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ORIGINAL ARTICLE

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Efficacy and Safety of Water-Free Lipid Formulation System Containing Calcipotriol Against Psoriasis Vulgaris

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ABSTRACT

Calcipotriol, a vitamin D analogue is widely used in the treatment of psoriasis. However, poor adherence to topical therapy has led to an ineffective use of the medication and built a barrier to the treatment's success. A water-free lipid-based formulation system has been developed to improve dosage and cosmetic properties along with patient compliance. This study was conducted to evaluate the efficacy and cutaneous safety of water-free lipid-based formulations containing calcipotriol (50 µg/g) as compared to their corresponding vehicles and marketed calcipotriol formulations in a psoriasis plaque test. In total, 24 subjects with chronic psoriasis vulgaris were enrolled in this single-center, randomized, vehicle, and comparator-controlled clinical trial and treated once daily over a 12-day period (10 applications). The anti-psoriatic effect was evaluated by sonographic measurement of psoriatic infiltrate and investigators' clinical efficacy assessments. The mean reduction in psoriatic infiltrate from baseline to day 12 (end of trial) with lipid-based calcipotriol formulations (-34% and -37%) was statistically significant (P<0.0001) when compared to their corresponding vehicles (6% and -4%) but not when compared with marketed calcipotriol solution and cream (-34% and -49% respectively). Mean total clinical assessment scores of these lipid-based calcipotriol formulations (1.7 each) were between those of the two comparators- greater than marketed calcipotriol solution (1.3) but lower than cream (2.0). Overall, nine mild non-serious treatment-emergent adverse effects related to all calcipotriol formulations were reported in four subjects, but all recovered at the follow-up visit. Therefore, novel lipid-based formulations of calcipotriol were clearly more efficacious than their corresponding vehicles and considered as safe therapy against psoriasis vulgaris.

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INTRODUCTION

Psoriasis is a common chronic inflammatory skin disease which affects 2 – 3 % of the European population.[1] Psoriasis vulgaris (chronic plaque psoriasis) is the most frequent form of psoriasis which is characterized by high degree of epidermal proliferation and damaged keratinocyte differentiation leading to thickened, scaly, and itchy skin plaques.[2] Blood vessels in the affected skin areas get dilated and are infiltrated by inflammatory cells which further triggers the pathophysiological processes of psoriasis.[3] Psoriatic infiltrate consists of variety of infiltrating cells that are distributed in the epidermis and upper dermis of the diseased skin and its analysis forms an important step in understanding the pathogenesis and therapeutics in psoriasis.[4]

Management of psoriasis includes regulation of epidermal proliferation and reduction of inflammatory reactions.[5] There are several topical treatments available, including corticoids and vitamin-D derivates.[6] Calcipotriol (vitamin D3-analogue) has been known to possess cutaneous safety and efficacy against psoriasis vulgaris in extensive, well-controlled clinical studies.[7,8] Calcipotriol was well tolerated in these studies, with only mild adverse events which later diminished on continuation of the treatment. The monotherapy with calcipotriol cream was reported to be as efficient as the topical corticosteroid betamethasone.[9] In recent years, treatment of topical agents under occlusive dressings has become a popular method of screening new drugs. A clinical study conducted on psoriasis vulgaris reported that the therapeutic response to calcipotriol increased with hydrocolloid occlusive dressing due to enhanced penetration.[10] Relatively shorter study duration (2 weeks or less) used under occlusive treatment is known to provide a better insight into novel compounds and their formulations, offering quick decisions in early phase of clinical development.[11,12] Shorter application duration also offers better standardization of protocol and a reduced cost of clinical trial.

Non-adherence to topical treatment has been identified as an important issue in the management of psoriasis and is likely to affect the treatment outcome.[13] New formulation and drug delivery systems may help to improve compliance and can increase the choices for the patient to find a product with acceptable properties.[14] An innovative dosage form, based on water-free lipid formulation system (AKVANO®, Lipidor AB, Danderyd, Sweden) for topical administration has been developed.[15,16] The active ingredients are dissolved in a volatile

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solvent system along with selected lipids, which provide different characteristics to the formulation. The resulting formulation is a clear, low-viscous solution which can be easily sprayed onto the affected skin. After quick drying, a smooth and non-greasy polar lipid film is formed on the skin surface for effective deposition of the active ingredient. Spray dosing is particularly attractive when treating the inflamed areas which may be sensitive to physical contact and prevents cross-infection of wounds after being applied using the fingers.[17] According to a consumer study, the cosmetic properties of our lipid-based spray formulation was preferred by majority of psoriasis patients in terms of its fine texture, non-greasiness, feeling after application, and overall grade when compared to calcipotriol cream (Daivonex, Leo Pharma A/S, Denmark) (P<0.001) (unpublished). Thus, this novel formulation system offers all advantages of a new topical spray formulation without the drawbacks of poor patient compliance linked with traditional topical agents.

The current study was designed to evaluate the clinical efficacy and safety of once-daily application (12 days, 10 treatments) of lipid-based calcipotriol formulations in comparison to their corresponding vehicle formulations (primary objective) and marketed calcipotriol formulations (Daivonex) (secondary objective). In addition to sonographic measurement and clinical assessment, cutaneous safety assessments were performed on subjects with chronic psoriasis vulgaris.

MATERIALS AND METHODS

This was a single-center, randomized, vehicle- and comparator-controlled clinical trial, double-blind for the novel formulations and vehicles, observer-blind for the comparators, with intra-individual comparison of treatments. The clinical trial was carried out at Bioskin GmbH, Berlin, Germany.

Ethics

Written informed consent was obtained from all subjects for inclusion before they participated in the study. The clinical trial was performed in accordance with the currently valid declaration of Helsinki as well as German regulations and the protocol was approved by the Ethics Committee of federal state Berlin (Reference number: 12/0548-ZS EK). The trial was registered at ClinicalTrials.gov (Identifier: NCT05488990). The ICH guideline for good clinical practices (GCP) was observed.

Subjects

Twenty-four subjects, both male and female, white (Caucasian), ages ranged from 32 to 69 (mean = 53.0) years, weight from 57 to 120 (mean = 89.9) kg, and height from 158 to 196 (mean = 176.5) cm, were enrolled in the clinical trial based on a clinical diagnosis of psoriasis vulgaris and mild or moderate chronic plaque(s) on different body regions (trunk or extremities, excluding palms/soles/knees). The plaques to be treated should have had a comparable psoriatic infiltrate thickness of at least 200 µm. Any patients who had received systemic or topical anti-psoriatic treatment in the three months before first study treatment were excluded. Other exclusion criteria included the need for concurrent use of anti-psoriatics, eg, corticosteroids, cytostatics, retinoids, etc, known allergic reactions or sensitivity to the active ingredients of investigational products, recent exposure to sun or ultraviolet treatments, a current diagnosis of other types of psoriasis, pregnancy or breastfeeding, evidence of drug or alcohol abuse, and the use of any other medications which are known to provoke or worsen psoriasis.

Treatments

Altogether six test fields (two active formulations, their corresponding vehicles, and two comparators; cf. Table 1) located on the torso, or the extremities were randomly assigned

FIGURE 1. Mean change in Infiltrate thickness (µm) from baseline at day 8 and 12 (FAS) (n=24).

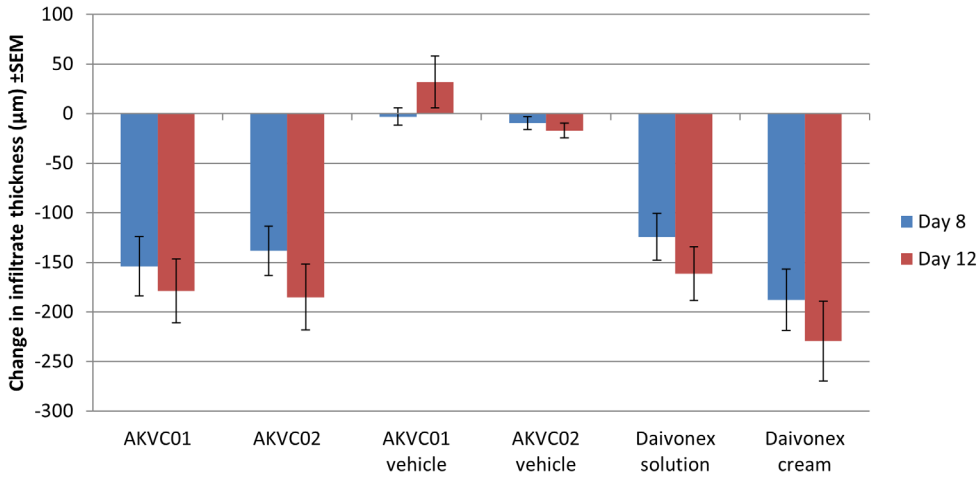

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TABLE 1.

Summary of the Investigational Products and Their Ingredients Used in the Study

Investigational Product	Formulation Type	Active Constituent	Additional Ingredients
AKVC01	AKVANO (solution)	Calcipotriol (50 µg/g)	Cyclomethicone 5-NF, anhydrous ethanol, glycerol caprylate, isopropyl myristate (IPM)
AKVC02	AKVANO (solution)	Calcipotriol (50 µg/g)	Cyclomethicone 5-NF, anhydrous ethanol, phospholipids from soybean, glycerol caprylate, isopropyl myristate (IPM)
AKVC01 Vehicle	AKVANO (Vehicle for AKVC01)	--	Cyclomethicone 5-NF, anhydrous ethanol, glycerol caprylate, isopropyl myristate (IPM)
AKVC02 Vehicle	AKVANO (Vehicle for AKVC02)	--	Cyclomethicone 5-NF, anhydrous ethanol, phospholipids from soybean, glycerol caprylate, isopropyl myristate (IPM)
Daivonex solution	Daivonex solution	Calcipotriol (50 µg/g)	Hyprolose, propane-2-ol, levomenthol, sodium citrate dihydrate, propylene glycol, purified water
Daivonex cream	Daivonex cream	Calcipotriol (50 µg/g)	Sodium edetate, sodium monohydrogen phosphate dihydrate, viscous paraffin, white petrolatum, glycerol 85%, cetomacrogol 1000, cetostearyl alcohol, 1-(3-chlorallyl)-3,5,7-triaza-1-azoniaadamantane chloride, all-rac-α-tocopherol, purified water

for treatments per subject. Approximately 150 µl of the formulations were applied to three layers of filter paper (except Daivonex cream which was applied directly on the skin/plaque) in special test chambers (Duhring chambers, 12 mm inside Ø, 14 mm outside Ø) to the test fields. This was the amount required to completely fill the test chamber. The filled Duhring chambers were seated in holes punched in a hydrocolloid dressing (Varihesive® E, ConvaTec, Munich, Germany) which was fixed before on the skin with adhesive patches (BSN, Hamburg, Germany). The lack of a therapeutic influence of the dressing on the psoriasis was verified by determination of the infiltrate thickness before and after application. The test fields were treated under occlusion once daily during a 12 day trial period (10 treatments, no application on days 7 and 12). Before each new application, remaining preparation residues were removed by gently cleansing each test field with a separate soft tissue.

Assessments

The thickness of psoriatic infiltrate was recorded as echo lucent psoriatic band (ELB)[18] using a 20 MHz high frequency sonograph (PROFI USB, Taberna pro Medicum, Lueneburg) at each visit on day 1 (baseline), day 8, and day 12 (end of treatment; EoT). Mean change of infiltrate thickness was determined. Clinical assessment of the test fields was made at visits on days 8 and 12 using a defined five-point scale of worsened (-1), unchanged (0), slight improvement (1), clear improvement but not completely healed (2), and completely healed (3). The comparison of single test fields was made to the untreated plaque(s) beneath the hydrocolloid dressing and next to the respective test field. Clinically apparent differences in erythema and infiltration contributed to this assessment.

FIGURE 2. Average clinical efficacy assessment score at day 8 and day 12 (FAS) (n=24).

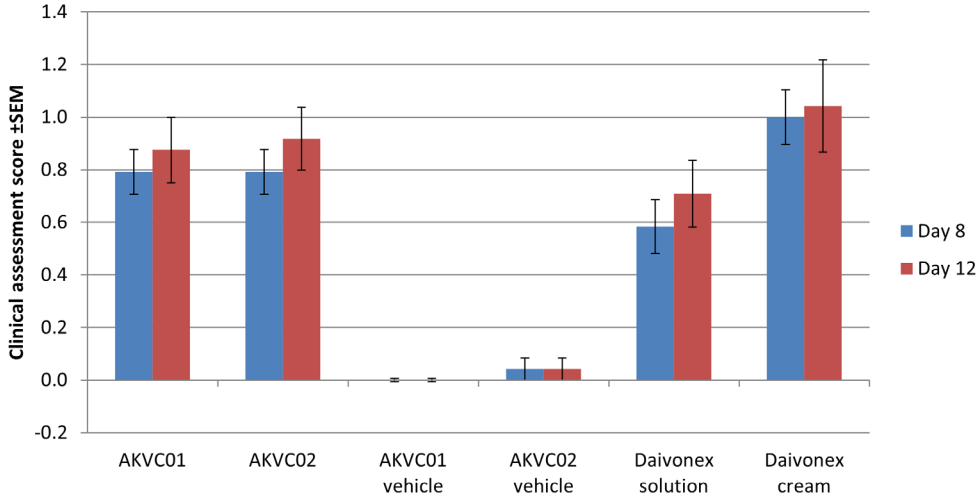

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TABLE 2.

Trial Flow Chart													
Procedure	Screening Period (Days)	Treatment Period (Day)											
	-14 to -1	1	2	3	4	5	6	7	8	9	10	11	12
Informed Consent	X												
Inclusion/Exclusion Criteria	X	X											
Demographics/Medical History	X												
Physical Examination of Skin	X												X
Vital Signs	X												X
Photographic Documentation		X											X
Sonography		X							X				X
Clinical Assessment									X				X
Product Application		X	X	X	X	X	X		X	X	X	X	
Prior and Concomitant Therapy	X	X	X	X	X	X	X		X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X		X	X	X	X	X

At baseline (day 1) the score was documented as "0" (unchanged). Physical examination of the skin and vital signs (blood pressure and pulse rate) was measured at baseline (day 1) and on EoT (day 12). Adverse events were recorded from the time point the subject had signed the informed consent form until subject's last visit. The primary efficacy endpoint was the comparison of lipid-based calcipotriol formulations (AKVC01 and AKVC02) to their corresponding vehicles in terms of change in infiltrate thickness from baseline to EoT. Secondary efficacy endpoint included the following: comparison of AKVC01 and AKVC02 to their corresponding comparators (Daivonex solution and cream) in terms of change in infiltrate thickness from baseline to EoT, comparison of AKVC01 and AKVC02 to their corresponding vehicles and comparators in terms of change in infiltrate thickness from baseline to day 8, and the clinical assessment of the treatment efficacy of all formulations at day 8 and EoT. All Adverse events (AEs) (non-treatment-emergent and treatment-emergent) were documented. AEs were regarded as "treatment emergent" if onset was on or after the time of the first investigational product application. A flow chart of trial procedures is presented in Table 2.

Sample Size and Statistics

Twenty-four volunteers were recruited for the clinical trial to get at least 22 evaluable cases. Based on a former in-house trial at Bioskin it was estimated that a sample size of 24 subjects would have had 90% power to detect this treatment effect using a two-sided paired t-test with significance level of 0.05. A sample size of 22 subjects would have reduced the power to 87 %.

Analysis populations

All 24 subjects were included in full analysis set (FAS), valid cases set (VCS) and safety evaluation set (SES). The Intent-To-Treat (ITT) analysis was based on the FAS ie, all randomized subjects who received at least one dose of the investigational product and had at least one post-baseline assessment. The PP analysis was based on the VCS ie, all subjects without any major protocol violation, who had not taken any interfering concomitant medication, who received the full trial medication doses, except for treatment related discontinuations. The safety population was based on the SES ie, all subjects who received any trial medication at least once.

Efficacy analysis

Primary analysis was evaluated using descriptive statistics including the number of cases, mean, standard deviation, minimum and maximum. Additionally, a two-sided 95%-confidence interval of the mean and its corresponding *P*-value was provided. No multiplicity adjustment was used. The *P*-values were interpreted descriptively. Secondary analysis was assessed using descriptive statistics of the pairwise differences, including the two-sided 95%-confidence interval.

Safety analysis

The extent of exposure to the investigational product was summarized by the number of days of dosing. For each treatment, descriptive statistics and a frequency table was recorded. The incidence of treatment-emergent AEs (TEAEs) was assessed and recorded. Other safety analyses such as vital signs and their changes from baseline were summarized by visits providing descriptive statistics.

RESULTS AND DISCUSSION

Efficacy

A 12-day treatment regimen was chosen to measure the clinical response to the novel lipid-based calcipotriol formulations, since both the extent and pace of efficacy of treatment are important. A previous study[12] showed that different formulations used once daily were effective within a short period of time,

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thus providing the basis for a 12-day treatment plan in this trial. In the current study, AKVC01 and AKVC02 showed a clear anti-psoriatic effect which was confirmed by sonographic measurement and clinical assessment. The sonographic results demonstrated a continuous decrease in mean thickness of the ELB (measure of infiltrate thickness) in the test fields treated with AKVC01 and AKVC02, reflecting a clear clinical improvement of psoriatic lesions. Both AKVC01 and AKVC02 showed statistically significant greater mean changes from baseline to day 12 in infiltrate thickness when compared to their corresponding vehicles (primary endpoint):

