Clinical trial results:
In vivo measurement of cefuroxime in subcutaneous and bone tissue using microdialysis

Summary

EudraCT number	2013-001138-17
Trial protocol	DK
Global end of trial date	12 June 2014

Results information

Result version number	v1 (current)
This version publication date	01 July 2016
First version publication date	20 June 2015

Trial information

Trial identification

Sponsor protocol code	240583

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Orthopedic Research in Aarhus (v/Kjeld Søballe)
Sponsor organisation address	Tage Hansens Gade 2, Aarhus C, Denmark,
Public contact	Mikkel Tøttrup, Orthopedic Research in Aarhus, mikkel.tottrup@ki.au.dk
Scientific contact	Mikkel Tøttrup, Orthopedic Research in Aarhus, mikkel.tottrup@ki.au.dk

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	01 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 June 2014
Global end of trial reached?	Yes
Global end of trial date	12 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to describe and compare plasma, subcutaneous tissue and bone pharmacokinetics of cefuroxime after traditional short-term infusion (STI) and continuous infusion (CI). The primary endpoint is time that the free cefuroxime concentration exceeds the minimal inhibitory concentration (fT>MIC) for the predominant staphylococcus aureus MIC of 1 mg/L. This endpoint is reported as the probability of attaining clinically relevant targets of 65% and 90% fT>MIC over the 8 hour observation period.

Protection of trial subjects:

All trial subjects were observed by an investigator during administration of cefuroxime and during the subsequent sample collection.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 September 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	Denmark: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	3
From 65 to 84 years	15

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment began in september 2013 and ended june 2014. All patients were recruited from department of Orthopaedic surgery, Horsens Regional Hospital, Denmark

Pre-assignment

Screening details:

Competent male patients were offered enrolment in the study if they were scheduled for a total knee replacement. Exclusion criteria included the following: allergy to cefuroxime or vancomycin, on-going treatment with cefuroxime, and clinically reduced renal function.

Period 1

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

Blinding implementation details:

The investigators were blinded blinded to the mode of cefuroxime administration during surgical placement of the microdialysis catheters, so that the procedure would not be affected by this knowlegde.

Arms

Are arms mutually exclusive?	Yes
Arm title	Short-term infusion (STI)

Arm description:

The patients in this arm were given 1,500 mg of cefuroxime (Fresenius Kabi AB, Sweden) intravenously in a peripheral catheter as STI (over 15 min)

Arm type	Active comparator
Investigational medicinal product name	Cefuroxim Fresenius Kabi
Investigational medicinal product code	J 01 DC 02
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The patients in this arm were given 1,500 mg of cefuroxime (Fresenius Kabi AB, Sweden) intravenously in a peripheral catheter as STI (over 15 min)

Arm title	Continuous infusion (CI)

Arm description:

The patients in this arm were given 1,500 mg of cefuroxime (Fresenius Kabi AB, Sweden) intravenously in a peripheral catheter as CI (500 mg as loading dose over 5 min followed by CI of the remaining 1,000 mg over 7 hours and 55 min)

Arm type	Active comparator
Investigational medicinal product name	Cefuroxim Fresenius Kabi
Investigational medicinal product code	J 01 DC 02
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The patients in this arm were given 1,500 mg of cefuroxime (Fresenius Kabi AB, Sweden) intravenously in a peripheral catheter as CI (500 mg as loading dose over 5 min followed by CI of the remaining 1,000 mg over 7 hours and 55 min)

Number of subjects in period 1	Short-term infusion (STI)	Continuous infusion (CI)
Started	9	9
Completed	9	9

Baseline characteristics

Reporting groups	
Reporting group title	Short-term infusion (STI)
Reporting group description:	
The patients in this arm were given 1,500 mg of cefuroxime (Fresenius Kabi AB, Sweden) intravenously in a peripheral catheter as STI (over 15 min)	
Reporting group title	Continuous infusion (CI)
Reporting group description:	
The patients in this arm were given 1,500 mg of cefuroxime (Fresenius Kabi AB, Sweden) intravenously in a peripheral catheter as CI (500 mg as loading dose over 5 min followed by CI of the remaining 1,000 mg over 7 hours and 55 min)	

Reporting group values	Short-term infusion (STI)	Continuous infusion (CI)	Total
Number of subjects	9	9	18
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)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	1	3
From 65-84 years	7	8	15
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	68.7	70	
full range (min-max)	58 to 76	60 to 75	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	9	9	18
Body mass index (kg/m2) Units: kg/m^2			
arithmetic mean	30.6	28.7	
full range (min-max)	21.8 to 36	23.9 to 35.8	-
Plasma creatinine Units: µmol/l			
arithmetic mean	76	87	
full range (min-max)	64 to 99	68 to 111	-
Plasma albumin Units: g/l			
arithmetic mean	42	42	
full range (min-max)	38 to 47	40 to 46	-

End points

End points reporting groups

Reporting group title	Short-term infusion (STI)

Reporting group description:

The patients in this arm were given 1,500 mg of cefuroxime (Fresenius Kabi AB, Sweden) intravenously in a peripheral catheter as STI (over 15 min)

Reporting group title	Continuous infusion (CI)

Reporting group description:

The patients in this arm were given 1,500 mg of cefuroxime (Fresenius Kabi AB, Sweden) intravenously in a peripheral catheter as CI (500 mg as loading dose over 5 min followed by CI of the remaining 1,000 mg over 7 hours and 55 min)

Primary: Probability of target attainment (for a target of 65% fT > MIC in cancellous bone for a MIC of 1 mg/L)

End point title	Probability of target attainment (for a target of 65% fT > MIC in cancellous bone for a MIC of 1 mg/L)[1]

End point description:

Using a non-linear mixed effects regression model with a random patient effect for each of the model parameters, a two-compartment model were fitted to the drug concentration data separately for the different tissues. Monte Carlo simulation was used to determine the probability of target attainment (PTA) for targets of 65% (low target) and 90% fT > MIC (high target) for the observation period of 8 hours, and to estimate the area under the concentration–time curve from 0 to infinity.

End point type	Primary

End point timeframe:

Cefuroxime concentrations were quantified within 6 weeks after sample collection using an ultra high performance liquid chromatography assay.

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: Population pharmacokinetic modelling and Monte Carlo Simulations provide probabilities of attaining specified targets (probality of target attainment, PTA). Comparison of PTA between groups are usually not supported by other statistical analyses.

End point values	Short-term infusion (STI)	Continuous infusion (CI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: percent				
number (not applicable)	100	100		

Statistical analyses

No statistical analyses for this end point

Primary: Probability of target attainment (for a target of 90% fT > MIC in cancellous bone for a MIC of 1 mg/L)

End point title	Probability of target attainment (for a target of 90% fT > MIC in cancellous bone for a MIC of 1 mg/L)[2]

End point description:

See the first primary endpoint.

End point type	Primary

End point timeframe:

See the first primary endpoint.

Notes:

[2] - 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: Population pharmacokinetic modelling and Monte Carlo Simulations provide probabilities of attaining specified targets (probality of target attainment, PTA). Comparison of PTA between groups are usually not supported by other statistical analyses.

End point values	Short-term infusion (STI)	Continuous infusion (CI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: percent				
number (not applicable)	100	100		

Statistical analyses

No statistical analyses for this end point

Primary: Probability of target attainment (for a target of 65% fT > MIC in cortical bone for a MIC of 1 mg/L)

End point title	Probability of target attainment (for a target of 65% fT > MIC in cortical bone for a MIC of 1 mg/L)[3]

End point description:

See the first primary endpoint.

End point type	Primary

End point timeframe:

See the first primary endpoint.

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: Population pharmacokinetic modelling and Monte Carlo Simulations provide probabilities of attaining specified targets (probality of target attainment, PTA). Comparison of PTA between groups are usually not supported by other statistical analyses.

End point values	Short-term infusion (STI)	Continuous infusion (CI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: percent				
number (not applicable)	99.9	99.1		

Statistical analyses

No statistical analyses for this end point

Primary: Probability of target attainment (for a target of 90% fT > MIC in cortical bone for a MIC of 1 mg/L)

End point title	Probability of target attainment (for a target of 90% fT > MIC in cortical bone for a MIC of 1 mg/L)[4]

End point description:

See the first primary endpoint.

End point type	Primary

End point timeframe:

See the first primary endpoint.

Notes:

[4] - 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: Population pharmacokinetic modelling and Monte Carlo Simulations provide probabilities of attaining specified targets (probality of target attainment, PTA). Comparison of PTA between groups are usually not supported by other statistical analyses.

End point values	Short-term infusion (STI)	Continuous infusion (CI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: percent				
number (not applicable)	96.5	97.1		

Statistical analyses

No statistical analyses for this end point

Primary: Probability of target attainment (for a target of 65% fT > MIC in subcutaneous tissue for a MIC of 1 mg/L)

End point title	Probability of target attainment (for a target of 65% fT > MIC in subcutaneous tissue for a MIC of 1 mg/L)[5]

End point description:

See the first primary endpoint.

End point type	Primary

End point timeframe:

See the first primary endpoint.

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: Population pharmacokinetic modelling and Monte Carlo Simulations provide probabilities of attaining specified targets (probality of target attainment, PTA). Comparison of PTA between groups are usually not supported by other statistical analyses.

End point values	Short-term infusion (STI)	Continuous infusion (CI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: percent				
number (not applicable)	99.8	100		

Statistical analyses

No statistical analyses for this end point

Primary: Probability of target attainment (for a target of 90% fT > MIC in subcutaneous tissue for a MIC of 1 mg/L)

End point title	Probability of target attainment (for a target of 90% fT > MIC in subcutaneous tissue for a MIC of 1 mg/L)[6]

End point description:

See the first primary endpoint.

End point type	Primary

End point timeframe:

See the first primary endpoint.

Notes:

[6] - 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: Population pharmacokinetic modelling and Monte Carlo Simulations provide probabilities of attaining specified targets (probality of target attainment, PTA). Comparison of PTA between groups are usually not supported by other statistical analyses.

End point values	Short-term infusion (STI)	Continuous infusion (CI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: percent				
number (not applicable)	62	99.9		

Statistical analyses

No statistical analyses for this end point

Primary: Probability of target attainment (for a target of 65% fT > MIC in free plasma for a MIC of 1 mg/L)

End point title	Probability of target attainment (for a target of 65% fT > MIC in free plasma for a MIC of 1 mg/L)[7]

End point description:

See the first primary endpoint.

End point type	Primary

End point timeframe:

See the first primary endpoint.

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: Population pharmacokinetic modelling and Monte Carlo Simulations provide probabilities of attaining specified targets (probality of target attainment, PTA). Comparison of PTA between groups are usually not supported by other statistical analyses.

End point values	Short-term infusion (STI)	Continuous infusion (CI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: percent				
number (not applicable)	100	100		

Statistical analyses

No statistical analyses for this end point

Primary: Probability of target attainment (for a target of 90% fT > MIC in free plasma for a MIC of 1 mg/L)

End point title	Probability of target attainment (for a target of 90% fT > MIC in free plasma for a MIC of 1 mg/L)[8]
End point description:	
See the first primary endpoint.	
End point type	Primary
End point timeframe:	
See the first primary endpoint.	

Notes:

[8] - 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: Population pharmacokinetic modelling and Monte Carlo Simulations provide probabilities of attaining specified targets (probality of target attainment, PTA). Comparison of PTA between groups are usually not supported by other statistical analyses.

End point values	Short-term infusion (STI)	Continuous infusion (CI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: percent				
number (not applicable)	41.5	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Cancellous bone area under the concentration–time curve from 0 to infinity

End point title	Cancellous bone area under the concentration–time curve from 0 to infinity
End point description:	
See the first primary endpoint.	
End point type	Secondary
End point timeframe:	
See the first primary endpoint.	

End point values	Short-term infusion (STI)	Continuous infusion (CI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: min mg/L				
number (confidence interval 95%)	6035 (3718 to 9831)	6256 (4276 to 8954)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cortical bone area under the concentration–time curve from 0 to infinity

End point title	Cortical bone area under the concentration–time curve from 0 to infinity
End point description: See the first primary endpoint.	
End point type	Secondary
End point timeframe: See the first primary endpoint.	

End point values	Short-term infusion (STI)	Continuous infusion (CI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: min mg/L				
number (confidence interval 95%)	2630 (1746 to 3945)	3357 (1375 to 7262)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subcutaneous tissue area under the concentration–time curve from 0 to infinity

End point title	Subcutaneous tissue area under the concentration–time curve from 0 to infinity
End point description: See the first primary endpoint.	
End point type	Secondary
End point timeframe: See the first primary endpoint.	

End point values	Short-term infusion (STI)	Continuous infusion (CI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: min mg/L				
number (confidence interval 95%)	3016 (1929 to 4675)	3764 (2164 to 6426)		

Statistical analyses

No statistical analyses for this end point

Secondary: Free plasma area under the concentration–time curve from 0 to infinity

End point title	Free plasma area under the concentration–time curve from 0 to infinity
End point description: See the first primary endpoint.	
End point type	Secondary
End point timeframe: See the first primary endpoint.	

End point values	Short-term infusion (STI)	Continuous infusion (CI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: min mg/L				
number (confidence interval 95%)	5801 (4902 to 7277)	5415 (4625 to 6670)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24 September 2013 until 13 June 2014.	
Assessment type	Systematic

Dictionary used	
Dictionary name	Eudralex (CT 3)
Dictionary version	10

Reporting groups	
Reporting group title	Short-term infusion group
Reporting group description: The patients in this arm were given 1,500 mg of cefuroxime (Fresenius Kabi AB, Sweden) intravenously in a peripheral catheter as STI (over 15 min)	
Reporting group title	Continuous infusion
Reporting group description: The patients in this arm were given 1,500 mg of cefuroxime (Fresenius Kabi AB, Sweden) intravenously in a peripheral catheter as CI (500 mg as loading dose over 5 min followed by CI of the remaining 1,000 mg over 7 hours and 55 min)	

Serious adverse events	Short-term infusion group	Continuous infusion	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
prosthetic infection (knee)	Additional description: One patient acquired prosthetic infection within a month after surgery, but this could not be related to the experiment. After replacement of mobile prosthetic components and antibiotic therapy, the patient was cured.		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Short-term infusion group	Continuous infusion	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
Nervous system disorders			

Vasovagal attack subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 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

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

Data were analysed using population pharmacokinetic modelling and Monte Carlo Simulations. It should be noted that other modellers/analysts may come to slightly different results because of different approaches, models and software.

Notes: