Clinical trial results:
Multinational, Randomized, Double-Blind, Double-Dummy, Comparative Study to Evaluate the Efficacy and Safety of Telithromycin 25 mg/kg Given Once Daily for 5 or 10 Days Depending on Age and Previous Treatment History Versus Cefuroxime Axetil 15 mg/kg, Given Twice Daily for 10 Days, in Children With Acute Otitis Media

Summary

EudraCT number	2004-000738-34
Trial protocol	DE
Global end of trial date	20 September 2007

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	11 June 2015

Trial information

Trial identification

Sponsor protocol code	EFC6131

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00174811
WHO universal trial number (UTN)	-
Other trial identifiers	Other ID: HMR3647B/3001

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 October 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 September 2007
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the noninferiority of telithromycin with respect to cefuroxime axetil in clinical efficacy at the posttherapy/test-of-cure (TOC) visit 3 (Days 13–17) in the per protocol population (PPc population) for analysis of clinical outcome in children with acute otitis media (AOM).

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 June 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 89
Country: Number of subjects enrolled	France: 60
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Peru: 35
Country: Number of subjects enrolled	Chile: 45
Country: Number of subjects enrolled	Dominican Republic: 16
Country: Number of subjects enrolled	Guatemala: 91
Country: Number of subjects enrolled	Mexico: 109
Country: Number of subjects enrolled	Costa Rica: 158
Country: Number of subjects enrolled	Panama: 30
Worldwide total number of subjects	639
EEA total number of subjects	61

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)	387
Children (2-11 years)	252
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 43 sites in 15 countries. A total of 648 subjects were screened between 27 June 2005 and 7 June 2006.

Pre-assignment

Screening details:

Of 648 screened subjects, 639 subjects were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Telithromycin

Arm description:

Telithromycin for 10 days for high risk subjects (=<24 months of age who received antibacterials for Acute Otitis Media within the past 30 days) and 5 days for all other subjects + placebo for 5 additional days.

Arm type	Experimental
Investigational medicinal product name	Telithromycin
Investigational medicinal product code	HMR3647B
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

25 mg/kg once daily.

Investigational medicinal product name	Placebo (for Cefuroxime axetil)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to cefuroxime axetil 15 mg/kg twice daily.

Arm title	Cefuroxime axetil

Arm description:

Cefuroxime axetil for 10 days - Depending on local health autority guideline.

Arm type	Active comparator
Investigational medicinal product name	Cefuroxime axetil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

15 mg/kg twice daily.

Investigational medicinal product name	Placebo (for Telithromycin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to telithromycin 25 mg/kg once daily.

Number of subjects in period 1	Telithromycin	Cefuroxime axetil
Started	321	318
Treated	317	316
Completed	284	289
Not completed	37	29
Consent withdrawn by subject	1	-
Randomized but not treated	4	2
Adverse event	12	6
Unspecified	9	11
Lost to follow-up	1	2
Lack of efficacy	10	8

Baseline characteristics

Reporting groups	
Reporting group title	Telithromycin
Reporting group description:	
Telithromycin for 10 days for high risk subjects (=<24 months of age who received antibacterials for Acute Otitis Media within the past 30 days) and 5 days for all other subjects + placebo for 5 additional days.	
Reporting group title	Cefuroxime axetil
Reporting group description:	
Cefuroxime axetil for 10 days - Depending on local health autority guideline.	

Reporting group values	Telithromycin	Cefuroxime axetil	Total
Number of subjects	321	318	639
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	193	193	386
Children (2-11 years)	124	123	247
Not treated	4	2	6
Gender categorical Units: Subjects			
Female	149	130	279
Male	168	186	354
Not available	4	2	6

End points

End points reporting groups

Reporting group title	Telithromycin
Reporting group description:	
Telithromycin for 10 days for high risk subjects (=<24 months of age who received antibacterials for Acute Otitis Media within the past 30 days) and 5 days for all other subjects + placebo for 5 additional days.	
Reporting group title	Cefuroxime axetil
Reporting group description:	
Cefuroxime axetil for 10 days - Depending on local health autority guideline.	

Primary: Percentage of Subjects According to Clinical Outcome in Clinically Evaluable Per-Protocol (PPc) Population

End point title	Percentage of Subjects According to Clinical Outcome in Clinically Evaluable Per-Protocol (PPc) Population[1]
End point description:	
Clinical cure was defined as absence of acute otitis media (AOM)-related fever, improvement in tympanic membrane and no need for surgical procedure/antibacterial administration for AOM or its complications. A subject was considered a clinical failure if a surgical procedure was performed. PPc population is defined as subjects randomized and treated and excluding for major protocol deviations, or classified as clinically indeterminate.	
End point type	Primary
End point timeframe:	
At posttherapy (Day 13-17)	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: This study was terminated early (randomization of 639 subjects / 900 planned) the type II error was not controlled as planned and only descriptive statistics were generated.	

