SYNOPSIS CLINICAL STUDY REPORT
(Laboratorios SALVAT, S.A.)

Study phase: III
Protocol No.: FLUOTIII/11ES01
EudraCT Nº: 2011-004172-11
Drug product: Fluocinolone Acetonide 0.025%
Formulation: Otic solution
Indication: Otic eczema

A multicenter, randomized, parallel, double-blind, clinical trial study to assess the efficacy and safety of Fluocinolone Acetonide 0.025% Otic Solution compared to Placebo in patients with otic eczema.

Sponsor:	Laboratorios SALVAT, S.A. Gall, 30-36 08950 – Esplugues de Llobregat Barcelona, Spain
Sponsor's Responsible Medical Officer:	Enrique Jiménez, MD. Medical Director Laboratorios SALVAT, S.A.
Date of Clinical Study Report:	25 June 2013
Version:	Final
First Patient First Visit :	09 March 2012
Last Patient Last Visit:	22 March 2013

This study was conducted according to the protocol and in compliance with the Good Clinical Practice guidelines of the International Conference on Harmonization, the Declaration of Helsinki, and applicable regulatory requirements.

1. SYNOPSIS

Name of Sponsor/Company: Laboratorios SALVAT, S.A.		
Name of medicinal product: Not applicable		
Name of drug substances: Fluocinolone Acetonide 0.025% otic solution		
Protocol No: FLUOTIII/11ES01 **Code No.:** EudraCT No.2011-004172-11		
Title of trial: A multicenter, randomized, parallel, double-blind, clinical trial study to assess the efficacy and safety of Fluocinolone Acetonide 0.025% otic solution compared to placebo in patients with otic eczema.		
Investigators and Centre(s): Multicentre study (see Appendix 16.1.4).		
Publication (reference): NA		
Studied period (years): **Date of first enrollment:** **Date of last completed:**	2012-2013 09 March 2012 22 March 2013	**Phase of development:** Phase III clinical trial

Objectives:

Primary objective: To assess the efficacy of Fluocinolone Acetonide 0.025% otic solution compared to placebo for the reduction of itching after 8 days of starting treatment in patients with otic eczema.

Secondary objectives:

1. To assess the efficacy of Fluocinolone Acetonide 0.025% otic solution compared to placebo for the reduction of itching after 15 days of starting treatment in patients with otic eczema.
2. To assess the efficacy of Fluocinolone Acetonide 0.025% otic solution compared to placebo for the reduction of signs (erythema, edema and scaling) after 8 and 15 days of starting treatment in patients with otic eczema.
3. To assess the safety of Fluocinolone Acetonide 0.025% otic solution compared to placebo, by the incidence of adverse events occurred during the study.

Methodology:

Multicenter, randomized, parallel, double-blind, phase III clinical trial, on male and female patients aged 12 years or over with a clinical diagnosis of otic eczema suitable for local treatment.

The patients were randomly assigned to one of the two treatment groups: Fluocinolone Acetonide 0.025% otic solution or placebo.

This study consisted of three visits: day 1 inclusion, day 8 end of treatment and day 15 follow- up visit. The total duration of treatment in each group was 7 days. The study was planned according to the following visits:

Inclusion visit (V1, day 1)

Demographic data, baseline data, evaluation of signs and symptoms (itching, erythema, edema and scaling) choice of target ear. Assignment of treatment and patient treatment diary delivery.

End of treatment visit (V2, day 8)

Evaluation of signs (erythema, edema and scaling). Compliance with study medication was assessed by reviewing the patient treatment diary. Patient treatment diary was collected and patient follow up diary was delivered.

Evaluation of safety.

Follow- up visit (V3, day 15)

Evaluation of signs (erythema, edema and scaling) and safety. Patient follow up diary was collected.

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Number of patients (planned and analyzed):

It was planned to recruit 128 patients (64 patients per treatment group).
Sixty-six patients were randomized to Fluocinolone Acetonide and sixty- nine patients to placebo. The safety population was composed of 135 patients, the FAS population of 131 patients and the PPAS population of 119 patients. The efficacy analysis was performed on the FAS population: 63 patients treated with Fluocinolone Acetonide and 68 patients treated with placebo.

Diagnosis and main criteria for inclusion:

- Male and female patients aged 12 years or over.
- Clinical diagnosis of otic eczema suitable for local treatment according to the investigator.
- Moderate or severe itching in the ear canal (with or without involvement of the pinna), and otoscopic image of scaling in the ear canal skin.
- Patients who agreed to participate in the study and signed informed consent.
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Investigational product, dose and mode of administration, batch number:

Fluocinolone Acetonide 0.025% otic solution
Therapeutic group: S02BA08
Route of administration: topical
Mode of administration: twice a day (every 12 hours) for 7 days.
Batch number: **E001**

Reference therapy, dose and mode of administration, batch number:

Placebo with characteristics identical to the investigational product as regards to visible physical characteristics, administered twice a day (every 12 hours) for 7 days.
Batch number: **DF277/027C**

Duration of treatment:

The duration of treatment for each patient was 7 days.

Criteria for evaluation:

Efficacy Criteria:

- Primary endpoint: The efficacy was measured from the change in itching at the end of treatment (mean itching on days 4-8 compared to baseline).
- Secondary endpoints:
  - Change in itching at follow-up (mean itching on days 9-15 compared to baseline).
  - Change in mean scores of otoscopic signs (erythema, edema and scaling) at the end of treatment (day 8) compared to baseline (day 1).
  - Change in mean scores of otoscopic signs (erythema, edema and scaling) at follow- up (day 15) compared to baseline (day 1).

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Safety Criteria:

Monitoring and recording of AE and SAE. The adverse events were coded according to the World Health Organisation classification for adverse events (MedDRA, version 16), and were described by a synonym (Preferred Term) and the system/organ (SOC) affected, severity, seriousness and causality relationship with the study treatment.

Statistical methods:

Primary efficacy analysis: The analysis of itching change at the end of treatment (mean itching on days 4-8 compared to baseline) was assessed using a lineal model (ANCOVA) that included the randomization treatment and baseline data as fixed values.

Difference between treatments is considered proven if the level of bilateral significance was less than 5% ($p<0.05$), and was estimated by the mean square differences and the 95% confidence interval.

Secondary efficacy analysis:

The analysis of itching change at follow- up (mean itching on days 9-15 compared to baseline) was conducted the same way as the primary analysis.

The analysis of the individual otoscopic signs (erythema, edema and scaling) was conducted using a lineal model ANCOVA.

However, since these variables are discrete and have a very narrow range (scores defined as 0=absent, 1=mild, 2=moderate and 3=severe), the use of an ANCOVA might be questioned. The non-parametric alternatives foreseen in the SAP for the case of non-normality might also be questioned due to the very high number of ties. For this reason, despite not being preplanned in the SAP, it was considered appropriate to conduct an additional analysis of these variables using a 3 df general association Cochrane-Mantel-Haenzel (CMH) test, to compare the distribution of signs among treatment groups adjusting by the baseline value. This analysis is not conducted on change scores, but rather on the categorical classification (absent, mild, moderate or severe) at each visit. However, the CMH analysis is made adjusting for baselines, which is conceptually equivalent to the analysis of change scores.

Safety analysis:

The safety population, which included all patients who took at least one dose of the study medication, was used. Adverse events were analyzed on a descriptive manner.

SUMMARY OF RESULTS/CONCLUSIONS

Efficacy results:

The trial demonstrated the efficacy of the Fluocinolone Acetonide 0.025% otic solution treatment, since the pre-specified primary FAS analysis of efficacy performed on the change in itching at day8 (end of treatment) showed that a significantly higher reduction was achieved with the Fluocinolone Acetonide treatment as compared to placebo ($p=0.005$). This result was similar in the Per Protocol Analysis Set (PPAS).

Secondary analyses of efficacy also showed significantly better results with Fluocinolone Acetonide treatment as compared to placebo: the itching improved at follow-up and in terms of individual and global otoscopic signs scores, both at end of treatment and at follow-up. Results were robust to change in analysis method and similar in FAS and PPAS sets.

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Safety results:
The incidence of adverse events was similar in both treatment groups, and no serious adverse events were reported. The number of study discontinuations due to adverse events was actually lower with Fluocinolone Acetonide 0.025% otic solution than it was with Placebo.

Final conclusion:
Fluocinolone Acetonide 0.025% otic solution administered twice a day (every 12 hours) for 7 days is an effective treatment against otic eczema. The results of clinical assessment of the target lesion show the superiority of Fluocinolone Acetonide 0.025% otic solution compared to placebo in the treatment of otic eczema. The safety profile of Fluocinolone Acetonide 0.025% otic solution is equivalent to that of placebo administered with the same posological regimen and for the same period of time.