- AKVC01 vs AKVC01 vehicle:
-178.9 µm (-34 %) vs 31.9 µm (6 %), *P*<0.0001
- AKVC02 vs AKVC02 vehicle:
- 185.1 µm (-37 %) vs -17.2 µm (- 4 %), *P*<0.0001

Statistically significant differences were also seen between AKVC01 and AKVC02 and their vehicles regarding mean change from baseline to day 8. The mean reduction in infiltrate thickness following treatment with AKVC01 and AKVC02 was comparable to Daivonex solution (change from baseline to day 12: 161.4 µm [-33 %]) and less compared to Daivonex cream (change from baseline to day 12: 229.5 µm [-49 %]) (Figure 1).

For the statistical comparison between the AKVC01, AKVC02, and the comparator Daivonex solution no significant differences were seen either for mean change from baseline to day 8 or day 12. Without compensation for multiple comparisons, AKVC01 vs Daivonex cream showed a statistically significant difference for mean change from baseline to day 12 and for AKVC02 vs Daivonex cream for mean change from baseline to day 8, all in favor of the comparator Daivonex cream. However, applying multiple comparison adjustments for the comparisons of AKVC01 or AKVC02 vs Daivonex cream, no statistically significant difference was found for any of the differences in anti-psoriatic effect. Moreover, it should be noted that this experimental set-up allowed for a direct and more intense contact of Daivonex cream with skin/plaque as it was applied under the filter papers, in contrast to the Daivonex and AKVC01 or AKVC02 solutions which were applied on the filter papers, the impact of which were plausibly affected by first being absorbed into filter papers prior to the application to the affected skin area. The use of the filter paper may have had an influence on the release and the penetration of the active constituent depending on the dosage form used. Hence, the comparison between different dosage forms (AKVC01 or AKVC02 solution and Daivonex cream) is influenced by the methodology used and needs to be interpreted with care.[12]

The results of the clinical assessment underscored the results of the sonographic measurements. All four calcipotriol formulations showed an overall slight improvement in psoriatic lesions. The mean total clinical assessment scores (sum of scores at Day 8 and 12) of AKVC01 and AKVC02 formulations (1.7 each) were between those of the two comparators: greater than Daivonex solution (1.3) but lower than Daivonex cream (2.0). Very low scores were calculated for the two corresponding active ingredient-free vehicles, indicating no effect (Figure 2).

Safety

A total of nine mild non-serious TEAEs all corresponding to a specific test field were reported in four subjects. Four TEAEs (erythema) were noted in the test fields of one subject and considered to be probably related to all formulations containing calcipotriol. An allergic contact dermatitis was seen in the test field treated with Daivonex cream in one subject and was certainly related. In two subjects erosions were noted in two test fields each: In one subject the erosions were unlikely related to any of the investigational products (AKVC01 or AKVC02), but in the other subject erosions were possibly related to the corresponding investigational products (AKVC01 and Daivonex solution). In the first subject, the erosions were only located on the edge of test fields and were most likely caused by mechanical stress due to prolonged sitting position. All nine TEAEs had occurred at EoT (day 12), but recovered at the follow-up visit. No other relevant findings with respect to safety were reported in this trial.

CONCLUSION

The results from the present clinical study show that both lipid-based formulations containing calcipotriol, AKVC01 and AKVC02 gave a significantly greater reduction in infiltrate thickness compared to their respective vehicles and had an anti-psoriatic effect comparable to Daivonex solution. No safety concerns for the two test products emerged from the study. Thus, lipid-based calcipotriol as a novel formulation system seems to have all the necessary features to be used against topical diseases like psoriasis owing to its enhanced efficacy and cutaneous safety. AKVC02 formulation has been chosen for further clinical development, which will be reported in a forthcoming article.

DISCLOSURES

Jan Holmbäck reports a relationship with Lipidor AB that includes employment and stocks. Anders Carlsson reports a relationship with Lipidor AB that includes consulting and stocks. Puneet Rinwa reports a relationship with Lipidor AB that includes employment.

Related Patents:

1. Carlsson A, Holmbäck J. Lipid Layer Forming Composition for Administration onto a Surface of a Living Organism. International patent application WO 2011/056115 A8, 30-06-2011.
2. Herslöf B, Holmbäck J. Sprayable Topical Carrier and Composition Comprising Phosphatidylcholine. International patent application WO 2015/072909 Al, 21-05-2015.

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