Benefits of Patient-Reported Outcomes in Dermatology Drug Development

Catherine Copley-Merriman,[1] Susan Zelt,[2] Marci Clark,[1] Ari Gnanasakthy[3]

[1] RTI Health Solutions, Ann Arbor, MI, United States; [2] GlaxoSmithKline, Research Triangle Park, NC, United States;
[3] RTI Health Solutions, Research Triangle Park, NC, United States

BACKGROUND

- A recent systematic literature review of randomized controlled dermatology–related trials showed that patient-reported outcomes (PROs) were mentioned in some form in only 25.6% of 125 trials conducted from 1994 to 2001.[1]

OBJECTIVE

- To characterize the benefits of PROs in dermatology drug development from the patient, prescriber, regulator, manufacturer, and payer perspectives using a case study approach.

METHODS

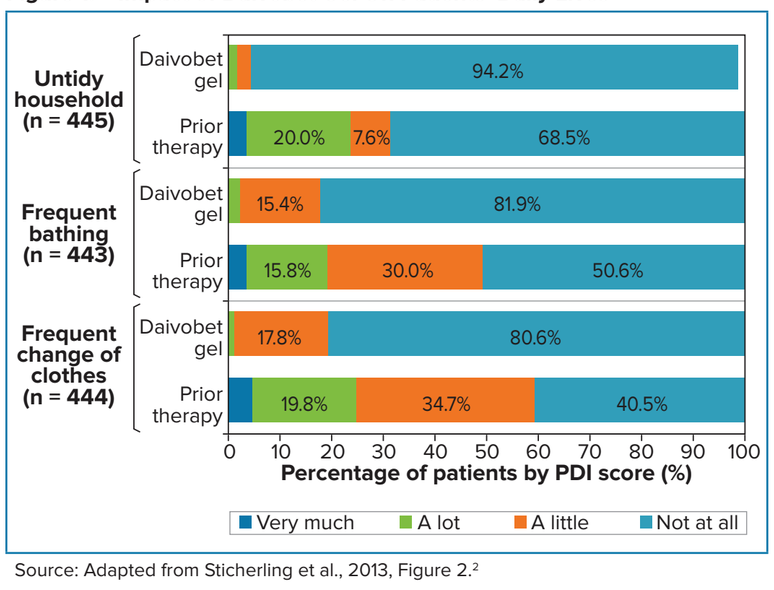
- Case studies were identified based on the use of PROs in pivotal clinical trials for dermatology drugs.
- A targeted literature review was conducted in PubMed from 2004 to 2014 for six products (Atopiclair for atopic dermatitis, botulinum toxin type A [Botox] for hyperhidrosis, calcipotriol plus betamethasone dipropionate gel for scalp psoriasis, pimecrolimus and tacrolimus for atopic dermatitis, and ustekinumab for psoriasis).
- Regulatory (Food and Drug Administration [FDA] and European Medicines Agency [EMA]) and health technology agency websites and publications were searched for documentation of PRO label claims and mentions.

RESULTS

Patients

- Inclusion of PROs ensured the full benefit of the product was demonstrated, including improvement in symptoms, quality of life, and treatment satisfaction.
- For example, in a noninterventional prospective trial conducted in Germany, 579 patients with psoriasis were treated with a once-daily fixed combination of calcipotriol 50 µg/g plus betamethasone 0.5 mg/g (Daivobet gel) for 4 weeks, and Daivobet gel was compared with prior therapy.
- PROs were assessed using the Dermatology Life Quality Index (DLQI), Psoriasis Disability Index (PDI), Patient Global Assessment of disease severity (PGA) (range, 0-5), and questions on how easy the new medication was to use.
  - Patient burden: As assessed by the PDI, patient burden was decreased when taking Daivobet gel compared with prior therapy (Figure 1).
  - Disease severity: As judged by patients, 83.6% had moderately severe, severe, or very severe involvement 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 Daivobet gel, while only 27.6% of the patients were very satisfied or satisfied with prior topical treatment.
  - Tolerability: 75.4% of patients were very satisfied with Daivobet gel, and 29.5% were very satisfied with prior treatment.[2]

Figure 1. Impact of Daivobet Gel On Patients' Daily Lives

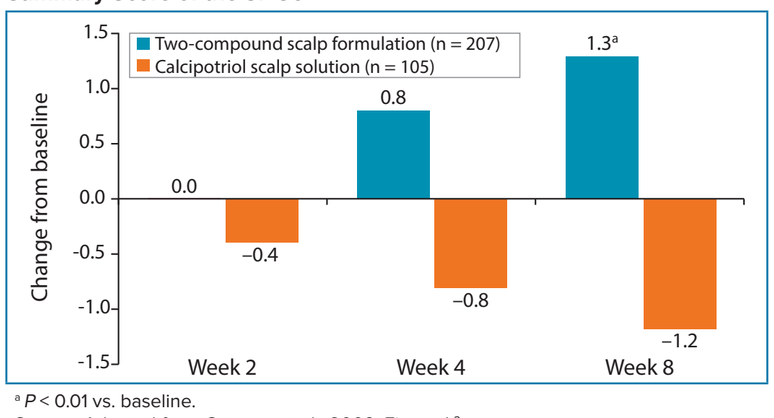


Source: Adapted from Sticherling et al., 2013, Figure 2.[2]

Prescribers

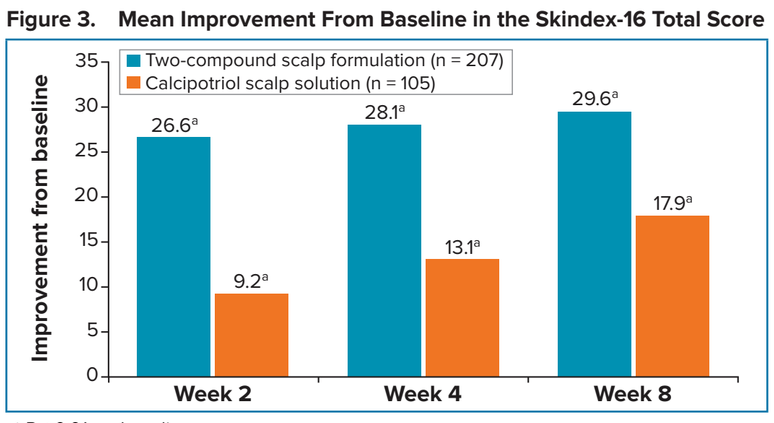
- Comparative trials evaluating the dermatology drugs reviewed reported PRO data information on each product's benefits and risks, and also which product was superior from the patient perspective.
- For example, Ortonne and colleagues (2009)[3] conducted an 8-week, randomized, investigator-blind study in 17 centers in five countries (Belgium, Canada, Denmark, France, and Sweden) comparing the once-daily, two-compound scalp formulation of calcipotriol 50 µg/g and betamethasone 0.5 mg/g (Xamiol gel) with twice-daily calcipotriol (50 µg/g) (Daivonex).
- PROs were assessed using the 36-Item Short Form Health Survey (SF-36) and the Skindex-16.

Figure 2. Mean Change From Baseline in the Physical Component Summary Score of the SF 36



[a] $P < 0.01$ vs. baseline.
Source: Adapted from Ortonne et al., 2009, Figure 1.[3]

Figure 3. Mean Improvement From Baseline in the Skindex-16 Total Score



[a] $P < 0.01$ vs. baseline.
Source: Adapted from Ortonne et al., 2009, Figure 3.[3]

Regulators and Manufacturers

- For regulators, PROs were included in the product label for all except one of the six products reviewed (Table 1). Similarly, for the manufacturer, the PRO data generated label claims and many publications that allowed extensive public dissemination of product benefits.
- PRO label claims were granted by the FDA for Atopiclair, Botox, pimecrolimus, tacrolimus, and ustekinumab. PRO claims were granted by the EMA for Botox, pimecrolimus, tacrolimus, and ustekinumab.[4] The types of PRO claims obtained for the drugs reviewed were as follows:
  - Symptom (e.g., itching, burning, pain) (n = 4); Atopiclair (FDA), pimecrolimus (FDA and EMA), tacrolimus (FDA and EMA), ustekinumab (FDA and EMA)
  - Interference with daily activities (n = 1): Botox (FDA and EMA)
  - Treatment satisfaction (n = 1): Botox (EMA)
  - Global subject assessment (n = 1): pimecrolimus (EMA)
  - Quality of life (n = 1): ustekinumab (Health Assessment Questionnaire-Disability Index [HAQ-DI]) (FDA); DLQI (EMA), SF-36 (EMA), Hospital Anxiety and Depression Scale (HADS) (EMA)
  - Work limitations (n = 1): ustekinumab (EMA)

Payers

- For payers, utility values based on PROs were used in cost-effectiveness evaluations for two of the six products for three indications.
  - Tacrolimus ointment for regular and maintenance treatment of moderate-to-severe atopic dermatitis
  - Pimecrolimus for treatment of mild and moderate atopic dermatitis

Table 1. Summary of PRO Label Claims for Approved Dermatology Drugs in the US and EU

Product Country: Brand Name (Generic Name)	Label Indication	US Approval Date/PRO Label Claim	EU Approval Date/SmPC PRO Claim
US and EU: Atopiclair (nonsteroidal cream) Not found in Drugs@FDA or EMA databases; identified by manufacturer's website: http://www.flexus.com/Atopiclair/healthcarepros01.html	Itching, burning, and pain experienced with various types of dermatoses, including atopic dermatitis and allergic contact dermatitis	January 2011 Not applicable (510(k) clearance for medical devices): prescribing information has a PRO claim for itching, burning, and pain	Not applicable
US: Botox (OnabotulinumtoxinA) EU: Botox/Clostridium botulinum type A neurotoxin complex	US: severe axillary hyperhidrosis EU: persistent severe primary hyperhidrosis of the axillae that interferes with the activities of daily living and is resistant to topical treatment	July 20, 2004 Primary axillary hyperhidrosis Most recent (January 18, 2013) Label 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"	February 20, 2003 CPMP positive opinion; final decision June 25, 2003: Annex II Scientific Conclusions on Benefit/Risk: "These clinical findings [reduction in mean sweat production], along with **high levels of patient satisfaction with treatment**, were consistently statistically superior to those seen with placebo." Annex III (SmPC) Indication: "...persistent severe primary hyperhidrosis of the axillae, **which interferes with the activities of daily living** and is resistant to topical treatment" Pharmacological Properties (Clinical Studies) section: no PROs
US: Taclonex gel (calcipotriol plus betamethasone dipropionate) EU: Daivobet/Dovobet gel (formerly Xamiol gel until 2012) (calcipotriol/betamethasone)	US: plaque psoriasis of the scalp and body EU: scalp psoriasis	June 2006 No PRO claims in latest label (July 2014)	Q4 2008; SmPC July 21, 2013 No PRO claims
US and EU: Elidel (pimecrolimus 1% cream)	US and EU: mild-to-moderate atopic dermatitis	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 hours prior to the visit."	May 29, 2006 SmPC 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] treatment showed better efficacy in all secondary assessments (Eczema Area Severity Index, IGA, **subject assessment**);" pruritus was controlled within a week with <pimecrolimus>
US and EU: Protopic (tacrolimus)	US: short-term and noncontinuous chronic treatment of moderate-to-severe atopic dermatitis EU: Flare treatment Moderate-to-severe atopic dermatitis Maintenance treatment Moderate-to-severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals	December 2000 Clinical Studies Section November 4, 2011 label: "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 ($P < 0.001$) was observed in the secondary efficacy endpoints of...**patient evaluation of pruritus erythema, edema, excoriation, oozing, scaling, and lichenification.**"	2002 "**Pruritus** decreased over time in the tacrolimus groups but not in the hydrocortisone group."
US and EU: Stelara (ustekinumab)	US and EU: moderate-to-severe plaque psoriasis and PSA	2009 Results: "Table 1. ACR 20, ACR 50, ACR 70 and PASI 75 responses in PSA STUDY 1 and PSA STUDY 2 at week 24" includes scores for: "Patient's assessment of **pain** (based on **visual analogue scale**; 0 = best, 10 = worst)" **"Disability Index of the Health Assessment Questionnaire**; 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." "STELARA® treated patients showed improvement in physical function compared to patients treated with placebo as assessed by **HAQ-DI** at week 24. In both studies, the proportion of **HAQ-DI** responders (≥0.3 improvement in **HAQ-DI** score) was greater in the STELARA® 45 mg and 90 mg groups compared to placebo at week 24."	2009 "Baseline disease characteristics were generally consistent across all treatment groups in Psoriasis Studies 1 and 2 with... median **DLQI** range from 10 to 12." "In Psoriasis Study 1, at week 2 and week 12, significantly greater improvements from baseline were demonstrated in the **DLQI** 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 **physical and mental component summary scores of the SF-36** and in the **Itch VAS** were also significant in each ustekinumab treatment group compared with placebo. In Psoriasis Study 2, the **HADS** and **WLQ** were also significantly improved in each ustekinumab treatment group compared with placebo."

ACR = American College of Radiology; CPMP = Committee for Proprietary Medicinal Products; EU = European Union; HDSS = Hyperhidrosis Disease Severity Scale; IGA = Investigators Global Assessment; PASI = Psoriasis Area Severity Index; PSA = psoriatic arthritis; SmPC = Summary of Product Characteristics; US = United States; VAS = visual analog scale; WLQ = Work Limitations Questionnaire.

DISCUSSION

- For all the dermatology drugs reviewed, inclusion of PROs in the clinical development program provided evidence of treatment benefits to patients, prescribers, regulators, manufacturers, and payers.
- Drug manufacturers of developmental drugs for atopic dermatitis, hyperhidrosis, and psoriasis should consider including the following:
  - PRO measures meeting FDA PRO guidance criteria[4] to support PRO labeling claims for their products, both in the US and EU
  - PRO measures (e.g., EQ-5D) that produce utility values for use in cost-effectiveness models and may facilitate reimbursement

CONCLUSION

- Including patient-reported assessment of the treatment impact on disease during development of dermatology drugs has many benefits for all stakeholders.

DISCLOSURE

This work was carried out by RTI Health Solutions and funded by Stiefel, a GSK company. C Copley-Merriman, M Clark, and A Gnanasakthy are each employees of RTI Health Solutions. S Zelt is an employee of GSK and holds shares in the company.

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CONTACT INFORMATION

Catherine Copley-Merriman, MS, MBA
Vice President, Outcomes Group

RTI Health Solutions
Phone: +1.734.213.5429
E-mail: kcmerriman@rti.org