Clinical trial results:
An Open Label, Randomized, Single Dose, Parallel Arm Study To Determine Pharmacokinetics Of Azithromycin Following Oral Administration Of Immediate-Release (IR) Or Extended-Release (ER) Formulation In Pediatric Subjects With Acute Otitis Media (AOM)

Summary

EudraCT number	2014-004164-38
Trial protocol	Outside EU/EEA
Global end of trial date	18 February 2009

Results information

Result version number	v1 (current)
This version publication date	30 May 2016
First version publication date	15 July 2015

Trial information

Trial identification

Sponsor protocol code	A0661190

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00796224
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc, 001 800-718-1021, ClinicalTrials.govCallCenter@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc, 001 800-718-1021, ClinicalTrials.govCallCenter@pfizer.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	23 July 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 February 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the pharmacokinetics of azithromycin following a single dose of either 30 milligram per kilogram (mg/kg) IR or 60 mg/kg ER formulation in pediatric subjects with AOM.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 December 2008
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	Costa Rica: 38
Worldwide total number of subjects	38
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)	0
Infants and toddlers (28 days-23 months)	19
Children (2-11 years)	19
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: -

Pre-assignment

Screening details:

Study started on 23 December 2008 and completed on 18 February 2009 in Costa Rica. Subjects were screened within 48 hours of dosing.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	60 mg/kg Azithromycin Extended-release (ER)

Arm description:

Subjects received Azithromycin ER single oral dose on Day 1.

Arm type	Experimental
Investigational medicinal product name	Azithromycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received 60 mg/kg Azithromycin ER single oral dose on Day 1.

Arm title	30 mg/kg Azithromycin Immediate-release (IR)

Arm description:

Subjects received Azithromycin IR single oral dose on Day 1.

Arm type	Reference
Investigational medicinal product name	Azithromycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received 30 mg/kg Azithromycin IR single oral dose on Day 1.

Number of subjects in period 1	60 mg/kg Azithromycin Extended-release (ER)	30 mg/kg Azithromycin Immediate-release (IR)
Started	19	19
Completed	18	18
Not completed	1	1
Adverse event	1	-

Protocol Violation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	60 mg/kg Azithromycin Extended-release (ER)
Reporting group description: Subjects received Azithromycin ER single oral dose on Day 1.	
Reporting group title	30 mg/kg Azithromycin Immediate-release (IR)
Reporting group description: Subjects received Azithromycin IR single oral dose on Day 1.	

Reporting group values	60 mg/kg Azithromycin Extended-release (ER)	30 mg/kg Azithromycin Immediate-release (IR)	Total
Number of subjects	19	19	38
Age categorical Units: Subjects			
1 month to less than (<) 2 years	13	6	19
2 years to <12 years	6	13	19
Gender categorical Units: Subjects			
Female	8	7	15
Male	11	12	23

End points

End points reporting groups

Reporting group title	60 mg/kg Azithromycin Extended-release (ER)
Reporting group description: Subjects received Azithromycin ER single oral dose on Day 1.	
Reporting group title	30 mg/kg Azithromycin Immediate-release (IR)
Reporting group description: Subjects received Azithromycin IR single oral dose on Day 1.	

Primary: Area Under the Curve From Time Zero to 72 Hours (AUC72Hours)

End point title	Area Under the Curve From Time Zero to 72 Hours (AUC72Hours)
End point description: AUC72 = Area under the plasma concentration versus time curve from time zero (pre-dose) to 72 hours. All subjects randomized and treated who had at least 1 of the pharmacokinetic parameters of primary interest.	
End point type	Primary
End point timeframe: Pre-dose/ 0 to 72 hours	

End point values	60 mg/kg Azithromycin Extended-release (ER)	30 mg/kg Azithromycin Immediate-release (IR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: nanogram*hour per milliliter (ng*hr/mL)				
arithmetic mean (standard deviation)	12173.02 (± 6305.032)	7950.949 (± 4759.301)		

Statistical analyses

Statistical analysis title	Analysis of AUC72
Statistical analysis description: Test (60 mg/kg Azithromycin ER)/ Reference (30 mg/kg Azithromycin IR). Analysis of variance (ANOVA) method was used for analysis.	
Comparison groups	60 mg/kg Azithromycin Extended-release (ER) v 30 mg/kg Azithromycin Immediate-release (IR)

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Ratio of Geometric Means
Point estimate	157.98
Confidence interval	
level	90 %
sides	2-sided
lower limit	98.87
upper limit	252.44

Secondary: Area Under the Curve From Time Zero to Extrapolated Infinite Time (AUC Inf)

End point title	Area Under the Curve From Time Zero to Extrapolated Infinite Time (AUC Inf)

End point description:

AUCinf = AUClast + (Clast* divided by kel), where AUClast is calculated by Linear-Log trapezoidal method, Clast* is the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis and kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. All subjects randomized and treated who had at least 1 of the pharmacokinetic parameters of primary interest.

End point type	Secondary

End point timeframe:

Pre-dose /0, 1, 2, 3, 4, 8, 24, 48, 72 hours post-dose

End point values	60 mg/kg Azithromycin Extended-release (ER)	30 mg/kg Azithromycin Immediate-release (IR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: ng*hr/mL				
arithmetic mean (standard deviation)	15536.19 (± 9310.399)	9645.63 (± 6062.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Azithromycin

End point title	Maximum Observed Plasma Concentration (Cmax) of Azithromycin

End point description:

All subjects randomized and treated who had at least 1 of the pharmacokinetic parameters of primary interest.

End point type	Secondary

End point timeframe:

Predose/0, 1, 2, 3, 4, 8, 24, 48, 72 hours

End point values	60 mg/kg Azithromycin Extended-release (ER)	30 mg/kg Azithromycin Immediate-release (IR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: ng/mL				
arithmetic mean (standard deviation)	774.75 (± 477.989)	901.644 (± 600.682)		

Statistical analyses

Statistical analysis title	Analysis of Cmax
Statistical analysis description:	
ANOVA method was used for analysis.	
Comparison groups	30 mg/kg Azithromycin Immediate-release (IR) v 60 mg/kg Azithromycin Extended-release (ER)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Ratio of Geometric Means
Point estimate	91.63
Confidence interval	
level	90 %
sides	2-sided
lower limit	56.21
upper limit	149.38

Secondary: Time to Reach Maximum Observed Plasma Concentration (Tmax) and Plasma Decay Half Life (t1/2) of Azithromycin

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax) and Plasma Decay Half Life (t1/2) of Azithromycin
End point description:	
Plasma decay half-life is the time measured for the plasma concentration to decrease by one-half. All subjects randomized and treated who had at least 1 of the pharmacokinetic parameters of primary interest.	
End point type	Secondary
End point timeframe:	
Pre dose/0, 1, 2, 3, 4, 8, 24, 48, 72 hours post-dose	

End point values	60 mg/kg Azithromycin Extended-release (ER)	30 mg/kg Azithromycin Immediate-release (IR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: hour				
median (full range (min-max))				
Tmax	3 (2 to 8)	2 (1 to 4.05)		
t1/2	30.303 (15 to 52.2)	28.959 (10.4 to 49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentrations of Azithromycin ER (Test) and Azithromycin IR (Reference)

End point title	Serum Concentrations of Azithromycin ER (Test) and Azithromycin IR (Reference)

End point description:

All subjects randomized and treated who had at least 1 of the pharmacokinetic parameters of primary interest.

End point type	Secondary

End point timeframe:

1, 2, 3, 4, 8, 24, 48, 72 hours

End point values	60 mg/kg Azithromycin Extended-release (ER)	30 mg/kg Azithromycin Immediate-release (IR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: ng/mL				
number (not applicable)				
Serum Concentration 1 hour post dose	99.96	152.75		
Serum Concentration 2 hour postdose	293.14	579.72		
Serum concentration 3 hour postdose	381.96	381.69		
Serum Concentration 4 hour postdose	441.79	267.86		
Serum Concentration 8 hour postdose	244.75	140.33		
Serum Concentration 24 hour postdose	142.41	82.31		
Serum Concentration 48 hour postdose	94.79	50.06		
Serum Concentration 72 hour postdose	56.03	30.6		

Statistical analyses

Statistical analysis title	Serum Concentration 1 hour postdose
Statistical analysis description:	
Ratio (percent) = Test/Reference multiplied by 100. ANOVA method was used for analysis.	
Comparison groups	60 mg/kg Azithromycin Extended-release (ER) v 30 mg/kg Azithromycin Immediate-release (IR)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Ratio of Geometric means (percent)
Point estimate	65.44
Confidence interval	
level	90 %
sides	2-sided
lower limit	23.56
upper limit	181.77

Statistical analysis title	Serum Concentration 2 hour postdose
Statistical analysis description:	
Ratio (percent) = Test/Reference multiplied by 100. ANOVA method was used for analysis.	
Comparison groups	60 mg/kg Azithromycin Extended-release (ER) v 30 mg/kg Azithromycin Immediate-release (IR)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Ratio of Geometric means (percent)
Point estimate	50.57
Confidence interval	
level	90 %
sides	2-sided
lower limit	25.24
upper limit	101.3

Statistical analysis title	Serum Concentration 3 hour postdose
Statistical analysis description:	
Ratio (percent) = Test/Reference multiplied by 100. ANOVA method was used for analysis.	
Comparison groups	60 mg/kg Azithromycin Extended-release (ER) v 30 mg/kg Azithromycin Immediate-release (IR)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Ratio of Geometric means (percent)
Point estimate	100.07
Confidence interval	
level	90 %
sides	2-sided
lower limit	57.91
upper limit	172.92

Statistical analysis title	Serum Concentration 4 hour postdose
Statistical analysis description:	
Ratio (percent) = Test/Reference multiplied by 100. ANOVA method was used for analysis.	
Comparison groups	60 mg/kg Azithromycin Extended-release (ER) v 30 mg/kg Azithromycin Immediate-release (IR)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Ratio of Geometric means (percent)
Point estimate	164.93
Confidence interval	
level	90 %
sides	2-sided
lower limit	103.78
upper limit	262.12

Statistical analysis title	Serum Concentration 8 hour postdose
Statistical analysis description:	
Ratio (percent) = Test/Reference multiplied by 100. ANOVA method was used for analysis.	
Comparison groups	60 mg/kg Azithromycin Extended-release (ER) v 30 mg/kg Azithromycin Immediate-release (IR)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Ratio of Geometric means (percent)
Point estimate	174.41
Confidence interval	
level	90 %
sides	2-sided
lower limit	110.07
upper limit	276.36

Statistical analysis title	Serum Concentration 24 hour postdose
Statistical analysis description:	
Ratio (percent) = Test/Reference multiplied by 100. ANOVA method was used for analysis.	
Comparison groups	60 mg/kg Azithromycin Extended-release (ER) v 30 mg/kg Azithromycin Immediate-release (IR)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Ratio of Geometric means (percent)
Point estimate	173.01

Confidence interval	
level	90 %
sides	2-sided
lower limit	111.45
upper limit	268.55

Statistical analysis title	Serum Concentration 48 hour postdose
Statistical analysis description:	
Ratio (percent) = Test/Reference multiplied by 100. ANOVA method was used for analysis.	
Comparison groups	60 mg/kg Azithromycin Extended-release (ER) v 30 mg/kg Azithromycin Immediate-release (IR)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Ratio of Geometric means (percent)
Point estimate	189.35
Confidence interval	
level	90 %
sides	2-sided
lower limit	129.76
upper limit	276.3

Statistical analysis title	Serum Concentration 72 hour postdose
Statistical analysis description:	
Ratio (percent) = Test/Reference multiplied by 100. ANOVA method was used for analysis.	
Comparison groups	60 mg/kg Azithromycin Extended-release (ER) v 30 mg/kg Azithromycin Immediate-release (IR)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Ratio of Geometric means (percent)
Point estimate	183.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	124.61
upper limit	269.14

Secondary: Number of Subjects With a Clinical Response

End point title	Number of Subjects With a Clinical Response

End point description:

Clinical response was assessed between Days 7 and 10, or when subjects discontinued the study prematurely (if applicable). Response was assessed by the investigator as cure or failure. Cure = Clinical signs and symptoms related to the acute illness have resolved, or clinical improvement is such that no additional therapy is necessary. Failure = One or more of the following: Signs and symptoms related to

the acute illness have persisted or worsened and additional therapy is necessary; New clinical signs and symptoms of acute illness have developed and additional therapy is necessary. Any worsening of existing signs and symptoms, or new signs and symptoms, were documented as adverse events.

End point type	Secondary

End point timeframe:

Day 7, 8, 9 or 10

End point values	60 mg/kg Azithromycin Extended-release (ER)	30 mg/kg Azithromycin Immediate-release (IR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: subjects				
Cure	18	16		
Failure	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events (AEs) and Serious AEs (SAEs)

End point title	Adverse Events (AEs) and Serious AEs (SAEs)

End point description:

All observed or volunteered AEs and SAEs regardless of treatment group or suspected causal relationship to the investigational product(s) was reported. All subjects who received at least 1 dose of study medication were included in the safety analyses.

End point type	Secondary

End point timeframe:

Baseline up to 35 days of last study treatment

End point values	60 mg/kg Azithromycin Extended-release (ER)	30 mg/kg Azithromycin Immediate-release (IR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: subjects				
AEs	4	5		
SAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline till 35 days after last study treatment	
Adverse event reporting additional description:	
EU BR specific AE tables were generated separately as per EU format. Latest coding dictionary has been used for EU BR tables.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	60 mg/kg Azithromycin ER
Reporting group description:	
Subjects received 60 mg/kg Azithromycin ER single oral dose on Day 1.	
Reporting group title	30 mg/kg Azithromycin IR
Reporting group description:	
Subjects received 30 mg/kg Azithromycin IR single oral dose on Day 1.	

Serious adverse events	60 mg/kg Azithromycin ER	30 mg/kg Azithromycin IR	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	60 mg/kg Azithromycin ER	30 mg/kg Azithromycin IR	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 19 (21.05%)	5 / 19 (26.32%)	
General disorders and administration site conditions			
Treatment failure			
subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	3 / 19 (15.79%)	1 / 19 (5.26%)	
occurrences (all)	3	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	

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