Dermatol Ther (Heidelb) (2024) 14:521–532
https://doi.org/10.1007/s13555-024-01102-6

ORIGINAL RESEARCH

Efficacy and Safety of Topical Tacrolimus Microemulsion Applied Twice Daily in Patients with Mild to Moderate Scalp Psoriasis

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Received: December 1, 2023 / Accepted: January 15, 2024 / Published online: February 12, 2024

ABSTRACT

Introduction: Involvement of the scalp is common in psoriasis and severely affects the quality of life of those affected. It is difficult to treat and places special demands on the galenics of a drug formulation. Tacrolimus is a calcineurin inhibitor and is approved as an ointment formulation for the treatment of atopic dermatitis. The efficacy and safety of topically applied tacrolimus have also been studied and proven for psoriasis. However, no proprietary pharmaceutical product is currently approved for this indication.

Methods: A multicenter, double-blind, vehicle-controlled phase 3 study was conducted to evaluate the efficacy and safety of 0.1% tacrolimus microemulsion when applied topically twice daily in 128 patients independently of sex with scalp psoriasis.

Results: The primary efficacy analysis showed a scalp Investigator Global Assessment (s-IGA) of 0 (absence of disease) or 1 (very mild disease) at 8 weeks in 28.6% of subjects in the tacrolimus group, indicating a significantly better response ($p = 0.0476$, chi-square test) versus 12.7% of subjects in the placebo group (difference of 15.9%-points). The Dermatology Life Quality Index (DLQI) improved over time and was more pronounced in the group treated with tacrolimus-containing microemulsion than in the placebo group, but showed no statistically significant difference after 8 weeks of use ($p = 0.193$, ANCOVA). The safety analysis revealed no evidence of cutaneous side effects other than those known. Toxicologically relevant serum levels of tacrolimus could be excluded.

Conclusion: The study data show that 0.1% tacrolimus microemulsion has good efficacy and safety in the treatment of scalp psoriasis.

Keywords: Microemulsion; Scalp psoriasis; Tacrolimus; Topical application

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Key Summary Points

Tacrolimus is a calcineurin inhibitor that is approved in topicals for atopic dermatitis, also has clinical data showing efficacy for the use in psoriasis, and has strong evidence regarding safety.

Microemulsions are colloidal vehicles that are particularly suitable for stably dissolving tacrolimus and transporting it into the skin. Because of their low viscosity as well as their thermodynamic properties, they are particularly suited to the special features of the capillitium and epidermal hyperplasia in psoriasis.

In a phase 3 study, the efficacy and safety of a 0.1% tacrolimus microemulsion was investigated in 128 subjects with mild to moderate scalp psoriasis testing a twice-daily application compared to vehicle.

The primary efficacy analysis showed a s-IGA (0/1) at 8 weeks in 28.6% (95% confidence interval (CI) 17.42, 39.73) in the tacrolimus group, indicating a significantly better response ($p = 0.0476$, chi-square test) versus 12.7% (95% CI 4.48, 20.92) in the placebo group (difference of 15.9%-points).

The safety analysis revealed no evidence of cutaneous side effects other than those known, and toxicologically relevant serum levels of tacrolimus could be excluded.

The study data show that 0.1% tacrolimus microemulsion has good efficacy and safety in the treatment of scalp psoriasis.

INTRODUCTION

Psoriasis is a T helper 1 (Th1)/Th17-mediated, chronic inflammatory systemic disease with phenotypic involvement of skin, skin appendages, joints, juxta-articular bones, and entheses [1]. Depending on the severity and duration of the disease as well as individual risk factors, comorbidity patterns may develop [2–4]. The prevalence of psoriasis in Europe is approximately 2% [5]. Topical, physical, and systemic therapeutic options are available for treatment, which have been evaluated by national and international guidelines. Depending on the severity of the disease, corresponding recommendations for action are outlined [6–9]. For the vast majority of patients with mild severity (approximately 80%), the use of topical agents is recommended as first-line therapy [7]. Topical agents are also used in combination with systemic therapies to accelerate the therapeutic response and to optimize local efficacy. For monotherapy, glucocorticoids of class II and III (according to Niedner), vitamin D derivatives, dithranol, tar preparations, and keratolytics are available [7]. In addition, combination preparations, especially of betamethasone dipropionate and calcipotriol or glucocorticoids and salicylic acid, have been proven effective for practical and pharmacological reasons.

Although topical monotherapy with calcineurin inhibitors is recommended in the guidelines, no preparation with a marketing authorization for the indication psoriasis is currently available [7]. The guideline recommendation for the use of tacrolimus is based on extensive data on the efficacy and safety of a 0.1% ointment preparation that is approved for atopic dermatitis [10–14]. These data are supplemented by study data on the therapy of psoriasis with experimental, partly higher-dose formulations [15–17]. From a pharmaceutical point of view, the problem with the tacrolimus formulations is predominantly the instability of the drug, which is thermally unstable and susceptible to hydrolysis. To circumvent this problem, an anhydrous vehicle in the form of a semi-solid ointment has been used so far. However, this vehicle does not meet the necessary requirements for a galenic therapy for psoriasis [18].

From a clinical point of view, affected areas of the body that do not sufficiently respond to conventional topical, and occasionally systemic

therapy, are of particular interest. These "difficult to treat areas" include above all the scalp with a frequency of approximately 50% [19, 20]. Here, the capillitium, the adjacent forehead, and neck areas, but also the retroauricular area and the external auditory canals are relevant. A major reason for this insufficient response is the lack of suitability of the galenic formulations used, which do not correspond to the characteristics of follicle-rich, hairy skin [21]. The scalp features special conditions for the cutaneous bioavailability of topically applied drugs that are different from the penetration properties of interfollicular skin [22]. These result primarily from the pore pathway of diffusion, which is based on the anatomical conditions of the follicular structure. In this context, a low viscosity and the associated flow properties of the vehicle are of particular importance. When conventional vehicles are used for scalp psoriasis, two problems occur: the severe hyperkeratosis, which makes it difficult for the formulation to penetrate the follicular openings, as well as reduced contact between vehicle and scalp due to the adhesion of vehicle components to the hair shafts.

In order to fulfill the galenic requirements for the topical application of tacrolimus for the therapy of scalp psoriasis, a microemulsion system was developed that ensures a stable formulation of the drug tacrolimus. It has a low viscosity with good spreadability and allows the penetration of the drug not only by diffusion but also by the solvent drag effect. Additionally, the intrinsic effect of the vehicle reduces the hyperkeratosis of the psoriatic skin by its keratoemulsifying properties [18, 23, 24]. We hypothesized that tacrolimus 0.1% microemulsion will be more effective than tacrolimus-free vehicle.

METHODS

Study Design

The study was a prospective, randomized, double blinded, placebo-controlled, multicenter, phase 3 study to evaluate efficacy and safety of a 0.1% tacrolimus-containing microemulsion in subjects with mild to moderate scalp psoriasis over an 8-week treatment period. After screening, subjects were randomized in a 1:1 ratio to tacrolimus-containing microemulsion twice daily or vehicle microemulsion without active ingredient twice daily. Thus 0.25 g per 1% body surface area (BSA), i.e., 5 to 6 drops of test preparation for an affected area equivalent to the size of the entire palm of the hand, was applied.

Ethical Approval

The study was performed in compliance with local laws and regulations, the Declaration of Helsinki, and the International Conference on Harmonization of Good Clinical Practice Guidelines. The study protocol was approved by the relevant independent ethics committees and national health authorities.

Subjects

The multicenter study was performed at 12 active sites in Germany ($n = 9$) and France ($n = 3$) between July 2019 and August 2020. A total of 128 Caucasian subjects with mild to moderate scalp psoriasis were randomized after giving written informed consent. All subjects were in otherwise good health as determined by clinical and laboratory examinations at screening and eligible for study participation as assessed by predefined inclusion and exclusion criteria.

Study Assessments

Efficacy Parameters

The efficacy of the 0.1% tacrolimus-containing microemulsion on scalp psoriasis was evaluated by clinical assessments using the s-IGA scale (6-point scale of "absence of disease" (score 0), "almost clear" (score 1), "mild disease" (score 2), "moderate disease" (score 3), "severe disease" (score 4), and "very severe disease" (score 5)) as primary parameter, the scalp-modified Psoriasis Area and Severity Index (S-mPASI), the subject assessment of scalp pruritus (itch) using a 100-mm visual analogue scale (VAS), and the

Dermatology Life Quality Index (DLQI) as secondary parameters [25–28].

Safety Parameters

Safety assessments included recording of adverse events (AEs), laboratory examinations including blood sampling for systemic bioavailability of tacrolimus (Synlab Analytics & Services Germany GmbH, München, Germany), and physical examinations.

Statistical Analyses

Data were summarized by means of summary statistics. Continuous data were presented with the number of observations, mean value, standard deviation (SD), minimum, 25th percentile, median, 75th percentile and maximum value. Categorical data were presented as counts and percentages. The data were presented for each treatment group by visit.

The primary endpoint, the proportion of subjects achieving an s-IGA after 8 weeks (visit 7) of treatment (tacrolimus-containing microemulsion vs. placebo) of 0 or 1, was analyzed using summary statistics: proportion of subjects in treatment group achieving s-IGA (0/1) as well as its 95% CI and the difference in proportions between the treatment groups. Furthermore, a continuity corrected chi-square test assessed whether the proportions of s-IGA (0/1) differed between the treatment groups. If the p value associated with this test was less than 0.05 and the proportion of subjects achieving an s-IGA (0/1) was greater in the group treated with the tacrolimus-containing microemulsion compared with the placebo treated group, it was concluded that the tacrolimus-containing microemulsion is efficacious.

The secondary efficacy analyses included the analysis of change from baseline for the ordered categorical variable s-IGA. Comparison of treatment group on each study visit was performed using Wilcoxon–Mann–Whitney test, as applicable. Comparison of category changes from baseline (visit 2) to each study visit by treatment groups was conducted using Friedman test.

Furthermore, the changes from baseline in the continuous variables S-mPASI, VAS (scalp pruritus), and DLQI were analyzed. Comparison of treatment group was performed using an analysis of covariance (ANCOVA). The ANCOVA model included treatment group and baseline value.

Non-compartmental analysis (NCA) was to be performed using tacrolimus plasma concentrations observed at visit 2 and visit 7, i.e., after the first and the last day of application of tacrolimus-containing microemulsion, respectively.

RESULTS

Study Population

A total of 139 subjects were screened, resulting in the randomization of 128 subjects (32.0% male and 68.0% female subjects aged between 19 and 83) (Table 1). All 128 subjects received blinded study medication (tacrolimus-containing microemulsion or placebo) at least once applied to the affected areas of the scalp. A total of 103 subjects completed the study, whereas 25 subjects were prematurely discontinued. The primary reasons for premature discontinuation were lack of efficacy (6 subjects), AEs (3 subjects), withdrawal by subject (5 subjects), lost to follow-up (5 subjects), use of prohibited medication (1 subject), and other (5 subjects).

The data of all 128 randomized subjects were included in the safety analyses set. Data from 126 subjects (63 per treatment group) were valid for the primary analyses (full analyses set (FAS) using non-responder imputation (NRI)). The reason for exclusion from the FAS was that the respective subjects did not have at least one post-baseline assessment.

Primary Analysis Results of Efficacy

The primary endpoint of the study was the proportion of subjects achieving an s-IGA after 8 weeks (visit 7) of treatment of 0 (absence of disease) or 1 (very mild disease). In the primary efficacy analysis based on the FAS, the

Table 1 Demographic and clinical characteristics of the patients at baseline

		Tacrolimus microemulsion (n = 64)	Vehicle (n = 64)	Total (n = 128)
Age [years]	Mean (SD)	45.4 (18.09)	46.6 (18.27)	46.0 (18.12)
	Minimum; maximum	19; 83	19; 83	19; 83
Gender	Male	15 (23.4%)	26 (40.6%)	41 (32.0%)
	Female	49 (76.6%)	38 (59.4%)	87 (68.0%)
Ethnicity	Caucasian	64 (100.0%)	64 (100.0%)	128 (100.0%)
Body mass index	Mean (SD)	26.68 (4.741)	26.68 (4.863)	26.68 (4.783)
	Minimum; maximum	17.7; 39.6	18.3; 47.6	17.7; 47.6
Scalp investigator's global assessment Score	2—Mild disease	10 (15.6%)	11 (17.2%)	21 (16.4%)
	3—Moderate disease	37 (57.8%)	36 (56.3%)	73 (57.0%)
	4—Severe disease	17 (26.6%)	17 (26.6%)	34 (26.6%)

S-mPASI scalp-modified psoriasis area and severity index

proportion of subjects achieving an s-IGA (0/1) was 28.6% (95% CI 17.42, 39.73) in the group treated with tacrolimus-containing microemulsion and 12.7% (95% CI 4.48, 20.92) in the placebo group, with a difference of 15.9%-points. The continuity corrected chi-square test indicates that the proportion of subjects with s-IGA (0/1) achieved under treatment with tacrolimus-containing microemulsion differed statistically significantly from the proportion under placebo treatment (p = 0.0476) and the proportion of subjects achieving an s-IGA (0/1) was greater in the group treated with tacrolimus-containing microemulsion compared with the placebo treatment group, showing efficacy of 0.1% tacrolimus-containing microemulsion.

The number of subjects with s-IGA (0/1) increased over time and was more pronounced in the group treated with tacrolimus-containing microemulsion compared with placebo group: after 8 weeks (visit 7) of treatment, there were 18 such subjects in the group treated with tacrolimus-containing microemulsion and 8 such subjects in the placebo group (Fig. 1).

Secondary Analysis Results

Secondarily the analysis of change from baseline for the ordered categorical variable s-IGA was performed. During the study, improvements in disease severity were obtained for both tacrolimus-containing microemulsion and placebo; however, improvements were more pronounced in the group treated with tacrolimus-containing microemulsion. After 8 weeks of treatment, a statistically significant difference (p = 0.0314) was achieved between the treatment groups. After 8 weeks of treatment (visit 7), the greatest proportion of subjects in the group treated with tacrolimus-containing microemulsion (38.5%) was in category 2 (mild disease), followed by category 1 (very mild disease; 30.8%). In the placebo group, these were 41.8% of the subjects in category 2 (mild disease) and 41.8% of the subjects in category 3 (moderate disease) (Fig. 2).

The S-mPASI improved over time and was more pronounced in the group treated with

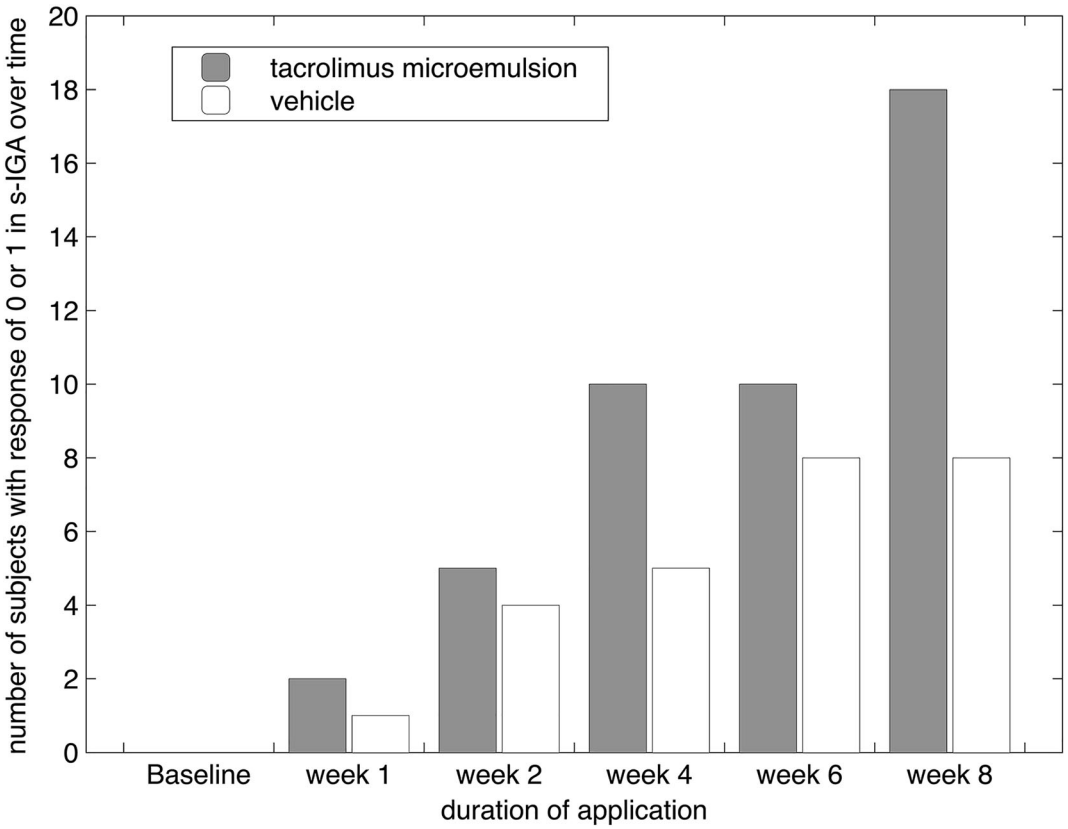

Fig. 1 Number of subjects with a response of 0 or 1 in s-IGA over time ("verum" means the treatment group). *s-IGA* scalp Investigator Global Assessment

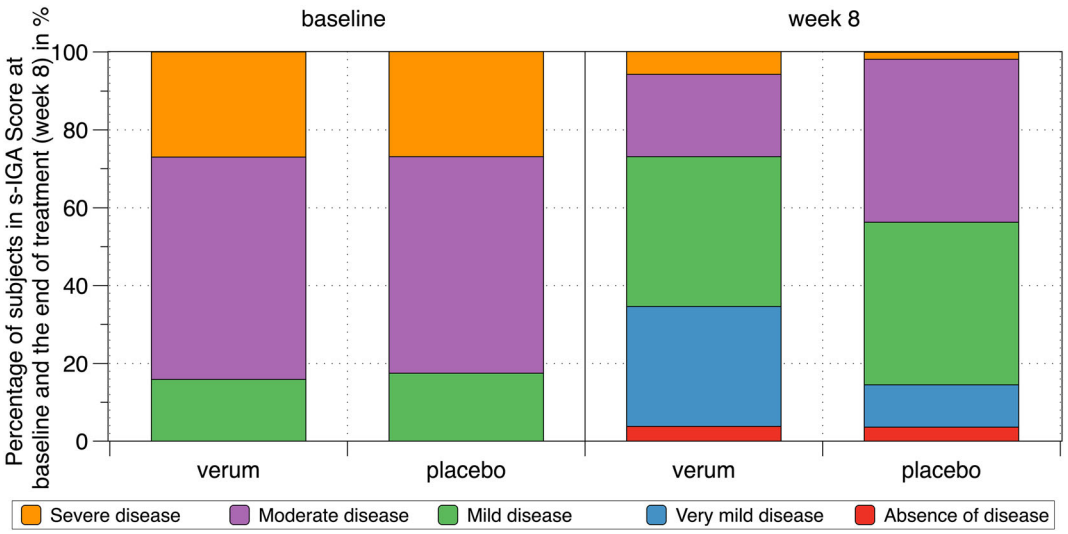

Fig. 2 Percentage of subjects in s-IGA Score at baseline and the end of treatment

tacrolimus-containing microemulsion compared with placebo group. After 8 weeks of treatment (visit 7), the mean S-mPASI was 1.0 in the group treated with tacrolimus-containing microemulsion and 1.2 in the placebo group, which corresponds to mean changes from baseline of − 1.1 and − 0.9, respectively. The ANCOVA showed no significant difference between the treatment group on the S-mPASI score at visit 7 ($p = 0.137$).

The VAS (scalp pruritus) improved over time in both treatment groups and was more pronounced in the group treated with tacrolimus-containing microemulsion compared with placebo group. However, the rating at baseline differed between treatment groups: the mean VAS in the group treated with tacrolimus-containing microemulsion was 61.0 compared with 53.8 in the placebo group. After 8 weeks of treatment (visit 7), VAS was 32.6 in the group treated with tacrolimus-containing microemulsion and 33.8 in the placebo group, which corresponds to mean changes from baseline of − 27.8 and − 18.9, respectively. The ANCOVA for VAS (scalp pruritus) showed that there was no significant effect between the treatment group on the VAS score after 8 weeks ($p = 0.357$).

The DLQI improved over time and was more pronounced in the group treated with tacrolimus-containing microemulsion compared with placebo group. However, the rating at baseline differed between treatment groups: the mean DLQI in the group treated with tacrolimus-containing microemulsion was 8.3 compared with 6.7 in the placebo group. After 8 weeks of treatment (visit 7), mean DLQI was 3.8 in the group treated with tacrolimus-containing microemulsion and 3.8 in the placebo group, which corresponds to mean changes from baseline of − 4.6 and − 2.4, respectively. The ANCOVA for DLQI showed that there was no statistically significant difference of the DLQI at visit 7 between the treatment groups ($p = 0.193$).

Analysis of Safety Parameters

Overall, AEs were similarly distributed between treatment groups. A total of 140 AEs were reported in 71 (55.5%) subjects; 70 occurred in 35 (54.7%) subjects in the group treated with tacrolimus-containing microemulsion and 70 AEs in 36 (56.3%) subjects in the placebo group.

During the study no deaths and no serious adverse events (SAEs) related to treatment occurred. The proportion of subjects with AEs related to treatment was higher in the group treated with tacrolimus-containing microemulsion (18 AEs in 12 (18.8%) subjects) than in the placebo group (10 AEs in 8 (12.5%) subjects). The most frequent AEs that were related to the tacrolimus-containing microemulsion were skin and subcutaneous tissue disorders (tacrolimus-containing microemulsion, 8 AEs in 6 subjects (9.4%); placebo, 8 AEs in 7 subjects (10.9%)). The most frequently reported preferred term within this system organ class (SOC) was pruritus (tacrolimus-containing microemulsion, 6.3% of the subjects; placebo, 3.1% of the subjects). Furthermore, for one subject in the placebo group, application site pruritus (SOC: General disorders and administration site conditions) was reported.

Three AEs led to permanent discontinuation of treatment. All three were skin and subcutaneous tissue disorders (tacrolimus-containing microemulsion, exacerbation of body psoriasis and diffuse alopecia; placebo group, psoriasis flare-up).

For the large panel of safety laboratory parameters, no notable difference was observed between the two treatment arms and only single abnormal clinically significant measurements were observed during the study (four subjects) within both treatment groups. For vital signs and for the physical examination, no clinically significant findings were noticed during the study and only a single abnormal clinically significant finding for dermatologic examination of the skin (one in each treatment group) and general appearance (one subject in the group treated with tacrolimus-containing microemulsion).

The analysis of the systemic bioavailability of tacrolimus showed that concentrations

observed both at visit 2 and at visit 7 were below the limit of quantification for all subjects and samples assessed. No subject showed blood concentrations greater than 1 ng/mL or greater than 5 ng/mL (the latter is associated with systemic immunosuppressive activity). Consequently, the presence of toxicologically relevant serum levels of tacrolimus could be excluded.

DISCUSSION

The clinical need for effective and safe topicals for the treatment of scalp psoriasis is ongoing and is not adequately met by the currently available proprietary medicinal products [22]. As a result of the macro- and micromorphological characteristics of scalp altered by psoriasis, a galenic formulation specifically designed for this area of application is necessary in order to achieve sufficient cutaneous bioavailability of the applied drug. Also, patients expect formulations for use on hairy and scaly skin to have special physicochemical properties, so a vehicle that facilitates practical applicability increases adherence to therapy [29]. Therefore, formulations designed for psoriasis of the skin have very limited suitability for use on the scalp [30]. Despite numerous available treatment options for scalp psoriasis, therapeutic experience of patients and physicians is disappointing, sometimes even frustrating. This statement is confirmed by a survey of 17,990 patients with psoriasis in seven European countries [31]. The two main complaints were “time consuming” and “ineffective.” Also, most physicians underestimate the impact of scalp diseases on quality of life [32].

From a clinical perspective, the application of a tacrolimus-containing microemulsion not only offers optimized cutaneous bioavailability in the scalp area compared to conventional formulations but has also keratoemulsifying effects that significantly improve the diffusion conditions of the drug. As an ointment, tacrolimus is approved for the treatment of atopic dermatitis. In contrast to atopic dermatitis, plaques in psoriatic skin represent a larger barrier for the penetration of drugs and the physicochemical properties of tacrolimus itself (large molecular size, structure, and lipophilicity) are very disadvantageous for dermal drug delivery through the skin. Earlier studies found that tacrolimus as ointment was no more effective than placebo [33]. Therefore, a new formulation of tacrolimus with a significantly better skin penetration profile and a higher acceptance by patients would close the gap in the treatment of scalp psoriasis [18].

The main result of the current study was the statistically significant improvement of psoriatic lesions on the scalp with the topical administration of 0.1% tacrolimus-containing microemulsion. A significantly greater proportion of subjects achieved a s-IGA (0/1) in the group treated with tacrolimus-containing microemulsion compared with the placebo group (28.6% vs. 12.7%). Although 28.6% may seem low, it must be considered that this only includes patients who achieved a score of 0 or 1.

In atopic dermatitis, tacrolimus has been shown to be comparably effective to class II (according to Niedner) corticosteroids [34, 35]. For scalp psoriasis class III and IV (according to Niedner) are commonly used, very often as combination therapy with either calcipotriene or salicylic acid [32, 35]. Since prolonged treatment of scalp psoriasis with topical corticosteroids is not recommended because of the lack of data supporting the long-term safety and efficacy of topical steroids, the use of these combination therapies is limited [36]. Because of the lower percutaneous absorption of corticosteroids, however, the scalp is more resistant to atrophy, but it does occur (e.g., percutaneous absorption of cortisol is 6% on forehead, 3.5% on the scalp) [37]. Thus, continuous twice-daily application of a corticosteroid should be limited to a 2-week course, which highlights the need for therapeutic alternatives.

The secondary efficacy endpoint analysis comprised the change from baseline to the end of treatment after 8 weeks for the severity scores s-IGA, S-mPASI, and VAS (scalp pruritus) as well as the DLQI. Improvements over time were observed in all scores analyzed in both treatment groups and were more pronounced in the group treated with tacrolimus-containing microemulsion but surprisingly also in the placebo group. This underlines not only the benefit

of the drug-related effect but also the improved outcome related to the vehicle itself, which has a keratoemulsifying effect, significantly improving mPASI by reducing scaling [23]. The keratoemulsifying effect of the vehicle is also a possible explanation for the relatively small difference between the treatment groups regarding the primary endpoint. The characteristics of the microemulsion also allow an effective administration to the hairy and psoriatic scalp. Visible ointment traces and oily and smeary hair that would further affect the quality of life are reduced, thereby improving the acceptance by patients.

In general, the results of this study are in line with a 2016 review of at least 23 studies involving more than 800 subjects evaluating topically applied tacrolimus, showing its general efficacy in treating different types of psoriasis in different areas [11, 38–41].

Study Limitations

As a result of the 8-week duration of the placebo-controlled phase 3 trial, the current analysis did not provide information about the long-term efficacy and safety of 0.1% tacrolimus-containing microemulsion in patients with mild to moderate scalp psoriasis. Also, no direct comparison to other treatments is possible as an active comparator arm was lacking in the study. Those aspects must be addressed in further studies. Furthermore, it has to be considered that the baseline values for S-mPASI, VAS, and DLQI differed between tacrolimus-containing microemulsion and vehicle, and that the number of subjects treated (64 per group) plus the defined inclusion and exclusion criteria cannot represent the average patient population.

CONCLUSION

Topical 0.1% tacrolimus-containing microemulsion appears to be an effective and safe option for treatment of scalp psoriasis.

ACKNOWLEDGEMENTS

The authors thank the participants of the study. Moreover, the authors wish to thank Dr. Walter Wigger-Alberti and Ragna Williams (bioskin GmbH, Hamburg, Germany) for involving in the background research and presentation of the study results on a contract research basis. Data analysis was performed by TFS Trial Form Support AB, Lund, Schweden.

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Weirich, Thomas Wildfeuer, Andreas Kleinheinz, Johannes Niesmann, Adrian Crainic, Ridwan Weber.

Author Contribution. AP: concept, study design, principal investigator, correction of manuscript. AT: co-investigator, correction of manuscript. AE: drafting manuscript, corresponding author.

Funding. The preparation of this article was supported by a grant from Bay Pharma GmbH, Hamburg, Germany.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available because the data has not yet been released by the sponsor of the study.

Declarations

Conflict of Interest. All authors have nothing to disclose. Andreas Pinter acted as principal investigator and Athanasios Tsianakas as investigator in the presented trial.

Ethical Approval. The final study protocol (final draft V3.0, 17-Jan-2019) was approved by the responsible ethics committee of Medical Faculty, Johann Wolfgang Goethe University, Frankfurt/Main (vote of 17 May 2019; no. 75/19 F). Furthermore, the study was approved by the ethics committees of the different study groups. The study was conducted in compliance with the protocol, regulatory requirements, good clinical practice (GCP) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

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