Clinical trial results:
Pharmacokinetics of penicillin, ampicillin and gentamicin in near- term and full-term neonates

Summary

EudraCT number	2012-002836-97
Trial protocol	EE
Global end of trial date	27 August 2014

Results information

Result version number	v1 (current)
This version publication date	29 November 2021
First version publication date	29 November 2021

Trial information

Trial identification

Sponsor protocol code	240193

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Tartu University Hospital
Sponsor organisation address	Puusepa 1A, Tartu, Estonia, 50406
Public contact	Children`s Clinic, Tartu University Hospital, +372 7319552, helgi.padari@kliinikum.ee
Scientific contact	Children`s Clinic, Tartu University Hospital, 5102696 7319552, helgi.padari@kliinikum.ee

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	12 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 August 2014
Global end of trial reached?	Yes
Global end of trial date	27 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To describe the PK of ampicillin, penicillin G and gentamicin in neonates with suspected or proven neonatal sepsis or pneumonia and GA of ≥ 32 week in order to define optimal dosing regimen of the studied antibiotics.

Protection of trial subjects:

Pharmacokinetics of penicillin, ampicillin and gentamicin was studied only in neonates to whom antibiotic treatment was clinically indicated.
Study included only neonates who had central venous or arterial catheter placed on clinical indication and no additional pain associated with pharmacokinetic samplings was caused.
Amount of blood drawn for pharmacokinetic samplings was restricted as guided by Committee for Medicinal Products for Human Use and Paediatric Committee of European Medicines Agency.
Epithelial lining fluid samples were taken only from patients who needed invasive ventilation (intubation) and tracheal aspiration was performed as part of the clinical routine.
Cerebrospinal fluid was taken for pharmacokinetic study only when lumbar puncture was clinically indicated.

Background therapy:

in this study no background therapy was used

Evidence for comparator:

In this study no comparator was used

Actual start date of recruitment	01 October 2012
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	Estonia: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	32

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
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:

Eligible were neonates with following criteria: 1.GA ≥ 32 weeks 2. PNA < 28 days 3. Informed consent (IC) given by parents or guardian 4. Central venous or arterial catheter placed or will be placed on clinical indication 5. Treatment with intravenous ampicillin or penicillin G with or without gentamicin for suspected or proven neonatal sepsis.

Pre-assignment

Screening details:

All neonates with GA ≥ 32 weeks and PNA 28 days who were hospitalised to NICU of Tartu University Hospital or Tallinn Children's Hospital with suspected or proven neonatal sepsis or pneumonia.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ampicillin-gentamicin

Arm description:

Neonates with GA ≥ 32 weeks and PNA < 28 days, who had central venous or arterial catheter placed on clinical indication and who were treated with intavenous ampicillin due to congenital sepsis or pneumonia. Informed consent for participation had given by parents or guardian.

Arm type	Experimental
Investigational medicinal product name	ampicillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Ampicillin was administered in a dose of 25 mg/kg based on current body weight of the neonate. The dosing interval was 12 h. No more than 10 minutes before administration to the patient 1 g of ampicillin (Sandoz GmbH) was reconstituted in 5 ml of 0.9% NaCl to a concentration of 200 mg/ml. Two ml (400 mg) of this solution was further diluted in 2 ml of 0.9% NaCl to a final concentration of 100 mg/ml. Ampicillin was administered as a bolus injection over 3 minutes into a central or peripheral venous cannula.

Arm title	penicillin-gentamicin

Arm description:

Neonates with GA ≥ 32 weeks and PNA < 28 days, who had central venous or arterial catheter placed on clinical indication and who were treated with intravenous penicillin due to congenital sepsis or pneumonia. All participants had informed consent obtained from parents or guardian

Arm type	Experimental
Investigational medicinal product name	penicillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in pre-filled syringe
Routes of administration	Intracavernous use

Dosage and administration details:

Penicillin G was administered in a dose of 25 000 IU/kg based on current body weight of the neonate. The dosing interval was 12 h. No more than 10 minutes before administration to the patient 1000000 IU of penicillin G (Sandoz GmbH) was reconstituted in 5 ml of 0.9% NaCl to a concentration of 200000 IU/ml. Two ml (400000 IU) of this solution was further be diluted in 2 ml of 0.9% NaCl to a final concentration of 100000 IU/ml.
Penicillin was administered as a bolus injection over 3 minutes into a central or peripheral venous cannula.

Number of subjects in period 1	ampicillin-gentamicin	penicillin-gentamicin
Started	15	17
Completed	15	17

Baseline characteristics

Reporting groups	
Reporting group title	ampicillin-gentamicin

Reporting group description:

Neonates with GA ≥ 32 weeks and PNA < 28 days, who had central venous or arterial catheter placed on clinical indication and who were treated with intavenous ampicillin due to congenital sepsis or pneumonia. Informed consent for participation had given by parents or guardian.

Reporting group title	penicillin-gentamicin

Reporting group description:

Neonates with GA ≥ 32 weeks and PNA < 28 days, who had central venous or arterial catheter placed on clinical indication and who were treated with intravenous penicillin due to congenital sepsis or pneumonia. All participants had informed consent obtained from parents or guardian

Reporting group values	ampicillin-gentamicin	penicillin-gentamicin	Total
Number of subjects	15	17	32
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	15	17	32
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
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	7	6	13
Male	8	11	19

End points

End points reporting groups

Reporting group title	ampicillin-gentamicin

Reporting group description:

Neonates with GA ≥ 32 weeks and PNA < 28 days, who had central venous or arterial catheter placed on clinical indication and who were treated with intavenous ampicillin due to congenital sepsis or pneumonia. Informed consent for participation had given by parents or guardian.

Reporting group title	penicillin-gentamicin

Reporting group description:

Neonates with GA ≥ 32 weeks and PNA < 28 days, who had central venous or arterial catheter placed on clinical indication and who were treated with intravenous penicillin due to congenital sepsis or pneumonia. All participants had informed consent obtained from parents or guardian

Primary: clearance

End point title	clearance[1][2]

End point description:

penicillin

End point type	Primary

End point timeframe:

steady state

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: median and quartiles were calculated only

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: the end point was for one arm

End point values	penicillin-gentamicin			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: L/h				
median (inter-quartile range (Q1-Q3))	0.21 (0.17 to 0.29)			

Statistical analyses

No statistical analyses for this end point

Primary: Volume of distribution

End point title	Volume of distribution[3][4]

End point description:

penicillin

End point type	Primary

End point timeframe:

steady state

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: median and quartiles were calculated only

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: median and quartiles were calculated only

End point values	penicillin-gentamicin			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: L/kg				
median (inter-quartile range (Q1-Q3))	0.50 (0.42 to 0.57)			

Statistical analyses

No statistical analyses for this end point

Primary: half-life

End point title	half-life[5][6]

End point description:

penicillin

End point type	Primary

End point timeframe:

steady state

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: median and quartiles were calculated only

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: the end point was for one arm

End point values	penicillin-gentamicin			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: h				
median (inter-quartile range (Q1-Q3))	3.65 (3.23 to 4.34)			

Statistical analyses

No statistical analyses for this end point

Primary: maximum concentration in serum

End point title	maximum concentration in serum[7][8]

End point description:

penicillin

End point type	Primary

End point timeframe:

steady state

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: median and quartiles were calculated only

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: the end point was for one arm

End point values	penicillin-gentamicin			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: mg/L				
median (inter-quartile range (Q1-Q3))	70.25 (57.35 to 84.56)			

Statistical analyses

No statistical analyses for this end point

Primary: minimum concentation in serum

End point title	minimum concentation in serum[9][10]

End point description:

penicillin

End point type	Primary

End point timeframe:

steady state

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: median and quartiles were calculated only

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: the end point was for one arm

End point values	penicillin-gentamicin			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: mg/L				
median (inter-quartile range (Q1-Q3))	4.63 (2.52 to 5.91)			

Statistical analyses

No statistical analyses for this end point

Primary: area under the concentration-time curve

End point title	area under the concentration-time curve[11][12]

End point description:

penicillin

End point type	Primary

End point timeframe:

steady state

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: median and quartiles were calculated only

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: the end point was for one arm

End point values	penicillin-gentamicin			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: hxmg/L				
median (inter-quartile range (Q1-Q3))	196.04 (139.46 to 218.20)			

Statistical analyses

No statistical analyses for this end point

Primary: clearance 1

End point title	clearance 1[13][14]

End point description:

ampicillin

End point type	Primary

End point timeframe:

steady state

Notes:

[13] - 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: arithmetic mean and standard deviation were calculated only

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: the end point was for one arm

End point values	ampicillin-gentamicin			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: L/h				
arithmetic mean (standard deviation)	0.20 (± 0.13)			

Statistical analyses

No statistical analyses for this end point

Primary: half-life 1

End point title	half-life 1[15][16]
End point description: ampicillin	
End point type	Primary
End point timeframe: steady state	

Notes:

[15] - 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: arithmetic mean and standard deviation were calculated only

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: the end point was for one arm

End point values	ampicillin-gentamicin			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: h				
arithmetic mean (standard deviation)	7.21 (± 7.97)			

Statistical analyses

No statistical analyses for this end point

Primary: Volume of distribution 1

End point title	Volume of distribution 1[17][18]
End point description: ampicillin	
End point type	Primary
End point timeframe: steady state	

Notes:

[17] - 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: arithmetic mean and standard deviation were calculated only

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: arithmetic mean and standard deviation were calculated only

End point values	ampicillin-gentamicin			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: L				
arithmetic mean (standard deviation)	1.07 (± 0.51)			

Statistical analyses

No statistical analyses for this end point

Primary: area under the concentration-time curve 1

End point title	area under the concentration-time curve 1[19][20]
End point description: ampicillin	
End point type	Primary
End point timeframe: steady state	

Notes:

[19] - 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: arithmetic mean and standard deviation were calculated only

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: the end point was for one arm

End point values	ampicillin-gentamicin			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: hxmg/L				
arithmetic mean (standard deviation)	348.92 (± 114.86)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Starting fom the day when study drug was administeed for pharmacokinetic studying. Finishing up to two days (+/-one day) after the end of treatment with all study dugs. Fom 22.12.2012 - 31.08.2014.

Adverse event reporting additional description:

Daily physical examination; daily monitoing of uine output; weight monitoing at least evey other day; continuous monitoring of heart rate, transcutaneous oxygen satuation; laboatoy tests when clinicallly indicated

Assessment type	Systematic

Dictionary used

Dictionary name	Predefined
Dictionary version	2

Reporting groups

Reporting group title	group I

Reporting group description:

ampicillin-gentamicin group

Reporting group title	group II

Reporting group description:

penicillin-gentamicin group

Serious adverse events	group I	group II	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (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: 0.1 %

Non-serious adverse events	group I	group II	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: We did not obseve any advese events

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

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

Due to small number of patients covariate analysis for population pharmacokinetics was not possible
Due to technical reasons we did not obtain enough samples of ELF and CSF for probability of target attainment simulations

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33591074

http://www.ncbi.nlm.nih.gov/pubmed/29463540