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Efficacy and safety of fluocinolone acetonide 0.025% otic solution in patients with otic eczema: a randomized, double-blind, placebo-controlled clinical trial

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Abstract

Objectives: To assess the efficacy and safety of fluocinolone acetonide 0.025% otic solution versus placebo in treating patients with otic eczema.

Methods: In this multicentre, randomized, double-blind, parallel-group phase 3 clinical trial, conducted at 12 Spanish centres between March 2012 and March 2013, patients received fluocinolone acetonide 0.025% or placebo otic solution twice daily for 7 days (days 1–7) with an 8-day follow-up (days 9–15). Outcome measures included change in itching from baseline (day 1) to study days 4–8 and 9–15, and change in otoscopic signs (erythema, oedema, and scaling) from baseline to the end of treatment (day 8) and end of follow-up (day 15).

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Results: Patients treated with fluocinolone acetonide 0.025% (n = 66), as compared with placebo-treated patients (n = 69), showed significantly higher reductions in itching from baseline to study days 4–8 and 9–15, and in individual and global otoscopic signs from baseline to the end of treatment (day 8) and end of follow-up (day 15). Incidence and severity of adverse events was similar between the fluocinolone and placebo groups.
Conclusions: Fluocinolone acetonide 0.025% otic solution, administered twice daily for 7 days, is an effective and safe treatment for otic eczema.

Keywords
Fluocinolone, otic eczema, efficacy, safety, randomized clinical trial

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Introduction

Otic eczema is a non-infectious form of otitis externa primarily caused by dermatologic and allergic reactions.[1,2] This otic disorder can arise from a broad range of systemic dermatologic conditions such as eczema, seborrhea, atopic dermatitis, or psoriasis; or from local dermatologic diseases, such as contact dermatitis.[3,4]

The most common symptom of otic eczema is itching (pruritus), often promoting a severe and persistent discomfort.[5] Scaling, that can become chronic and produce lichenification affecting the entire pinna, is the most frequently detected otoscopic sign, followed by erythema and oedema. Clinical manifestations of otic eczema can range from mild to severe depending on the underlying dermatologic condition and disease progression: otic eczema caused by atopic dermatitis usually presents with erythema and scaling, underlying psoriasis is associated with scaling, and causal contact dermatitis is often accompanied by lichenification.[6]

Otic eczema is often a chronic and relapsing condition. Depending on the severity and frequency of recurrent clinical manifestations, otic eczema may develop into a chronic condition that will become difficult to manage if inadequately treated. For this reason, management of otic eczema requires the selection of effective treatment approaches to improve signs and symptoms and to minimize the risk of adverse events (AEs).[7–9]

Because of the dermatologic and inflammatory nature of otic eczema, corticosteroids (such as hydrocortisone, dexamethasone, or fluocinolone) are widely recommended to treat this pathology.[10–12] However, specific treatment approaches for otic eczema are scarce, as are randomized controlled trials (RCTs) investigating specific options to treat this condition. Fluocinolone acetonide 0.01% is currently the only otic medication approved by the US Food and Drug Administration (FDA) for the indication of otic eczema.

Fluocinolone, a low-to-medium fluorinated corticosteroid, exhibits anti-inflammatory, anti-pruritic, and vasoconstrictive properties[13] and has been employed for the management of diverse inflammatory diseases including psoriasis, atopic dermatitis, and macular oedema.[14–16] The efficacy and safety of fluocinolone acetonide at 0.01 and 0.025% has been demonstrated when used as a single agent or in combination with antibiotics in different formulations

(creams, ointments, oils, or ophthalmic and otic solutions).[16–21]

The aim of the present study was to evaluate the efficacy and safety of fluocinolone acetonide 0.025% otic solution versus placebo in patients with otic eczema.

Patients and methods

Study population

This multicentre, randomized, double-blind, placebo-controlled, parallel-group trial (clinicaltrials.gov identifier: NCT01996748) was conducted at 12 Spanish centres between March 2012 and March 2013. The study adhered to the tenets of the Declaration of Helsinki and complied with Good Clinical Practice guidelines according to the International Council for Harmonization of Technical requirements for pharmaceuticals for human use (http://www.ich.org/home.html). The study was approved by the Clinical Research Ethics Committee of Vall d'Hebron Hospital (Barcelona, Spain), and written informed consent was obtained from all participants.

Patients who attended otolaryngology outpatient clinics were assessed for eligibility according to the following criteria: age over 12 years, clinical diagnosis of otic eczema suitable for locally applied treatment, moderate or severe itching in the ear canal (with or without involvement of the pinna), and/or scaling in the skin of the ear canal evidenced by otoscopic imaging.

Patients were excluded from the trial if, among other conditions, they presented with clinical and/or exploratory findings of complicated otic eczema; fungal or bacterial otitis media or otitis externa; significant concomitant diseases such as tuberculosis, psoriasis, or impetigo; traumatism or otologic surgery within the past 2 months; earwax at inclusion or within the past 2 weeks; use of immunosuppressant drugs, antihistamines, or topical non-steroidal drugs; use of topical otic, ophthalmic, or intranasal steroids; concomitant use of oral anti-inflammatory drugs; use of topical antiseptics, antibiotics, or antipruritic medications on the target lesion the day before inclusion; history of adverse reactions to any component of the study medication; and/or disorders that could alter the interpretation of the results, such as seborrheic dermatitis or local dermatitis.

Study design and intervention

Patients were randomly assigned to receive either fluocinolone acetonide 0.025% otic solution or placebo otic solution. A 1:1 allocation ratio was performed using a computer-generated randomization list with masked block size to randomize patients to each treatment arm. Study personnel, sponsor, and patients were blinded to treatment randomization. Both treatment arms were supplied in vials of identical characteristics (single-dose vials containing 0.40 ml of a clear, colourless, homogeneous solution). The placebo otic solution was formulated with the same ingredients as the active treatment, except for fluocinolone acetonide 0.025%.

The study comprised a 7-day treatment period (study days 1–7) and a subsequent 8-day follow-up period (study days 8–15). During this period the patient was scheduled to attend three visits: three visits: baseline (treatment day 1), end of treatment (day 8, first follow-up day), and end of follow-up (day 15). At baseline, signs and symptoms of otic eczema were evaluated in each patient followed by their randomization to receive the active treatment (fluocinolone acetonide 0.025%) or the comparator treatment (placebo). Patients were instructed to properly administer the otic medication twice daily for 7 days (study days 1–7). In case of bilateral otic eczema, the ear most affected by itching was selected. In case of identical itching in both ears,

the evaluable ear was selected based on higher severity of scaling, erythema or oedema, according to the investigator's criteria.

A study diary was provided to each patient, with detailed instructions of how to record itching twice daily (described below) and treatment adherence. Compliance was calculated from the number of doses taken by the patient divided by the number of doses the patient was expected to take, and patients who scored $\geq$80% were considered to be compliant. At the end of treatment, efficacy and safety parameters, and treatment compliance were evaluated. At follow-up, efficacy and safety parameters were assessed.

Efficacy assessment

The primary efficacy endpoint was the change in itching on days 4–8 of the study relative to baseline (day 1). Mean itching score during days 4–8 was calculated from the punctuations recorded in the patient diary twice daily on these days. Itching was graded by the patient according to the 4-point, internationally validated scale, in which 0 = absent, 1 = mild, 2 = moderate, and 3 = severe.[22]

Secondary endpoints were: change in itching during follow-up (mean itching score on days 9–15 relative to baseline), and change in global and individual otoscopic signs (erythema, oedema, and scaling) at the end of treatment (day 8) and at the end of follow-up (day 15) relative to baseline (day 1). Otoscopic signs were measured on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) as follows: erythema using a partly subjective visual scale, and oedema and scaling according to the percentage of occlusion (mild <25%; moderate 25–50%; or severe >50%).

Safety assessment

Safety was evaluated by the incidence and severity of AEs. The severity of AEs was recorded as mild, moderate, or severe. The potential relationship between AEs and study treatment was classified as unrelated, unlikely, possible, probable, certain, or unclassifiable. AEs were classified by system organ class (SOC) or preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) (version 16).[23]

Statistical analyses

A sample size of 64 patients per group (128 in total) was calculated to detect a difference between means equal to half of the standard deviation (SD), with a 2-sided 5% significance level and 80% power. Primary and secondary endpoints were primarily evaluated in the full analysis set population, defined as all randomized patients with a baseline value for the primary efficacy variable. Analyses were also performed in the per-protocol population for confirmatory purposes. The per-protocol population was defined as the full analysis set of patients who took $\geq$80% of the assigned treatment, had a post-treatment value for the primary variable ($\geq$four assessments during days 4–8), and did not receive concomitant treatment with systemic non-steroidal anti-inflammatory drugs, or systemic or topical steroidal anti-inflammatory drugs. Safety data were analysed in the safety population (all randomized patients). Missing data for itching change in the full analysis set were imputed using the last observation carried forward method. Other analyses were conducted using available data only.

