



Clinical trial results:

A Phase III, Multicenter, Randomized, Double-Blind Clinical Trial to Assess the Efficacy and Safety of Clotrimazole 1% Otic Solution Compared to Placebo for the Treatment of Fungal Otitis Externa (Otomycosis).

Summary

EudraCT number	2019-003463-22
Trial protocol	ES PT BG RO
Global end of trial date	19 October 2021

Results information

Result version number	v1 (current)
This version publication date	30 December 2022
First version publication date	30 December 2022

Trial information

Trial identification

Sponsor protocol code	CLOTOT3-16IA03
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03686397
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Laboratorios Salvat, S.A
Sponsor organisation address	Gall 30-36, Barcelona, Spain, 08950
Public contact	Enrique Jiménez, Laboratorios Salvat, S.A, 34 933946400, ejimenez@svt.com
Scientific contact	Enrique Jiménez, Laboratorios Salvat, S.A, 34 933946400, ejimenez@svt.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2021
Global end of trial reached?	Yes
Global end of trial date	19 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superior efficacy of Clotrimazole vs placebo in the treatment of otomycosis, with respect to the therapeutic cure at test of cure in the MITT population.

Protection of trial subjects:

If patient reported no improvement in otomycosis signs/symptoms, the investigator might treat patient with other medication (rescue medication) at their discretion.

For patients who required analgesic medication for otalgia, the recommended medication was paracetamol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 June 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 15
Country: Number of subjects enrolled	Romania: 34
Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	Bulgaria: 103
Worldwide total number of subjects	193
EEA total number of subjects	193

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	145

From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The principal investigator was an otolaryngologist

Pre-assignment

Screening details:

A fungal cultures was performed at baseline to know if subject had an ear infection due to *Aspergillus* and/or *Candida* spp.

The main efficacy population of the study was the MITT population (evaluable patients): randomized subjects who had a positive baseline culture for *Aspergillus* spp and/or *Candida* spp.

Period 1

Period 1 title	Baseline MITT Population (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

All study medication products had the same packaging and labels

Arms

Are arms mutually exclusive?	Yes
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Arm title	Clotrimazole
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Clotrimzole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, solution
Routes of administration	Auricular use

Dosage and administration details:

1 vial in the affected ear(s) twice a day during 14 days

Arm title	Placebo
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Arm description: -

Arm type	Placebo
Investigational medicinal product name	Saline solution 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, solution
Routes of administration	Auricular use

Dosage and administration details:

1 vial in the affected ear(s) twice a day during 14 days

Number of subjects in period 1^[1]	Clotrimazole	Placebo
Started	75	35
Completed	70	27
Not completed	5	8
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	1
covid pandemia, bacterial ear culture	2	-
Lack of efficacy	3	5
Protocol deviation	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A fungal culture was performed at baseline to know if subject had an ear infection due to Aspergillus and/or Candida spp.

The main efficacy population of the study was the MITT population (evaluable patients): randomized subjects who had a positive baseline culture for Aspergillus and/or Candida spp.

From the 193 randomized patients, only 110 patients showed positive fungal culture for Aspergillus and/or Candida spp.

Baseline characteristics

Reporting groups

Reporting group title	Baseline MITT Population
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Reporting group description: -

Reporting group values	Baseline MITT Population	Total	
Number of subjects	110	110	
Age categorical			
Units: Subjects			
Adults (18-64 years)	78	78	
From 65-84 years	32	32	
85 years and over	0	0	
Age continuous			
Units: years			
median	52.4		
standard deviation	± 15.53	-	
Gender categorical			
Units: Subjects			
Female	50	50	
Male	60	60	

End points

End points reporting groups

Reporting group title	Clotrimazole
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Therapeutic cure (Clinical and Mycological Cure)

End point title	Therapeutic cure (Clinical and Mycological Cure)
End point description:	
Proportion of subjects with therapeutic cure	
End point type	Primary
End point timeframe:	
Test of cure on day 24	

End point values	Clotrimazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75 ^[1]	35 ^[2]		
Units: Count of participants				
number (not applicable)	59	8		

Notes:

[1] - MITT Population

[2] - MITT Population

Statistical analyses

Statistical analysis title	Therapeutic cure
Statistical analysis description:	
Therapeutic cure is defined as both mycological cure and clinical cure. Mycological cure is defined as eradication (culture does not show growth of any fungal pathogen) or presumed eradication (there is no material to culture and the overall clinical outcome is clinical cure). Subjects who received rescue medication are considered therapeutic failure. Missing endpoints are set to therapeutic failure.	
Comparison groups	Clotrimazole v Placebo
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall study period (about 4 weeks)

Adverse event reporting additional description:

If pre-existing signs and symptoms of otomycosis worsen during the study, this was considered treatment failure instead of an adverse event (AE).

The AE were reviewed in the safety population (subjects who received at least 1 dose of study medication)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Clotrimazole
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Clotrimazole	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 127 (0.00%)	1 / 64 (1.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholesteatoma			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 127 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Labyrinthitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 127 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Clotrimazole	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 127 (0.00%)	3 / 64 (4.69%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 127 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported