Clinical trial results:
Denosumab and male infertility: a randomized double-blinded intervention study

Summary

EudraCT number	2016-003546-84
Trial protocol	DK
Global end of trial date	20 October 2020

Results information

Result version number	v1 (current)
This version publication date	29 March 2022
First version publication date	29 March 2022

Trial information

Trial identification

Sponsor protocol code	01112016

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Dept. of growth and reproduction
Sponsor organisation address	Blegdamsvej 9, copenhagen, Denmark, 2100
Public contact	Secretariat, Dpt.of Growth and Reproduction, 0045 35455085, vaekst-repro@rh.dk
Scientific contact	Secretariat, Dpt.of Growth and Reproduction, 0045 35455085, vaekst-repro@rh.dk
Sponsor organisation name	Dept. of growth and reproduction
Sponsor organisation address	Blegdamsvej 9, copenhagen, Denmark, 2100
Public contact	Dept of growth and reproduction, Rigshospitalet, group of skeletal, mineral and gonadal endocrinology, +45 30221014, li.juel.mortensen@regionh.dk
Scientific contact	Dept of growth and reproduction, Rigshospitalet, group of skeletal, mineral and gonadal endocrinology, +45 30221014, li.juel.mortensen@regionh.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	09 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 January 2020
Global end of trial reached?	Yes
Global end of trial date	20 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this intervention is to investigate whether Denosumab can improve semen quality of infertile men

Protection of trial subjects:

extra bloodsample on day 14 to ensure calcium homeostasis unaffected

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2016
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: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	100
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

recruited through our andrological clinic at dept of growth and reproduction, RH, Denmark

Pre-assignment

Screening details:

reffered for evaluation of low semen quality

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Denosumab

Arm description:

60 mg denosumab s.c. once

Arm type	Experimental
Investigational medicinal product name	denosumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

60 mg once

Arm title	placebo

Arm description:

saline

Arm type	Placebo
Investigational medicinal product name	NaCl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 ml NaCl once

Number of subjects in period 1	Denosumab	placebo
Started	50	50
Completed	46	47
Not completed	4	3
Lost to follow-up	4	3

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	100	100	
Age categorical			
mean age at baseline			
Units: Subjects			
Adults (18-64 years)	100	100	
Age continuous			
mean age for all included at baseline			
Units: years			
arithmetic mean	34.09		
standard deviation	± 6.24	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	100	100	

End points

End points reporting groups	
Reporting group title	Denosumab
Reporting group description: 60 mg denosumab s.c. once	
Reporting group title	placebo
Reporting group description: saline	

Primary: semen quality	
End point title	semen quality
End point description: increase in semen concentration 80 days after injection	
End point type	Primary
End point timeframe: 80 days	

End point values	Denosumab	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	44		
Units: mio/mL				
number (not applicable)	45	44		

Statistical analyses

Statistical analysis title	kruskal wallis
Comparison groups	Denosumab v placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.749
Method	Kruskal-wallis
Parameter estimate	Median difference (net)
Point estimate	11.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	16
Variability estimate	Standard deviation
Dispersion value	15.6

Primary: live birth rate	
End point title	live birth rate
End point description:	
End point type	Primary
End point timeframe:	
160 days + 9 months	

End point values	Denosumab	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	39		
Units: pregnancies				
number (not applicable)	36	39		

Statistical analyses

Statistical analysis title	kruskal wallis
Comparison groups	Denosumab v placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.835
Method	Kruskal-wallis
Parameter estimate	Mean difference (final values)
Point estimate	62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	100
Variability estimate	Standard deviation
Dispersion value	0.48

Secondary: inhibin B	
End point title	inhibin B
End point description:	
End point type	Secondary
End point timeframe:	
80 days	

End point values	Denosumab	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	46		
Units: nmol/L				
number (not applicable)	47	46		

Statistical analyses

Statistical analysis title	kruskal wallis
Comparison groups	Denosumab v placebo
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.348
Method	Kruskal-wallis
Parameter estimate	Mean difference (final values)
Point estimate	129.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	89
upper limit	172
Variability estimate	Standard deviation
Dispersion value	53

Secondary: change in reproductive hormones

End point title	change in reproductive hormones
End point description:	
End point type	Secondary
End point timeframe:	
80 days	

End point values	Denosumab	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	46		
Units: pmol/L				
number (not applicable)	47	46		

Statistical analyses

Statistical analysis title	kruskal wallis
Statistical analysis description: testosterone day 80	
Comparison groups	Denosumab v placebo
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.836
Method	Kruskal-wallis
Parameter estimate	Mean difference (final values)
Point estimate	18.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	13
upper limit	23
Variability estimate	Standard deviation
Dispersion value	6.9

Secondary: DNA fragmentation

End point title	DNA fragmentation
End point description:	
End point type	Secondary
End point timeframe: 80 days	

End point values	Denosumab	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: percentage				
number (not applicable)	40	40		

Statistical analyses

Statistical analysis title	kruskal wallis
Comparison groups	Denosumab v placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Kruskal-wallis

Statistical analysis title	kruskal wallis
Comparison groups	placebo v Denosumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.299
Method	Kruskal-wallis
Parameter estimate	Mean difference (final values)
Point estimate	24
Confidence interval	
level	95 %
sides	2-sided
lower limit	15
upper limit	30
Variability estimate	Standard deviation
Dispersion value	13.27

Adverse events

Adverse events information	
Timeframe for reporting adverse events: anytime during study period of 160 days (interview at day 14, 80 and 160).	
Adverse event reporting additional description: by personal interview at planned visits	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	none
Dictionary version	0

Reporting groups	
Reporting group title	Denosumab
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	

Serious adverse events	Denosumab	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Skin and subcutaneous tissue disorders			
Malignant melanoma			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Denosumab	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 50 (34.00%)	24 / 50 (48.00%)	
Musculoskeletal and connective tissue disorders			
Joint swelling	Additional description: unspecifik musculoskeletal pain		
subjects affected / exposed	17 / 50 (34.00%)	24 / 50 (48.00%)	
occurrences (all)	17	24	

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