End point values	Telithromycin	Cefuroxime axetil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	259		
Units: percentage of subjects				
number (not applicable)				
Cure	90	92.7		
Failure	10	7.3		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects According to Clinical Outcome in Modified Intent To Treat (mITT) Population

End point title	Percentage of Subjects According to Clinical Outcome in Modified Intent To Treat (mITT) Population[2]
End point description:	
mITT population is defined as all randomized and treated subjects . Protocol deviations were not	

considered and indeterminate clinical outcome were considered as failure.

End point type	Primary

End point timeframe:

At posttherapy (Day 13-17)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was terminated early (randomization of 639 subjects / 900 planned) the type II error was not controlled as planned and only descriptive statistics were generated.

End point values	Telithromycin	Cefuroxime axetil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: percentage of subjects				
number (not applicable)				
Cure	80.2	79.7		
Failure	19.8	20.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Symptom Resolution in PPc Population

End point title	Time to Symptom Resolution in PPc Population

End point description:

Analysis not performed due to early termination.

End point type	Secondary

End point timeframe:

Baseline up to day 10

End point values	Telithromycin	Cefuroxime axetil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: subjects				

Notes:

[3] - The number of subjects analysed were zero for this outcome measure.

[4] - The number of subjects analysed were zero for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Symptom Resolution in mITT Population

End point title	Time to Symptom Resolution in mITT Population

End point description:

The time to symptom resolution was defined as mentioned in outcome measure 3. Analysis was carried out on mITT population.

End point type	Secondary

End point timeframe:

Baseline up to day 10

End point values	Telithromycin	Cefuroxime axetil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: days				
median (inter-quartile range (Q1-Q3))	2.5 (1 to 5.5)	3 (1 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events of special interest

End point title	Number of subjects with adverse events of special interest

End point description:

Analysis was carried out on safety population defined as all randomized and treated subjects. One subject was randomized to receive telithromycin, but received cefuroxime and is included in the cefuroxime safety population.

End point type	Secondary

End point timeframe:

Day 1 up to 14 days after the last intake of medication, or Visit 4

End point values	Telithromycin	Cefuroxime axetil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317	316		
Units: subjects				
Cardiac events	0	0		
Hepatic events	4	5		
Visual disturbances	1	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (day 24 to 28) regardless of seriousness or relationship to investigational product. Analysis was performed on safety population.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (from the first dose of study medication and up to 7 days after the last dose of study medication or, up to 17 days after the first dose of study medication, whichever is later).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Telithromycin

Reporting group description:

Telithromycin for 10 days for high risk subjects (=<24 months of age who received antibacterials for Acute Otitis Media within the past 30 days) and 5 days for all other subjects + placebo for 5 additional days.

Reporting group title	Cefuroxime axetil

Reporting group description:

Cefuroxime axetil for 10 days - Depending on local health autority guideline.

Serious adverse events	Telithromycin	Cefuroxime axetil	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 317 (2.21%)	5 / 316 (1.58%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 317 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 317 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Bilirubin Increased			

subjects affected / exposed	1 / 317 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Enzyme Increased			
subjects affected / exposed	1 / 317 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Face Oedema			
subjects affected / exposed	1 / 317 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 317 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 317 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Staring			
subjects affected / exposed	1 / 317 (0.32%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 317 (0.00%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis Media			

subjects affected / exposed	1 / 317 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis Media Acute			
subjects affected / exposed	1 / 317 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 317 (0.32%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Infection			
subjects affected / exposed	1 / 317 (0.32%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Telithromycin	Cefuroxime axetil	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 317 (18.61%)	48 / 316 (15.19%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	37 / 317 (11.67%)	33 / 316 (10.44%)	
occurrences (all)	39	34	
Vomiting			
subjects affected / exposed	29 / 317 (9.15%)	22 / 316 (6.96%)	
occurrences (all)	36	25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2005	- Inclusion criteria were modified to include otalgia or ear tugging (interfering with normal activity) for more accurate diagnosis of AOM. - Exclusion criteria were expanded to exclude subjects with abnormalities of the eye. - Performance of the visual assessment at any unscheduled visits prior to Visit 3 was specified. - The tympanometry procedure was removed from the protocol.
10 March 2006	- One inclusion criterion was corrected from <59 months of age to <60 months of age as the upper limit of subject age. - Contact information for the study managers was updated. - Paracentesis was included as an authorized procedure (in addition to tympanocentesis) to be performed by the Investigators according to their usual practice. - Performance of Gram staining was recommended any time an middle ear fluid (MEF) sample was collected. - Fever was defined as a minimum level of body temperature of >38° Celsius for baseline evaluation. - Instructions were added for the visual acuity results to be reported by the site Investigator in the case report form (CRF). - Text was modified to cover cases of assignment of more than 1 investigational product lot number per subject.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
27 June 2006	In June 2006, the Sponsor voluntarily paused enrollment in pediatric clinical trials with no subsequent recruitment of subjects. On 20 September 2007, the Sponsor informed the study sites that the trial was terminated.	-

Notes:

Limitations and caveats

None reported