Clinical trial results:
Efficacy, safety and impact on antimicrobial resistance of duration and dose of amoxicillin treatment for young children with Community-Acquired Pneumonia (CAP): a randomised controlled trial.

Summary

EudraCT number	2016-000809-36
Trial protocol	GB IE
Global end of trial date	21 May 2019

Results information

Result version number	v1 (current)
This version publication date	01 May 2020
First version publication date	01 May 2020

Trial information

Trial identification

Sponsor protocol code	CAP-IT

Additional study identifiers

ISRCTN number	ISRCTN76888927
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCL
Sponsor organisation address	Gower St, London, United Kingdom,
Public contact	CAP-IT Trial Manager, Medical Research Council Clinical Trials Unit at UCL, 0044 02076704763, mrcctu.capit@ucl.ac.uk
Scientific contact	CAP-IT Trial Manager, Medical Research Council Clinical Trials Unit at UCL, 0044 02076704763, mrcctu.capit@ucl.ac.uk

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 May 2019
Global end of trial reached?	Yes
Global end of trial date	21 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal objectives are to determine whether:
1. lower dose oral amoxicillin treatments is as effective as higher dose oral amoxicillin treatment for uncomplicated childhood pneumonia
2. shorter duration (3 days) amoxicillin treatment is as effective as longer duration (7 days) amoxicillin treatment for uncomplicated childhood pneumonia

CAP-IT is a 2x2 factorial trial. Main effects for the two randomisations (1. lower dose versus higher dose; 2. shorter duration versus longer duration) are estimated by collapsing across levels of the other randomisation group.

Protection of trial subjects:

Inclusion/exclusion criteria and follow-up visits were carefully chosen to minimise the risk to trial subjects. For example, children with severe underlying chronic disease with an increased risk of developing complicated pneumonia including sickle cell anaemia, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis were excluded from the trial.
Amoxicillin is a widely used licensed drug and adverse events caused by drug toxicity were known to be rare. Furthermore, the inclusion/exclusion criteria prevented patients with penicillin allergy or any other known contra-indications to amoxicillin from entering the trial.
Patients were monitored closely and a review of clinical signs and symptoms were performed at each face-to-face visit and if they were unwell or showed signs of pneumonia they wold be seen by a doctor.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	01 February 2017
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 Kingdom: 820
Country: Number of subjects enrolled	Ireland: 4
Worldwide total number of subjects	824
EEA total number of subjects	824

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)	307
Children (2-11 years)	517
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:

Participants were recruited from 01/02/2017 to 23/04/2019 across 29 sites, (28 in the UK and 1 in Ireland). They were enrolled by research nurses and paediatric teams from paediatric emergency departments and wards.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	2642[1]
Number of subjects completed	824

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Eligible but parents did not want to participate: 665
Reason: Number of subjects	Language barrier: 148
Reason: Number of subjects	Failed additional WARD eligibility criteria: 671
Reason: Number of subjects	Discharged on other than amoxicillin: 334

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported to have started the pre-assignment period relates to the number screened for eligibility. Not all patients screened have been enrolled.

Period 1

Period 1 title	Main trial (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	Lower + shorter

Arm description:

Lower dose (target dose 40mg/kg per day; range 35-50 mg/kg per day) oral amoxicillin treatment for 3 days

Arm type	Experimental
Investigational medicinal product name	Amoxicillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

35-50 mg/kg per day, according to a weight-banded dosing chart.
The total daily dose was administered as two daily doses, for 3 days

Arm title	Lower + longer

Arm description:

Lower dose (target dose 40mg/kg per day; range 35-50mg/kg per day) oral amoxicillin treatment for 7 days

Arm type	Experimental

Investigational medicinal product name	Amoxicillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

35-50 mg/kg per day, according to a weight-banded dosing chart.
The total daily dose was administered as two daily doses, for 7 days.

Arm title	Higher + shorter

Arm description:

Higher dose (target dose 80mg/kg per day; range 70-90mg/kg per day) oral amoxicillin treatment for 3 days.

Arm type	Experimental
Investigational medicinal product name	Amoxicillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

70-90 mg/kg per day, according to a weight-banded dosing chart.
The total daily dose was administered as two daily doses for 3 days.

Arm title	Higher + longer

Arm description:

Higher dose (target dose 80mg/kg per day; range 70-90mg/kg per day) oral amoxicillin treatment for 7 days.

Arm type	Experimental
Investigational medicinal product name	Amoxicillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

70-90 mg/kg per day, according to a weight-banded dosing chart.
The total daily dose was administered as two daily doses for 7 days.

Number of subjects in period 1	Lower + shorter	Lower + longer	Higher + shorter
Started	209	203	207
Completed	209	203	207

Number of subjects in period 1	Higher + longer
Started	205
Completed	205

Baseline characteristics

Reporting groups	
Reporting group title	Lower + shorter
Reporting group description:	
Lower dose (target dose 40mg/kg per day; range 35-50 mg/kg per day) oral amoxicillin treatment for 3 days	
Reporting group title	Lower + longer
Reporting group description:	
Lower dose (target dose 40mg/kg per day; range 35-50mg/kg per day) oral amoxicillin treatment for 7 days	
Reporting group title	Higher + shorter
Reporting group description:	
Higher dose (target dose 80mg/kg per day; range 70-90mg/kg per day) oral amoxicillin treatment for 3 days.	
Reporting group title	Higher + longer
Reporting group description:	
Higher dose (target dose 80mg/kg per day; range 70-90mg/kg per day) oral amoxicillin treatment for 7 days.	

Reporting group values	Lower + shorter	Lower + longer	Higher + shorter
Number of subjects	209	203	207
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	71	73	73
Children (2-11 years)	138	130	134
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	98	102	100
Male	111	101	107
Stratum Units: Subjects			
PED	154	150	148
WARD	55	53	59

Reporting group values	Higher + longer	Total	
Number of subjects	205	824	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	

Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	90	307	
Children (2-11 years)	115	517	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	97	397	
Male	108	427	
Stratum Units: Subjects			
PED	147	599	
WARD	58	225	

Subject analysis sets

Subject analysis set title	Analysis population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Excluding all randomised participants who did not receive any trial medication.

Reporting group values	Analysis population		
Number of subjects	814		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	305		
Children (2-11 years)	509		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	393		
Male	421		
Stratum Units: Subjects			
PED	591		
WARD	223		

End points

End points reporting groups

Reporting group title	Lower + shorter
Reporting group description:	
Lower dose (target dose 40mg/kg per day; range 35-50 mg/kg per day) oral amoxicillin treatment for 3 days	
Reporting group title	Lower + longer
Reporting group description:	
Lower dose (target dose 40mg/kg per day; range 35-50mg/kg per day) oral amoxicillin treatment for 7 days	
Reporting group title	Higher + shorter
Reporting group description:	
Higher dose (target dose 80mg/kg per day; range 70-90mg/kg per day) oral amoxicillin treatment for 3 days.	
Reporting group title	Higher + longer
Reporting group description:	
Higher dose (target dose 80mg/kg per day; range 70-90mg/kg per day) oral amoxicillin treatment for 7 days.	
Subject analysis set title	Analysis population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Excluding all randomised participants who did not receive any trial medication.	

Primary: Primary endpoint: any clinically indicated systemic antibacterial treatment prescribed for respiratory tract infection (including CAP) other than trial medication.

End point title	Primary endpoint: any clinically indicated systemic antibacterial treatment prescribed for respiratory tract infection (including CAP) other than trial medication.
End point description:	
An Endpoint Review Committee (ERC), blinded to randomised allocations, will review all cases where the participant was prescribed non-trial systemic antibacterial treatment. The main role of the Committee is to adjudicate, based on all available data, whether the primary outcome was met. Clinical indication of non-trial systemic antibacterial treatment for respiratory tract infection will be classified as "definitely/probably", or "possibly" or "unlikely" or "too little information". Those categorised as "CAP" or "other respiratory tract infection" and the likelihood that non-trial medication was indicated is "definitely/probably" or "possibly" will be regarded as fulfilling the primary endpoint.	
End point type	Primary
End point timeframe:	
up to and at final follow-up 4 weeks after randomisation	

End point values	Lower + shorter	Lower + longer	Higher + shorter	Higher + longer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	208[1]	202[2]	205[3]	199[4]
Units: Subjects				
Had primary endpoint	25	26	26	23
Did not have primary endpoint	183	176	179	176

Notes:

[1] - Patients in analysis population

[2] - Patients in analysis population

[3] - Patients in analysis population

[4] - Patients in analysis population

End point values	Analysis population			
Subject group type	Subject analysis set			
Number of subjects analysed	814[5]			
Units: Subjects				
Had primary endpoint	100			
Did not have primary endpoint	714			

Notes:

[5] - Patients in analysis population

Statistical analyses

Statistical analysis title	Primary endpoint, dose randomisation, primary
Statistical analysis description:	
Primary analysis of the primary endpoint for the dose randomisation	
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	814
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Risk difference (RD)
Point estimate	0.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.7
upper limit	4

Notes:

[6] - 8% non-inferiority margin assessed against an upper 2-sided 90% CI: Lower dose is non-inferior to Higher dose

Statistical analysis title	Primary endpoint, duration randomisation, primary
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	814
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	Risk difference (RD)
Point estimate	0.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.8
upper limit	3.9

Notes:

[7] - 8% non-inferiority margin assessed against an upper 2-sided 90% CI: Shorter duration is non-inferior to Longer duration

Secondary: Secondary endpoint: adherence, early cessation of IMP

End point title	Secondary endpoint: adherence, early cessation of IMP
End point description:	
Early cessation of trial treatment	
End point type	Secondary
End point timeframe:	
From trial entry to day 8.	

End point values	Lower + shorter	Lower + longer	Higher + shorter	Higher + longer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	208[8]	202[9]	205[10]	199[11]
Units: subjects				
Trial treatment completed	173	182	185	181
Early cessation for clinical improvement	4	3	1	0
Early cessation for clinical deterioration	7	9	3	8
Early cessation for other reason	24	8	16	10

Notes:

[8] - Participants who took at least one dose of trial medication

[9] - Participants who took at least one dose of trial medication

[10] - Participants who took at least one dose of trial medication

[11] - Participants who took at least one dose of trial medication

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint, cough

End point title	Secondary endpoint, cough
End point description:	
End point type	Secondary
End point timeframe:	
From trial entry until week 4.	

End point values	Lower + shorter	Lower + longer	Higher + shorter	Higher + longer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	200	197	198	190
Units: Subjects with cough resolution				
Resolved	144	151	141	148
Not resolved	56	46	57	42

Statistical analyses

Statistical analysis title	Time to resolution of cough: dose randomisation
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.807
Method	Logrank

Statistical analysis title	Time to resolution of cough: duration randomisati
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04 [12]
Method	Logrank

Notes:

[12] - Longer treatment was associated with a faster time to resolution than shorter treatment.

Secondary: Secondary endpoint, fever

End point title	Secondary endpoint, fever

End point description:

End point type	Secondary

End point timeframe:

From trial entry until week 4.

End point values	Lower + shorter	Lower + longer	Higher + shorter	Higher + longer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	168	159	162	159
Units: Subjects with fever resolution				
Resolved	164	155	157	156
Not resolved	4	4	5	3

Statistical analyses

Statistical analysis title	Time to resolution of fever: dose randomisation
Comparison groups	Lower + longer v Higher + shorter v Higher + longer v Lower + shorter
Number of subjects included in analysis	648
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.095
Method	Logrank

Statistical analysis title	Time to resolution of fever: duration randomisatio
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	648
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	Logrank

Secondary: Secondary endpoint, phlegm

End point title	Secondary endpoint, phlegm

End point description:

End point type	Secondary

End point timeframe:

From trial entry until week 4.

End point values	Lower + shorter	Lower + longer	Higher + shorter	Higher + longer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	146	143	146	132
Units: Participants with phlegm resolution				
Resolved	129	124	125	114
Not resolved	17	19	21	18

Statistical analyses

Statistical analysis title	Time to resolution of phlegm: dose randomisation
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	567
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.168
Method	Logrank

Statistical analysis title	Time to resolution of phlegm: duration randomisati
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	567
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.806
Method	Logrank

Secondary: Secondary endpoint, wheeze

End point title	Secondary endpoint, wheeze

End point description:

End point type	Secondary

End point timeframe:

From trial entry until week 4.

End point values	Lower + shorter	Lower + longer	Higher + shorter	Higher + longer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	97	102	105
Units: Subjects with wheeze resolution				
Resolved	112	93	95	95
Not resolved	5	4	7	10

Statistical analyses

Statistical analysis title	Time to resolution of wheeze: dose randomisation
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	Logrank

Statistical analysis title	Time to resolution of wheeze: duration randomisati
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.783
Method	Logrank

Secondary: Secondary endpoint, sleep disturbed by cough

End point title	Secondary endpoint, sleep disturbed by cough

End point description:

End point type	Secondary

End point timeframe:

From trial entry until week 4.

End point values	Lower + shorter	Lower + longer	Higher + shorter	Higher + longer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	178	173	174	163
Units: Subjects with resolution of sleep distur				
Resolved	154	162	157	147
Not resolved	24	11	17	16

Statistical analyses

Statistical analysis title	Time to resolution of sleep disturbance: dose rand
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	688
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.127
Method	Logrank

Statistical analysis title	Time to resolution of sleep disturbance: duration
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	688
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026 [13]
Method	Logrank

Notes:

[13] - Longer treatment was associated with a faster time to resolution than shorter treatment.

Secondary: Secondary endpoint, vomiting

End point title	Secondary endpoint, vomiting

End point description:

End point type	Secondary

End point timeframe:

From trial entry until week 4.

End point values	Lower + shorter	Lower + longer	Higher + shorter	Higher + longer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	90	77	93	74
Units: Subjects with resolution of vomiting				
Resolved	87	75	88	72
Not resolved	3	2	5	2

Statistical analyses

Statistical analysis title	Time to resolution of vomiting: dose randomisation
Comparison groups	Lower + longer v Higher + shorter v Higher + longer v Lower + shorter
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.477
Method	Logrank

Statistical analysis title	Time to resolution of vomiting: duration randomisa
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.224
Method	Logrank

Secondary: Secondary endpoint, eating/drinking less

End point title	Secondary endpoint, eating/drinking less

End point description:

End point type	Secondary

End point timeframe:

From trial entry until week 4.

End point values	Lower + shorter	Lower + longer	Higher + shorter	Higher + longer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	182	176	188	174
Units: Subjects with normal eating/drinking				
Resolved	166	165	170	158
Not resolved	16	11	18	16

Statistical analyses

Statistical analysis title	Time to normal eating/drinking: dose randomisation
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	720
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.647
Method	Logrank

Statistical analysis title	Time to normal eating/drinking: duration randomisa
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	720
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.132
Method	Logrank

Secondary: Secondary endpoint, normal activity

End point title	Secondary endpoint, normal activity

End point description:

End point type	Secondary

End point timeframe:

From trial entry until week 4.

End point values	Lower + shorter	Lower + longer	Higher + shorter	Higher + longer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	177	169	178	179
Units: Subjects with normal activity				
Resolved	161	163	167	166
Not resolved	16	6	11	13

Statistical analyses

Statistical analysis title	Time to normal activity: dose randomisation
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	703
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.901
Method	Logrank

Statistical analysis title	Time to normal activity: duration randomisation
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	703
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Logrank

Secondary: Secondary endpoint, fast breathing

End point title	Secondary endpoint, fast breathing

End point description:

End point type	Secondary

End point timeframe:

From trial entry until week 4.

End point values	Lower + shorter	Lower + longer	Higher + shorter	Higher + longer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	167	182	160	170
Units: Subjects with fast breathing resolution				
Resolved	165	179	151	161
Not resolved	2	3	9	9

Statistical analyses

Statistical analysis title	Time to resolution of fast breathing: dose r
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	679
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.058
Method	Logrank

Statistical analysis title	Time to resolution of fast breathing: duration r
Comparison groups	Lower + shorter v Lower + longer v Higher + shorter v Higher + longer
Number of subjects included in analysis	679
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063
Method	Logrank

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From trial entry to week 4.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	Lower + shorter
Reporting group description: Lower dose (target dose 40mg/kg per day; range 35-50 mg/kg per day) oral amoxicillin treatment for 3 days	
Reporting group title	Lower + longer
Reporting group description: Lower dose (target dose 40mg/kg per day; range 35-50mg/kg per day) oral amoxicillin treatment for 7 days	
Reporting group title	Higher + shorter
Reporting group description: Higher dose (target dose 80mg/kg per day; range 70-90mg/kg per day) oral amoxicillin treatment for 3 days.	
Reporting group title	Higher + longer
Reporting group description: Higher dose (target dose 80mg/kg per day; range 70-90mg/kg per day) oral amoxicillin treatment for 7 days.	

Serious adverse events	Lower + shorter	Lower + longer	Higher + shorter
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 208 (6.73%)	9 / 202 (4.46%)	11 / 205 (5.37%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Cerebellar Tumour			
subjects affected / exposed	0 / 208 (0.00%)	1 / 202 (0.50%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile seizure			
subjects affected / exposed	1 / 208 (0.48%)	0 / 202 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Coffee ground vomiting			
subjects affected / exposed	0 / 208 (0.00%)	0 / 202 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiploic appendagitis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 202 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonella Gastroenteritis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 202 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 208 (0.00%)	0 / 202 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 208 (0.00%)	0 / 202 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	2 / 208 (0.96%)	0 / 202 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 208 (0.48%)	0 / 202 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection viral			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 208 (0.48%)	2 / 202 (0.99%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 208 (0.96%)	3 / 202 (1.49%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Distress			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 208 (2.40%)	2 / 202 (0.99%)	7 / 205 (3.41%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Cyanosis peripheral			
subjects affected / exposed	0 / 208 (0.00%)	1 / 202 (0.50%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex oral			
subjects affected / exposed	0 / 208 (0.00%)	0 / 202 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Higher + longer		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 199 (4.52%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Cerebellar Tumour			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile seizure			

subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Coffee ground vomiting			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epiploic appendagitis			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Salmonella Gastroenteritis			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 199 (1.01%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchiolitis			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Lower respiratory tract infection viral			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 199 (2.51%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory Distress			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 199 (1.01%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Cyanosis peripheral			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes simplex oral			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Lower + shorter	Lower + longer	Higher + shorter
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 208 (36.06%)	61 / 202 (30.20%)	70 / 205 (34.15%)
Gastrointestinal disorders			
Diarrhoea	Additional description: New Diarrhoea after baseline or worse than at baseline		
alternative dictionary used: Parent reported n/a			
alternative assessment type: Systematic			

subjects affected / exposed	56 / 208 (26.92%)	42 / 202 (20.79%)	52 / 205 (25.37%)
occurrences (all)	56	42	52
Skin and subcutaneous tissue disorders			
Skin rash	Additional description: New Skin rash after baseline or worse than at baseline		
alternative dictionary used: Parent reported n/a			
alternative assessment type: Systematic			
subjects affected / exposed	25 / 208 (12.02%)	28 / 202 (13.86%)	25 / 205 (12.20%)
occurrences (all)	25	28	25
Infections and infestations			
Thrush	Additional description: New Oral thrush after baseline or worse than at baseline		
alternative dictionary used: Parent reported n/a			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 208 (3.37%)	9 / 202 (4.46%)	7 / 205 (3.41%)
occurrences (all)	7	9	7

Non-serious adverse events	Higher + longer		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 199 (35.68%)		
Gastrointestinal disorders			
Diarrhoea	Additional description: New Diarrhoea after baseline or worse than at baseline		
alternative dictionary used: Parent reported n/a			
alternative assessment type: Systematic			
subjects affected / exposed	50 / 199 (25.13%)		
occurrences (all)	50		
Skin and subcutaneous tissue disorders			
Skin rash	Additional description: New Skin rash after baseline or worse than at baseline		
alternative dictionary used: Parent reported n/a			
alternative assessment type: Systematic			
subjects affected / exposed	34 / 199 (17.09%)		
occurrences (all)	34		
Infections and infestations			
Thrush	Additional description: New Oral thrush after baseline or worse than at baseline		
alternative dictionary used: Parent reported n/a			
alternative assessment type: Systematic			
subjects affected / exposed	9 / 199 (4.52%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2016	•Correction to the higher amoxicillin dose from 70-120mg/kg to 70-90mg/kg • Trial Assessment Schedule: o Inclusion of an additional phone call at day 4. o Clarification regarding the physical exam at the final visit o Change to duration of the symptom diary • Section 3 - clarifications and changes to the inclusion and exclusion criteria. • Section 6.1.2 – clarification on procedures for face to face visits • Section 6.2.1 – additional detail regarding the collection of nasopharyngeal swabs • Section 6.3.1 – additional detail regarding the collection of EDTA blood sample • Section 6.7.1 – additional information regarding storing parent/guardians email address and phone number and additional phone call at day 4. • Section 10.3 – addition of methodology sub-study. Amendments to all PISs and consent forms, as below: • Clarification regarding storage of contact details • Change in duration of symptom diary • Clarifications regarding sample collection and storage • Update to trial schedule • Addition of methodology sub-study • Clarification regarding storage of participant data GP Letter, version 3.0 12Aug16 • Corrected higher dose of amoxicillin CAP-IT Symptom Diary, version 2.0 12Aug16 • Change in duration of symptom diary • Updated schedule • Change to severity categories for symptoms • Change to wellbeing scale CAP-IT Wellbeing Questionnaire (EQ-5D-Y), version 2.0 12Aug16 • Correction of typo on visit label CAP-IT Study Medicine Information Sheet for Parents, version 2.0 12Aug16 • Change ‘syrup’ to ‘medicine’ throughout Addition of 15 new sites and change of PI to one site. Updated IMP details
20 December 2016	Updated child trial diary - Minor formatting changes. New Trial Patient-parent card - To be given to parents/guardians of the CAP-IT participants at the time of study enrolment

01 September 2017	New wording: Previous PED and WARD specific patient information sheet, summary information sheet and consent forms have been merged together into CAP-IT patient information sheet, summary information sheet and consent form. These will replace the PED and WARD specific documents. Patients from both groups will be now consented using the same CAP-IT information sheets. CAP-IT Protocol, Version 3.0 30Aug2017: • Throughout - minor typographical corrections and amendments for consistency and clarity. • Throughout - version and date updated to v3.0, 30-Aug-2017. • Throughout – addition of CTA number "17141803" • Page iii-iv – trial contact details updated • Trial assessment schedule updated: - Addition of blood sample sub-study in PED group. - Addition of optional medical history, physical examination, symptom review, nasopharyngeal swab, saliva sample, haematology, biochemistry, virology, chest x-ray and stool sample taken at pre-randomisation n WARD group. - Nasopharyngeal and saliva samples added to randomisation (d1) for WARD group • Section 1 - background re-ordered and partially re-worded in parts for clarity and reference to recent literature added. In addition, previously unavailable results from CAP-IT feasibility work (service evaluation) have been included. • Section 3 – clarifications and changes to the inclusion and exclusion criteria • Section 3/9.6 – change of pilot timeframe from initial 6 months of the study to 3 months during the first winter of recruitment • Section 5.6.1 – additional instruction added for cases of tolerability issues. Section 6.2.1 - The nasopharyngeal sample for WARD patients will be collected at randomisation to ensure availability of a baseline sample for comparison with the final sample. An optional additional sample may be taken prior to antibiotic treatment at admission. Appendices updated Updated IMP details
01 September 2017	Addition of CAP-IT information poster to be displayed in A&E departments targeted towards parents of potential CAP-IT participants to give a brief overview of the research.
02 March 2018	The IMP dossier for the placebo used in the CAP-IT study has been updated with i) a broader release specification for viscosity, ii) up to date stability data. In the IMPD placebo version 1, the release specification for viscosity is 150-400mPA. In version 3.0, this has been widened to 150-550mPA. The broadening of the release specification is supported by a declaration from the manufacturer of the placebo, which contains data confirming that the difference in viscosity in the range of 239 to 556mPa*s are not visibly distinguishable and therefore should not affect IMP blinding. Based on our overall assessment, the broadening of the viscosity specification will allow shelf life extension of the placebo according to ICH guideline (i.e. maximum of 12 months extrapolation from last analysed time-point) without comprising the safety or integrity of the clinical trial.

21 June 2018	As part of the written informed consent for the CAP-IT study, parents/ guardians give consent for their child's GP to provide information on any antibiotic prescriptions given during the planned 29 day duration of the study for that patient. Where a participant is lost to follow up, information on antibiotic prescriptions during this period will be elicited through contact with the participant's GP. In the case of a parent/guardian decision to withdraw from the study, parent/guardians will be asked whether they consent to further data collection through hospital notes and NHS records. If consent is given, information on antibiotic prescriptions during the planned 29 day duration of the study for that patient will be elicited through contact with the participant's GP. A template GP letter and form has been designed for use by sites to collect this data and approval is requested for this. In addition, several new investigator sites are being added to the protocol and a change of PI at a current site has occurred.
07 December 2018	Summary of changes to protocol: •Statistical changes: Joint analysis of the PED & WARD groups, change to the primary endpoint definition, change to the non-inferiority margin (4-8%) and a consequent reduction in sample size from 2400 to 800 children. •Addition of an Endpoint Review Committee (ERC). •Addition of a procedure for collecting primary endpoint data from primary care for patients who are lost to follow-up or withdrawn. •Modification of the WARD criteria to allow outpatient systemic antibacterial treatment prior to presentation as long as total treatment is <48 hours before randomisation. •Removal of saliva sample collection information as this has been stopped. Summary of changes to the PIS and summary PIS: •Removal of reference to the saliva samples, which are no longer being collected •Additional information about the stool sub-study •Additional and modified wording of section relating to patient data Summary of changes to the symptom diary: •Removal of reference to the Wellbeing Questionnaire as this is performed as part of telephone follow-up calls

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Final results on phenotypic resistance to penicillin not available yet

Notes: