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Original article

# Treatment of seborrhoeic dermatitis of the scalp with a topical solution of urea, lactic acid, and propylene glycol (K301): results of two double-blind, randomised, placebo-controlled studies

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## Summary

Alternative treatments for seborrhoeic dermatitis are needed because of the increasing risk of anti-fungal resistance to existing therapies. To investigate the efficacy, safety and tolerability of topical scalp treatment with K301 solution. Two multi-centre, randomised, double-blind studies were conducted. Study I: 4 weeks of once-daily treatment with either one form of K301 (a or b) or placebo, followed by 4 weeks of maintenance treatment three times-per-week. Study II: 4 weeks of K301 (a) or placebo once-daily. Study I: 98 patients enrolled (K301a + b, $n = 51$; placebo, $n = 47$) and 83 completed; 201 entered Study II (K301a, $n = 136$; placebo, $n = 65$) and 195 completed. Erythema and desquamation sum score at 4 weeks, mean (SD) values were 2.4 (2.0) for K301a + b and 3.2 (2.2) for placebo in Study I ($P = 0.025$) and 2.5 (1.9) for K301a and 3.2 (1.8) for placebo in Study II (not significant). In both studies, 4-week desquamation scores were significantly improved for K301 vs. placebo ($P < 0.05$). Both studies showed significant improvements in symptomatic investigator and patient assessments for K301 over placebo after 4 weeks ($P < 0.05$). Treatment-related adverse events were generally mild and included some smarting or burning upon application. The K301 was well tolerated and associated with clinically meaningful improvements in seborrhoeic dermatitis endpoints.

**Key words:** Desquamation scores, dermatologic therapy, erythema scores, K301, seborrhoeic dermatitis, skin diseases.

## Introduction

Seborrhoeic dermatitis is a common skin condition that predominantly affects the scalp and the face, and is characterised by erythematous patches and scaling of the skin. The condition requires repeated treatment and regular prophylaxis as it follows a chronic course punctuated by relapses and remissions. Anti-fungal agents such as ketoconazole and ciclopirox provide the cornerstone of treatment for seborrhoeic dermatitis following the confirmation of the relationship between seborrhoeic dermatitis [1] and *Malassezia* yeast, and there is a substantial body of evidence demonstrating their clinical utility.[2–7] Recently, it has been shown that *M. globosa* and *M. restricta* are the most commonly isolated species from patients with seborrhoeic dermatitis and dandruff.[8,9] However, anti-fungal drug resistance has been reported in a number of pathogenic fungi [10,11] and because of the risk of development of anti-fungal resistance in seborrhoeic dermatitis there is a need for alternative therapeutic agents with differing modes of action.

The K301 (Kaprolac®) is a newly developed topical solution based on a patented combination of ingredients with well-established use in dermatology. It is a homogeneous mixture of urea, propylene glycol and

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lactic acid with small amounts of glycerol and water, all of which are biodegradable. It constitutes a clear, colourless and virtually odourless liquid. Urea is known to be keratolytic and hygroscopic and may also have an anti-pruritic effect.[12,13] Propylene glycol is used extensively as an excipient in cosmetics and pharmaceuticals and has both keratolytic and hygroscopic effects.[14] Lactic acid is a common additive to skin care products where it is included mainly for its exfoliating and hydrating properties. Propylene glycol,[15,16] lactic acid[17] and urea[12] have all been shown to inhibit growth of bacteria and/or fungi. Propylene glycol has also demonstrated efficacy against seborrhoeic dermatitis.[18] When combined, the ingredients of K301 provide a solution with keratolytic, exfoliating, anti-fungal and hydrating activities. The K301 has a physical mode of action, thus decreasing the risk of development of resistance upon repeated application. During the development of K301, a number of studies were undertaken to determine the minimum inhibitory concentration for *M. furfur* and several other common microorganisms using the individual active components as well as the binary and tertiary mixtures and the final K301 solution. The final K301 solution provided the highest level of activity. As yet, unpublished clinical data have demonstrated application of K301 relieved symptoms of seborrhoeic dermatitis and provided an acceptable tolerability profile. In addition to the patented formulation (termed K301a), a modified formulation of K301 (K301b) that included isopropyl alcohol was developed. Isopropyl alcohol is used in topical solutions to improve their cosmetic qualities, for example, to reduce stickiness. As it is inert, the inclusion of isopropyl alcohol in the formulation was not expected to affect the efficacy of K301.

A series of randomised, double-blind, placebo-controlled studies was conducted to investigate the efficacy, safety and tolerability of topical application of K301 solution in patients with seborrhoeic dermatitis. The first study (Study I) assessed K301a and K301b in patients with mild to severe seborrhoeic dermatitis. The formulation considered most preferable in terms of cosmetic qualities and tolerability was assessed in Study II, which evaluated topical application of K301a in patients with mild to moderate seborrhoeic dermatitis. A pooled analysis of the data from both studies was also conducted.

## Materials and methods

Two clinical studies, both randomised, double-blind and placebo-controlled, were undertaken. Both studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and International Conference on Harmonization/Good Clinical Practice, and after approval by the local ethics committees. All patients provided written informed consent to participate. Study I (protocol number: K40-3) and Study II (protocol number: K301-I) were conducted at 10 and 21 centres in Sweden, respectively.

### Study I

*Study population*

The study population comprised men and women aged 18–65 years, inclusive, with mild to severe seborrhoeic dermatitis of the scalp for at least 2 months. Patients were considered ineligible for the study if they had used topical anti-fungal, selenium sulphide or corticosteroid therapy for their seborrhoeic dermatitis in the previous 2 weeks, or if they had any other cutaneous disease requiring the use of specified topical treatments during the previous 15 days. Other exclusion criteria included seborrhoeic dermatitis associated with Parkinson's disease or human immunodeficiency virus infection; and recent use of oral cyclines, lithium or anti-fungals, inhaled corticosteroids, systemic corticosteroids and retinoids.

*Study design*

This study assessed two topical formulations of K301 (K301a and K301b). The K301a was a liquid consisting of propylene glycol, urea, lactic acid, glycerol and water, whereas K301b additionally included isopropyl alcohol. The K301 was compared against a placebo formulation that consisted of water (>90%) with glycerol, isopropyl alcohol and the preservative nipasept sodium. Eligible patients were randomised to treatment with K301a, K301b or placebo in a 1 : 1 : 2 ratio. After eligibility screening, patients attended a baseline visit (week 0) where they underwent instruction on how to apply the treatment to affected areas of the scalp before bed. Patients were also instructed on how to grade their symptoms using symptom scales. Following the baseline visit, patients started a 4-week period of daily application and a subsequent 4-week maintenance period of application three times per week. The investigator monitored adherence; patients returned for visits at weeks 2, 4 and 8.

*Investigator assessment of efficacy*

At each visit, the investigator used a series of assessment scales that were modifications of previously published scales.[6–8] At baseline, the lesion that displayed the most severe erythematic and desquamation symptoms was

selected for assessment throughout the study. Erythema was rated as 0 = absent (no erythema or barely visible: pale or pink); 1 = slight (erythema was slightly visible or just visible: light red); 2 = mild (erythema was visible: red); 3 = moderate (erythema was clearly visible: red); 4 = pronounced (erythema was clearly visible: clear red); or 5 = severe (brisk erythema: clear red-violet red, dark red). Desquamation score was rated as 0 = absent (no desquamation); 1 = slight (some desquamation: a few small loose flakes as a sparse and coarse, white or greyish powder); 2 = mild (some desquamation: small loose flakes as a coarse, white or greyish powder); 3 = moderate (vivid desquamation: large partially adherent flakes, irregular whitish appearance loosely large attached flakes, adherent small white flakes); 4 = pronounced (mostly adherent desquamation: large mostly adherent flakes as scarce white or yellow plates); or 5 = severe (brisk desquamation: adherent flakes as white or yellow plates).

Investigators also performed a global evaluation of seborrhoeic dermatitis rating patients' conditions as 0 = cleared – fully healed; 1 = almost healed; 2 = some clearance; 3 = no response/no change; or 4 = worsening.

*Patient subjective score assessments*

Patients rated their scalp pruritus as 0 = absent (no pruritus or burning, when asked); 1 = slight (some pruritus or burning, when asked, but did not interfere with daily activities or sleep); 2 = moderate (pruritus or burning, spontaneously reported, now and then interfering with daily activities or sleep); or 3 = severe (pruritus or burning, spontaneously reported, interfering with daily activities or sleep). Dandruff was rated as 0 = absent (no dandruff was noticed); 1 = slight (some dandruff was noticed, but not evident, without provocation); 2 = moderate (visible and evident dandruff); or 3 = severe (brisk dandruff). Patients also performed a global evaluation of seborrhoeic dermatitis using the same scale as that used by the investigator. Patients completed the Dermatology Life Quality Index (DLQI).[17]

Patients rated the cosmetic properties of the treatment using three visual analogue scales on a 100 mm horizontal line. For ease of application, the extremes on the scales were 'very easy' on the left to 'very difficult' on the right; for stickiness, 'no stickiness' to 'worst possible stickiness'; and for effects on hair quality, 'very good' to 'very poor'.

*Safety assessments*

Adverse event data, including intensity and relationship to treatment, were recorded at each visit.

### Study II

*Study population*

Entry criteria were identical to those in Study I except for an increased upper age limit (70 years) and the maximum disease severity at screening (moderate). Patients who had previously participated in Study I were ineligible.

*Study design*

Screening, the 4-week daily application phase, randomisation and maintenance treatment were performed as for Study I. At baseline (week 0) patients were allocated to treatment with K301a or placebo in a 2 : 1 ratio. Patients returned for study visits at weeks 2 and 4.

*Investigator assessments of efficacy*

Investigators assessed a selected lesion using the same scales as described for Study I. The investigator also performed a global evaluation of seborrhoeic dermatitis using a six-point scale where 0 = fully healed; 1 = markedly improved; 2 = moderately improved; 3 = slightly improved; 4 = unchanged; and 5 = deteriorated.

*Patient subjective score assessments*

Patients assessed the extent of their pruritus and dandruff using scales similar to those used in Study I: 0 = absent; 1 = slight; 2 = mild; 3 = moderate; 4 = pronounced; or 5 = severe. Patients also performed a global evaluation of seborrhoeic dermatitis using the same scale as that used by the investigator.

*Safety assessments.*

Adverse event data were captured as in Study I.

### Statistical methods

Both studies were powered for the primary efficacy endpoint of the sum of erythema and desquamation scores at week 4. The sample size was calculated under the assumption of the proportional odds model for sum scores. A sample size of 80 patients in Study I and 153 patients in Study II would have 80% power to detect a difference between active treatment and placebo for the primary endpoint, using a proportional odds model with a 5% two-sided significance level. To allow for premature withdrawal it was decided that 100 patients would provide sufficient power in Study I, and 180 patients in Study II. All statistical analyses were conducted using SAS version 8.02 (SAS Institute Inc, Cary, NC, USA).

The primary efficacy analysis population comprised the full analysis dataset, defined as all randomised patients who applied at least one dose of study medication and for whom at least one post-dose erythema and desquamation score was recorded. The study also included a per-protocol population: a subset of the full analysis set including patients whose adherence was 'Good' and who provided a measurement of the primary endpoint. The safety analysis set comprised all randomised patients who applied study medication at least once.

The primary efficacy endpoint was analysed for K301a and K301b combined (Study I) or K301a (Study II) vs. placebo using a proportional odds model with baseline sum score included as a covariate. In Study II the Cochran–Mantel–Haenszel model was to be used where the assumptions of the proportional odds model were not fulfilled for any endpoint. The proportion of responders was assessed using a logistic regression model, with baseline erythema/desquamation sum score as a covariate. Responders in Study I were defined as patients with complete (sum of erythema and desquamation = 0) or partial remission (sum score = 1 or 2). Study II used the definitions 'Responders$_0$' (complete remission) and 'Responders$_{0–2}$' (complete or partial remission). Global evaluation and patient functional symptom scores were analysed using a proportional odds model. Scores for DLQI were analysed by analysis of covariance (ANCOVA) with baseline as a covariate, and data for cosmetic properties were analysed by ANCOVA. Significance was defined as $P$ <0.05.

The *post-hoc* analysis of pooled data from Study I and Study II included only patients randomised to K301a; patients with severe or pronounced erythema or desquamation at baseline were excluded. The sum of erythema and desquamation scores was analysed for the full analysis set. As the proportional odds assumption was not fulfilled, the Cochran–Mantel–Haenszel model was used controlling for study sum score at baseline. Significance was defined as $P$ <0.05.

## Results

### Patient disposition and baseline characteristics

In Study I, 98 patients were randomised to treatment and applied the solution at least once; 83 patients completed the study. A summary of analysis populations is presented in Fig. 1a. In Study II, 201 patients were randomised to treatment and 200 applied the solution at least once; 196 patients completed the study. A summary of analysis populations is presented in Fig. 1b. Treatment groups were well matched with regard to demographic and baseline characteristics in Study I and Study II (Table 1). The pooled analysis of efficacy data from Studies I and II included 255 patients, 152 who received K301a and 103 who received placebo.

### Study I

*Investigator assessment of target lesions*

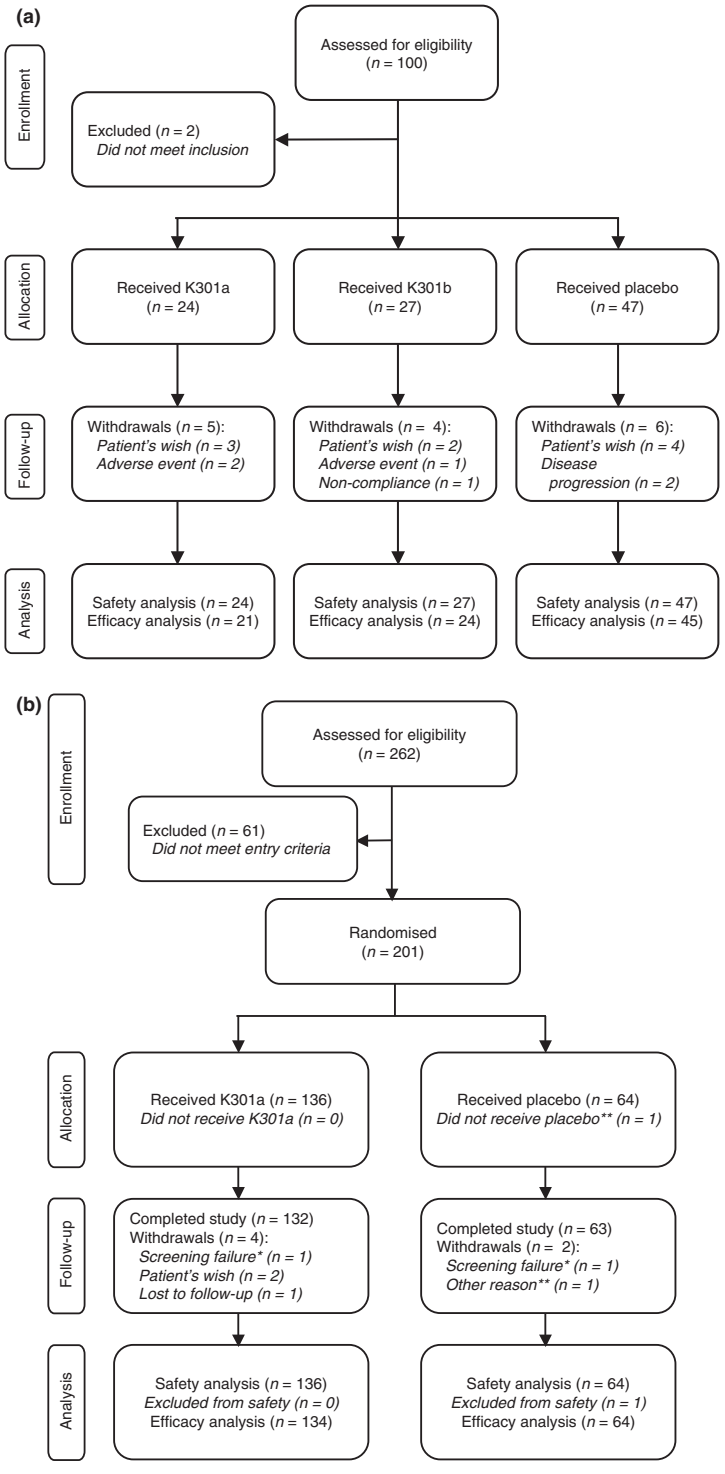
For the primary endpoint, sum of erythema and desquamation, marked improvements were seen at week 4 compared with baseline in patients who applied K301: mean (standard deviation) values were 2.4 (2.0) at week 4 compared with 4.9 (1.2) at baseline for K301a + b and 3.2 (2.2) compared with 5.0 (1.5) for placebo (full analysis set). The difference between K301a + b and placebo at week 4 achieved statistical significance ($P$ = 0.025) (Fig. 2). Similar results were obtained for the per-protocol population ($P$ = 0.004). Improvements were observed for K301a + b vs. placebo at other time points: the sum score was 3.2 (1.9) vs. 3.8 (2.0) at week 2 and 2.4 (1.9) vs. 3.2 (2.4) at week 8. The difference between K301a + b and placebo achieved statistical significance at week 2 ($P$ = 0.043; full analysis set). At week 8, the difference was not statistically significant although sum score values of erythema and desquamation did not return to baseline levels.

For the full analysis set, application of K301a and K301b increased the proportion of responders at 4 weeks compared with placebo: 67% vs. 40% ($P$ = 0.008). The proportion of responders was also greater after 2 and 8 weeks of application of K301a + b than for placebo: 38% vs. 29% at 2 weeks, and 56% vs. 44% at 8 weeks, although in neither case did the difference achieve statistical significance.

Marked improvements in desquamation were observed after 4 weeks of K301 application; the difference between K301a + b and placebo achieved statistical significance ($P$ = 0.003; Table 2). Improvements were also observed for K301a + b vs. placebo at week 2 and at week 8, with the difference at week 8 achieving statistical significance ($P$ = 0.0265). Although differences were observed in erythema between K301a + b and placebo, statistical significance was not achieved (Table 2).

*Global evaluation scores*

In both the investigator (Fig. 3a) and patient (Fig. 3b) global evaluations at week 4, the proportion of patients




*The screening failures were discovered after inclusion.

**The patient was discovered to be participating in another clinical study (an exclusion criterion).

**Figure 1** CONSORT diagrams of patient disposition in Study I (panel a) and Study II (panel b).

whose seborrhoeic dermatitis was cleared or almost healed was greater following application of K301a + b than placebo (investigator evaluation: $P = 0.005$; patient evaluation: $P = 0.033$). At week 8, no statistically significant difference was observed for either evaluation.

**Table 1** Baseline characteristics in the full analysis set population in Studies I and II.

| | Study I | | | Study II | |
|---|---|---|---|---|---|
| | Placebo ($n$ = 45) | K301a ($n$ = 21) | K301b ($n$ = 24) | Placebo ($n$ = 64) | K301a ($n$ = 134) |
| Age; years | | | | | |
| Median (range) | 48.0 (18–67) | 44.0 (21–71) | 50.0 (18–64) | 56.0 (18–70) | 59.5 (20–70) |
| Gender; n (%) | | | | | |
| Male | 22 (49) | 12 (57) | 17 (71) | 35 (55) | 74 (55) |
| Female | 23 (51) | 9 (43) | 7 (29) | 29 (45) | 60 (45) |
| Ethnic origin; n (%) | | | | | |
| Caucasian/white | 41 (91) | 19 (91) | 24 (100) | 64 (100) | 134 (100) |
| Mixed/multi-racial | 3 (7) | 2 (10) | 0 | 0 | 0 |
| Other | 1 (2) | 0 | 0 | 0 | 0 |
| Erythema score; mean (standard deviation) | 2.3 (0.7) | 2.3 (0.7) | 2.3 (0.8) | 2.5 (0.5) | 2.4 (0.5) |
| Desquamation score; mean (standard deviation) | 2.7 (0.9) | 2.4 (0.7) | 2.8 (0.8) | 2.5 (0.5) | 2.5 (0.5) |

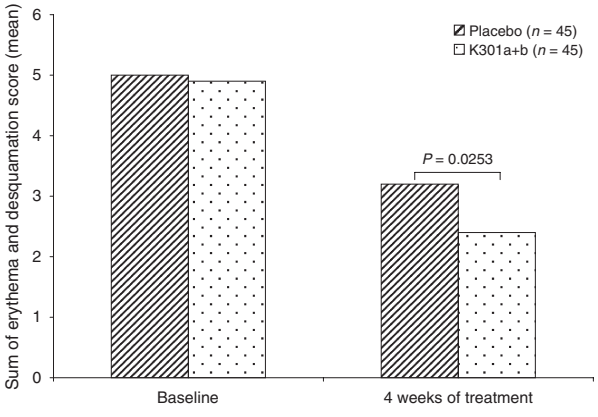



**Figure 2** Sum of erythema and desquamation at baseline and week 4 in Study I.

*Patient score of functional symptoms*

Improvements in patient score for dandruff were observed for K301a + b compared with placebo after 4 weeks: in patients who applied K301a or K301b, 20% had no dandruff and 60% had slight dandruff, compared with 11% and 36%, respectively, in the placebo group. In contrast, 18% of patients who applied K301a or K301b had moderate dandruff and 2% had severe dandruff at week 4, compared with 38% and 16%, respectively, in the placebo group. The overall analysis showed a statistically significant difference in favour of K301a + b over placebo at week 4 ($P$ = 0.001); the difference was also statistically significant at week 2 ($P$ = 0.005) but not at week 8.

For pruritus score at 4 weeks, 29% of patients who applied K301a or K301b reported no pruritus and 33% had slight pruritus, compared with 13% and 40%, respectively, in the placebo group. Thirty-three percent of patients who applied K301 had moderate pruritus and 4% had severe pruritus, compared with 40% and 7%, respectively, in the placebo group at week 4. Differences between the treatments for the pruritus score did not reach statistical significance at any time point.

**Table 2** Summary of erythema and desquamation in the full analysis set in Study I and Study II.

| | Study I mean (SD) | | | | Study II mean (SD) | |
|---|---|---|---|---|---|---|
| | Placebo ($n$ = 45) | K301a ($n$ = 21) | K301b ($n$ = 24) | K301a + b ($n$ = 45) | Placebo ($n$ = 64) | K301a ($n$ = 134) |
| Erythema | | | | | | |
| Baseline | 2.3 (0.7) | 2.3 (0.7) | 2.3 (0.8) | 2.3 (0.7) | 2.5 (0.5) | 2.4 (0.5) |
| Week 2 | 1.8 (1.1) | 1.6 (1.1) | 1.3 (0.9) | 1.5 (1.0) | 1.8 (1.0) | 1.6 (1.0) |
| Week 4 | 1.4 (1.2) | 1.0 (1.0) | 1.2 (0.9) | 1.1 (1.0) | 1.5 (1.1) | 1.2 (1.1) |
| Week 8 | 1.4 (1.2) | 1.1 (0.9) | 1.2 (1.1) | 1.2 (1.0) | NA | NA |
| Desquamation | | | | | | |
| Baseline | 2.7 (0.9) | 2.4 (0.7) | 2.8 (0.8) | 2.6 (0.8) | 2.5 (0.5) | 2.5 (0.5) |
| Week 2 | 2.1 (1.0) | 1.7 (1.1) | 1.8 (1.0) | 1.7 (1.0) | 2.0 (1.0) | 1.5 (0.9) |
| Week 4 | 1.9 (1.2) | 1.1 (1.0) | 1.4 (1.3) | 1.3 (1.2) | 1.7 (1.1) | 1.3 (1.0) |
| Week 8 | 1.8 (1.3) | 1.0 (1.0) | 1.3 (1.2) | 1.2 (1.1) | NA | NA |

NA, not applicable; SD, standard deviation.

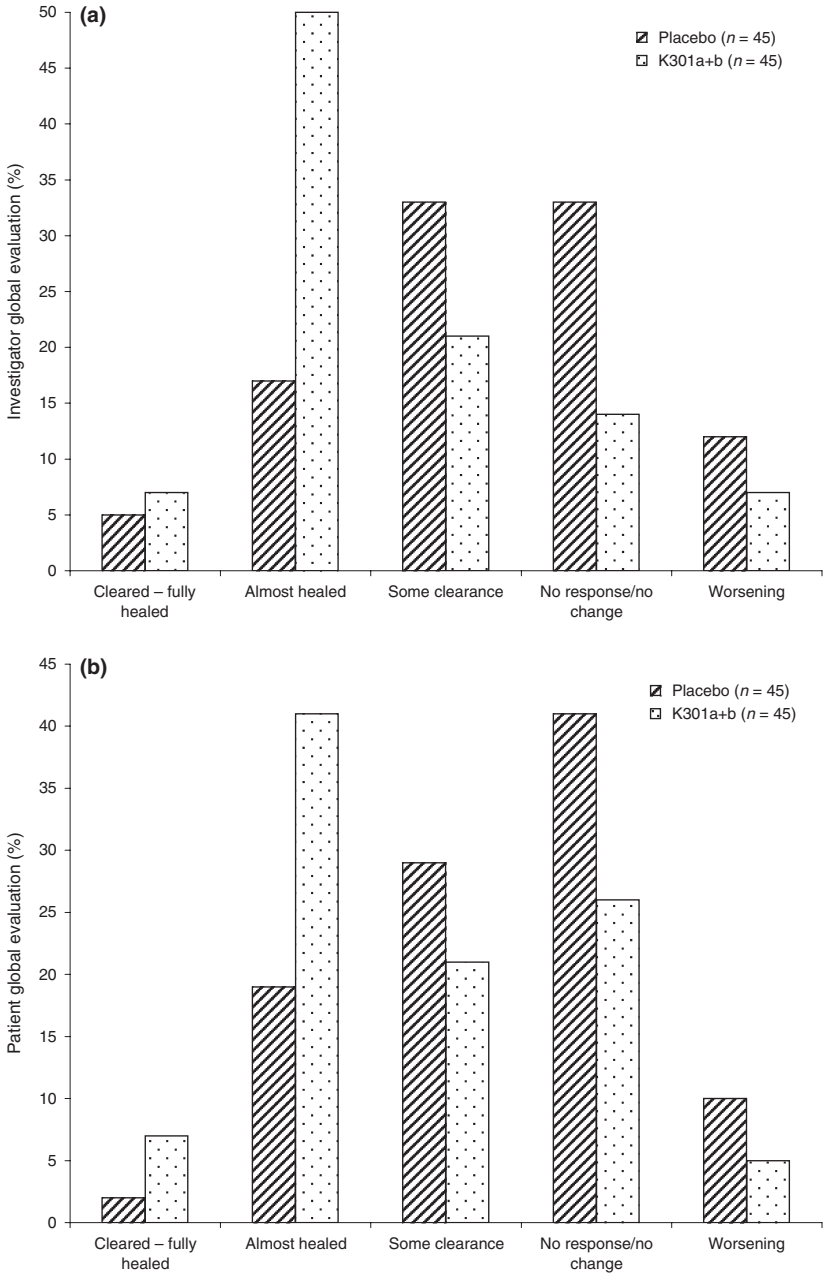



**Figure 3** Global assessment of seborrhoeic dermatitis in Study I at week 4: investigator global evaluation (panel a) and patient global evaluation (panel b).

*Dermatology life quality index scores*

No statistically significant difference was observed between K301 and placebo regarding DLQI after 4 or 8 weeks of treatment.

*Cosmetic properties*

Patients regarded K301a to be less sticky than K301b. Mean (standard deviation) stickiness score at week 4 was 26 (21) for K301a, 41 (28) for K301b and 12 (13) for placebo, although this difference was not statistically significant. Mean (standard deviation) stickiness score at week 8 was 20 (20) for K301a, 36 (27) for K301b and 14 (22) for placebo ($P = 0.037$). There was no evidence of a difference between K301a and K301b with regard to ease of application or effect on hair quality.

## Study II

*Investigator assessment of target lesions*

At baseline, mean (standard deviation) sum of erythema and desquamation scores were 4.8 (0.8) for

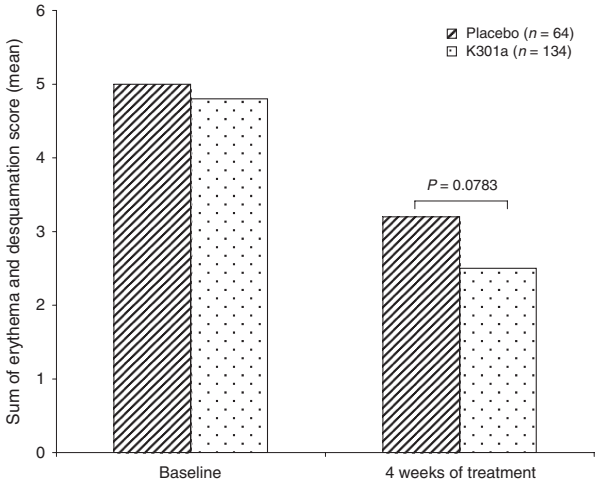



**Figure 4** Sum of erythema and desquamation at baseline and week 4 in study II.

K301a and 5.0 (0.7) for placebo. Sum scores were significantly lower in the K301a group compared with placebo after 2 weeks: mean (standard deviation) sum score for K301a was 3.1 (1.6) compared with 3.8 (1.7) in the placebo group ($P = 0.020$). At week 4, K301a was also associated with an improved score: mean (standard deviation) sum score for K301a was 2.5 (1.9) compared with 3.2 (1.8) in the placebo group, although this difference did not achieve statistical significance (Fig. 4). At 2 weeks, 43% of patients who applied K301a and 22% of patients who applied placebo had responded to treatment ($P = 0.018$). After 4 weeks the proportion of patients regarded as responders$_{0\text{-}2}$ was 55% for K301a patients compared with 42% of placebo patients ($P = 0.315$). In the per-protocol analysis set at week 4, an improvement was also seen with K301a, but statistical significance was not achieved.

The K301a was associated with statistically significant improvements in desquamation at 4 weeks in the full analysis population: mean (standard deviation) score for K301a was 1.3 (1.0) compared with 1.7 (1.1) for placebo ($P = 0.013$; Table 2). A statistically significant difference between K301a and placebo was also demonstrated for desquamation at 2 weeks ($P = 0.001$). However, no statistically significant differences were observed for erythema at 2 weeks or 4 weeks (Table 2).

*Global evaluation scores*

The proportion of patients whose seborrhoeic dermatitis was fully healed, markedly improved or moderately improved was greater following treatment with K301a than placebo; differences achieved statistical significance in both the investigator ($P = 0.012$; Fig. 5a) and patient ($P = 0.009$; Fig. 5b) evaluations.

*Patient score of functional symptoms*

There was a significant difference between K301a and placebo at 2 weeks ($P = 0.044$), with 9% of patients who applied K301a reporting no dandruff and 35% slight dandruff, vs. 8% and 20%, respectively, in the placebo group. No significant differences were observed for pruritus score at 2 weeks or dandruff and pruritus scores at 4 weeks.

### Pooled analysis of efficacy

Mean (standard deviation) sum score of erythema and desquamation at baseline was 4.8 (0.8) for patients randomised to K301a and 4.8 (0.9) for patients randomised to placebo. After 4 weeks, sum scores were lower for pooled K301a compared with placebo: mean (standard deviation) sum score for K301a was 2.4 (1.9) compared with 3.1 (1.9) for placebo ($P = 0.009$).

### Safety assessments overall

No serious adverse events were reported in either study. Smarting pain upon application or burning sensation was the most frequently reported adverse event across both studies (Table 3). In Study I, adverse events judged possibly related to treatment were reported in 8% (4/51) of the patients who applied K301a or K301b. Three patients discontinued treatment with K301 because of adverse events judged to be related to study treatment by the investigator: one patient experienced smarting and burning; one patient experienced rash and itching; and one patient experienced eczema and ulceration. In Study II, no patients discontinued the study as a consequence of adverse events. Adverse events that the investigator judged to be possibly related to treatment were reported in 11% (15/136) of patients who applied K301a and were generally transient application site reactions of mild severity, i.e. smarting pain and redness.

## Discussion

In the two studies presented, topical applications of K301 to the scalp resulted in clinical improvement in the expression of seborrhoeic dermatitis. The effects were established in the absence of any significant concerns over safety or local tolerance. The results of both studies indicate that K301 has a relatively early onset of action,

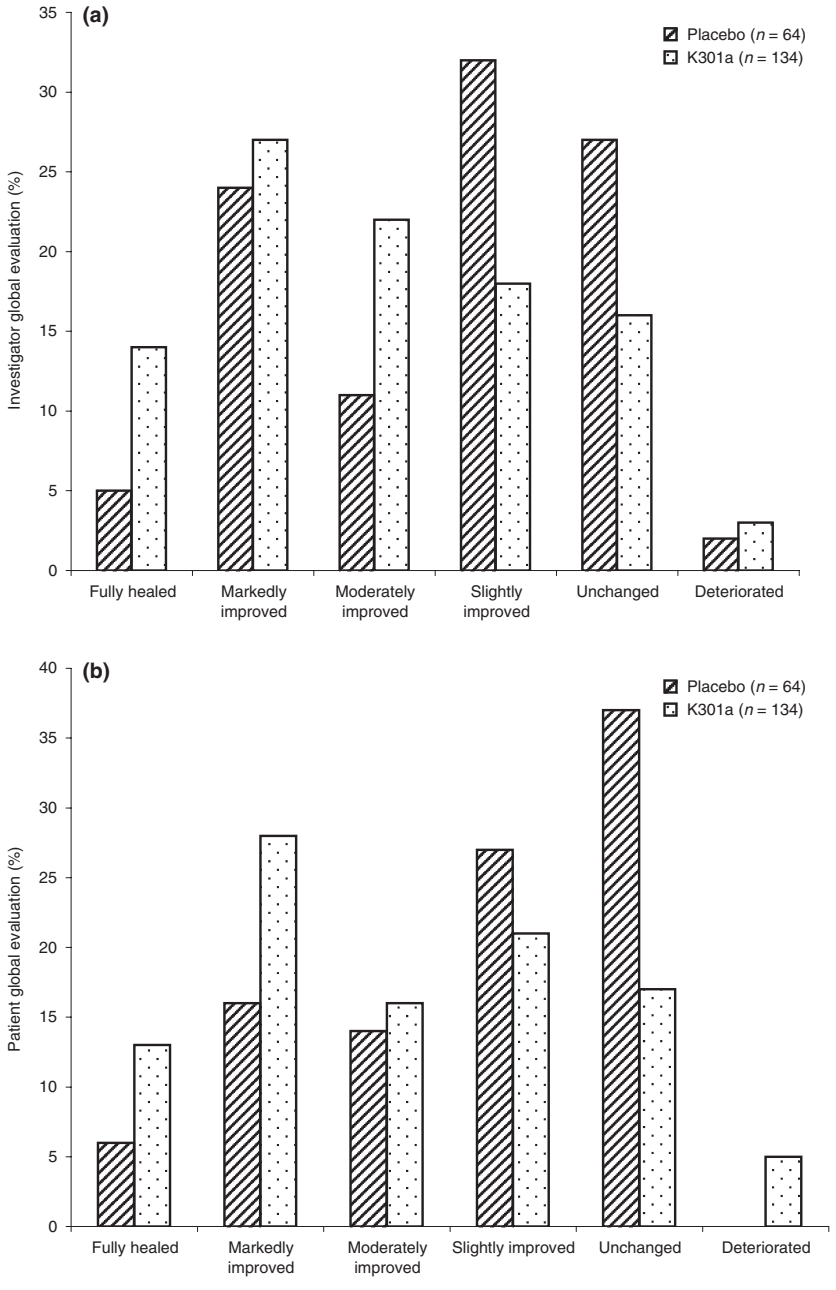



**Figure 5** Global assessment of seborrhoeic dermatitis in Study II: investigator global evaluation (panel a) and patient global evaluation (panel b).

particularly for desquamation and dandruff where significant responses were observed after 2 weeks of application. In Study I, there was a statistically significant difference between K301 and placebo after 8 weeks of application for desquamation but not for any other endpoint, possibly indicating that the once daily application schedule should be continued rather than reduced in frequency to a maintenance schedule.

In Study II, a statistically significant reduction was observed in desquamation at week 4. No significant reduction was observed for erythema and the primary endpoint (the sum of erythema and desquamation scores) was not achieved. The absence of a significant effect on erythema may not be unexpected as a previous study of ketoconazole (2%) and ciclopirox (1.5%) shampoos in patients with seborrhoeic dermatitis also found no statistically significant difference in the response of erythema for either agent compared with placebo.[19]

Analyses of pooled data from two or more studies provide a useful tool to evaluate apparently conflicting study results and to provide a different perspective of the

**Table 3** Adverse events and application site reactions (safety analysis set).

| | Study I | | | Study II | |
|---|---|---|---|---|---|
| | Placebo (*n* = 47) | K301a (*n* = 24) | K301b (*n* = 27) | Placebo (*n* = 64) | K301a (*n* = 136) |
| Any event; n (%) | 11 (23) | 6 (25) | 6 (22) | 6 (9) | 22 (16) |
| Any related event; n (%)[1] | 1 (2) | 2 (8) | 2 (7) | 1 (2) | 15 (11) |
| Most frequent events: (>one patient in any group) | | | | | |
| Burning sensation | 0 | 0 | 0 | 0 | 6 (4) |
| Pruritus | 0 | 2 (8) | 1 (4) | 1 (2) | 2 (1) |
| Erythema | 0 | 2 (8) | 0 | 0 | 2 (1) |
| Pain | 1 (2) | 0 | 0 | 0 | 4 (3) |
| Nasopharyngitis | 2 (4) | 1 (4) | 2 (7) | 1 (2) | 0 |
| Patients with pain, smarting or irritation on application; *n* (%) | | | | | |
| Week 2 | 8 (17) | 5 (21) | 8 (30) | NA | NA |
| Week 4 | 5 (11) | 5 (21) | 6 (22) | NA | NA |
| Week 8 | 4 (9) | 3 (13) | 5 (19) | NA | NA |

NA, not applicable.

[1]Treatment-related adverse event judged possibly or probably related to study medication.

overall effects of treatment.[20] The pooled data from patients who applied K301a supported a positive clinical effect of K301a on the primary endpoint, although not all assumptions for the planned proportional odds model were fulfilled and this should be considered when interpreting the results.

The present work does not consider the long-term benefit of K301 and whether it has the potential to add benefit over existing treatment in terms of remission and relapse rates. Consideration of this possibly could form part of further work allied with the prophylactic use of K301. A direct comparison of K301 with an anti-fungal agent such as ketoconazole was not conducted in this study because these agents are presented as shampoos in Sweden. Any direct comparison would have required a complicated double-dummy design that would have increased the complexity of the study design and implementation. The placebo solutions in the current studies contained the anti-fungal agent nipasept sodium. It cannot be excluded that nipasept sodium exerted an antifungal activity in this study, although no information is available on its activity against *Malassezia* spp.

There is a lack of standardisation in terms of the outcome measurements used to assess seborrhoeic dermatitis in the published literature. Several different variables have been used as primary endpoints to assess treatments, including investigator-assessed rating scales of various combinations of symptoms such as itching, scaling and inflammation,[7,8,21] the measured area of seborrhoeic dermatitis,[19] relapse rate within 3 months,[22] an 'effective treatment' endpoint based on investigator-assessed rating scales [6] and success rate, defined as complete remission.[2] This range of outcome measures makes it difficult to compare treatments across studies. However, statistically significant improvements compared with placebo have been reported for a number of anti-fungal agents including ketoconazole [9,23] and ciclopirox shampoo [7,8,24] using similar outcome variables to those in this study. There is also a lack of validated ratings scales available to assess erythema and desquamation. For this study, we used modified versions of scales that have been used in other clinical studies[6–8] and did not conduct any assessments of inter- and intra-assessor-related error.

The K301 was generally well tolerated and there were no significant safety concerns. As might be expected for a topical application, adverse events were generally located around the area of application and were most frequently a sensation of burning with pain, pruritus or erythema.

In conclusion, K301 was observed to have an effect on clinical markers of seborrhoeic dermatitis within 2 weeks, leading to statistically significant and clinically meaningful improvements in a range of endpoints used to assess disease severity. The clear clinical benefits following treatment with K301 coupled with its excellent safety and tolerability profiles, that appear to raise no concerns over chronic topical use, suggest that it represents a possible new treatment for seborrhoeic dermatitis that should undergo further investigation.

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## Conflict of interest

Lennart Emtestam reports having received consulting fees and grants for this study from Moberg Derma AB. Åke Svensson: none declared. Kjell Rensfeldt is an employee of Moberg Derma AB, the manufacturer of K301 and sponsor of these studies.

## References

1 Shuster S. The aetiology of dandruff and the mode of action of therapeutic agents. *Br J Dermatol* 1984; **111**: 235–42.
2 Ford GP, Farr PM, Shuster S. The response of seborrhoeic dermatitis to ketoconazole. *Br J Dermatol* 1984; **111**: 603–7.
3 Gupta A, Bluhm R. Seborrheic dermatitis. *J Eur Acad Dermatol Venereol* 2004; **18**: 13–26.
4 Lebwohl M, Plott T. Safety and efficacy of ciclopirox 1% shampoo for the treatment of seborrheic dermatitis of the scalp in the US population: results of a double-blind, vehicle-controlled trial. *Int J Dermatol* 2004; **43**(Suppl 1): 17–20.
5 Abeck D, Loprox Shampoo Dosing Study Group. Rationale of frequency of use of ciclopirox 1% shampoo in the treatment of seborrheic dermatitis: results of a double-blind, placebo-controlled study comparing the efficacy of once, twice, and three times weekly usage. *Int J Dermatol* 2004; **43**(Suppl 1): 13–6.
6 Altmeyer P, Hoffmann K, Loprox Shampoo Dosing Concentration Study Group. Efficacy of different concentrations of ciclopirox shampoo for the treatment of seborrheic dermatitis of the scalp: results of a randomized, double-blind, vehicle-controlled trial. *Int J Dermatol* 2004; **43**(Suppl 1): 9–12.
7 Elewski BE, Abramovits W, Kempers S *et al.* A novel foam formulation of ketoconazole 2% for the treatment of seborrheic dermatitis on multiple body regions. *J Drugs Dermatol* 2007; **6**: 1001–81.
8 Gupta AK, Batra R, Bluhm R, Boekhout T, Dawson TL. Skin diseases associated with *Malassezia* species. *J Am Acad Dermatol* 2004; **51**: 785–98.
9 De Angelis YM, Gemmer CM, Kaczvinsky JR, Kenneally DC, Schwartz JR, Dawson TL Jr. Three etiologic facets of dandruff and seborrhoeic dermatitis: *Malassezia* fungi, sebaceous lipids, and individual sensitivity. *J Investig Dermatol Symp Proc* 2005; **10**: 295–7.
10 Vanden Bossche H, Dromer F, Improvisi I, Lozano-Chiu M, Rex JH, Sanglard D. Antifungal drug resistance in pathogenic fungi. *Med Mycol* 1998; **36**(Suppl 1): 119–28.
11 Gupta AK, Kohli Y. Evaluation of in vitro resistance in patients with onychomycosis who fail antifungal therapy. *Dermatology* 2003; **207**: 375–80.
12 Ashton H, Frenk E, Stevenson CJ. Urea as a topical agent. *Br J Dermatol* 1970; **84**: 194–96.
13 Swanbeck G. Urea in the treatment of dry skin. *Acta Derm Venereol Suppl (Stockh)* 1992; **177**: 7–8.
14 Goldsmith LA. Propylene glycol. *Int J Dermatol* 1978; **17**: 703–5.
15 Kinnunen T, Koskela M. Antibacterial and antifungal properties of propylene glycol, hexylene glycol, and 1,3–butylene glycol in vitro. *Acta Derm Venereol* 1991; **71**: 148–50.
16 Faergemann J, Fredriksson T. Propylene glycol in the treatment of tinea versicolor. *Acta Derm Venereol* 1980; **60**: 92–3.
17 Finlay AY, Khan GK. Dermatology life quality index (DLQI) – a simple measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**: 210–6.
18 Faergemann J. Propylene glycol in the treatment of seborrheic dermatitis of the scalp, a double–blind study. *Cutis* 1988; **42**: 69–71.
19 Ratnavel RC, Squire RA, Boorman GC. Clinical efficacies of shampoos containing olamine (1.5%) and ketoconazole (2.0%) in the treatment of seborrhoeic dermatitis. *J Dermatol Treat* 2007; **18**: 88–96.
20 European Medicines Agency. ICH Topic E9: Statistical Principles for Clinical Trials. CPMP/ICH/363/96. September 1998.
21 Warshaw EM, Wohlhuter RJ, Liu A *et al.* Results of a randomised, double-blind, vehicle-controlled efficacy trial of pimecrolimus cream 1% for the treatment of moderate to severe facial seborrhoeic dermatitis. *J Am Acad Dermatol* 2007; **57**: 257–64.
22 Peter RU, Richarz-Barthauer UR. Successful treatment and prophylaxis of scalp seborrhoeic dermatitis and dandruff with 2% ketoconazole shampoo: results of a multicentre, double-blind, placebo-controlled trial. *Br J Dermatol* 1995; **132**: 441–5.
23 Elewski B, Ling MR, Phillips TJ. Efficacy and safety of a new once-daily ketoconazole 2% gel in the treatment of seborrhoeic dermatitis: a phase III trial. *J Drugs Dermatol* 2006; **5**: 646–50.
24 Shuster S, Meynadier J, Kerl H, Nolting S. Treatment and prophylaxis of seborrhoeic dermatitis of the scalp with antipityrosporal 1% ciclopirox shampoo. *Arch Dermatol* 2005; **141**: 47–52.