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ORIGINAL ARTICLE

Efficacy of a fixed combination of calcipotriol/betamethasone dipropionate topical gel in adult patients with mild to moderate psoriasis: blinded interim analysis of a phase IV, multicenter, randomized, controlled, prospective study

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Abstract

Background Psoriasis is a common, chronic, inflammatory skin disease with the majority of individuals having limited disease, treated with topical medication. However, special attributes of topical treatments like galenic/cosmetic properties or an inconvenient treatment schedule may result in low preference for topical treatments. Hence, there is strong medical need for a topical medication, which is highly efficacious, easy-to-use and preferred by both physicians and patients.

Objective Blinded interim analysis with the purpose to assess efficacy of (both from the physician's and patient's perspective) and the patients' preference with a highly efficacious and easy-to-use fixed combination of calcipotriol/betamethasone dipropionate topical gel after 8 weeks of once daily treatment in a large patient population.

Methods In this phase IV, international, multicentre, randomized, controlled, prospective, parallel group study, adult patients with active, mild to moderate psoriasis despite previous topical psoriasis treatment, i.e. unsuccessful in the 8 weeks preceding study participation, are followed over 64 weeks. During the first 8 weeks the patients apply their medication once a day followed by a 56-weeks maintenance period according to SmPC. Blinded interim analysis of all patients included demographics, Physician's Global Assessment, the novel Patient's self Global Assessment (PsGA) and Patient Preference Questionnaire (PPQ).

Results 1795 patients were analysed. At week 8, 36.5% of the physicians rated the patients' psoriasis as clear/almost clear. Similarly, based on the patients' self-assessment, 34.2% had a clear/almost clear score of PsGA in week 8. Analysis of the PPQ showed that the vast majority of the patients judged their 8-week treatment to be preferable compared with their previous treatments.

Conclusion Results of this blinded interim analysis indicate that the fixed combination of calcipotriol/betamethasone dipropionate gel is highly efficacious and preferred by the majority of analysed patients.

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Conflict of Interest

K Reich has received honoraria as consultant and/or advisory board member and/or acted as paid speaker and/or participated in clinical trials sponsored by Abbott, AbbVie, Amgen, Basilea, Biogen-Idec, Celgene, Centocor, Eli Lilly, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Medac, MSD (Essex Pharma, Schering-Plough), Novartis, Ocean Pharma, Pfizer (Wyeth) and UCB. I Zschocke has declared no conflict of interest. H Bachelez has been a consultant for Abbvie, Amgen, Boehringer, Celgene, Janssen, LEO Pharma, Lilly, MSD, Novartis, Pfizer, Pierre Fabre, Takeda. EMGJ de Jong has received research research grants for the independent research fund of the

department of dermatology of 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, Janssen, MSD, and Pfizer. P Gisondi has received honoraria to be a speaker for AbbVie, Janssen-Cilag, MSD (Essex Pharma, Schering-Plough) and Pfizer. L Puig has perceived honoraria from Leo-Pharma as a speaker and/or advisor on Dovobet and Picato and has participated in the presented phase IV clinical trial. RB Warren has acted as a consultant and or speaker for Amgen, Abbvie, Janssen, LEO Pharma, Lilly, Novartis and Pfizer and has received grant support from Abbvie, Janssen, Novartis and Pfizer. U Mrowietz has been an advisor and/or received speakers honoraria and/or received grants and/or participated in clinical trials of the following companies: Abbott/AbbVie, Almirall-Hermal, Amgen, BASF, Biogen Idec, Celgene, Centocor, Eli Lilly, Forward Pharma, Galderma, Janssen, Leo Pharma, Medac, MSD, Miltenyi Biotech, Novartis, Pfizer, Teva, VBL, Xenoport.

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Other information

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Introduction

Psoriasis, a chronic, inflammatory skin disease, has a prevalence of approximately 2–3% in the western population.[1] With 80% of the affected patients the most common clinical form is psoriasis vulgaris (plaque psoriasis).[2] As more than 90% of the patients show a chronic course, continuous treatment is crucial.[3] Psoriasis impacts the disease-related quality of life and is associated with a variety of comorbidities.[4–6]

Available therapies for psoriasis include topical treatments, phototherapy and systemic therapies. Topical treatments are first-line therapies for the majority of patients since approximately 80% of the patients have mild or moderate psoriasis.[7] Most commonly prescribed are topical corticosteroids, vitamin D analogues (e.g. calcipotriol) or combination therapy.[7–10] In recent years, several studies have reported the efficacy and safety of a fixed combination of calcipotriol and betamethasone dipropionate and advantages compared with its individual components.[8,10–12] Adherence to therapy is generally crucial and depends on the conditions and the complexity of regimens prescribed. Throughout various diseases adherence to any treatment is generally poor.[13] In psoriasis non-adherence to topical treatments ranges from 40% to 70%.[14] Thus, in psoriasis adherence to therapy is a major issue with non-adherence leading not only to poor disease management but also to inefficient use of health care resources and an increased risk for the development of comorbidities.[15–18] Special attributes of topical treatments like galenic/cosmetic properties or a time-consuming or inconvenient treatment schedule may results in low preference for topical treatments, both by the physician and the patient.[19] Hence, there is strong medical need for a topical medication, which is highly efficacious, easy-to-use and preferred by both physicians and patients.

Within the scopes of an ongoing phase IV study, a large patient population is treated with a fixed combination gel of calcipotriol and betamethasone dipropionate under controlled, yet long-term real-life conditions.

The purpose of this blinded interim analysis is to assess efficacy of and patients' preference with the fixed combination topical gel compared with their previous treatments with the aim to confirm the fixed combination gel as the optimal choice for the study. It is also intended to compare the psoriasis severity assessment from both a physician's and a patient's perspective.

Material and methods

Study design and patients

Within this phase IV, multicentre, randomized, controlled, prospective, parallel group study data from approximately 1630 adult patients estimated to finish the study per protocol are collected. Main inclusion criterion was active, mild to moderate psoriasis (Physician's Global Assessment (PGA) ≥ 2 [20] and a Body Surface Area (BSA) of $\leq 10\%$) despite previous topical psoriasis treatment, i.e. topical treatment (except gel combination products containing 50 μg calcipotriol/0.5 mg betamethasone/g) in the 8 weeks preceding study participation was ineffective. The study is conducted in eight European countries (Denmark, France, Germany, Italy, The Netherlands, Spain, Sweden and United Kingdom). Planned treatment duration for each patient is 64 weeks including 10 visits (baseline (week 0), weeks 4, 8, 16, 24, 32, 40, 48, 56, 64). Overall aim of this study is to show clinically the importance of (an) optimized relationship/communication between the patient and health care professional. For this purpose, the Topical Treatment Optimization Program (TTOP) has been developed together with patient boards and an

expert advisory board to address patients' non-adherence in topical psoriasis therapy and the resulting underperformance of such treatments.[21] The study is aimed at showing the efficacy of TTOP compared with standardized regular care ('non-TTOP'). Patients were randomized in a 1 : 1 ratio to either participation in the TTOP or without (non-TTOP). To exclude the medication's influence on patients' adherence patients of both arms received the same standardized topical treatment of a fixed combination gel with 50 µg calcipotriol/0.5 mg betamethasone/g according to SmPC (once daily application to the affected areas for the first 8 weeks followed by a 56-week maintenance period).

This study is conducted in accordance with applicable national and international laws and regulations, including but not limited to the ICH-GCP guideline and the ethics principles that have their origins in the Declaration of Helsinki. Prior to study start, an independent Ethics Committee and the competent authority reviewed and approved the study. Patients provided written informed consent prior to study participation.

Assessments

The parameters relevant for the blinded interim analysis included demographic data and baseline information regarding psoriasis, including Psoriasis Area and Severity Index (PASI).[22] Furthermore, PGA and Patient's self Global Assessment (PsGA) were analysed at baseline and week 8, while Patient Preference Questionnaire (PPQ) was analysed at week 8.

The PGA,[20] with a 7-point scale from 0 = clear to 6 = severe, is used as the main parameter for the evaluation of efficacy. The newly developed PsGA is based on the PGA, however, using more general category descriptions and simplified wording enabling the patients to assess their psoriasis severity themselves (Table 1). The newly developed PPQ collected data on the patient's preference for their current compared with their previous treatments. The PPQ contains 10 questions scaled in a 4-point Likert format (0 = strongly disagree, 1 = disagree, 2 = agree and 3 = strongly agree) and a supplementary option 'Does not apply to me' (Table 2).

Statistical analysis

A blinded interim analysis of the aforementioned parameters was performed for the total population using the statistical package SAS (Statistical Analysis System) for Windows Version 9.3 (SAS Institute Inc., Cary, NC, USA). The analysis included descriptive statistics, confirmatory analyses of and correlations between PGA and PsGA at baseline and week 8. PGA and PsGA were considered as endpoints for the interim analysis. Descriptive statistics, percentages and frequencies (where appropriate) were performed for demographic data, other baseline characteristics, PGA and PsGA. For PGA and PsGA, a Wilcoxon rank-sum test (5% significance level) was performed to compare the mean between baseline and week 8. Scatterplots were performed and Spearman's rank correlation coefficients calculated for PGA and PsGA correlation at baseline and week 8. For PPQ, frequencies were calculated for the levels of each item at week 8 by pretreatment.

Results

Characteristics of the study population

In total, 1803 patients were randomized in 104 study sites in Denmark, France, Germany, Italy, The Netherlands, Spain, Sweden and United Kingdom. Recruitment was stopped when the calculated statistical sample size of 1630 patients was reached with 1654 patients performing visit 3 at week 8. Eight patients were excluded from the analysis: five due to dubious data quality, two withdrew consent before dispensing of medication and one was withdrawn after randomization despite lack of fulfilment of inclusion criteria concerning pretreatment. From the 1795 analysed patients, 761 were female and 1034 male. Demographic data and other baseline characteristics are presented in Table 3 and Table S1.

Importantly, as stated above, all patients had been unsuccessfully treated with another topical agent in the 8 weeks preceding inclusion. At the time of interim analysis, documentation of previous topical psoriasis treatment was recorded and coded for 1285 patients. Thereof, 22.1% had received calcipotriol/betamethasone combination (=ointment), 47.8% a potent corticosteroid (group II-IV, according to WHO ATC codes level 4), 22.7% Vitamin D analogues and 7.4% either a combination of the above or another topical treatment (e.g. weak corticosteroids of group I).

Efficacy evaluation

Assessment of psoriasis severity between week 0 and 8 was done by via PGA and PsGA. At baseline, 33.4% of the patients had a

Table 1 Patient's Global Assessment (PsGA)

Score	Category	Description
0	Clear	The skin looks normal with no signs of lesions
1	Almost clear	There are only faint lesions with some slight redness, barely elevated and a few scales
2	Mild	The skin lesions have a light red colour, may be slightly elevated and a bit scaly
3	Mild to moderate	The skin lesions have a reddish colour, are a bit elevated and somewhat scaly
4	Moderate	The skin lesions are clearly red, elevated and scaly
5	Moderate to severe	The skin lesions are really red, thick and with a lot of scales
6	Severe	The skin lesions are very red, really thick and with heavy scaling

Table 2 Patient Preference Questionnaire (PPQ)

Item No.	Question
1	The current treatment is more effective than the previous topical treatments
2	The current treatment is easier to use than the previous topical treatments
3	The current treatment has fewer side-effects than the previous topical treatments
4	I consider the current treatment to be better tolerable than the previous topical treatments
5	I prefer the current treatment to previous topical treatments
6	The current treatment is more effective than previous systemic treatments
7	The current treatment is easier to use than previous systemic treatments
8	The current treatment has fewer side-effects than previous systemic treatments
9	I consider the current treatment to be better tolerated than previous systemic treatments
10	I prefer the current treatment to previous systemic treatments

Table 3 Demographics and other characteristics at baseline

Parameter	Total $n = 1795$
Female, *n* (%)	761 (42.4%)
Male, *n* (%)	1034 (57.6%)
Age (years)	50.9 (15.22)
Height (cm)	170.9 (10.01)
Weight (kg)	80.2 (17.30)
BMI (kg/m^2)	27.34 (5.02)
Duration of psoriasis (months)	212.6 (176.36)
Recently treated	
Yes	1795 (100.0%)
Involvement of nails	
Yes	1295 (72.1%)
No	500 (27.9%)
Psoriatic arthritis	
Yes	153 (8.5%)
No	1642 (91.5%)
PASI – score (H + UL + T + LL)	4.50 (2.19)

Data represent mean values (standard deviation), unless otherwise specified.

BMI, body mass index; H, head; LL, lower limbs; T, trunk; UL, upper limbs.

PGA of 2 (mild) and 66.5% a PGA >2; median PGA was 3.0. According to PsGA, 25.0% of the patients had a score of 2 (mild) and 72.2% a PsGA of >2; median PsGA was 3.0. After 8 weeks, the PGA was almost clear or clear for 36.5%. Likewise, 34.2% of the patients rated their psoriasis severity as being almost clear or clear. The median PGA as well as median PsGA improved to 2.0. Further details are shown in Table 4 (PGA) and Table 5 (PsGA).

Table 4 Summary of PGA at Baseline and Week 8

	Week 0	Week 8
N	1795	1655
Mean	3.0	1.9
SD	0.86	1.03
Median	3.0	2.0
Min	2	0
Max	6	6
Clear		93 (5.6%)
Almost clear		512 (30.9%)
Mild	600 (33.4%)	623 (37.6%)
Mild to moderate	736 (41.0%)	304 (18.4%)
Moderate	381 (21.2%)	109 (6.6%)
Moderate to severe	70 (3.9%)	13 (0.8%)
Severe	8 (0.4%)	1 (0.1%)
Wilcoxon rank-sum test (*P*-value)		$P < 0.001$

Table 5 Summary of PsGA at Baseline and Week 8

	Week 0	Week 8
N	1793	1653
Mean	3.2	2.0
SD	1.02	1.11
Median	3.0	2.0
Min	1	0
Max	6	6
Clear		89 (5.4%)
Almost clear	50 (2.8%)	459 (27.8%)
Mild	449 (25.0%)	640 (38.7%)
Mild to moderate	653 (36.4%)	287 (17.4%)
Moderate	487 (27.2%)	144 (8.7%)
Moderate to severe	125 (7.0%)	27 (1.6%)
Severe	29 (1.6%)	7 (0.4%)
Wilcoxon rank-sum test (*P*-value)		$P < 0.001$

Moreover, for both PGA and PsGA the null hypothesis of no treatment effect between week 0 and 8 could be rejected at a 5% significance level ($P < 0.001$). The shift of PGA from week 0–8 is shown in Fig. 1 for all patients ($n = 1795$) and in Fig. 2 according to pretreatments ($n = 1285$).

The correlation between PGA and PsGA using Spearman's correlation coefficient with 0.75 ($P < 0.0001$) shows a correlation at medium level. Generally, the patients rated their condition at baseline worse compared with the physicians' ratings (Fig. 3).

Patients' preference

Assessment of patients' preference using the PPQ showed that the vast majority judged their 8-week treatment with the current study medication (fixed combination topical gel) to be highly

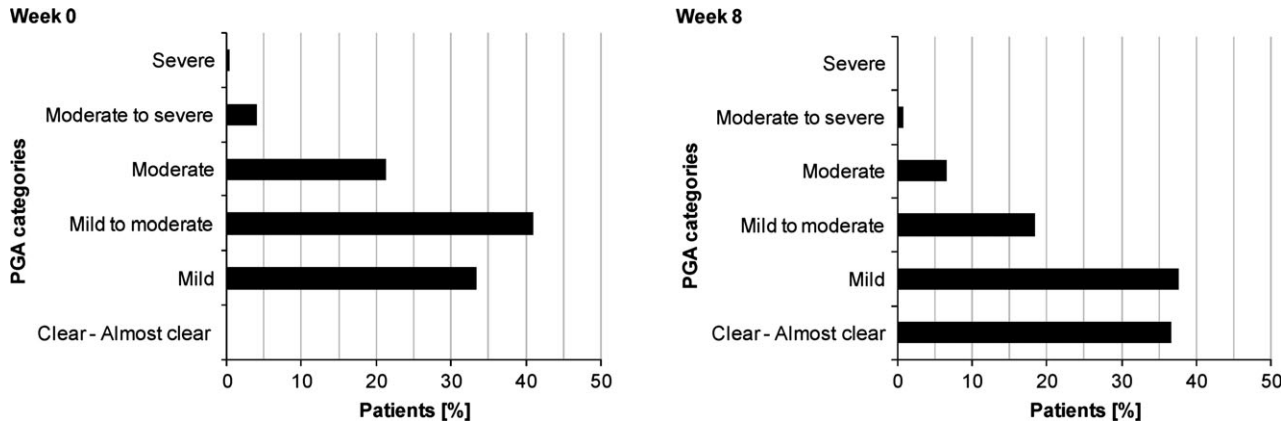

Figure 1 Physician's Global Assessment (PGA) according to severity: baseline vs. week 8 (n = 1795).

preferable when compared with their previous treatments. This was the case for both topical and potentially systemic treatments, whichever treatments the patients had previously received. Preference for the current medication was actually observed for each of the 10 items and was independent from the treatment that the patient had received preceding inclusion. More precisely, the patients rated the current topical treatment as being more effective, easier to use, having fewer side-effects and to be better tolerable compared with their previous treatments. Importantly, as a global statement, the patients preferred the current topical treatment compared with their previous topical treatments and/or systemic treatments (Item 5 and 10). The frequencies for the levels of each of the 10 items of PPQ at week 8 is shown in Fig. 4; Fig. S1 shows the PPQ results according to pretreatments.

Discussion

Topical agents are the mainstay in the treatment of psoriasis. However, given their specific characteristics the overall adherence and compliance are poor.[19] Factors contributing to this poor adherence rate are various and complex: topical therapies are often considered to be ineffective/not effective enough, messy and the application is time-consuming and inconvenient.[23–25] It has been shown that the prescribed regimen significantly affects adherence with once daily regimens resulting in 84% adherence, while for thrice-daily regimens reported adherence is only 59%.[13] Therefore, the fixed combination gel of calcipotriol and betamethasone dipropionate was chosen for the study as it is an easy-to-use, effective, generally safe and well-tolerated combination product, which only has to be applied once daily in the first weeks until full therapeutic effect is reached, after which it may be used 'as needed' for further disease control.[26–29]

An aim of this study is the documentation of the patients' perception of this specific topical therapy and to re-establish the value of topical therapy. The PPQ was newly developed for this study to collect data on the patients' preference for the current treatment with the fixed combination topical gel compared with their previous treatments. Acceptance of the study medication was very high as the patients rated this current topical treatment as being more effective, easier to use, having fewer side-effects and to be better tolerable, irrespective of the previous treatments – topical or systemic – they had received. In addition to the unsuccessful topical treatment in the 8 weeks prior to study participation, several patients had also received systemic treatment, previously, however, documentation of the 4 months prior to study participation was not intended and therefore for most of them neither type or duration of prior systemic treatment were known. Nevertheless, those patients who previously received systemic treatment interestingly also rated the current treatment with the fixed combination gel to be highly preferable when compared with their previous systemic treatment. However, regarding a high number of answers for items relating to previous systemic treatment it has to be considered that the terms topical and systemic might not be clear to some of the patients. Furthermore, the presented results of treatment with a fixed combination calcipotriol/betamethasone dipropionate gel are comparable with previous observations with a fixed combination ointment of calcipotriol and betamethasone dipropionate.[8] However, the presented analysis showed that the fixed combination gel was highly preferred, although containing the same active ingredients, when compared to previously available combination treatment, i.e. ointment. Possible explanations might be a better adherence and therefore better efficacy of the gel formulation due to less greasiness and/or less time spent for application or the use within the scope of a clinical study. The latter might be a general limitation concerning the comparison with the patients' previous treatments, which were all used according to daily practice and not within controlled conditions of a clinical study. Nevertheless, the high patient preference verifies the selection of the fixed combination gel as medication for the study.

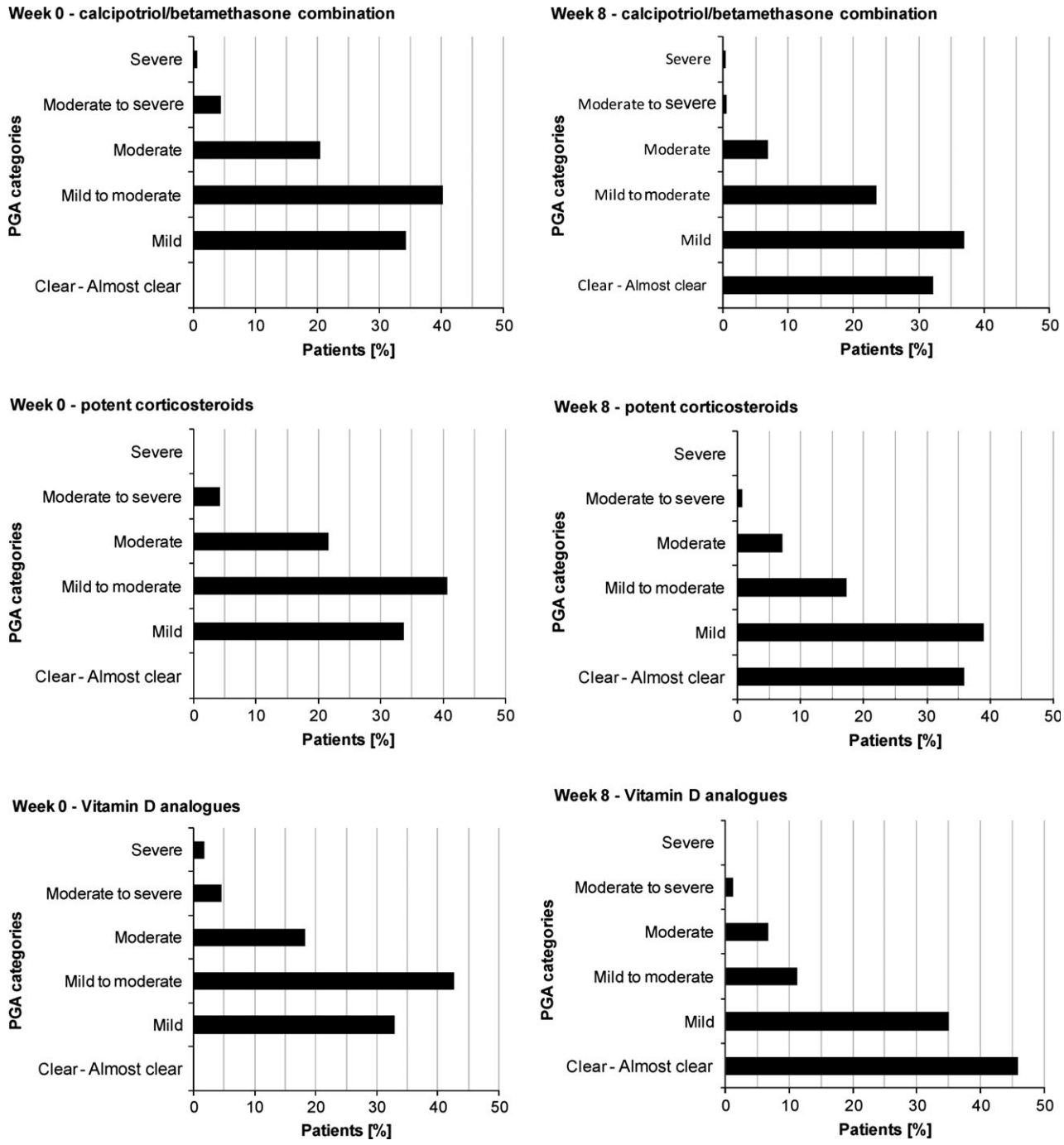

Figure 2 Physician's Global Assessment (PGA) according to severity by pretreatment (calcipotriol/betamethasone combination, potent corticosteroids, Vitamin D analogues): baseline vs. week 8 (n = 1285).

Within the scopes of this study it was aimed to positively select the patient population as being unsuccessfully treated with topical antipsoriatic agents other than the fixed combination gel for at least 8 weeks preceding inclusion. Importantly, to classify this pretreatment as ineffective, the PGA had to be 2 or higher at inclusion. PGA and PsGA at baseline were in the range of mild to moderate disease. After 8 weeks of once daily treatment with the fixed combination topical gel significant improvements were

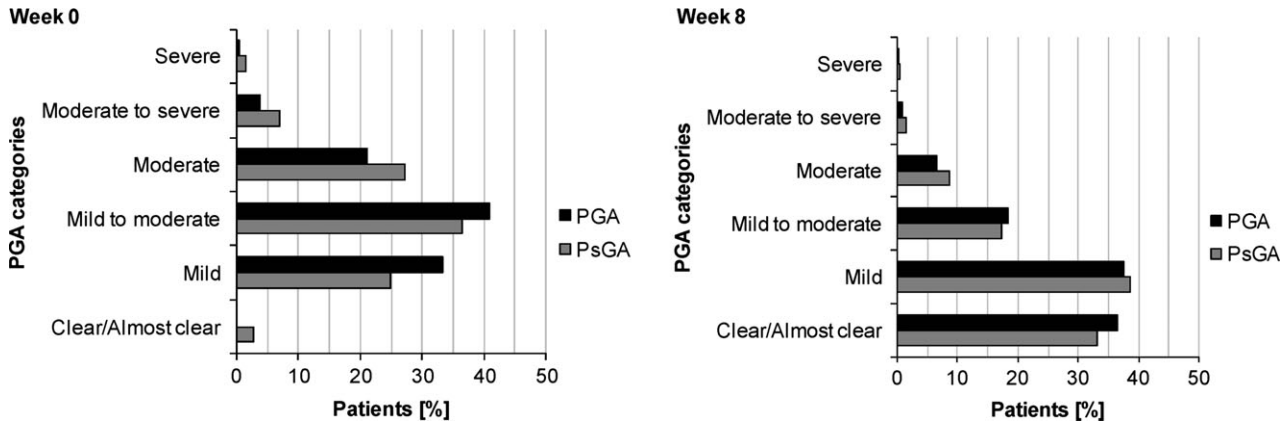

Figure 3 Physician's Global Assessment (PGA) vs. Patient's Global Assessment (PsGA) according to severity: baseline vs. week 8 (n = 1795).

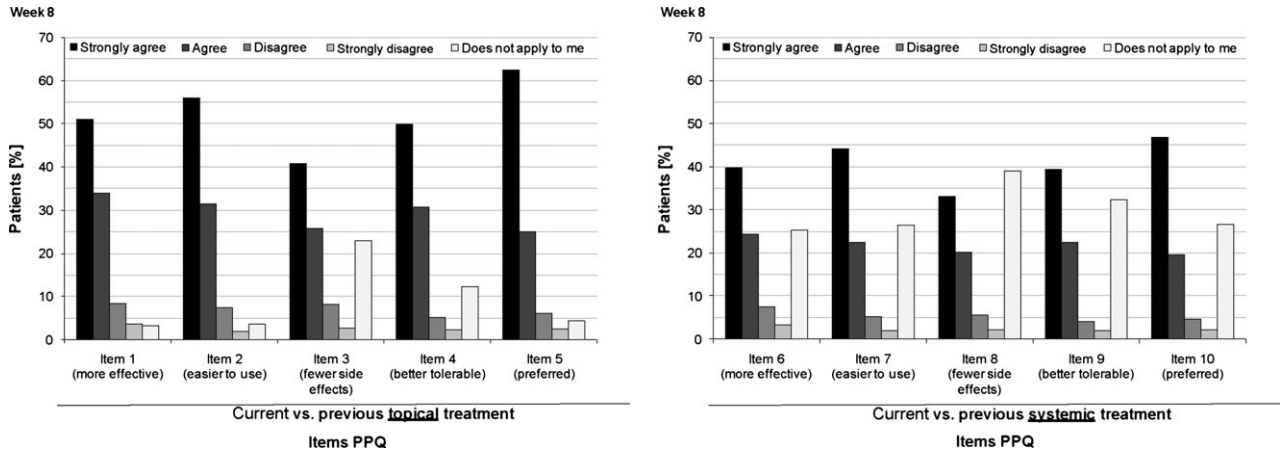

Figure 4 Patient Preference Questionnaire (PPQ) at week 8 (n = 1795). Item 1: The current treatment is more effective than the previous topical treatments, Item 2: The current treatment is easier to use than the previous topical treatments, Item 3: The current treatment has fewer side-effects than the previous topical treatments, Item 4: I consider the current treatment to be better tolerable than the previous topical treatments, Item 5: I prefer the current treatment to previous topical treatments, Item 6: The current treatment is more effective than previous systemic treatments, Item 7: The current treatment is easier to use than previous systemic treatments, Item 8: The current treatment has fewer side-effects than previous systemic treatments, Item 9: I consider the current treatment to be better tolerated than previous systemic treatments, Item 10: I prefer the current treatment to previous systemic treatments.

shown for both PGA and PsGA. Remarkably, both PGA and PsGA had comparable severity ratings, indicating the usefulness and comparability of the patient's self-assessment tool with the physician's assessment tool. This is the first study that attempts to compare the perspectives of both the physician as well as the patient with similar tools. At baseline, the physicians tend to rate the patient's condition severity less severe than the patients themselves, indicating that they might be more desensitized or conversely, that the patients consider due to psychological impairment that they are more severely affected than they actually are. In any case, the different perceptions tend to converge after 8 weeks. This trend might be explained by a certain "training effect" regarding the self-assessment of the patients. Additionally, the self-perception of the patients might have been changed after having received more information about severity and outcome of the disease, which could be assumed at least for the patients of the TTOP group. Particularly, possible differences between the TTOP and non-TTOP group will be interesting in the final analysis at the end of the study.

In summary, interim analysis of a large patient population after 8 weeks of treatment indicated that the fixed combination calcipotriol/betamethasone dipropionate topical gel is highly

efficacious and highly preferred by the patients compared with their previous treatments. This is beneficial to re-establish the value of topical therapy to both the physicians as well as the patients.

As the main goal of the PSO-TOP study is the assessment of the effectiveness of the TTOP-intervention, the results of the ongoing study are eagerly awaited to see how the TTOP-intervention influences the patient's adherence.

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Supporting information

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

Figure S1. Patient Preference Questionnaire (PPQ) at week 8 by pretreatment (calcipotriol/betamethasone combination, potent corticosteroids, Vitamin D analogues; n = 1285). Item 1: The current treatment is more effective than the previous topical treatments, Item 2: The current treatment is easier to use than the previous topical treatments, Item 3: The current treatment has fewer side-effects than the previous topical treatments, Item 4: I consider the current treatment to be better tolerable than the previous topical treatments, Item 5: I prefer the current treatment to previous topical treatments, Item 6: The current treatment is more effective than previous systemic treatments, Item 7: The current treatment is easier to use than previous systemic treatments, Item 8: The current treatment has fewer side-effects than previous systemic treatments, Item 9: I consider the current treatment to be better tolerated than previous systemic treatments, Item 10: I prefer the current treatment to previous systemic treatments.

Table S1. Demographics and other baseline characteristics.