

A Topical Treatment Optimization Programme (TTOP) improves clinical outcome for calcipotriol/betamethasone gel in psoriasis: results of a 64-week multinational randomized phase IV study in 1790 patients (PSO-TOP)*

K. Reich,^{1,2} I. Zschocke,² H. Bachelez,³ E.M.G.J. de Jong,⁴ P. Gisondi,⁵ L. Puig,⁶ R.B. Warren,⁷ C. Ortland⁸ and U. Mrowietz⁹ for the PSO-TOP study group

¹Dermatologikum Hamburg, Hamburg, Germany

²SCIderm GmbH, Hamburg, Germany

³Sorbonne Paris Cité Université Paris-Diderot, AP-HP Hôpital Saint-Louis, Paris, France

⁴Radboud University Medical Centre and Radboud University, Nijmegen, the Netherlands

⁵Dermatology and Venerology Section, University of Verona, Verona, Italy

⁶Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

⁷The Dermatology Centre, Salford Royal NHS Foundation Trust, The University of Manchester, Manchester Academic Health Science Centre, Manchester, U.K.

⁸Das Forschungsdock Service for Clinical Development, Schenefeld, Germany

⁹Psoriasis Center, Department of Dermatology, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany

Summary

Correspondence

Kristian Reich.

E-mail: kreich@dermatologikum.de

Accepted for publication

8 March 2017

Funding sources

This study was supported by a grant from LEO Pharma to K.R. Writing assistance and editorial support was provided by Andrew Jones PhD from Mudskipper Business Ltd., which was funded by LEO Pharma.

Conflicts of interest

See Appendix.

*Plain language summary available online

DOI 10.1111/bjd.15466

Background Around two-thirds of patients with psoriasis do not adhere to topical treatment. The Topical Treatment Optimization Programme (TTOP), a five-element tool, includes guidance for the conversation between dermatologists/nurses and patients, patient information material, telephone/e-mail helpdesks and treatment reminders. It has been developed by patients and dermatologists to help increase adherence to treatment in psoriasis.

Objectives To compare TTOP with standard of care ('non-TTOP') within a large European investigator-initiated study, PSO-TOP (clinicaltrials.gov NCT01587755). **Methods** Patients with mild-to-moderate psoriasis received calcipotriol/betamethasone dipropionate gel as standardized study medication and were randomized 1 : 1 to either TTOP or non-TTOP management. Study medication was applied once daily for 8 weeks followed by 'as needed' application for an additional 56 weeks. Response was defined as a Physician's Global Assessment (PGA) of 'clear' or 'almost clear'.

Results In 1790 patients (full analysis set), response rates after 8 weeks (primary objective) were significantly higher for TTOP (36.3%) than for non-TTOP (31.3%, $P = 0.0267$). Better clinical outcome was accompanied by higher rates of patients feeling well informed about their skin condition, treatment and other factors related to adherence, but the Dermatology Life Quality Index was not statistically different. TTOP patients regarded the structured one-to-one conversations with their dermatologist/nurse as the most important element of TTOP.

Conclusions Patients randomized to the TTOP intervention had a better clinical response than patients receiving standard of care. Improved communication between the healthcare provider and patient might be an important element in increasing adherence to topical therapy in psoriasis.

What's already known about this topic?

- Adherence rates in chronically ill patients, particularly those with psoriasis, are generally low.
- Poor adherence is linked to worse clinical outcomes and reduced quality of life, in addition to increased direct and indirect costs.
- Interventions are needed to improve adherence in patients with psoriasis, which should be multifaceted and tailored to the patient's individual needs so that these interventions are suitable for long-term use.

What does this study add?

- The Topical Treatment Optimization Programme (TTOP) was designed based on input from experts and patients and comprises structured guidance for one-to-one conversations between dermatologist/nurse and patients, patient information materials, telephone/e-mail helpdesks and treatment reminders.
- Patients randomized to TTOP had a significantly better clinical outcome than patients receiving standard of care, despite using less study medication.
- Improved communication between the dermatologist/nurse and patient might be important for increasing adherence to topical therapy in psoriasis.

The World Health Organization defines adherence to long-term therapy in chronic diseases as 'the extent to which a person's behaviour... corresponds with agreed recommendations from a healthcare provider'.¹ Adherence, therefore, differs from compliance in that it requires the patient's agreement. Adherence rates in chronically ill patients, particularly those with psoriasis, are generally low. In an outpatient study where prescriptions for initial treatments with a new medication were tracked, patients with psoriasis were the least adherent group assessed, with only 50% redeeming their prescriptions.² Adherence rates to topical therapies in psoriasis are around 50–70%,^{3–5} although rates can be as low as 40% for topical corticosteroids and in patients with severe disease.^{4,6} Poor adherence is linked to worse clinical outcomes and reduced quality of life, in addition to increased direct and indirect costs.^{7–9}

Interventions are clearly needed to improve adherence to treatment in psoriasis; these interventions should be multifaceted and tailored to the patient's individual needs so that they are suitable for long-term use.⁴ The factors impacting on adherence can be grouped into three main categories, i.e. disease-, patient- and treatment-related factors. Treatment-related factors include lack of efficacy and side-effects^{4,6} and, for topical therapies, low cosmetic acceptability, as patients prefer less messy/sticky medication that is quick and easy to apply.^{6,9,10} As some of these factors cannot easily be changed (e.g. educational status of the patient), the focus should be on those factors that can be influenced. For example, effective communication between healthcare professionals and the patient plays a significant role in adherence; in some diseases > 40% of patients misunderstand, forget or simply ignore the advice of their healthcare professional.¹¹ The Topical Treatment Optimization Programme (TTOP) was designed based on input from experts and patients.¹² TTOP comprises structured guidance for one-to-

one conversations between the dermatologist/nurse and patients, patient information materials, telephone/e-mail helpdesks and treatment reminders for the patients. To evaluate whether this tool could improve adherence, TTOP was assessed in the large, investigator-initiated, long-term PSO-TOP study, in which all patients received the same topical treatment but were randomized to either standard of care (non-TTOP arm) or management with the TTOP programme. Fixed combination calcipotriol (Cal) 50 µg and betamethasone dipropionate (BD) 0.5 mg gel was selected as topical therapy based on its favourable patient satisfaction.^{9,13}

Patients and methods**Patients**

Eligible patients were men and women aged ≥ 18 years. All patients were required to have active, mild-to-moderate plaque psoriasis with a Physician's Global Assessment (PGA) of disease severity of ≥ 2 and an affected body surface area (BSA) of $\leq 10\%$. Each patient was required to have been receiving topical treatment for at least 8 weeks prior to enrolment and be naive to treatment with Cal/BD gel. The main exclusion criteria were systemic treatment with biological therapies or phototherapy during a given period prior to study inclusion; severe renal or hepatic insufficiency; known hypercalcaemia; erythrodermic, exfoliative, pustular or guttate psoriasis or facial or genital psoriasis; pregnancy or breastfeeding; hypersensitivity to the active substances or to the excipients of the study medication or fulfilment of at least one contraindication according to the study medications summary of product characteristics (SmPC);¹⁴ suspected noncompliance and/or current participation in another clinical trial.

This study was conducted in accordance with the Declaration of Helsinki. An independent ethics committee and the competent authority reviewed and approved the study. All patients provided written informed consent (Data S1; see Supporting Information).

Study design

PSO-TOP was a phase IV, 64-week, randomized controlled study (EudraCT number 2011-001697-26). It was an investigator-led (K.R.) study, designed, developed and conducted by dermatology experts from Denmark, France, Germany, Italy, the Netherlands, Spain, Sweden and the U.K., with additional input from patient focus-group interviews.¹² During the first 8 weeks, all patients applied Cal/BD gel once daily, then on an 'as needed' basis in the following 56 weeks as per the SmPC.¹⁴ At baseline, patients were randomly assigned 1 : 1 to either the TTOP or non-TTOP intervention.¹² An electronic randomization list was generated by an independent third party using the software RandList 1.2, and was stored in the electronic case report form so that a randomization number was automatically assigned in ascending order as soon as the investigator confirmed the randomization of the patient. The seven-digit randomization number was a combination of the letter R (one digit), the combined site number (four digits; comprising the country number and the site number – two digits each) and the patient number (two digits).

TTOP contains the following five elements (Data S2–S6; see Supporting Information):

1. Visit checklist with instructions for a one-to-one conversation between dermatologist and patient
2. Visit checklist with instructions for a one-to-one conversation between nurse and patient
3. Patient information material (the 'TTOP Patient Brochure')
4. Telephone and e-mail helpdesk for patients
5. Treatment reminders, where the nurse contacted the patient at a given time.

Participating investigators and nurses from each study site were carefully trained for the TTOP intervention by means of a specific TTOP training programme, which included communication exercises and written background and instruction materials (the 'PSO-TOP Manual'). Study teams were asked to have the same personnel managing patients longitudinally to minimize inter-rater variability.

Objectives and assessments

The primary objective was to demonstrate a difference in treatment responses to study medication in the TTOP and non-TTOP arms. The primary efficacy end point was PGA response after 8 weeks of treatment, with a responder having a PGA of 0 (clear) or 1 (almost clear). Visits were planned at weeks 4 and 8 (\pm 3-day and \pm 7-day window at each visit, respectively), then every 8 weeks during the 'as needed' period up to week 64. PGA and affected BSA were assessed at all

visits.^{15,16} Patient-reported outcomes – Patient's self Global Assessment (PsGA),¹² Dermatology Life Quality Index (DLQI)¹⁷ and the Topical Therapy Adherence Questionnaire (TTAQ)¹⁸ – were collected at baseline, weeks 8, 40 and 64 (Data S1; see Supporting Information). At weeks 8 and 64, patients randomized to the TTOP arm were asked to rank the five TTOP elements from one (most important) to five (least important). From baseline to week 8, treatment compliance was assessed by measuring the patient-reported number of days of Cal/BD gel application, while the extent of exposure was measured by weighing the returned study medication for all patients. The time required for consultations between the patient and dermatologist/nurse were recorded at each visit. Adverse events (AEs) were monitored throughout the study.

Statistical analysis

For the sample size calculation, it was assumed that the PGA responder rate at week 8 would be around 40% in the non-TTOP arm and 47% in the TTOP arm. To be able to show this absolute difference of 7% with a type I error rate of 5% and a power of 80%, and taking uneven distribution of patients among the participating countries (depending on their size) into account, a sample size of 1630 patients (815 per study arm) was calculated. This analysis was originally based on the full analysis set (FAS; all patients with any postrandomization data) without imputation of missing values (i.e. as observed); considering a 20% dropout rate, the target enrolment was planned to be 1956 patients. However, owing to a lower-than-expected dropout rate, the target number of 815 patients per arm was achieved with a lower overall number of enrolled patients (Fig. 1). As primary end point analyses of clinical trials in psoriasis are usually performed using a more conservative approach,^{19–21} in this paper we show the primary end point analysis and all main long-term efficacy outcomes based on the FAS with imputation of all patients with missing values as non-responders (nonresponder analysis). Based on this method, the number of enrolled patients ($n = 893$ in the TTOP and $n = 897$ in the non-TTOP arm, respectively) allowed detection of a 7% response difference between the arms with a power of 83% and detection of a 5% difference with a power of 58%.

Efficacy analyses were conducted on the FAS, while safety analyses were performed in all randomized patients who received the study drug. The primary study objective was tested statistically in a hierarchical order. A two-sided Cochran–Mantel–Haenszel test (continuity corrected) was used to test for the overall effect (data from all countries) at $\alpha = 5\%$. In case of significance ($P \leq 0.05$), a Breslow–Day test of homogeneity within countries was used at $\alpha = 5\%$. Two-sided χ^2 -tests (5% significance level) were performed by visit and country to test the null hypothesis that the PGA responder rate did not differ between treatment arms for weeks 16–64. For exploratory reasons, the influence of possible prognostic factors on PGA responder rate at week 8 was assessed using a logistic regression model with the study arm, country and sex as factors, and months since psoriasis diagnosis, age and

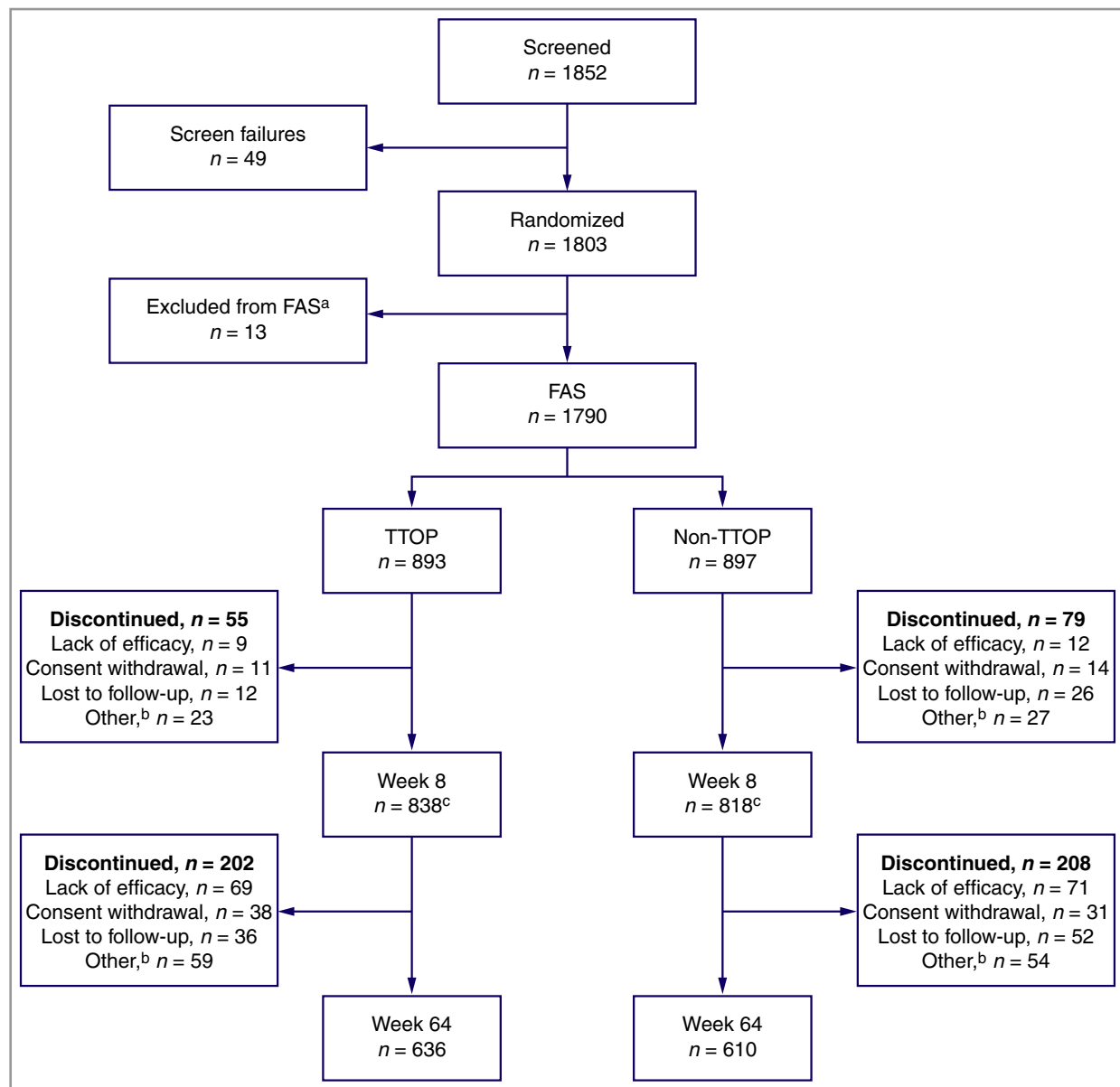


Fig 1. Patient disposition. TTOP, Topical Treatment Optimization Programme. ^aNo informed consent ($n = 8$); data issues at investigational site ($n = 5$). ^b'Other' includes adverse events/serious adverse events, major protocol deviation, pregnancy or unspecified. ^cThe primary end point analysis at week 8 was based on the full analysis set (FAS) using nonresponder imputation.

baseline Psoriasis Area and Severity Index score as covariates. To compare mean PGA, PsGA and BSA from weeks 8 to 64 between the two study arms, Wilcoxon rank-sum tests (5% significance level) were performed. Correlations between PGA and DLQI and PGA and PsGA were calculated, and Spearman's rank correlation coefficient is provided.

Results

Patients

Between 24 February 2012 and 25 June 2014, 1852 patients were screened and 1803 were randomized to either

TTOP or non-TTOP (Fig. 1); a total of 13 patients were excluded from the FAS and 1246 patients completed the study.

Overall, patient demographics and characteristics were comparable between TTOP and non-TTOP arms (Table 1).

Use of study medication

From baseline to week 8 (i.e. 56 ± 7 days), the mean \pm SD number of days where Cal/BD gel was applied was 53.5 ± 9.9 in the TTOP arm and 53.5 ± 10.2 in the non-TTOP arm. Patients randomized to non-TTOP had a consistently higher mean use of study medication per percentage of

Table 1 Patient demographics and baseline characteristics (full analysis set)

	TTOP arm (n = 893)	Non-TTOP arm (n = 897)
Men	509 (57.0)	521 (58.1)
Age (years)	50.9 ± 15.0	51.0 ± 15.4
BMI (kg m ⁻²)	27.2 ± 4.8	27.5 ± 5.0
Duration of psoriasis (months) ^a	215.8 ± 178.3	208.2 ± 173.6
PASI	4.5 ± 2.2	4.5 ± 2.2
PGA		
Mild	312 (34.9)	287 (32.0)
Mild-to-moderate	349 (39.1)	384 (42.8)
Moderate	192 (21.5)	188 (21.0)
Moderate-to-severe	35 (3.9)	35 (3.9)
Severe	5 (0.6)	3 (0.3)
BSA (%)	5.1 ± 2.7	5.0 ± 2.6
Patients with		
Nail involvement	248 (27.5)	250 (27.9)
Psoriatic arthritis	76 (8.5)	74 (8.2)
Obesity	147 (16.5)	174 (19.4)
(Essential) hypertension	172 (19.3)	180 (20.1)
Patients with previous systemic therapy	6 (0.7)	7 (0.8)
Patients with previous phototherapy	5 (0.6)	3 (0.3)
Patients with previous topical therapy		
Corticosteroids	328 (36.7)	278 (31.0)
Vitamin D only	126 (14.1)	127 (14.2)
Combination	185 (20.7)	184 (20.5)
Other	35 (3.9)	36 (4.0)

Data are presented as mean ± SD or n (%). BMI, body mass index; BSA, body surface area; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment of disease severity; TTOP, Topical Treatment Optimization Programme. ^aDuration of psoriasis could not be calculated for one patient in the TTOP arm.

Table 2 Consumption of study medication (gram per interval) per percentage of body surface area affected (full analysis set)

	TTOP arm	Non-TTOP arm
Baseline to week 4	7.3 ± 9.9 (865)	8.0 ± 9.5 (860)
Week 4–8	7.0 ± 7.3 (817)	7.8 ± 9.7 (807)
Week 8–16	10.7 ± 11.7 (794)	12.0 ± 17.8 (766)
Week 16–24	10.5 ± 12.5 (752)	11.6 ± 13.6 (716)
Week 24–32	10.4 ± 12.0 (701)	11.6 ± 17.3 (682)
Week 32–40	10.4 ± 12.3 (655)	11.5 ± 15.0 (645)
Week 40–48	9.5 ± 11.1 (617)	11.0 ± 14.0 (601)
Week 48–56	9.8 ± 11.2 (606)	11.3 ± 15.6 (589)
Week 56–64	9.5 ± 10.7 (580)	11.3 ± 15.7 (563)

Data are mean ± SD (n). TTOP, Topical Treatment Optimization Programme.

affected BSA than patients in the TTOP arm (Table 2), although the magnitude of the SDs suggests considerable variation in both arms.

Efficacy

The primary efficacy end point was fulfilled as 36.3% of TTOP patients and 31.3% of non-TTOP patients had a PGA of 0 (clear) or 1 (almost clear) at week 8 ($P = 0.0267$; Fig. 2). There was no difference in responder rates between countries ($P = 0.775$), and the treatment effect at week 8 remained significant after adjusting for potential confounding factors, such as age, sex, disease duration and baseline severity ($P = 0.0399$). From week 8 onwards, the numerical differences between the TTOP and non-TTOP arms were maintained to week 64; statistically significant differences were noted at weeks 4, 8, 24, 32 and 48 (Fig. 2). The mean PGA of TTOP and non-TTOP patients over weeks 8–64 was significantly different ($P = 0.0343$). The mean BSA affected from baseline to week 64 decreased from 5.1 to 2.4 in the TTOP arm and from 5.0 to 2.7 in the non-TTOP arm, with no statistically significant difference between arms ($P = 0.1196$). In both arms of the study, mean PsGA values decreased from baseline to week 64 (TTOP 3.2 ± 1.0 to 1.8 ± 1.3 ; non-TTOP 3.1 ± 1.0 to 1.9 ± 1.2); there were no statistically significant differences between arms. The correlation between PsGA and PGA was moderate at baseline in both arms (0.56, $P < 0.001$ for both; Spearman's rank correlation). At week 64, the correlation increased to 0.85 in the TTOP arm and 0.82 in the non-TTOP arm ($P < 0.001$ for both).

Patient-reported outcomes

Dermatology Life Quality Index

Mean baseline DLQI scores were similar in the TTOP (5.2 ± 4.7) and non-TTOP (5.0 ± 4.5) arms (66.5% and 66.7% had a baseline DLQI of ≤ 5 , respectively; while 18.8% and 21.5% had a baseline DLQI of 0/1, respectively). The mean decrease in DLQI from baseline to week 8 (decrease of 2.6 ± 3.7 for TTOP; decrease of 2.2 ± 3.4 for non-TTOP) and to week 64 (2.4 ± 4.1 for TTOP; 2.2 ± 3.8 for non-TTOP) was similar across arms. When patients who had a DLQI of ≤ 5 were evaluated, the proportions in the TTOP and non-TTOP arms were 81.5% and 77.3% at week 8, and 60.1% and 58.4% at week 64, respectively. The proportion of patients achieving a DLQI of 0/1 in the TTOP and non-TTOP arms was 47.9% and 44.1% at week 8, and 39.9% and 35.7% at week 64, respectively.

Topical Therapy Adherence Questionnaire

It is not known whether the DLQI is a suitable tool to assess adherence-relevant factors in the topical therapy of psoriasis. Therefore, we additionally used the TTAQ, a patient questionnaire more specifically designed to address patient confidence and treatment satisfaction, in addition to other parameters known to influence adherence.¹⁸ For the statements related to patient empowerment and adherence there was a significant difference between TTOP and non-TTOP patients at week 8. This indicates that TTOP positively influenced these factors

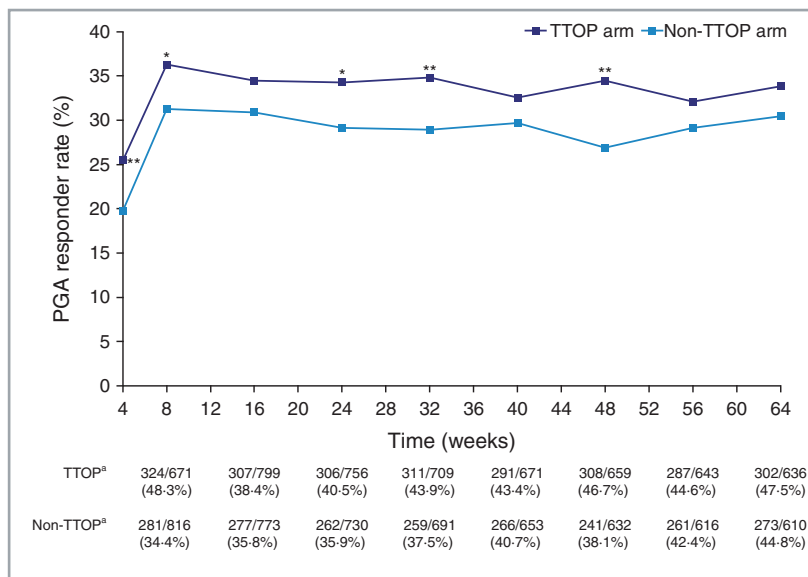


Fig 2. Physician's Global Assessment (PGA) responder rates by study arm from week 4 to week 64. The numbers shown in the figure are based on the full analysis set using nonresponder imputation. * $P < 0.05$; ** $P < 0.01$ vs. non-TTOP. ^aFor comparison, the numbers shown below the x-axis given as n/N (%) represent an 'as observed' analysis, where n = number of patients reaching a PGA response; N = number of patients with a PGA value and % = PGA response rate based on number of patients with PGA value. TTOP, Topical Treatment Optimization Programme.

beyond the self-assessment of disease severity, which was rated similarly in both groups (Table 3).

Assessment of Topical Treatment Optimization Programme elements

The patients' ranking of TTOP elements was similar at weeks 8 and 64, with one-to-one conversations with the dermatologist/nurse being of greatest importance at both time points (Table 4). Telephone/e-mail helpdesk and reminder calls were consistently regarded as being of least importance.

The time required for consultations decreased from baseline to week 64 in both the TTOP (dermatologist 33.5 ± 13.9 min to 18.0 ± 8.8 min; nurse 31.1 ± 13.2 min to 14.6 ± 8.3 min) and non-TTOP arms (dermatologist 25.2 ± 12.9 min to 9.2 ± 5.3 min; nurse 18.9 ± 11.2 min to 8.1 ± 5.2 min). Visits for TTOP patients generally lasted around 9–10 min longer than non-TTOP visits.

Safety and tolerability

Overall, 46.6% of the patients reported at least one AE (49.8% of TTOP patients and 43.4% of non-TTOP patients; Table 5). The frequency of patients with serious AEs was 6.8% in the TTOP arm and 4.9% in the non-TTOP arm. One male patient died during week 8 (TTOP arm), but neither the investigator nor study sponsor considered the event to be related to the study drug; the patient had a history of hypertension, hypercholesterolaemia and obesity.

Drug-related AEs were reported in 4.5% of patients in the TTOP arm and 3.7% in the non-TTOP arm; the most common were pruritus and application-site pain (Table 5). Of the drug-related AEs, four were severe (pruritus, skin irritation, guttate psoriasis and drug intolerance). In addition, one AE of moderate severity fulfilled the criteria for seriousness. A 23-year-old woman experienced Quincke oedema and was hospitalized overnight, receiving intravenous treatment with

Table 3 Selected Topical Therapy Adherence Questionnaire (TTAQ) statements – proportion of patients who strongly agreed (week 8)

TTAQ	Response	TTOP arm (n = 893)	Non-TTOP arm (n = 897)
A. 'I am satisfied with the efficacy of the treatment'	Strongly agree	413 (46.2)	358 (39.9)
B. 'I am more confident as a result of the treatment'	Strongly agree	412 (46.1)	328 (36.6)
C. 'I feel well informed about my skin condition'	Strongly agree	660 (73.9)	537 (59.9)
D. 'My doctor has taken enough time to explain the condition to me'	Strongly agree	674 (75.5)	565 (63.0)
E. 'I have understood how to implement the treatment to ensure that I can easily handle my condition'	Strongly agree	667 (74.7)	576 (64.2)

Data are n (%). TTOP, Topical Treatment Optimization Programme. Patients could rate each statement as 'strongly disagree', 'disagree', 'agree' and 'strongly agree'. Overall answers to the above questions were statistically different between the two groups (Wilcoxon rank-sum test with Bonferroni correction for multiple comparison, $P = 0.01$). Based on Fisher's exact test, the responses to statements B, C, D and E were significantly different ($P = 0.001$, $P < 0.001$, $P < 0.001$ and $P < 0.001$, respectively), but were not significantly different for statement A ($P = 0.033$).

prednisolone and dimetindene; she recovered fully. The investigator and sponsor classified the AE as possibly related to the study drug.

Table 4 Ranking of importance of Topical Treatment Optimization Programme (TTOP) elements by patients randomized to the TTOP arm at week 8 and week 64 (full analysis set)

TTOP element	Mean week-8 score (median)	Mean week-64 score (median)	Overall ranking
One-to-one conversation with dermatologist	1.6 (1.0)	1.5 (1.0)	1
One-to-one conversation with nurse	2.1 (2.0)	2.0 (2.0)	2
Patient information material	3.3 (3.0)	3.5 (3.0)	3
Telephone/e-mail helpdesk	3.8 (4.0)	3.9 (4.0)	4
Reminders for using treatment	4.0 (4.0)	4.0 (4.0)	5

Discussion

There is substantial evidence highlighting that adherence rates are low in psoriasis,^{4,9,10} which can lead to poor efficacy and wasted healthcare resources.^{9,22,23} However, to the best of our knowledge, there have not been any large, high-quality studies that document improved outcomes as a consequence of the implementation of adherence strategies. TTOP was developed to provide tools that may help to improve adherence in daily practice. Specifically, the TTOP intervention aimed to augment the quantity/quality of information provided to the patient and improve the relationship with the healthcare provider,¹² as these factors are known to impact on adherence.^{3,4} It was thought that this patient-centric approach would help patients feel more empowered in the treatment of their psoriasis, which would ultimately result in optimized outcomes. The value of the TTOP intervention was tested against standard of care in a large randomized 64-week study (PSO-TOP). To avoid confounding by different topical treatments and formulations, Cal/BD gel was used in all patients. According to the study concept, the main outcomes included assessment of the objective clinical response (i.e. PGA) and a patient questionnaire related to relevant factors involved in empowerment and adherence (i.e. TTAQ).

After 8 weeks of therapy significantly more patients achieved a PGA of 'clear' or 'almost clear' in the TTOP arm than those in the non-TTOP arm (36.3% vs. 31.3%, $P = 0.0267$); this superiority was maintained across countries and when different disease- and patient-related factors were included. The PGA response rate of $\geq 30\%$ demonstrates that Cal/BD gel is effective for treating psoriasis, even in patients who had previously failed topical treatment. The data align with previous Cal/BD gel studies,^{24,25} underlining the robustness of the results collected in PSO-TOP. Significant differences between the TTOP arm and the non-TTOP arm were observed as early as 4 weeks, and at different time points during the 'as needed' period. Mean PGA over the 'as needed' period was

Table 5 Adverse drug reactions

Adverse reaction	TTOP arm (n = 891)	Non-TTOP arm (n = 897)	Total (n = 1788)
Any AE	444 (49.8)	389 (43.4)	833 (46.6)
Any drug-related AE	40 (4.5)	33 (3.7)	73 (4.1)
Any serious AE	61 (6.8)	44 (4.9)	105 (5.9)
Any drug-related serious AE	0 (0.0)	1 (0.1)	1 (0.1)
Common AEs ^a			
Nasopharyngitis	72 (8.1)	66 (7.4)	138 (7.7)
Influenza	27 (3.0)	29 (3.2)	56 (3.1)
Upper respiratory tract infection	19 (2.1)	17 (1.9)	36 (2.0)
Lower respiratory tract infection	14 (1.6)	20 (2.2)	34 (1.9)
Worsening psoriasis	22 (2.5)	15 (1.7)	37 (2.1)
Headache	18 (2.0)	13 (1.4)	31 (1.7)
Diarrhoea	22 (2.5)	12 (1.3)	34 (1.9)
Back pain	33 (3.7)	24 (2.7)	57 (3.2)
Arthralgia	19 (2.1)	21 (2.3)	40 (2.2)
Common drug-related AEs ^b			
Pruritus	4 (0.4)	6 (0.7)	10 (0.6)
Application-site pain	6 (0.7)	4 (0.4)	10 (0.6)
Worsening psoriasis	5 (0.6)	1 (0.1)	6 (0.3)
Erythema	0 (0.0)	5 (0.6)	5 (0.3)
Application-site irritation	3 (0.3)	2 (0.2)	5 (0.3)

Data are provided as n (%). TTOP, Topical Treatment Optimization Programme. ^aAdverse events (AEs) occurring in at least 2% of patients in either treatment arm. ^bDrug-related AEs occurring in at least five patients overall.

also significantly higher for the TTOP arm than for the non-TTOP arm, providing further support for a longer-term superiority of the TTOP approach.

At all time points, mean overall and BSA-calculated use of Cal/BD gel was higher in the non-TTOP arm than in the TTOP arm, which is notable given that TTOP patients had a significantly better clinical outcome based on PGA-defined responder rates. We can speculate that because TTOP patients were trained in the correct application and use of Cal/BD gel at their first visit, with additional training at week 4 if necessary, they used the medication in a more considered way, applying it more accurately to the affected plaques and avoiding excessive use. In line with this assumption, at week 8, significantly more patients in the TTOP than in the non-TTOP arm expressed that they understood the treatment.

As assessed by the TTAQ, the improved PGA response rate at week 8 in the TTOP arm was accompanied by more patients being confident as a result of the treatment, feeling informed about the disease and stating that their doctor had taken enough time to explain the condition, which are all parameters that are likely to have an impact on adherence. However, the changes in the DLQI and the self-assessment of global disease severity (PsGA) were not significantly different between the arms, although both clearly indicated

improvement from baseline.²⁶ This may be because the observed difference in the PGA response rate was relatively small and/or suggest a limited suitability of the DLQI to address adherence factors specifically. This also reflects a number of potential limitations linked to the approach of testing adherence strategies in a clinical trial such as PSO-TOP; in particular, the controlled setting including a preselection of patients, in this case patients who had already failed previous topical therapy; a structured visit scheme and the use of a standardized high-quality treatment, all of which are necessary to limit confounding; the increased awareness of physicians and patients owing to participation in a clinical trial; and the fact that most sites could not provide two separate investigational teams for TTOP and non-TTOP arms, thereby limiting discrimination between the two strategies. All of these limitations will have an impact on the factors that may lead to non-adherence in a 'real-world' setting and/or potentially minimize the likelihood of being able to differentiate between the TTOP and non-TTOP intervention.

Our positive finding demonstrates that measures against nonadherence are useful and can be tested and validated in clinical trials. In this regard, the analyses of the ranking of TTOP elements should be informative for future programmes aimed at optimizing adherence. An improved quality of life is a desirable treatment goal that could not be documented in this study, but the TTAQ findings clearly indicate that patients recognize the value of TTOP. This is particularly true for the communication with a healthcare professional; of the five TTOP elements, patients ranked the one-to-one conversations with the dermatologist and nurse as being of the highest importance. Information material, helpdesks and reminder calls were not as relevant. As one might expect from the design of the TTOP tool, its application led to longer consultations (on average 9–10 min longer in the TTOP than the non-TTOP arm). While this extra time may be reduced in the future by the development of more effective communication strategies, it may have to be accepted that better objective clinical outcomes and higher patient satisfaction levels, in the case of a chronic illness such as psoriasis, can only be achieved if dermatologists and nurses invest more time communicating with and training their patients.

Overall, Cal/BD gel was well tolerated in both treatment arms. The type and frequency of adverse reactions were comparable with those listed in the fixed combination Cal/BD SmPC and reported in a pooled safety analysis.^{14,27} There was one report of a serious adverse reaction (Quincke oedema), which is a rare but known adverse reaction to Cal.

In conclusion, the PSO-TOP study provides evidence that optimized management of patients with psoriasis, based on the five-element TTOP tool, can improve clinical outcome compared with standardized topical therapy and positively influences patient attitudes related to empowerment and adherence as assessed by a novel questionnaire (TTAQ). Of the elements contained in TTOP, patients rated the structured one-to-one communication with dermatologists and nurses to

be the most important. The TTOP-optimized patient management was associated with lower overall medication use than standard of care, suggesting that TTOP might lead to better adherence to topical medication. Overall, this study demonstrates that interventions beyond the treatment itself can influence treatment outcome and encourages further research on treatment-independent measures to overcome nonadherence.

Acknowledgments

This study was supported by a grant from LEO Pharma to K.R., who designed the study with help from I.Z., C.O. and U.M. The experts originally involved in developing the TTOP intervention were K.R., I.Z., C.O., U.M., E.H.B., E.M.G.J.J., P.G., L.P. and R.B.W. The TTAQ was developed by patient-reported outcome specialists at SCIderm. The data were collected and analysed by SCIderm, with input from K.R. and U.M. The manuscript was prepared by K.R., I.Z., U.M. and C.O., with input from all authors. Writing assistance and editorial support were provided by Andrew Jones PhD from Mudskipper Business Ltd, which was funded by LEO Pharma. We thank all participating sites for their support and are grateful to all patients who took part in the trial.

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Appendix

Conflicts of interest

K.R. has received honoraria as a consultant and/or advisory board member and/or acted as paid speaker and/or participated in clinical trials sponsored by AbbVie, Amgen, Biogen, Boehringer Ingelheim Pharma, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Lilly, Medac, Merck Sharp & Dohme Corp., Novartis, Ocean Pharma, Pfizer, Regeneron, Takeda, UCB Pharma, Xenoport. I.Z. is an employee of SCIderm. H.B. has received honoraria as a consultant and/or advisory board member and/or speaker for AbbVie, Amgen, Baxalta, Boehringer Ingelheim Pharma, Celgene, Janssen, LEO Pharma, Lilly, Merck Sharp & Dohme Corp., Novartis, Pfizer, Pierre Fabre, Sun Pharmaceuticals and Takeda, and has received research grants from Pfizer. E.M.G.J. has received research grants for the independent research fund of the Department of Dermatology of the University Medical Centre, St Radboud, Nijmegen, the Netherlands, from AbbVie, Pfizer and Janssen, and has acted as consultant and/or paid speaker for and/or participated in research sponsored by companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Celgene, Lilly, Janssen, Merck Sharp & Dohme Corp., Novartis and Pfizer; P.G. has received honoraria to be a speaker for AbbVie, Janssen, Merck Sharp & Dohme Corp. and Pfizer. L.P. has received honoraria from LEO Pharma as a speaker and/or advisor on Dovobet and Picato, and has participated in the presented phase IV clinical trial. R.B.W. has acted as a consultant and/or speaker for, or received grant support, from AbbVie, Allmirall, Amgen, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Medac, Xenoport and UCB. C.O. worked as a freelance Project Manager, GCP consultant and medical writer for SCIderm. U.W. has been an advisor and/or received speaker's honoraria and/or received grants and/or participated in clinical trials of the following companies: Abbott, AbbVie, Almirall, Amgen, BASF, Biogen Idec, Celgene, Centocor, Lilly, Forward Pharma, Galderma, Janssen, LEO Pharma, Medac, Merck Sharp & Dohme Corp., Miltenyi Biotech, Novartis, Pfizer, Teva, VBL and Xenoport.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Data S1. Supplementary methods.

Data S2. Investigator script for the Topical Treatment Optimization Programme arm.

Data S3. Nurse script for the Topical Treatment Optimization Programme arm.

Data S4. Investigator script for the non-Topical Treatment Optimization Programme arm.

Data S5. Nurse script for the non-Topical Treatment Optimization Programme arm.

Data S6. Patient information material (the 'Topical Treatment Optimization Programme Patient Brochure').

Video S1. Author video.