Clinical trial results:
A Multicenter, Randomized, Double-Blind Clinical Trial to Assess the Efficacy and Safety of Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% Otic Solution Compared to Ciprofloxacin 0.3% Otic solution and to Fluocinolone Acetonide 0.025% Otic Solution in the Treatment of Acute Otitis Media with Tympanostomy Tubes (AOMT) in Pediatric Patients.

Summary

EudraCT number	2010-023239-40
Trial protocol	ES SE FI DK CZ
Global end of trial date	29 May 2013

Results information

Result version number	v1 (current)
This version publication date	16 February 2016
First version publication date	12 June 2015

Trial information

Trial identification

Sponsor protocol code	CIFLOTIII/10IA04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01404611
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Laboratorios SALVAT, S.A.
Sponsor organisation address	Gall 30-36, Esplugues de Llobregat, Spain, 08950
Public contact	Medical Department, Laboratorios SALVAT, S.A., +34 93 394 64 00, clinicaltrials@salvatbiotech.com
Scientific contact	Medical Director, Laboratorios SALVAT, S.A., +34 93 394 64 70, ejimenezv@salvatbiotech.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	02 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 May 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the efficacy and safety of topical Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution twice a day for 7 days and the primary endpoint is to demonstrate therapeutic superiority for time to cessation of otorrhea over Ciprofloxacin 0.3% otic solution and over Fluocinolone Acetonide 0.025% otic solution, in patients suffering from AOMT. Otorrhea will be defined as ending on the first day on which the otorrhea is absent and remains absent until the end of the study.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 August 2011
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	Spain: 73
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	South Africa: 26
Country: Number of subjects enrolled	United States: 229
Worldwide total number of subjects	331
EEA total number of subjects	74

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)	140
Children (2-11 years)	187

Adolescents (12-17 years)	4
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment period was from August 2011 to May 2013 in Europe (Czech Republic, Denmark, Finland,
Spain and Sweden), South Africa, Canada and USA

Pre-assignment

Screening details:

Patients between 6 months and 12 years with AOMT. Patients had to suffer from otorrhea for 3 weeks or less. Otorrhea had to be moderate or severe and purulent.

Period 1

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

Blinding implementation details:

The patient was randomized using IWRS.
All study medication products (test and comparators) had the same packaging and labels, and the boxes in which the study medication was packaged, shipped, and dispensed were identical in appearance.
The central laboratory was blinded to the treatment assignment of the patient from whom the sample was collected.

Arms

Are arms mutually exclusive?	Yes
Arm title	CIPRO+FLUO

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ciprofloxacin plus Fluocinolone acetonide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, solution in single-dose container
Routes of administration	Auricular use

Dosage and administration details:

Administer the contents of one 0.25ml single dose vial twice a day to the affected ear(s) for seven days

Arm title	CIPRO

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Ciprofloxacin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, solution in single-dose container
Routes of administration	Auricular use

Dosage and administration details:

Administer the contents of one 0.25ml single dose vial twice a day to the affected ear(s) for seven days

Arm title	FLUO

Arm description: -

Arm type	Active comparator

Investigational medicinal product name	Fluocinolone acetonide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, solution in single-dose container
Routes of administration	Auricular use

Dosage and administration details:

Administer the contents of one 0.25ml single dose vial twice a day to the affected ear(s) for seven days

Number of subjects in period 1	CIPRO+FLUO	CIPRO	FLUO
Started	111	112	108
Completed	106	104	89
Not completed	5	8	19
Consent withdrawn by subject	-	2	1
Physician decision	-	-	1
Lack of comunication	1	-	-
Adverse event, non-fatal	-	2	3
Lost to follow-up	2	-	4
Protocol deviation	2	-	-
Lack of efficacy	-	4	10

Baseline characteristics

Reporting groups	
Reporting group title	CIPRO+FLUO
Reporting group description: -	
Reporting group title	CIPRO
Reporting group description: -	
Reporting group title	FLUO
Reporting group description: -	

Reporting group values	CIPRO+FLUO	CIPRO	FLUO
Number of subjects	111	112	108
Age categorical Units: Subjects			
6 months to 12 years	111	112	108
Gender categorical Units: Subjects			
Female	46	43	49
Male	65	69	59

Reporting group values	Total		
Number of subjects	331		
Age categorical Units: Subjects			
6 months to 12 years	331		
Gender categorical Units: Subjects			
Female	138		
Male	193		

End points

End points reporting groups

Reporting group title	CIPRO+FLUO
Reporting group description: -	
Reporting group title	CIPRO
Reporting group description: -	
Reporting group title	FLUO
Reporting group description: -	

Primary: Time to cessation of otorrhea

End point title	Time to cessation of otorrhea
End point description:	
End point type	Primary
End point timeframe:	
During all study (22 days)	

End point values	CIPRO+FLUO	CIPRO	FLUO	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111	112	108	
Units: day				
median (confidence interval 95%)	4.94 (3.74 to 5.52)	6.83 (5.49 to 7.74)	22 (13.93 to 22)	

Statistical analyses

Statistical analysis title	Time to cessation of otorrhea

Statistical analysis description:

The time to cessation of otorrhea was calculated in days. Survival analysis was done using nonparametric
Kaplan-Meier method. Patients who did not discontinue prematurely and for whom the otorrhea still persists at the end of the study (or Day 22 if earlier) are censored at Day 22. Patients who discontinued for any reason or took rescue medication are censored at Day 22.

Comparison groups	CIPRO+FLUO v CIPRO v FLUO
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Logrank

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All the study	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13

Reporting groups	
Reporting group title	CIPRO+FLUO
Reporting group description: -	
Reporting group title	CIPRO
Reporting group description: -	
Reporting group title	FLUO
Reporting group description: -	

Serious adverse events	CIPRO+FLUO	CIPRO	FLUO
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 111 (0.00%)	0 / 112 (0.00%)	0 / 107 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	CIPRO+FLUO	CIPRO	FLUO
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 111 (2.70%)	5 / 112 (4.46%)	5 / 107 (4.67%)
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	1 / 111 (0.90%)	1 / 112 (0.89%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Tympanic membrane disorder			
subjects affected / exposed	1 / 111 (0.90%)	0 / 112 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Deafness neurosensory			
subjects affected / exposed	0 / 111 (0.00%)	1 / 112 (0.89%)	0 / 107 (0.00%)
occurrences (all)	0	1	0

Otorrhoea			
subjects affected / exposed	0 / 111 (0.00%)	1 / 112 (0.89%)	2 / 107 (1.87%)
occurrences (all)	0	1	2
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 111 (0.00%)	1 / 112 (0.89%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 111 (0.00%)	0 / 112 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Infections and infestations			
Otitis media			
subjects affected / exposed	1 / 111 (0.90%)	0 / 112 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
otitis externa candida			
subjects affected / exposed	0 / 111 (0.00%)	1 / 112 (0.89%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 112 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 March 2012	• Revised the medical monitor for Canada and the United States and added contact information for medical monitors • Increased the number of study sites and add new countries
20 June 2012	• Added a new country to the list of countries for planned study sites • Updated procedure for return of study medication

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported