Clinical trial results:
Pharmacokinetics of vancomycin in cancellous and cortical bone obtained by microdialysis

Summary

EudraCT number	2014-000258-12
Trial protocol	DK
Global end of trial date	29 April 2016

Results information

Result version number	v1 (current)
This version publication date	03 March 2017
First version publication date	03 March 2017

Trial information

Trial identification

Sponsor protocol code	230189

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ortopædkirurgisk afdeling, Aarhus Universitetshospital
Sponsor organisation address	Tage Hansens Gade 2, Aarhus C, Denmark, 8000
Public contact	Mats Bue, Hospital Unit Horsens, 25599294 25599294, matsbue@hotmail.com
Scientific contact	Mats Bue, Hospital Unit Horsens, 25599294 25599294, matsbue@hotmail.com

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	29 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 January 2016
Global end of trial reached?	Yes
Global end of trial date	29 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial is to asses the penetration of vancomycin into bone tissue using the pharmacokinetic tool microdialysis.
The primary endpoint is the area under the concentration-time curve (AUC) above the MIC (minimal inhibitory concentration) for staphylococcus aureus. Secondary endpoints are standard pharmacokinetic parameters.

Protection of trial subjects:

Measures to trial subjects a good experience with clinical trials.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2014
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: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	0
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

- The patients must be scheduled for a knee prosthesis. The indication must be arthrosis.
- Normal kindey function. Serum creatnine must be within the range of 60-100 umol/l.
- Male gender.
- The patiens must be competent

Exclusion criteria: Allergic to vancomycin or cefuroxime, ongoing treatment with vancomycin, female gender

Pre-assignment period milestones

Number of subjects started	10
Number of subjects completed	10

Period 1

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

Arms

Arm title	Overall trial

Arm description:

All subjects recieved the same amount of drug. No randomisation.

Arm type	All subjects recieved the same amount of drug
Investigational medicinal product name	Vancomycin "Hospira"
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg milligram(s) administered over 100 min

Number of subjects in period 1	Overall trial
Started	10
Completed	10

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	10	10	
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)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	10	10	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	10	10	

End points

End points reporting groups

Reporting group title	Overall trial

Reporting group description:

All subjects recieved the same amount of drug. No randomisation.

Primary: Time to MIC 1

End point title	Time to MIC 1[1]

End point description:

Time (min) to mean concentrations of 1 for plasma, subcutaneous adipose tissue and cancellous and cortical bone (MICs).

End point type	Primary

End point timeframe:

From 0 to 8 hours of sampling

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: By use of Microsoft Excel, the time to mean MICs of 1, 2, 4 and 8 mg/L was estimated using linear interpolation

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Time (min)				
Plasma	1			
Subcutaneous adipose tissue	20			
Cancellous bone	17			
Cortical bone	18			

Statistical analyses

No statistical analyses for this end point

Primary: Tissue penetration ratios

End point title	Tissue penetration ratios[2]

End point description:

tissue penetration expressed as the ratio of free AUCtissue/free AUCplasma

End point type	Primary

End point timeframe:

From 0 to 8 hours of sampling

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: The free tissue AUC0-last to free plasma AUC0-last ratio (fAUCtissue/fAUCplasma) was calculated as a measure for tissue penetration.

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Percentage				
arithmetic mean (confidence interval 95%)				
Subcutaneous adipose tissue	0.31 (0.16 to 0.46)			
Cancellous bone	0.45 (0.29 to 0.62)			
Cortical bone	0.17 (0.11 to 0.24)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to MIC 2

End point title	Time to MIC 2[3]

End point description:

Time (min) to mean concentrations of 2 for plasma, subcutaneous adipose tissue and cancellous and cortical bone (MICs).

End point type	Primary

End point timeframe:

From 0 to 8 hours of sampling

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: By use of Microsoft Excel, the time to mean MICs of 1, 2, 4 and 8 mg/L was estimated using linear interpolation

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Time (min)				
Plasma	3			
Subcutaneous adipose tissue	36			
Cancellous bone	27			
Cortical bone	110			

Statistical analyses

No statistical analyses for this end point

Primary: Time to MIC 4

End point title	Time to MIC 4[4]

End point description:

Time (min) to mean concentrations of 4 ug/ml for plasma, subcutaneous adipose tissue and cancellous

and cortical bone (MICs).

End point type	Primary

End point timeframe:

From 0 to 8 hours of sampling

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: By use of Microsoft Excel, the time to mean MICs of 1, 2, 4 and 8 mg/L was estimated using linear interpolation.

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Time (min)				
Plasma	6			
Subcutaneous adipose tissue	68			
Cancellous bone	44			

Statistical analyses

No statistical analyses for this end point

Primary: Time to MIC 8

End point title	Time to MIC 8[5]

End point description:

Time (min) to mean concentrations of 8 mg/L for plasma, subcutaneous adipose tissue and cancellous and cortical bone (MICs).

End point type	Primary

End point timeframe:

From 0 to 8 hours of sampling

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: By use of Microsoft Excel, the time to mean MICs of 1, 2, 4 and 8 mg/L was estimated using linear interpolation

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Time (min)				
Plasma	11			
Cancellous bone	105			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC	
End point title	AUC
End point description:	
AUC0–last, area under the concentration–time curve from 0 to the last measured value	
End point type	Secondary
End point timeframe:	
From 0 to 8 hours of sampling	

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: min ug/ml				
median (confidence interval 95%)				
Plasma	6296 (5883 to 6709)			
Subcutaneous adipose tissue	1545 (698 to 2392)			
Cancellous bone	2636 (1527 to 3744)			
Cortical bone	1016 (661 to 1371)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax	
End point title	Cmax
End point description:	
Cmax, peak drug concentration	
End point type	Secondary
End point timeframe:	
From 0 to 8 hours of sampling	

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ug/ml				
arithmetic mean (confidence interval 95%)				
Plasma	34.3 (31.3 to 37.2)			
Subcutaneous adipose tissue	6.6 (3.4 to 9.8)			
Cancellous bone	10.8 (6.3 to 15.3)			

Cortical bone	4 (2.5 to 5.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax

End point title	Tmax
End point description: Tmax, time to Cmax	
End point type	Secondary
End point timeframe: From 0 to 8 hours of sampling	

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: minute				
median (confidence interval 95%)				
Plasma	100 (64 to 136)			
Subcutaneous adipose tissue	200 (120 to 281)			
Cancellous bone	148 (73 to 223)			
Cortical bone	152 (81 to 223)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the preoperative cefuroxime administration to the end of sampling (8 hours after vancomycin administration)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	Produktresumé
Dictionary version	21.okt2011

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
All subjects recieved the same amount of drug. No randomisation.	

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)		
Product issues			
Membrane default	Additional description: When pulling out one of the catheters, the membrane fell of the catheter and stayed in the subcutaneous tissue. The membrane is very small and biocompatible and the manufactor of the product, MDialysis, recommended to leave it behind.		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	10		

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