Clinical trial results:
Multinational, Randomized, Double-Blind, Double-Dummy, Comparative Study to Evaluate the Efficacy and Safety of 5 Days of Telithromycin Oral Suspension 25 mg/kg, Given Once Daily, Versus 5 Days of Azithromycin Oral Suspension, Given Once as 10 Mg/Kg Followed by 5 Mg/Kg Given Once Daily for 4 Days, in Children With Acute Otitis Media

Summary

EudraCT number	2014-004637-47
Trial protocol	Outside EU/EEA
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	03 July 2015

Trial information

Trial identification

Sponsor protocol code	EFC6132, HMR3647B/3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00315003
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi U.S Services Inc.
Sponsor organisation address	55 Corporate Drive Bridgewater, New Jersey, United States, 08807
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	22 September 2008
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:

The primary objective of this study was to assess the efficacy of telithromycin versus azithromycin in children with acute otitis media (AOM) with regard to superiority of time to symptom resolution in the modified intent-to-treat (mITT) population and noninferiority of clinical outcome at the test-of-cure (TOC) visit (Days 13 to 17) in the per protocol (PPc) population.

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	30 January 2006
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: 321
Worldwide total number of subjects	321
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	49

Infants and toddlers (28 days-23 months)	103
Children (2-11 years)	169
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 27 sites in the United States. A total of 346 subjects were screened between 30 January 2006 and 8 June 2006.

Pre-assignment

Screening details:

Of 346 screened subjects, 321 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 5 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 (not to exceed 1200 mg/day).

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

Dosage and administration details:

Placebo matched to azithromycin for 5 days.

Arm title	Azithromycin

Arm description:

Azithromycin for 5 days.

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

Dosage and administration details:

10 mg/kg once on Day 1 followed by 5 mg/kg on Days 2-5 (not to exceed 500 mg on Day 1 and 250 mg/day on Days 2-5).

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 for 5 days.

Number of subjects in period 1[1]	Telithromycin	Azithromycin
Started	156	163
Treated	157	161
Completed	141	155
Not completed	17	8
Randomized but not treated	1	2
Adverse event	2	2
Subject did not wish to continue	3	-
Unspecified	6	-
Lost to follow-up	1	2
Lack of efficacy	4	2
Joined	2	0
Transferred in from other group/arm	2	-

Notes:

[1] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.
Justification: Two subjects were initially randomized to Azithromycin group but actually received Telithromycin. Hence these two subjects were considered in Telithromycin group (Transferred in from other group/arm).

Baseline characteristics

Reporting groups	
Reporting group title	Telithromycin
Reporting group description: Telithromycin for 5 days.	
Reporting group title	Azithromycin
Reporting group description: Azithromycin for 5 days.	

Reporting group values	Telithromycin	Azithromycin	Total
Number of subjects	158	163	321
Age categorical Units: Subjects			
Newborns (0-27 days)	28	21	49
Infants and toddlers (28 days-23 months)	45	58	103
Children (2-11 years)	85	84	169
Gender categorical Units: Subjects			
Female	70	70	140
Male	87	93	180
Not available	1	0	1

End points

End points reporting groups

Reporting group title	Telithromycin
Reporting group description: Telithromycin for 5 days.	
Reporting group title	Azithromycin
Reporting group description: Azithromycin for 5 days.	

Primary: Percentage of Subjects According to Clinical Outcome in Clinically Evaluable Per

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 321 subjects / 1500 planned) the type II error was not controlled as planned and only descriptive statistics were generated.

End point values	Telithromycin	Azithromycin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	139		
Units: percentage of subjects				
number (not applicable)				
Cure	78.5	82.7		
Failure	21.5	17.3		

Statistical analyses

No statistical analyses for this end point

Primary: Time to Symptom Resolution in Modified Intent To Treat (mITT) Population

End point title	Time to Symptom Resolution in Modified Intent To Treat (mITT) Population[2]

End point description:

The definition of resolution of symptoms was based on fever and the 4 components: ear pain, appetite, behavior, and nighttime sleep. mITT population was defined as all randomized and treated subjects. Protocol deviations were not considered and indeterminate clinical outcome were considered as failure. One subject in the azithromycin group was excluded in mITT population due to lack of confirmation of

AOM.

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 321 subjects / 1500 planned) the type II error was not controlled as planned and only descriptive statistics were generated.

End point values	Telithromycin	Azithromycin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	162		
Units: days				
median (inter-quartile range (Q1-Q3))	3 (1.5 to 5)	2.75 (1.5 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 .Two subjects were randomized to receive azithromycin, but received telithromycin and were included included in the telithromycin safety population.

End point type	Secondary

End point timeframe:

Study duration up to 28 Days

End point values	Telithromycin	Azithromycin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	161		
Units: subjects				
Cardiac events	0	0		
Hepatic events	0	0		
Visual disturbances	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects According to Clinical Outcome in mITT Population

End point title	Percentage of Subjects According to Clinical Outcome in mITT

	Population

End point description:

Clinical outcome is defined in first primary end point section. Analysis was carried out on mITT population.

End point type	Secondary

End point timeframe:

At posttherapy (Day 13-17)

End point values	Telithromycin	Azithromycin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	162		
Units: percentage of subjects				
number (not applicable)				
Cure	69	74.7		
Failure	31	25.3		

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 24-28) 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' (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	10.1

Reporting groups

Reporting group title	Azithromycin
Reporting group description:	
Azithromycin for 5 days.	
Reporting group title	Telithromycin
Reporting group description:	
Telithromycin for 5 days.	

Serious adverse events	Azithromycin	Telithromycin	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 161 (0.00%)	1 / 157 (0.64%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Infections and infestations			
Viral Infection			
subjects affected / exposed	0 / 161 (0.00%)	1 / 157 (0.64%)	
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: 5 %

Non-serious adverse events	Azithromycin	Telithromycin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 161 (8.70%)	18 / 157 (11.46%)	
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	8 / 161 (4.97%) 9	10 / 157 (6.37%) 10	
Infections and infestations Otitis Media subjects affected / exposed occurrences (all)	8 / 161 (4.97%) 9	9 / 157 (5.73%) 9	

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? 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