Clinical trial results:
Osseointegrated transdermal femoral amputation prostheses - Denusomab Trial

Summary

EudraCT number	2012-003574-66
Trial protocol	DK
Global end of trial date	06 September 2017

Results information

Result version number	v1 (current)
This version publication date	21 December 2019
First version publication date	21 December 2019

Trial information

Trial identification

Sponsor protocol code	34964

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Blvd. 99, Aarhuc, Denmark, 8200
Public contact	Rehne Hansen, Ortopædkirurgisk Forskning , 0045 78450000,
Scientific contact	Rehne Hansen, Ortopædkirurgisk Forskning , 0045 78450000,

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	16 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2017
Global end of trial reached?	Yes
Global end of trial date	06 September 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Investigate the possibility to optimize patients' rehabilitation progress through the assessment of BMD at the OI-prosthesis and prescription of denusomab

H1: BMD increases in the group Denusomab (DXA) compared to controls.

Protection of trial subjects:

Patients were given the recommended dose of denusomab with 6 months interval and followed closely in the outpatient clinic.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 October 2013
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: 6
Worldwide total number of subjects	6
EEA total number of subjects	6

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)	5
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was based on a medical evaluation

Pre-assignment

Screening details:

Recruitment was based on a medical evaluation

Pre-assignment period milestones

Number of subjects started	6
Number of subjects completed	6

Period 1

Period 1 title	Intervention (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

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

The test drug was injected subcutaneously in the shoulder region using an aseptic procedure with a syringe containing 1ml of denosumab solution 60mg/ml (Prolia, Amgen)

Arm type	Experimental
Investigational medicinal product name	Denosumab (Prolia, Amgen)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

It was injected subcutaneously in the shoulder region using an aseptic procedure with a syringe containing 1ml denosumab solution 60mg/ml (Prolia, Amgen)

Arm title	Placebo

Arm description:

The placebo drug was injected subcutaneously in the shoulder region using an aseptic procedure with a syringe containing 1ml of saline solution 9 mg/ml (Takeda Pharma

Arm type	Placebo
Investigational medicinal product name	Saline solution (Takeda Pharma)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

It was injected subcutaneously in the shoulder region using an aseptic procedure with a syringe containing 1ml of saline solution 9 mg/ml (Takeda Pharma)

Number of subjects in period 1	Intervention	Placebo
Started	3	3
Completed	3	3

Baseline characteristics

Reporting groups

Reporting group title	Intervention (Overall trial)

Reporting group description: -

Reporting group values	Intervention (Overall trial)	Total	
Number of subjects	6	6	
Age categorical Units: Subjects			
18-65	6	6	
Age continuous Units: years			
arithmetic mean	55.5		
full range (min-max)	36 to 66	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	6	6	

Subject analysis sets

Subject analysis set title	Group difference at 18 months follow-up
Subject analysis set type	Full analysis

Subject analysis set description:

The analysis is based on a pilot analysis, defined as reaching 18 months follow-up for three patients in each treatment arm. As the study is underpowered due to a small study population the data are analysed using 99% confidence interval (99% CI) and the significance level was set to p <0.01.

Reporting group values	Group difference at 18 months follow-up		
Number of subjects	6		
Age categorical Units: Subjects			
18-65	6		
Age continuous Units: years			
arithmetic mean			
full range (min-max)			
Gender categorical Units: Subjects			
Female	0		
Male	6		

End points

End points reporting groups

Reporting group title	Intervention

Reporting group description:

The test drug was injected subcutaneously in the shoulder region using an aseptic procedure with a syringe containing 1ml of denosumab solution 60mg/ml (Prolia, Amgen)

Reporting group title	Placebo

Reporting group description:

The placebo drug was injected subcutaneously in the shoulder region using an aseptic procedure with a syringe containing 1ml of saline solution 9 mg/ml (Takeda Pharma

Subject analysis set title	Group difference at 18 months follow-up
Subject analysis set type	Full analysis

Subject analysis set description:

The analysis is based on a pilot analysis, defined as reaching 18 months follow-up for three patients in each treatment arm. As the study is underpowered due to a small study population the data are analysed using 99% confidence interval (99% CI) and the significance level was set to p <0.01.

Primary: ROI1

End point title	ROI1

End point description:

End point type	Primary

End point timeframe:

18 months followup

End point values	Intervention	Placebo	Group difference at 18 months follow-up	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3[1]	3[2]	6[3]	
Units: g/cm2				
arithmetic mean (confidence interval 99%)	0.01 (-0.69 to 0.70)	-0.24 (-1.06 to 0.59)	0.24 (-0.26 to 0.74)	

Notes:

[1] - 3 in intervention arm

[2] - 3 in placebo arm

[3] - group difference

Statistical analyses

Statistical analysis title	analysis
Comparison groups	Intervention v Placebo

Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.09
Method	two sample ttest

Notes:

[4] - Normal distribution was assessed by qq-plots and equal variance was checked by f-test. Parametric data were analysed using paired t tests

Primary: ROI2

End point title	ROI2

End point description:

End point type	Primary

End point timeframe:

18 months follow-up

End point values	Intervention	Placebo	Group difference at 18 months follow-up	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3[5]	3[6]		
Units: g/cm2				
arithmetic mean (confidence interval 99%)	0.18 (-0.03 to 0.38)	-0.18 (-1.55 to 1.19)	0.35 (-0.29 to 1)	

Notes:

[5] - intervention

[6] - placebo

Statistical analyses

Statistical analysis title	analysis roi2
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.06
Method	two sample ttest

Primary: ROI3

End point title	ROI3

End point description:

End point type	Primary

End point timeframe:

18 months follow-up

End point values	Intervention	Placebo	Group difference at 18 months follow-up	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3[7]	3[8]	6[9]	
Units: g/cm2				
arithmetic mean (confidence interval 99%)	0.08 (-0.53 to 0.68)	-0.43 (-1.55 to 0.69)	0.51 (-0.08 to 1.10)	

Notes:

[7] - intervention

[8] - placebo

[9] - group difference

Statistical analyses

Statistical analysis title	analysis
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02
Method	two sample ttest

Primary: ROI4

End point title	ROI4

End point description:

End point type	Primary

End point timeframe:

18 months follow-up

End point values	Intervention	Placebo	Group difference at 18 months follow-up	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3[10]	3[11]	6[12]	
Units: g/cm2				
arithmetic mean (confidence interval 99%)	0.07 (-0.93 to 1.08)	-0.51 (-2.06 to 1.04)	0.58 (-0.28 to 1.44)	

Notes:

[10] - intervention

[11] - placebo

[12] - group difference

Statistical analyses

Statistical analysis title	analysis
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.04
Method	two sample ttest

Primary: ROI5

End point title	ROI5

End point description:

End point type	Primary

End point timeframe:

18 months follow-up

End point values	Intervention	Placebo	Group difference at 18 months follow-up	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3[13]	3[14]	6[15]	
Units: g/cm2				
arithmetic mean (confidence interval 99%)	0.14 (-0.72 to 1.00)	-0.35 (-1.66 to 0.96)	0.49 (-0.24 to 1.22)	

Notes:

[13] - intervention

[14] - placebo

[15] - group difference

Statistical analyses

Statistical analysis title	analysis
Comparison groups	Intervention v Placebo

Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.04
Method	two sample ttest

Primary: ROI6

End point title	ROI6

End point description:

End point type	Primary

End point timeframe:

18 months follow-up

End point values	Intervention	Placebo	Group difference at 18 months follow-up	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3[16]	3[17]	6[18]	
Units: g/cm2				
arithmetic mean (confidence interval 99%)	0.07 (-0.48 to 0.62)	-0.58 (-2.23 to 1.07)	0.65 (-0.16 to 1.45)	

Notes:

[16] - intervention

[17] - placebo

[18] - group difference

Statistical analyses

Statistical analysis title	analysis
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02
Method	two sample ttest

Primary: ROI7

End point title	ROI7

End point description:

End point type	Primary

End point timeframe:

18 months follow-up

End point values	Intervention	Placebo	Group difference at 18 months follow-up	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3[19]	3[20]	6[21]	
Units: g/cm2				
arithmetic mean (confidence interval 99%)	-0.19 (-0.72 to 0.34)	-0.57 (-2.94 to 1.80)	0.39 (-0.74 to 1.51)	

Notes:

[19] - 3 in intervention arm

[20] - 3 in placebo arm

[21] - group differenve

Statistical analyses

Statistical analysis title	analysis
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.19
Method	two sample ttest

Adverse events

Adverse events information

Timeframe for reporting adverse events:

18 months

Assessment type	Systematic

Dictionary used

Dictionary name	unknown
Dictionary version	x

Reporting groups

Reporting group title	intervention

Reporting group description:

One patient developed a large exostosis in the distal part of the residual femur a few months after S1-surgery and could not use the socket prothesis. Two weeks after the second dmab injection the patient developed ischaemia in the intact lower leg due to a popliteal aneurysm with a thrombosis and excessive arteriosclerosis in the anterior and posterior tibial artery. The patient was successfully treated with thrombolysis and vascular surgery.

One patient reported pain during partial weightbearing after one year and was not able to successfully weight bear on the external prosthesis. Due to septic loosening (staphylococcus aureus) the implant was later removed

Reporting group title	placebo

Reporting group description:

One patient suffered an iatrogenic fissure in the distal femur bone at S1-surgery. The patient reported pain during partial weight bearing after S2 surgery which gradually improved during the following nine months.
Another patient had a traumatic incident one year after S1 surgery that caused the prosthetic leg to rotate externally without releasing the safety device (OPRA AXOR II, Integrum AB, Sweden), thus the torsion was transferred to the bone-anchored fixture. Afterwards, the abutment could rotate a few degrees from side to side (bone fixation was lost), weight bearing on the implant was painful and the implant (fixture + abutment) was removed at 18-month follow-up.

Serious adverse events	intervention	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
thrombosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (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: 5 %

Non-serious adverse events	intervention	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	
Musculoskeletal and connective tissue disorders			
periprosthetic changes			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	
occurrences (all)	1	2	

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? Yes

Date	Interruption	Restart date
01 June 2016	Even though information letters regarding the project were sent to all collaborators in the primary sector of the Danish Central Region inclusion of new patients was stopped by June 2016 after a long period of no new patient referrals.	-

Notes:

Limitations and caveats

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

This study was designed as a Level 1 prospective, randomised study, but only six out of 16 planned patients were included before the trial ended and the pilot analysis was conducted. Due to a small sample size the risk of type-II error pertained to t

Notes: