Clinical trial results:
A Multicenter, Open-Label Study To Assess The Efficacy And Safety Of Potassium Clavulanate/Amoxicillin (CVA/AMPC 1:14 combination) In The Treatment Of Children With Acute Bacterial Rhinosinusitis

Summary

EudraCT number	2015-004907-22
Trial protocol	Outside EU/EEA
Global end of trial date	07 November 2013

Results information

Result version number	v1 (current)
This version publication date	08 October 2016
First version publication date	08 October 2016

Trial information

Trial identification

Sponsor protocol code	117150

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 8664357343,
Scientific contact	GSK Response Center, GlaxoSmithKline, +1 8664357343,

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?	
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	21 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Acute Bacterial Rhinosinusitis (ABRS) is a respiratory inflammation commonly seen in clinical practice, which has with respiratory symptoms including nasal congestion, rhinorrhoea, postnasal discharge and cough and is associated with headache, cheek pain, facial pressure and other conditions. The principal bacterial pathogens in causing ABRS include Streptococcus pneumoniae, Haemophilus influenzae and Moraxella (Branhamella) catarrhalis. These three bacteria account for approximately 90% of ABRS in children <= to 5 years of age. Combination of Potassium Clavulanate (CVA) and Amoxicillin (AMPC) produces higher antibiotic activity against beta-lactamase-producing bacteria. The present study is designed to assess the clinical efficacy, bacteriological efficacy and safety of CVA/AMPC (1:14) administered in children aged from 3 months to less than 15 years with ABRS. It is an open-label study consisting of a 7-day treatment phase and a post-treatment follow-up phase for 7 to 14 days.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 August 2013
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	Japan: 27
Worldwide total number of subjects	27
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)	1
Children (2-11 years)	25
Adolescents (12-17 years)	1

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:

This study assessed the efficacy and safety of potassium clavulanate/amoxicillin (CVA/AMPC 1:14 combination) in the treatment of children with acute bacterial rhinosinusitis.

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	CVA/AMPC (1:14)

Arm description:

Participants received an oral dose of dry syrup potassium clavulanate (CVA)/amoxicillin hydrate (APMC) for 7 days. The daily dose of CVA/AMPC (1:14) was equal to CVA 6.4 milligrams (mg) (potency)/kilogram (kg)/day and AMPC 90 mg (potency)/kg/day in two divided doses (every 12 hours) just before lactation or meal depending on body weight at the start of treatment (Day 1).

Arm type	Experimental
Investigational medicinal product name	Potassium Clavulanate/ Amoxicillin Hydrate (CVA/AMPC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for syrup
Routes of administration	Oral use

Dosage and administration details:

Participants received CVA/AMPC corresponding 6.4/90 mg/kg/day for 7 days. The daily dose of CVA/AMPC in concentration of 6.4/90 mg/kg/day was given in two divided doses (every 12 hours) just before lactation or meal for 7 days depending on his/her body weight at the start of treatment (Day 1)

Number of subjects in period 1	CVA/AMPC (1:14)
Started	27
Completed	27

Baseline characteristics

Reporting groups	
Reporting group title	CVA/AMPC (1:14)

Reporting group description:

Participants received an oral dose of dry syrup potassium clavulanate (CVA)/amoxicillin hydrate (APMC) for 7 days. The daily dose of CVA/AMPC (1:14) was equal to CVA 6.4 milligrams (mg) (potency)/kilogram (kg)/day and AMPC 90 mg (potency)/kg/day in two divided doses (every 12 hours) just before lactation or meal depending on body weight at the start of treatment (Day 1).

Reporting group values	CVA/AMPC (1:14)	Total	
Number of subjects	27	27	
Age categorical Units: Subjects			
Age continuous Units: years geometric mean standard deviation	 6.6 ± 2.42	 -	
Gender categorical Units: Subjects			
Female	11	11	
Male	16	16	
Race Units: Subjects			
Asian - Japanese Heritage	27	27	

End points

End points reporting groups

Reporting group title	CVA/AMPC (1:14)

Reporting group description:

Participants received an oral dose of dry syrup potassium clavulanate (CVA)/amoxicillin hydrate (APMC) for 7 days. The daily dose of CVA/AMPC (1:14) was equal to CVA 6.4 milligrams (mg) (potency)/kilogram (kg)/day and AMPC 90 mg (potency)/kg/day in two divided doses (every 12 hours) just before lactation or meal depending on body weight at the start of treatment (Day 1).

Primary: Number of participants with a clinical outcome of "cure" at Test of Cure (TOC: Day 15)

End point title	Number of participants with a clinical outcome of "cure" at Test of Cure (TOC: Day 15)[1]

End point description:

Clinical assessment of acute bacterial rhinosinusitis was performed at TOC (Day 15) on the basis of: "Cure" is defined as sufficient resolution or improvement of the signs and symptoms (SS) such that no additional antibiotic (Ab) therapy is needed. Failure is defined as no change or deterioration of the SS or as additional Ab therapy being needed. The outcome was unable to be determined if no information was available regarding the SS or, despite improvement of the SS, the use of a non-study Ab was administered, indicating that there was a protocol deviation (Pd). Per Protocol Population: all participants (Par) randomized to treatment (Tr) who received the study drug for at least the first 3 days of study Tr and had evaluable data on both Day 8 and Day 15 with Tr compliance between 80% and 100% and no major pd. The estimated parameter (88.5) with 95% Confidence interval of 69.85- 97.55 represents the rate of cure (number of Par with an outcome of "Cure"/number of Par analyzed) * 100.

End point type	Primary

End point timeframe:

Day 15

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	CVA/AMPC (1:14)			
Subject group type	Reporting group			
Number of subjects analysed	26[2]			
Units: Participants				
number (not applicable)				
Cure	23			
Failure	3			
Unable to Determine	0			

Notes:

[2] - Per protocol (PP) Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with a clinical outcome of "cure" at the End of Treatment (EOT: Day 8)

End point title	Number of participants with a clinical outcome of "cure" at the End of Treatment (EOT: Day 8)

End point description:

Clinical assessment of acute bacterial rhinosinusitis was performed by the investigator (or subinvestigator) at the EOT (Day 8) on the basis of the following criteria: "Cure" is defined as sufficient resolution or improvement of the signs and symptoms such that no additional antibiotic therapy is needed. Failure is defined as no change or deterioration of the signs and symptoms or as additional antibiotic therapy being needed. The outcome was unable to be determined if no information was available regarding the signs and symptoms or, despite improvement of the signs and symptoms, the use of a non-study antibiotic was administered, indicating that there was a protocol deviation.

End point type	Secondary

End point timeframe:

Day 8

End point values	CVA/AMPC (1:14)			
Subject group type	Reporting group			
Number of subjects analysed	26[3]			
Units: Participants				
number (not applicable)				
Cure	25			
Failure	1			
Unable to Determine	0			

Notes:

[3] - PP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with a clinical outcome of "cure" at both the End of Treatment and Test of Cure (EOT and TOC: Day 8 and Day 15)

End point title	Number of participants with a clinical outcome of "cure" at both the End of Treatment and Test of Cure (EOT and TOC: Day 8 and Day 15)

End point description:

Clinical assessment of acute bacterial rhinosinusitis was performed by the investigator (or subinvestigator) at the EOT (Day 8) and TOC (Day 15) on the basis of the following criteria: "Cure" is defined as sufficient resolution or improvement of the signs and symptoms such that no additional antibiotic therapy is needed. Failure is defined as no change or deterioration of the signs and symptoms or as additional antibiotic therapy being needed. The outcome was unable to be determined if no information was available regarding the signs and symptoms or, despite improvement of the signs and symptoms, the use of a non-study antibiotic was administered, indicating that there was a protocol deviation. In order to be categorized as "cure," participants had to meet the criteria for "cure" at both Day 8 and Day 15.

End point type	Secondary

End point timeframe:

Day 8 and Day 15

End point values	CVA/AMPC (1:14)			
Subject group type	Reporting group			
Number of subjects analysed	26[4]			
Units: Participants				
number (not applicable)				
Cure	23			
Failure	3			
Unable to Determine	0			

Notes:

[4] - PP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated severity of symptoms and nasal cavity findings at Day 4, Day 8, and Day 15

End point title	Number of participants with the indicated severity of symptoms and nasal cavity findings at Day 4, Day 8, and Day 15

End point description:

The investigator (or sub-investigator) categorized the severity of symptoms such as rhinorrhoea and bad mood/productive cough as none, mild/small amount (M/SA), or moderate or severe (M or S). For the nasal cavity finding of nasal/postnasal discharge (N/PD) the categozation was serous [containing serum]), mucopurulent (MU/SA [containing both mucus and pus]), and moderate or larger amount (M/LA). In cases in which both sides of the nasal cavity were affected and there was no difference in severity between the sides, the right-side results were recorded. If there was a difference in severity, the more severe-side results were recorded.

End point type	Secondary

End point timeframe:

Baseline (BL), Day 4, Day 8, and Day 15

End point values	CVA/AMPC (1:14)			
Subject group type	Reporting group			
Number of subjects analysed	26[5]			
Units: Participants				
number (not applicable)				
Rhinorrhoea: BL, None	0			
Rhinorrhoea: BL, M/SA	5			
Rhinorrhoea: BL, M or S	21			
Rhinorrhoea: Day 4, None	7			
Rhinorrhoea: Day 4, M/SA	16			
Rhinorrhoea: Day 4, M or S	3			
Rhinorrhoea: Day 8, None	13			
Rhinorrhoea: Day 8, M/SA	13			
Rhinorrhoea: Day 8, M or S	0			
Rhinorrhoea: Day 15, None	18			
Rhinorrhoea: Day 15, M/SA	8			
Rhinorrhoea: Day 15, M or S	0			
Bad mood/productive cough: BL None	4			

Bad mood/productive cough: BL, M/SA	20			
Bad mood/productive cough: BL, M or S	2			
Bad mood/productive cough: Day 4, None	16			
Bad mood/productive cough: Day 4, M/SA	10			
Bad mood/productive cough: Day 4, M or S	0			
Bad mood/productive cough: Day 8, None	21			
Bad mood/productive cough: Day 8, M/SA	5			
Bad mood/productive cough: Day 8, M or S	0			
Bad mood/productive cough: Day 15, None	24			
Bad mood/productive cough: Day 15, M/SA	2			
Bad mood/productive cough: Day 15, M or S	0			
N/PD: BL, Serous	0			
N/PD: BL, MU/SA	6			
N/PD: BL, M/LA	20			
N/PD: Day 4, Serous	14			
N/PD: Day 4, MU/SA	10			
N/PD: Day 4, M/LA	2			
N/PD: Day 8, Serous	22			
N/PD: Day 8, MU/SA	4			
N/PD: Day 8, M/LA	0			
N/PD: Day 15, Serous	21			
N/PD: Day 15, MU/SA	5			
N/PD: Day 15, M/LA	0			

Notes:

[5] - PP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants (par.) with the specified bacteriological (bact.) outcome per pathogen (path.) at the End of Treatment (EOT) at Day 8

End point title	Number of participants (par.) with the specified bacteriological (bact.) outcome per pathogen (path.) at the End of Treatment (EOT) at Day 8

End point description:

The investigator used the sample collected at the start of study treatment (trt) to isolate and identify the pathogenic bacteria. The sample collected at the EOT was used to evaluate the bact. response to the investigational product of each path. If the same pathogen was not detected at the EOT, this pathogen was classified as "eradication" (E). If the same pathogen was detected at the EOT, this pathogen was classified as "persistence" (P). Bacteriology PP Population: all participants in the PP Population, excluding the participants who were classified as “Unable to determine” for the bacteriological outcome and who had no identified pathogen at Day 1.

End point type	Secondary

End point timeframe:

Day 8

End point values	CVA/AMPC (1:14)			
Subject group type	Reporting group			
Number of subjects analysed	24[6]			
Units: Participants				
number (not applicable)				
Streptococcus pneumoniae (StPn), E	8			
StPn, P	1			
Penicillin Susceptible (PenSusc) StPn, E	7			
PenSuscStPn, P	1			
Pen Intermediate (PenInt) StPn, E	1			
PenIntStPn, P	0			
Pen Resistant (PenR) StPn, E	0			
PenRStPn, P	0			
Moraxella (Branhamella) catarrhalis (MBC), E	6			
MBC, P	0			
MBC beta-lactamase (BL) positive, E	6			
MBC BL positive, P	0			
MBC BL negative (N), E	0			
MBC BLN, P	0			
Haemophilus influenzae (HI), E	8			
HI, P	6			
HI BLN ampicillin (A) susceptible (S), E	8			
HI BLNAS, P	2			
HI BLNA resistant (R), E	0			
HI BLNAR, P	3			
HI BL Producing (Pr) AR, E	0			
HI BLPrAR, P	1			
Staphylococcus aureus (Staph Ar), E	5			
Staph Ar, P	0			
Methicillin R Staph Ar, E	0			
Methicillin R Staph Ar, P	0			
Streptococcus pyogenes, E	1			
Streptococcus pyogenes, P	0			
Enterobacter species (sp), E	1			
Enterobacter sp., P	0			
Coagulase (Coag) NStaph, E	3			
CoagNStaph, P	0			
Corynebacterium sp., E	1			
Corynebacterium sp., P	0			
Streptococcus sp., E	1			
Streptococcus sp., P	0			
Pseudomonas aeruginosa, E	0			
Pseudomonas aeruginosa, P	0			

Notes:

[6] - Bacteriology PP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants (par.) with the specified bacteriological (bact.) outcome per participant at EOT (Day 8)

End point title	Number of participants (par.) with the specified bacteriological (bact.) outcome per participant at EOT (Day 8)

End point description:

The investigator used the sample collected at the start of study treatment (trt) to isolate and identify the pathogenic bacteria. The sample collected at the EOT was used to evaluate the bact. response to the investigational product of each par. using the following classification: Bact. eradication (erad.), presumed bact. erad. and colonization were categorized as erad. Bact. persistence (pers.), presumed bact. pers. and superinfection were categorized as pers. Bact. erad. elimination of the pathogen (path.) after trt; presumed bact. erad.-resolution of signs/symptoms (s/s) after trt; colonization-resolution of s/s but initial path. still recovered from sample; bact. pers.-no improvement in s/s and initial path. was recovered from sample; presumed bact. pers.-no improvement in s/s and isolation of initial path. was impossible/not performed; superinfection-initial path. was eradicated but a new path. was recovered; unable to determine-bact. test could not be performed.

End point type	Secondary

End point timeframe:

Day 8

End point values	CVA/AMPC (1:14)			
Subject group type	Reporting group			
Number of subjects analysed	24[7]			
Units: Participants				
number (not applicable)				
Eradication	24			
Persistence	0			

Notes:

[7] - Bacteriology PP Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of study medication until follow-up (up to Study Day 22).

Adverse event reporting additional description:

SAEs and non-serious AEs were reported for members of the Safety Population, comprised of all participants randomized to treatment who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	CVA/AMPC (1:14)

Reporting group description:

Participants received an oral dose of dry syrup potassium clavulanate (CVA)/amoxicillin hydrate (APMC) for 7 days. The daily dose of CVA/AMPC (1:14) was equal to CVA 6.4 milligrams (mg) (potency)/kilogram (kg)/day and AMPC 90 mg (potency)/kg/day in two divided doses (every 12 hours) just before lactation or meal depending on body weight at the start of treatment (Day 1).

Serious adverse events	CVA/AMPC (1:14)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	CVA/AMPC (1:14)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 27 (18.52%)		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Infections and infestations			

Otitis media subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3		

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