPC clinical data: "Both studies showed a significant reduction in the incidence of flares ( $P < 0.001$ ) in favour of < Invented Name > [pimecrolimus] treatment; < Invented Name > [pimecrolimus] showed better efficacy in all secondary assessments (Eczema Area Severity Index, IGA, <b>subject assessment</b> )"

**Table 1** continued

Product country: generic name	Product labeling indication	US approval date/product PRO labeling	EU approval date/SmpPC PRO claim
USA and EU: Tacrolimus [45, 46]	<p>USA: PROTOPIC ointment, both 0.03 % and 0.1 % for adults, and only 0.03 % for children aged 2–15 years, is indicated as <i>second-line therapy</i> for the short-term and noncontinuous chronic treatment of moderate-to-severe atopic dermatitis in nonimmunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable</p> <p>EU: Flare treatment <i>Adults and adolescents (16 years of age and above)</i> Treatment of moderate-to-severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids <i>Children (2 years of age and above)</i> Treatment of moderate-to-severe atopic dermatitis in children who failed to respond adequately to conventional therapies such as topical corticosteroids Maintenance treatment Treatment of moderate-to-severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (i.e., occurring 4 or more times per year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared, or mildly affected)</p>	<p>Approved December 2000; Clinical Studies section, 4 November 2011 product labeling: “In both PROTOPIC Ointment treatment groups in adults and in the PROTOPIC Ointment 0.03 % treatment group in pediatric patients, a significantly greater improvement compared to vehicle (<math>p &lt; 0.001</math>) was observed in the secondary efficacy endpoints of ... <b>patient evaluation of pruritus erythema, edema, excoriation, oozing, scaling, and lichenification</b>”</p>	<p>Approved 2002; “<b>Pruritus</b> decreased over time in the tacrolimus groups but not in the hydrocortisone group”</p>

Table 1 continued

Product country: generic name	Product labeling indication	US approval date/product PRO labeling	EU approval date/SmpPC PRO claim
US and EU: Ustekinumab [47, 48]	<p>USA: Moderate-to-severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy</p> <p>PSA, alone or in combination with methotrexate</p> <p>EU: Treatment of moderate-to-severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate, or PUVA treatment of PSA in adult patients when the response to previous nonbiological DMARD therapy has been inadequate</p>	<p>Approved 2009;</p> <p>Results "Table 1. ACR20, ACR50, ACR70 and PASI75 responses in PSA STUDY 1 and PSA STUDY 2 at week 24" includes scores for:</p> <p>"Patient's assessment of <b>pain</b> (based on <b>visual analogue scale</b>; <b>0 = best, 10 = worst</b>)"</p> <p>"<b>Disability Index of the Health Assessment Questionnaire</b>; <b>0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity</b>"</p> <p>"STELARA® treated patients showed improvement in physical function compared to patients treated with placebo as assessed by <b>HAQ-DI</b> at week 24. In both studies, the proportion of <b>HAQ-DI</b> responders (<math>\geq 0.3</math> improvement in <b>HAQ-DI</b> score) was greater in the STELARA® 45 mg and 90 mg groups compared to placebo at week 24"</p>	<p>Approved 2009;</p> <p>"Baseline disease characteristics were generally consistent across all treatment groups in Psoriasis Studies 1 and 2 with ... median <b>DLQI</b> range from 10 to 12"</p> <p>"In Psoriasis Study 1, at week 2 and week 12, significantly greater improvements from baseline were demonstrated in the <b>DLQI</b> in each ustekinumab treatment group compared with placebo. The improvement was sustained through week 28. Similarly, significant improvements were seen in Psoriasis Study 2 at week 4 and 12, which were sustained through week 24. In Psoriasis Study 1, improvements in nail psoriasis (Nail Psoriasis Severity Index), in the <b>physical and mental component summary scores of the SF-36</b> and in the <b>Itch VAS</b> were also significant in each ustekinumab treatment group compared with placebo. In Psoriasis Study 2, the <b>HADS</b> and <b>WLQ</b> were also significantly improved in each ustekinumab treatment group compared with placebo"</p>

PRO measures are listed in bold

ACR American College of Rheumatology, CPMP Committee for Proprietary Medicinal Products, DLQI Dermatology Life Quality Index, DMARD disease-modifying antirheumatic drug, EMA European Medicines Agency, HADS Hospital Anxiety and Depression Scale, HAQ-DI Health Assessment Questionnaire-Disability Index, HDSS Hyperhidrosis Disease Severity Scale, IGA Investigators Global Assessment, PASI Psoriasis Area and Severity Index, PRO patient-reported outcomes, PSA psoriatic arthritis, PUVA psoriatic arthritis, PUVA psoralen and ultraviolet A, SF-36 SF-36 Health Survey, SmpPC Summary of Product Characteristics, VAS visual analog scale, WLQ Work Limitations Questionnaire



5 % of patients reporting a severe dissatisfaction with current therapy had extensive disease covering a large body surface area, and many individuals with minimal psoriasis involvement at the time of the survey considered the disease to be a large problem in their everyday life. However, it should be noted that developing and validating PRO measures in dermatology to assess symptoms, feelings, and function can be both time and resource intensive, particularly if the sponsor aims to follow the currently accepted guidelines [33, 34] and/or plans to pursue product labeling in the USA [5] or EU [16] based on clinical trial data from the new PRO measure.

Many symptoms associated with dermatologic diseases are also not captured by clinician assessments. Symptoms such as pruritus and pain may be among the most bothersome aspects of dermatologic diseases (e.g., Pariser et al. [35]), and patient self-reports are required to accurately capture the presence and severity of these symptoms. There also may be discrepancies between clinician and patient assessments of the severity of a dermatologic disease [21]. Moreover, self-assessed, but not clinician assessed, disease severity was statistically associated with psychological morbidity (e.g., depression or anxiety) in this study. The psychological and emotional burden of dermatologic diseases indeed may be considerable: a large observational case–control study conducted in Europe found that patients with various dermatologic conditions including psoriasis, nonmelanoma skin cancer, skin infections, and eczema had a significantly higher prevalence of clinical depression, anxiety disorder, and suicidal ideation compared with controls [36].

Dermatologic diseases clearly can be burdensome for individual patients, and these diseases are also widely prevalent, burdening healthcare systems worldwide. Yet, despite the individual and global burden of dermatologic diseases, dermatology is often a neglected field of research because many dermatologic conditions are not life threatening. Nevertheless, the authors of the Global Burden of Disease [2] strongly recommend that prevention and treatment of dermatologic diseases be included in future global health strategies. We strongly suggest that global health strategies focusing on dermatologic diseases incorporate PROs in addition to traditional clinical measures of disease burden and treatment response.

Although there is increasing regulatory focus on the voice of the patient in drug development in general [14], there is no regulatory guidance specific to the use of PROs in dermatology. Regardless, patient perspectives are critical in determining treatment success—particularly in dermatology, where these perspectives have been long underrepresented—and sponsors and researchers are urged to include PROs in clinical trial programs for emerging dermatology products. Specifically, drug manufacturers developing drugs

for diseases such as atopic dermatitis, hyperhidrosis, or psoriasis should consider including the PRO measures meeting FDA PRO guidance criteria to support product labeling and SmPC claims for their products, in both the USA and Europe [5], as well as PRO measures (e.g., the EuroQol 5 Dimensions [EQ-5D]) that produce utility values for use in economic evaluation of new technologies to potentially facilitate reimbursement. However, beyond considerations of product labeling, sponsors should include PRO assessments in clinical trials to enable regulators and payers to assess the risk–benefit profile of drugs in a holistic manner. For prescribers, PRO assessments inform patient-centered treatment strategies, providing clinicians with data on which treatments show the greatest likelihood of improving a patient’s HRQOL. There is evidence that PRO data used in treatment decision making in a real-world clinical setting positively influence patients’ QOL [37]. Finally, the inclusion of PROs in clinical trials enable patients to evaluate which treatments have offered the greatest benefits to other patients with the same disease.

## 5 Limitations

Limitations to this study include using a structured search strategy to identify the relevant case studies. Systematic literature review methodology was not employed, and studies were identified for inclusion by a single reviewer. The case studies selected for review were intended to explore the potential impact of measuring PROs in dermatology clinical trials and not to review negative examples where PROs were not useful. Therefore, the findings may not be generalizable.

## 6 Conclusion

For the dermatology drugs reviewed in this study, inclusion of PROs in the clinical development program provided evidence of treatment benefits to patients, prescribers, regulators, manufacturers, and payers.

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### Compliance with Ethical Standards

**Author contributions** Catherine Copley-Merriman and Marci Clark were involved in all aspects of this research and development of the manuscript. Ari Gnanasakthy and Susan Zelt reviewed the research report and manuscript.

**Conflicts of interest** Catherine Copley-Merriman, Marci Clark, and Ari Gnanasakthy are employees of RTI Health Solutions. Susan Zelt is an employee of GlaxoSmithKline.

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