Baseline demographic characteristics are presented as mean (±SD), median, and extremes (min, max) for numerical (continuous) variables; and as number and

percentage for categorical variables. Statistically significant between-group differences in itching, and global and individual otoscopic signs (erythema, oedema and scaling) were calculated using the analysis of covariance (ANCOVA); randomization treatment and baseline data were included as fixed effects. Statistical tests were two-sided, and a P-value < 0.05 was considered statistically significant. AEs were assessed using descriptive statistical analyses in the safety population. All statistical analyses were performed using SAS software for Windows, version 9.2 (SAS Institute, Cary, SC, USA).

Results

Patient population

A total of 136 patients with diagnosis of otic eczema were recruited, of whom 135 were randomly assigned to receive either fluocinolone acetonide 0.025% otic solution (66 patients) or placebo otic solution (69 patients). One patient was not included as only attendance at the first visit, and no other data (randomization visit, randomization number) were recorded. Fourteen patients withdrew from the study: eight in the fluocinolone group and six in the placebo group. Primary reasons for discontinuation were the presence of AEs in the placebo group (four patients) and lost to follow-up in the treatment group (four patients). A total of 22 protocol deviations were identified in 16 patients. The safety population comprised 135 patients, the full analysis set population comprised 131 patients (63 patients in the fluocinolone group; and 68 patients in the placebo group) and the per-protocol population comprised 119 patients (Figure 1).

Baseline characteristics were balanced between the fluocinolone and placebo groups in terms of age, sex and race. Mean age (±SD) was 53.6 (±13.8) years in the fluocinolone group and 52.4 (±11.8) years in the placebo group. Of note, a female predominance (80.6%) was observed overall, with no statistically significant between-group differences: 46 (73%) females and 17 (27%) males in the fluocinolone group, and 60 (88%) females and 8 (12%) males in the placebo group. Most patients experienced bilateral otic eczema: 53 (84.1%) and 52 (76.5%) in the fluocinolone and placebo groups, respectively. Mean baseline scores were comparable between the fluocinolone and placebo groups for itching (2.4 versus 2.3), erythema (1.4 versus 1.5), oedema (1.0 versus 1.1), and scaling (1.9 versus 1.8), respectively.

Efficacy evaluation

Mean itching values were almost identical between the fluocinolone and placebo groups at baseline and decreased on study days 4–8 (primary efficacy endpoint). This decrease was significantly more pronounced in the fluocinolone group (mean change, –1.62) than in the placebo group (mean change, –1.26; $P = 0.005$, ANCOVA; Figure 2). The estimated difference between treatments for the change in itching from baseline to days 4–8 was –0.36 (95% CI –0.60, –0.11). Mean itching values were also decreased during the follow-up period (days 9–5) compared with baseline, with a statistically higher reduction in the fluocinolone group compared with the placebo group (mean change, –1.79 versus –1.27, respectively; $P < 0.001$, ANCOVA; Figure 2). These results were corroborated by analyses of the per-protocol population ($P < 0.001$ for the change in itching on days 4–8 and 9–15 relative to baseline; data not shown).

Scores for each otoscopic sign (erythema, oedema, and scaling) decreased from baseline to the end of treatment (study day 8) and to the end of the follow-up period (study day 15), being significantly higher in patients treated with fluocinolone

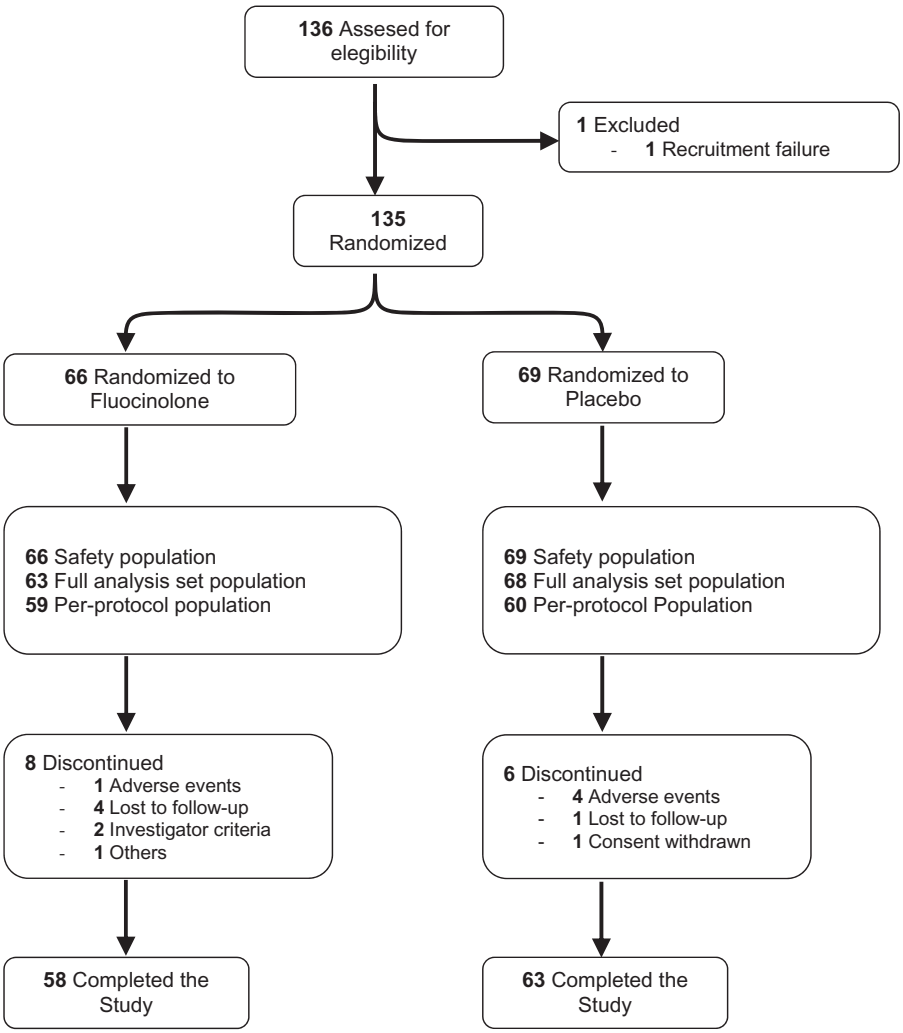

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

acetonide 0.025% compared with placebo-treated patients ($P < 0.05$, ANCOVA; Table 1). Global scores for otoscopic signs (erythema, oedema, and scaling combined) were highly comparable between fluocinolone- and placebo-treated patients at baseline (mean $\pm$ SD score, 1.41 ± 0.63 and 1.49 ± 0.64, respectively), were decreased at the end of treatment (study day 8), and showed slight variations at the end of the follow-up period (study day 15) in both study groups. Between-group differences showed statistically higher reductions in global otoscopic signs scores in the fluocinolone group at the end of treatment and at the end of follow-up ($P < 0.001$, ANCOVA; Table 1). The significantly higher efficacy of fluocinolone in reducing the score for otoscopic signs was corroborated by analyses of the per-protocol population at the end of treatment

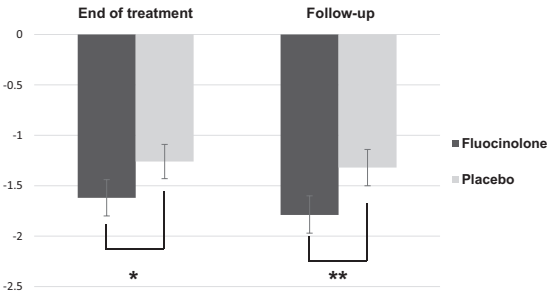

Figure 2. Mean change in itching from baseline to study days 4–8 and 9–15 in the full analysis set of patients with otic eczema treated with 0.025% fluocinolone ($n = 63$) or placebo ($n = 68$) otic solution. Data presented as mean change in itching ± confidence intervals (CI); *$P = 0.005$ and **$P < 0.001$, statistically significant between-group differences (analysis of covariance).

Table 1. Mean change in global and individual otoscopic signs from baseline (day 1) to the end of treatment (day 8) and end of follow-up (day 15) in the full analysis set of patients with otic eczema.

	Change in mean score			
Variable	Fluocinolone ($n = 63$)	Placebo ($n = 68$)	Estimated difference (95% CI)	Statistical significance
Erythema				
End of treatment	–1.23	–0.77	–0.46 (–0.70, –0.23)	$P < 0.001$
End of follow-up	–1.14	–0.79	–0.35 (–0.61, –0.09)	$P = 0.009$
Oedema				
End of treatment	–0.89	–0.49	–0.40 (–0.62, –0.19)	$P < 0.001$
End of follow-up	–0.85	–0.56	–0.29 (–0.49, –0.09)	$P = 0.005$
Scaling				
End of treatment	–1.58	–1.04	–0.55 (–0.79, –0.30)	$P < 0.001$
End follow-up	–1.66	–0.89	–0.77 (–1.02, –0.51)	$P < 0.001$
Global Score				
End of treatment	–1.23	–0.77	–0.46 (–0.66, –0.27)	$P < 0.001$
End of follow-up	–1.22	–0.76	–0.46 (–0.66, –0.26)	$P < 0.001$

Data presented as mean score for each group.
CI, confidence interval.
Statistically significant between-group differences at $P < 0.05$ (analysis of covariance).

and end of the follow-up period (data not shown).

Safety evaluation

A total of 33 AEs were reported: 17 in participants treated with fluocinolone otic solution and 16 in those receiving placebo (Table 2). The most frequently reported AEs belonged to ear and labyrinth disorders SOC: nine (52.9%) in the fluocinolone group (related to ear discomfort, ear disorder, ear pain, external ear inflammation, and vertigo PT), and 12 (75%) in the placebo group (classified as ear discomfort, ear pain, otitis externa, and tinnitus PT).

Table 2. Number of adverse events (AEs) classified by system organ class (SOC), preferred term (PT) and severity in the safety population of patients with otic eczema.

	Study group		
	Fluocinolone ($n = 66$)	Placebo ($n = 69$)	Total ($n = 135$)
Number of AEs	17	16	33
Patients with ≥1 AE, *n* (%)	15 (22.7)	15 (21.7)	30 (22.2)
Patients with ≥1 study-drug related AE, *n* (%)	5 (7.6)	9 (13)	14 (10.4)
SOC/PT, *n* (% out of total number of AEs)			
Ear and labyrinth disorders			
Ear discomfort	5 (29.4)	5 (31.3)	10 (30.3)
Ear disorder	1 (5.9)	0	1 (3.0)
Ear pain	1 (5.9)	1 (6.3)	2 (6.1)
External ear inflammation	1 (5.9)	0	1 (3.0)
Otitis externa	0	5 (31.3)	5 (15.2)
Tinnitus	0	1 (6.3)	1 (3.0)
Vertigo	1 (5.9)	0	1 (3.0)
General disorders and administration site conditions			
Application site pruritus	1 (5.9)	0	1 (3.0)
Infections and infestations			
Bronchitis	0	1 (6.3)	1 (3.0)
Nasopharyngitis	1 (5.9)	0	1 (3.0)
Nervous system disorders			
Headache	2 (11.8)	0	2 (6.1)
Tension headache	0	1 (6.3)	1 (3.0)
Reproductive system and breast disorders			
Dysmenorrhoea	0	1 (6.3)	1 (3.0)
Respiratory, thoracic and mediastinal disorders			
Dry throat	1 (5.9)	0	1 (3.0)
Nasal obstruction	1 (5.9)	0	1 (3.0)
Skin and subcutaneous tissue disorders			
Pruritus generalised	0	1 (6.3)	1 (3.0)
Eyelid disorder	1 (5.9)	0	1 (3.0)
Surgical and medical procedures			
Dental implantation	1 (5.9)	0	1 (3.0)
Severity, *n* (% out of total number of AEs)			
Mild	17 (100)	11 (68.8)	28 (84.8)
Moderate	0	4 (25.0)	4 (12.1)
Severe	0	1 (6.3)	1 (3.0)

Data presented as *n* or *n* (%) incidence.
Study-drug related AEs include those scored as: 2 = possible, 3 = probable and 4 = certain.

Other AEs reported in the fluocinolone and placebo groups are summarized in Table 2.

Thirty patients reported at least one AE: 15 (22.7%) in the fluocinolone group and 15 (21.7%) in the placebo group. AEs related to study drug were observed in five patients (7.6%) in the fluocinolone group and in nine patients (13.0%) in the placebo group, comprising a total of six related AEs in the fluocinolone group, classified as ear discomfort (4), ear disorder (1), and application site pruritus (1); and a total of nine

related AEs in the placebo group, corresponding to ear discomfort (4), ear pain (1), and otitis externa (4). When stratified by severity, 68.8% of participants in the placebo group reported AEs of mild intensity whereas all AEs in the fluocinolone group were mild. The remaining AEs in the placebo group were moderate (25%) or severe (6.3%) (Table 2). Compliance was high in both groups, with only one patient (1.5%) and six patients (8.7%) showing noncompliance (<80% compliance) in the fluocinolone and placebo groups, respectively.

Discussion

Although otic eczema is a common otic disease,[6,8] evidence-based results from RCTs on this condition are lacking. To the best of the authors' knowledge, the present study comprises one of the few RCTs designed to evaluate the efficacy of a specific treatment option for otic eczema. Itching improvement was found to be statistically superior in the fluocinolone group compared with the placebo group ($P = 0.005$). Importantly, the beneficial effect of fluocinolone acetonide 0.025% was observed shortly after treatment initiation (during study days 4–8). This relatively fast response is of key importance, since it likely contributes to treatment compliance and may be associated with a rapid improvement in patients' quality of life. Moreover, a clear pattern of decreased itching was observed over time, showing a higher reduction during the follow-up period (days 9–15) than during days 4–8 of the study. These results indicate that itching alleviation is progressive, making fluocinolone acetonide 0.025% a particularly suitable agent for patients affected by chronic otic eczema.

Analyses of secondary outcome measures also demonstrated the higher efficacy of fluocinolone acetonide 0.025% in improving other well-known signs of otic eczema such as erythema, oedema, and scaling. Although the vehicle showed some improvement in otoscopic signs, statistically significant differences favouring the fluocinolone group were observed for individual and global otoscopic signs scores, at the end of treatment and at the end of follow-up and regardless of the population analysed. At the end of treatment (study day 8), scaling showed the greatest improvement in the fluocinolone group and displayed the highest difference between groups. During days 9–15 of follow-up, itching exhibited the greatest improvement in the fluocinolone group and scaling was the otoscopic sign with the largest between-group difference. Taken together, the present data demonstrate the efficacy of fluocinolone acetonide 0.025% in resolving well-characterized signs and symptoms of otic eczema, by promoting their rapid and sustained relief.

Otic eczema can occur as a chronic condition;[24,25] thus, it is of prime importance to prevent AEs and recurrences. In the present study, all AEs reported in patients treated with fluocinolone acetonide were of mild intensity, while five AEs in the placebo group were classified as moderate or severe. These results concur with previous studies demonstrating the good tolerability of fluocinolone acetonide treatment.[17–19] In two RCTs, fluocinolone acetonide 0.01% in peanut oil showed a good efficacy response,[20,21] although this formulation raised concerns about possible peanut-derived allergies. Multiple single-entity and combination products containing fluocinolone acetonide at 0.01% and 0.025% have been commercialized in different formulations (creams, ointments, oils, ophthalmic solutions).[16–19] The only product specifically indicated for otic eczema and approved by the FDA is an oil formulation of fluocinolone acetonide at 0.01%. In the present study, fluocinolone acetonide was

assessed at 0.025% based on previous results reporting the safety and good tolerability of this fluocinolone concentration in combination with antibiotics,[17,18] with the hypothesis that 0.025% fluocinolone acetonide would achieve high biological activity and induce a rapid response, at a minimum risk of AEs. In addition, otic solutions can release high local concentrations of the active ingredient within the external auditory canal,[26] thus becoming efficacious alternatives to other formulations, such as ointments or creams. Moreover, single-dose formats are expected to favour the correct instillation of the appropriate volume and to increase patient compliance.[27,28]

In conclusion, the efficacy, safety, and compliance results shown in this study demonstrate that fluocinolone acetonide 0.025% is a suitable treatment option for patients with otic eczema.

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Laboratorios Salvat, S.A. contributed to the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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