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.

Estudio multicéntrico, randomizado, doble ciego para evaluar la eficacia y seguridad de Ciprofloxacino 0,3% más Fluocinolona Acetónido 0,025% solución ótica en comparación con Ciprofloxacino 0,3% solución ótica y con Fluocinolona Acetónido 0,025% solución ótica en el tratamiento de Otitis Media Aguda con Tubos de Timpanostomía en Pacientes Pediatricos

Summary

EudraCT number	2010-023238-22
Trial protocol	ES SE FI DK CZ
Global end of trial date	23 June 2014

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/10IA02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01395966
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 933946400, clinicaltrials@salvatbiotech.com
Scientific contact	Medical Director, Laboratorios SALVAT, S.A, +34 933946470, ejimenezv@salvatbiotech.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric	No

investigation plan (PIP)	
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	16 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of topical Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic
solution. The primary endpoint was to demonstrate therapeutic superiority of Ciprofloxacin plus Fluocinolone Acetonide relative to Ciprofloxacin alone and to Fluocinolone Acetonide alone for time to cessation of otorrhea in pediatric patients suffering from acute otitis media with tympanostomy tubes (AOMT).

Protection of trial subjects:
Not applicable
Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	15 July 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: 13
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	South Africa: 62
Country: Number of subjects enrolled	United States: 243
Worldwide total number of subjects	331
EEA total number of subjects	26

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)	121
Children (2-11 years)	209
Adolescents (12-17 years)	1
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 July 2011 to June 2014 in Europe (Czech Republic, Denmark, Finland, Spain and Sweden), South Africa 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.

Pre-assignment period milestones

Number of subjects started	331
Number of subjects completed	331

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	112	109	110
Completed	104	99	91
Not completed	8	10	19
Consent withdrawn by subject	1	1	3
Physician decision	-	-	2
Adverse event, non-fatal	3	3	4
early temination	-	-	1
Lost to follow-up	2	1	1
Tube absent	1	-	-
Lack of efficacy	1	4	7
Protocol deviation	-	1	1

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	112	109	110
Age categorical Units: Subjects			
6 months to 12 years	112	109	110
Gender categorical Units: Subjects			
Female	48	43	42
Male	64	66	68

Reporting group values	Total		
Number of subjects	331		
Age categorical Units: Subjects			
6 months to 12 years	331		
Gender categorical Units: Subjects			
Female	133		
Male	198		

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	112	109	110	
Units: day				
median (confidence interval 95%)	3.75 (3.04 to 4.39)	7.69 (4.78 to 11.44)	22 (7.43 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 non-parametric 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	13.0
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 / 113 (0.00%)	0 / 108 (0.00%)	0 / 106 (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	7 / 113 (6.19%)	4 / 108 (3.70%)	9 / 106 (8.49%)
Ear and labyrinth disorders			
Auricular swelling			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	0 / 106 (0.00%)
occurrences (all)	1	0	0
Ear pain			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	2 / 106 (1.89%)
occurrences (all)	1	1	2
Otorrhoea			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	0 / 106 (0.00%)
occurrences (all)	1	0	0

Ear canal erythema			
subjects affected / exposed	0 / 113 (0.00%)	0 / 108 (0.00%)	1 / 106 (0.94%)
occurrences (all)	0	0	1
Ear discomfort			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	0 / 106 (0.00%)
occurrences (all)	0	1	0
Ear haemorrhage			
subjects affected / exposed	0 / 113 (0.00%)	0 / 108 (0.00%)	1 / 106 (0.94%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Excessive granulation tissue			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	1 / 106 (0.94%)
occurrences (all)	1	0	1
Rash			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	1 / 106 (0.94%)
occurrences (all)	1	0	1
Dermatitis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	0 / 106 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 113 (0.00%)	0 / 108 (0.00%)	1 / 106 (0.94%)
occurrences (all)	0	0	1
Infections and infestations			
Otitis media			
subjects affected / exposed	2 / 113 (1.77%)	1 / 108 (0.93%)	3 / 106 (2.83%)
occurrences (all)	2	1	3
Otitis media acute			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	0 / 106 (0.00%)
occurrences (all)	1	1	0
Ear infection fungal			
subjects affected / exposed	0 / 113 (0.00%)	0 / 108 (0.00%)	1 / 106 (0.94%)
occurrences (all)	0	0	1
Otitis externa			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	0 / 106 (0.00%)
occurrences (all)	0	1	0

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
16 May 2013	Changed sponsor contact Added and revised the medical monitors in all countries

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported