Clinical trial results:
Chronic non bacterial osteomyelitis treated with pamidronat in a randomised placebo controlled trial

Summary

EudraCT number	2015-002038-36
Trial protocol	DK
Global end of trial date	30 October 2019

Results information

Result version number	v1 (current)
This version publication date	29 May 2020
First version publication date	29 May 2020

Trial information

Trial identification

Sponsor protocol code	48438

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02594878
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital, Denmark
Sponsor organisation address	Palle Juul-Jensens Boukevard 99, Aarhus, Denmark, 8200
Public contact	Caroline Marie Andreasen, Aarhus University Hospital, Department of Rheumatology, +45 7846 4252, carand@rm.dk
Scientific contact	Caroline Marie Andreasen, Aarhus University Hospital, Department of Rheumatology, +45 7846 4252, carand@rm.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	30 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 October 2019
Global end of trial reached?	Yes
Global end of trial date	30 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In a randomized double blind placebo controlled design in patients with chronic non bacterial osteomyelitis to investigate whether it is possible by treating with pamidronat to achieve a
1. Reduction of the inflammatory activity in the osteomyelytic boneproces measured by whole body MRIafter 9 months
2. Healing of the inflammatory activity in the osteomyelytic boneproces measured by whole body MRI after 9 months

Full length article has been accepted for publication Scandinavian Journal of Rheumatology, Accepted January 2020.

Protection of trial subjects:

Clinical evaluation and blood samples included laboratory screening for inflammation, renal and liver functional parameters

Background therapy:

Placebo (NaCl)

Evidence for comparator: -

Actual start date of recruitment	01 October 2015
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	Denmark: 14
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	1

Adolescents (12-17 years)	0
Adults (18-64 years)	13
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Fifty-six patients were approached of whom 23 adults and one child/family provided written consent and were assessed for eligibility. Randomisation was performed in 13 of 23 adults. One child completed the study but was excluded from the analyses for methodological reasons.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	14
Number of subjects completed	14

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

The hospital pharmacy performed the randomization. Pamidronate or placebo were identically packed at the hospital pharmacy.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pamidronate

Arm description:

Pamifos 3mg/ml, Medac, Hamburg, Germany

Arm type	Active comparator
Investigational medicinal product name	Pamifos 3mg/ml, Medac, Hamburg, Germany
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

pamidronate 1 mg pamidronate kg/day, max 60 mg, first dose first series 0.5 mg/kg, administered for three consecutive days at baseline, week 12 and week 24.

Arm title	Sodium chloride

Arm description:

sodium chloride 9g/l

Arm type	Placebo
Investigational medicinal product name	Sodium chloride 9g/l
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

intravenous sodium chloride 9g/l

Number of subjects in period 1	Pamidronate	Sodium chloride
Started	7	7
Completed	6	7
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	14	14	
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)	1	1	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	13	13	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	32		
inter-quartile range (Q1-Q3)	23 to 57	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	3	3	

Subject analysis sets

Subject analysis set title	Data analysis
Subject analysis set type	Full analysis

Subject analysis set description:

Randomisation was performed in 14. One patient in the pamidronate group dropped out of the study for personal reasons after the first pamidronate cycle. One child completed the study but was excluded from the analyses for methodological reasons. Analysis were performed in placebo (n=6) and IMP (pamidronatedinatrium) (n=6)

Reporting group values	Data analysis		
Number of subjects	12		
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)	0		
Children (2-11 years)	0		

Adolescents (12-17 years)	0		
Adults (18-64 years)	12		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
median	32		
inter-quartile range (Q1-Q3)	23 to 57		
Gender categorical Units: Subjects			
Female	9		
Male	3		

End points

End points reporting groups

Reporting group title	Pamidronate
Reporting group description: Pamifos 3mg/ml, Medac, Hamburg, Germany	
Reporting group title	Sodium chloride
Reporting group description: sodium chloride 9g/l	
Subject analysis set title	Data analysis
Subject analysis set type	Full analysis
Subject analysis set description: Randomisation was performed in 14. One patient in the pamidronate group dropped out of the study for personal reasons after the first pamidronate cycle. One child completed the study but was excluded from the analyses for methodological reasons. Analysis were performed in placebo (n=6) and IMP (pamidronatedinatrium) (n=6)	

Primary: Endpoints listed in table attached

End point title	Endpoints listed in table attached
End point description: Primary endpoint: Changes in disease activity score of the anterior chest wall assessed by whole body magnetic resonance imaging Secondary endpoint: Changes in disease chronicity score of the anterior chest wall assessed by whole body magnetic resonance imaging Changes in disease chronicity score of the anterior chest wall assessed by computered tomography Changes in diseaseactivity score of the spine assessed by whole body magnetic resonance imaging Changes in disease chronicity score of the spine assessed by whole body magnetic resonance imaging Changes in VAS pain Changes in VAS global Changes in biomarkers of boneresorption, boneformation and inflammation	
End point type	Primary
End point timeframe: Baseline and week 36	

End point values	Pamidronate	Sodium chloride	Data analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	6	12[1]	
Units: variable				
arithmetic mean (standard deviation)	2.3 (± 1.5)	0 (± 2.3)	1 (± 1)	

Notes:

[1] - See reuslts attached

Attachments (see zip file)	Results CNOPAM/Results CNOPAM.pdf

Statistical analyses

Statistical analysis title	See results attached
Comparison groups	Pamidronate v Sodium chloride v Data analysis
Number of subjects included in analysis	24
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Assessment of AE was performed at week 1,4,12,24 and week 36 and if an extra visit was acquired.

Adverse event reporting additional description:

Reporting of all adverse event follows The European Commission and Danish law: ”Guidelines on medical devices. Clinical investigations: Serious adverse event reporting” MEDDEV 2.7/3.

Assessment type	Systematic

Dictionary used

Dictionary name	MEDDEV 2.7
Dictionary version	3

Reporting groups

Reporting group title	Adverse events

Reporting group description:

Non- serious adverse events were reported in the pamidronate group/placebo group were: gastrointestinal symptoms (n=1/2), aching joints (n=2/1), flu-like symptoms (n=3/1), headache (n=5/1), mild hypophosphatemia (n=1/0), mild hypocalcaemia (n=1/0) and phlebitis in cubitalis vein (n=1/1). Adverse events were mainly seen following the first treatment cycle.

Serious adverse events	Adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Adverse events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)		
General disorders and administration site conditions			
Specified below	Additional description: Non- serious adverse events were reported in the pamidronate group/placebo group: gastrointestinal symptoms (n=1/2), tender joints (n=2/1), flu-like symptoms (n=3/1), headache (n=5/1), mild hypophosph (n=1/0), mild hypocalcaemi (n=1/0)		
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	6		

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 recruitment challenges, only 12 adults and one child completed the study and because of inadequate sample size the study was a posteriori converted to a pilot study. The child was excluded from analyses for methodological reasons.

Notes: