



Clinical trial results:

An open label study to determine the pharmacokinetic profiles of amoxicillin and clavulanate in adolescent patients weighing at least 40 kg and no more than 16 years of age receiving AUGMENTIN™XR (amoxicillin 2000 mg/clavulanate 125 mg) orally twice daily for 10 days.

Summary

EudraCT number	2015-004874-13
Trial protocol	Outside EU/EEA
Global end of trial date	02 April 2007

Results information

Result version number	v1 (current)
This version publication date	30 November 2016
First version publication date	30 November 2016

Trial information

Trial identification

Sponsor protocol code	AUG102821
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	13 July 2007
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 April 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To obtain pharmacokinetic data on amoxicillin/clavulanate and time above MIC (T>MIC) for amoxicillin when AUGMENTIN XR (amoxicillin 2000 mg/clavulanate 125 mg) is given orally twice daily to adolescents weighing at least 40 kg.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 January 2006
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	United States: 44
Worldwide total number of subjects	44
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)	0
Children (2-11 years)	15
Adolescents (12-17 years)	29
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible participants received amoxicillin 2000 milligrams (mg)/clavulanate 125 mg tablets twice daily for 10 days. The study consisted of a follow-up visit (within 3 days of the final dose).

Pre-assignment

Screening details:

Adolescent participants with acute bacterial sinusitis, who weigh at least 40 kilograms (kg) and are no more than 16 years old were enrolled into the study. A total of 52 participants who met eligibility criteria were screened, and 44 participants were randomized.

Period 1

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

Arms

Arm title	Amoxicillin 2000 mg/Clavulanate 125 mg BD
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Arm description:

Participants received 2 tablets of combination product prolonged release amoxicillin 1000 mg/clavulanate 62.5 mg twice daily (BD) orally with food for 10 days.

Arm type	Experimental
Investigational medicinal product name	Amoxicillin 1000 mg/clavulanate 62.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two tablets (approximately every 12 hours apart) twice daily with food were administered for 10-days.

Number of subjects in period 1	Amoxicillin 2000 mg/Clavulanate 125 mg BD
Started	44
Completed	42
Not completed	2
Consent withdrawn by subject	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Overall study
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Reporting group description:

Overall study

Reporting group values	Overall study	Total	
Number of subjects	44	44	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	12.2		
standard deviation	± 2.2	-	
Gender categorical			
Units:			
Female	13	13	
Male	31	31	
Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Units: Subjects			
African American/African Heritage	4	4	
American Indian or Alaska Native	2	2	
White - Arabic/North African heritage	1	1	
White - White/Caucasian/European heritage	37	37	

End points

End points reporting groups

Reporting group title	Amoxicillin 2000 mg/Clavulanate 125 mg BD
Reporting group description: Participants received 2 tablets of combination product prolonged release amoxicillin 1000 mg/clavulanate 62.5 mg twice daily (BD) orally with food for 10 days.	

Primary: Time (percentage) above the minimum inhibitory concentration (T>MIC) for amoxicillin MIC of 2 microgram/milliliter (µg/mL) and 4 µg/mL/ over the 12 hour dosing interval

End point title	Time (percentage) above the minimum inhibitory concentration (T>MIC) for amoxicillin MIC of 2 microgram/milliliter (µg/mL) and 4 µg/mL/ over the 12 hour dosing interval ^[1]
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End point description:

MIC is defined as the lowest concentration of antimicrobial that prevents visible growth of an organism. T>MIC was calculated for an amoxicillin MIC of 2 µg/mL (T>MIC2)) and 4 µg/mL (T>MIC4). Blood samples for pharmacokinetic (PK) analyses of amoxicillin were collected during one dosing interval (i.e., 12-hour period) after administration of medication on any of the 10 days in the dosing period. PK Parameter Population is defined as all participants in the PK Concentration Population (all participants for whom PK data had been collected for any dosing day and analyzed) who had provided PK parameters.

End point type	Primary
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End point timeframe:

Predose, and 0.5, 1, 1.5, 2, 4, 5, 6, 7, 8, 10 and 12 hours post-dose, during one of the dosing interval in any of the 10-day treatment period

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: There are no statistical data to report.

End point values	Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Subject group type	Reporting group			
Number of subjects analysed	24 ^[2]			
Units: Percentage				
geometric mean (confidence interval 95%)				
T>MIC2	77.2 (69.4 to 84.92)			
T>MIC4	50.1 (43.21 to 57.01)			

Notes:

[2] - PK Parameter Population

Statistical analyses

No statistical analyses for this end point

Primary: Time (hours) above the minimum inhibitory concentration (T>MIC) for amoxicillin MIC of 2 microgram/milliliter (µg/mL) and 4 µg/mL/ over the 12 hour dosing interval

End point title	Time (hours) above the minimum inhibitory concentration (T>MIC) for amoxicillin MIC of 2 microgram/milliliter (µg/mL) and 4 µg/mL/ over the 12 hour dosing interval ^[3]
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End point description:

MIC is defined as the lowest concentration of antimicrobial that prevents visible growth of an organism. Blood samples PK analyses of amoxicillin were collected during one dosing interval (i.e., 12-hour period) after administration of medication on any of the 10 days in the dosing period. The mean time above MIC (T>MIC) for amoxicillin MIC of 2 µg/mL and 4 µg/mL was calculated.

End point type	Primary
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End point timeframe:

Predose, and 0.5, 1, 1.5, 2, 4, 5, 6, 7, 8, 10 and 12 hours post-dose, during one of the dosing interval in any of the 10-day treatment period

Notes:

[3] - 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: There are no statistical data to report.

End point values	Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Subject group type	Reporting group			
Number of subjects analysed	24 ^[4]			
Units: Hours				
geometric mean (confidence interval 95%)				
T>MIC2	9.26 (8.33 to 10.19)			
T>MIC4	6.01 (5.19 to 6.84)			

Notes:

[4] - PK Parameter Population

Statistical analyses

No statistical analyses for this end point

Primary: Maximum plasma drug concentration (Cmax) for amoxicillin and clavulanate

End point title	Maximum plasma drug concentration (Cmax) for amoxicillin and clavulanate ^[5]
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End point description:

Maximum plasma drug concentration (Cmax) for amoxicillin and clavulanate was analyzed. Blood samples for PK analyses of amoxicillin and clavulanate were collected during one dosing interval (i.e 12-hour period) after administration of medication on any of the 10 days in the dosing period. Only those participants available at the indicated time points were assessed (represented by n=X in the category titles).

End point type	Primary
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End point timeframe:

Predose, and 0.5, 1, 1.5, 2, 4, 5, 6, 7, 8, 10 and 12 hours post-dose, during one of the dosing interval in any of the 10-day treatment period

Notes:

[5] - 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: There are no statistical data to report.

End point values	Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Subject group type	Reporting group			
Number of subjects analysed	24 ^[6]			
Units: Micrograms per milliliter				
geometric mean (confidence interval 95%)				
Cmax, Amoxicillin, n=24	10.5 (9.37 to 11.86)			
Cmax, Clavulanate, n=23	1.02 (0.808 to 1.276)			

Notes:

[6] - PK Concentration Population

Statistical analyses

No statistical analyses for this end point

Primary: Apparent terminal phase half-life (T1/2) for amoxicillin and clavulanate

End point title	Apparent terminal phase half-life (T1/2) for amoxicillin and clavulanate ^[7]
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End point description:

Apparent terminal phase half life (T1/2) for amoxicillin and clavulanate was analyzed. Blood samples for PK analyses of amoxicillin and clavulanate were collected during one dosing interval (i.e 12-hour period) after administration of medication on any of the 10 days in the dosing period. Only those participants available at the indicated time points were assessed (represented by n=X in the category titles).

End point type	Primary
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End point timeframe:

Predose, and 0.5, 1, 1.5, 2, 4, 5, 6, 7, 8, 10 and 12 hours post-dose, during one of the dosing interval in any of the 10-day treatment period

Notes:

[7] - 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: There are no statistical data to report.

End point values	Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Subject group type	Reporting group			
Number of subjects analysed	24 ^[8]			
Units: Hours				
geometric mean (confidence interval 95%)				
Amoxicillin, n=18	2.71 (1.95 to 3.75)			
Category title 2. Clavulanate, n=17	0.93 (0.86 to 1)			

Notes:

[8] - PK Concentration Population

Statistical analyses

No statistical analyses for this end point

Primary: Time to reach maximum observed concentration (Tmax) for amoxicillin and clavulanate

End point title	Time to reach maximum observed concentration (Tmax) for amoxicillin and clavulanate ^[9]
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End point description:

Time to reach maximum observed concentration (Tmax) for amoxicillin and clavulanate was analyzed. Blood samples for PK analyses of amoxicillin and clavulanate were collected during one dosing interval (i.e 12-hour period) after administration of medication on any of the 10 days in the dosing period. Only those participants available at the indicated time points were assessed (represented by n=X in the category titles).

End point type	Primary
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End point timeframe:

Predose, and 0.5, 1, 1.5, 2, 4, 5, 6, 7, 8, 10 and 12 hours post-dose, during one of the dosing interval in any of the 10-day treatment period

Notes:

[9] - 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: There are no statistical data to report.

End point values	Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Subject group type	Reporting group			
Number of subjects analysed	24 ^[10]			
Units: Hours				
median (full range (min-max))				
Amoxicillin, n=24	2 (1 to 5)			
Clavulanate, n=23	2 (1 to 4)			

Notes:

[10] - PK Concentration Population

Statistical analyses

No statistical analyses for this end point

Primary: Area under the plasma concentration-time curve over the dosing interval on multiple dosing AUC(0-tau) of amoxicillin and clavulanate.

End point title	Area under the plasma concentration-time curve over the dosing interval on multiple dosing AUC(0-tau) of amoxicillin and clavulanate. ^[11]
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End point description:

Area under the plasma concentration – time curve from time zero to the time of last detectable concentration AUC (0-tau) for amoxicillin and clavulanate was analyzed. Blood samples for PK analyses of amoxicillin and clavulanate were collected during one dosing interval (i.e 12-hour period) after administration of medication on any of the 10 days in the dosing period. Only those participants available at the indicated time points were assessed (represented by n=X in the category titles).

End point type	Primary
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End point timeframe:

Predose, and 0.5, 1, 1.5, 2, 4, 5, 6, 7, 8, 10 and 12 hours post-dose, during one of the dosing interval in any of the 10-day treatment period

Notes:

[11] - 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: There are no statistical data to report.

End point values	Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Subject group type	Reporting group			
Number of subjects analysed	24 ^[12]			
Units: Micrograms per hour per milliliter				
geometric mean (confidence interval 95%)				
AUC(0-tau), amoxicillin, n=24	55.7 (49.41 to 62.68)			
AUC(0-tau), clavulanate, n=23	2.92 (2.44 to 3.51)			

Notes:

[12] - PK Concentration Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any adverse events (AEs) and any serious adverse events (SAE) during the treatment period

End point title	Number of participants with any adverse events (AEs) and any serious adverse events (SAE) during the treatment period
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End point description:

An adverse event (AE) is any untoward medical occurrence in a participant temporally of a medicinal product, whether or not considered related to the medicinal. A serious adverse event is any untoward medical occurrence that, at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity and is a congenital anomaly/birth defect. Safety Population is defined as all participants who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Up to Day 13

End point values	Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Subject group type	Reporting group			
Number of subjects analysed	44 ^[13]			
Units: Participants				
Any AE	22			
Any SAE	0			

Notes:

[13] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Alanine amino transferase and aspartate amino transferase values at the indicated time points

End point title	Alanine amino transferase and aspartate amino transferase values at the indicated time points
End point description: Clinical chemistry included analysis of alanine amino transferase and aspartate amino transferase at screening and follow-up (within 3 days of receipt of the last dose) period. Only those participants available at the indicated time points were assessed (represented by n=X in the category titles).	
End point type	Secondary
End point timeframe: Screening and Follow-up (up to Day 13)	

End point values	Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Subject group type	Reporting group			
Number of subjects analysed	44 ^[14]			
Units: International unit per liter				
arithmetic mean (standard deviation)				
Alanine amino transferase, Screening, n=44	21 (± 8.07)			
Alanine amino transferase, Follow-up, n=41	23.8 (± 10.84)			
Aspartate amino transferase, Screening, n=44	23 (± 4.82)			
Aspartate amino transferase, Follow-up, n=41	25 (± 7.08)			

Notes:

[14] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Basophils, eosinophils, lymphocytes, monocytes, total neutrophils, platelet count and white blood cell count values at the indicated time points

End point title	Basophils, eosinophils, lymphocytes, monocytes, total neutrophils, platelet count and white blood cell count values at the indicated time points
End point description: Hematology included analysis of basophils, eosinophils, lymphocytes, monocytes, total neutrophils, platelet count and white blood cell count during screening and follow-up (within 3 days of receipt of the last dose) period. Only those participants available at the indicated time points were assessed (represented by n=X in the category titles).	
End point type	Secondary
End point timeframe: Screening and Follow-up (up to Day 13)	

End point values	Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Subject group type	Reporting group			
Number of subjects analysed	44 ^[15]			
Units: Giga per liter				
arithmetic mean (standard deviation)				
Basophils, Screening, n=44	0.055 (± 0.052)			
Basophils, Follow-up, n=37	0.053 (± 0.049)			
Eosinophils, Screening, n=44	0.239 (± 0.249)			
Eosinophils, Follow-up, n=40	0.255 (± 0.279)			
Lymphocytes, Screening, n=44	2.293 (± 0.741)			
Lymphocytes, Follow-up, n=41	2.611 (± 0.823)			
Monocytes, Screening, n=44	0.606 (± 0.206)			
Monocytes, Follow-up, n=40	0.526 (± 0.217)			
Total neutrophils, Screening, n=44	4.769 (± 2.085)			
Total neutrophils, Follow-up, n=37	4.423 (± 2.062)			
Platelet count, Screening, n=44	314.4 (± 74.15)			
Platelet count, Follow-up, n=42	326.8 (± 80.81)			
White blood cell count, Screening, n=44	7.942 (± 2.23)			
White blood cell count, Follow-up, n=42	7.709 (± 2.848)			

Notes:

[15] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Hemoglobin values at the indicated time points

End point title	Hemoglobin values at the indicated time points
End point description: Hematology included analysis of hemoglobin during screening and follow-up (within 3 days of receipt of the last dose) period. Only those participants available at the indicated time points were assessed (represented by n=X in the category titles).	
End point type	Secondary
End point timeframe: Screening and Follow-up (up to Day 13)	

End point values	Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Subject group type	Reporting group			
Number of subjects analysed	44 ^[16]			
Units: Gram per liter				
arithmetic mean (standard deviation)				
Screening, n=44	138.6 (± 12.98)			
Follow-up, n=42	135.8 (± 11.42)			

Notes:

[16] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Total bilirubin and creatinine values at the indicated time points

End point title	Total bilirubin and creatinine values at the indicated time points
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End point description:

Clinical chemistry included analysis of total bilirubin and creatinine during screening and follow-up (within 3 days of receipt of the last dose) period. Only those participants available at the indicated time points were assessed (represented by n=X in the category titles).

End point type	Secondary
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End point timeframe:

Screening and Follow-up (up to Day 13)

End point values	Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Subject group type	Reporting group			
Number of subjects analysed	44 ^[17]			
Units: Micromole per liter				
arithmetic mean (standard deviation)				
Total bilirubin, Screening, n=43	7.512 (± 3.293)			
Total bilirubin, Follow-up, n=41	7.582 (± 3.733)			
Creatinine, Screening, n=44	59.871 (± 11.731)			
Creatinine, Follow-up, n=42	61.67 (± 11.631)			

Notes:

[17] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Carbon Dioxide content or bicarbonate, sodium, potassium and urea values at the indicated time points

End point title	Carbon Dioxide content or bicarbonate, sodium, potassium and urea values at the indicated time points
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End point description:

Clinical chemistry included carbon dioxide content/bicarbonate, potassium, sodium and urea during screening and follow-up (within 3 days of receipt of the last dose) period. Only those participants available at the indicated time points were assessed (represented by n=X in the category titles).

End point type	Secondary
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End point timeframe:

Screening and Follow-up (up to Day 13)

End point values	Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Subject group type	Reporting group			
Number of subjects analysed	44 ^[18]			
Units: Millimole per liter				
arithmetic mean (standard deviation)				
CO2 content /bicarbonate, Screening, n=44	25.93 (± 2.473)			
CO2 content /bicarbonate, Follow-up, n=42	25.67 (± 2.301)			
Sodium, Screening, n=44	139.2 (± 2.2)			
Sodium, Follow-up, n=42	139.4 (± 2.61)			
Potassium, Screening, n=44	4.32 (± 0.311)			
Potassium, Follow-up, n=42	4.22 (± 0.329)			
Urea, Screening, n=44	4.946 (± 2.083)			
Urea, Follow-up, n=42	5.068 (± 1.838)			

Notes:

[18] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Red blood cell count values at the indicated time points

End point title	Red blood cell count values at the indicated time points
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End point description:

Hematology included analysis of red blood cell count during screening and follow-up (within 3 days of receipt of the last dose) period. Only those participants available at the indicated time points were assessed (represented by n=X in the category titles).

End point type	Secondary
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End point timeframe:

Screening and Follow-up (up to Day 13)

End point values	Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Subject group type	Reporting group			
Number of subjects analysed	44 ^[19]			
Units: 10 ¹² per liter				
arithmetic mean (standard deviation)				
Screening, n=44	4.838 (± 0.486)			
Follow-up, n=42	4.733 (± 0.379)			

Notes:

[19] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Heart rate values at the indicated time points

End point title	Heart rate values at the indicated time points
End point description:	
Heart rate was recorded during screening, telephone clinic visit and follow-up (within 3 days of receipt of the last dose) period. Only those participants available at the indicated time points were assessed (represented by n=X in the category titles).	
End point type	Secondary
End point timeframe:	
Screening and Follow-up (up to Day 13)	

End point values	Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Subject group type	Reporting group			
Number of subjects analysed	44 ^[20]			
Units: Beats per minute				
arithmetic mean (standard deviation)				
Screening, n=44	86.9 (± 12.36)			
Telephone clinic visit, n=3	83.3 (± 13.32)			
Follow-up, n=42	84.1 (± 14.07)			

Notes:

[20] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Temperature values at the indicated time points

End point title	Temperature values at the indicated time points
End point description:	
Temperature was recorded during screening, telephone clinic visit and follow-up (within 3 days of	

receipt of the last dose) period. Only those participants available at the indicated time points were assessed (represented by n=X in the category titles).

End point type	Secondary
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End point timeframe:

Screening and Follow-up (up to Day 13)

End point values	Amoxicillin 2000 mg/Clavulanate 125 mg BD			
Subject group type	Reporting group			
Number of subjects analysed	44 ^[21]			
Units: Degree centigrade				
arithmetic mean (standard deviation)				
Temperature, Screening, n=44	36.73 (± 0.635)			
Temperature, Telephone clinic visit, n=3	37.07 (± 1.29)			
Temperature, Follow-up, n=42	36.57 (± 0.709)			

Notes:

[21] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse events (SAEs) and AEs will be analyzed up to Day 13.

Adverse event reporting additional description:

Adverse events were monitored throughout the study by spontaneous patient/parent-guardian reporting, direct questioning, observation, clinical responses, and clinical laboratory tests.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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Reporting groups

Reporting group title	Amoxicillin 2000 mg/Clavulanate 125 mg BD
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Reporting group description:

Participants received 2 tablets of combination product prolonged release amoxicillin 1000 mg/clavulanate 62.5 mg twice daily (BD) orally with food for 10 days.

Serious adverse events	Amoxicillin 2000 mg/Clavulanate 125 mg BD		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Amoxicillin 2000 mg/Clavulanate 125 mg BD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 44 (50.00%)		
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		

Dizziness subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Lethargy subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3		
Ear and labyrinth disorders Otorrhoea subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	9 / 44 (20.45%) 9 3 / 44 (6.82%) 3 2 / 44 (4.55%) 2 1 / 44 (2.27%) 1 1 / 44 (2.27%) 1 1 / 44 (2.27%) 1		
Respiratory, thoracic and mediastinal disorders Cough			

subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Asthma			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Pharyngolaryngeal pain			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash pruritic			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		

Viral infection			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Viral rash			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	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