Clinical trial results:
Translational therapy in patients with Osteogenesis imperfecta - a pilot trial on treatment with the RANKL-antibody Denosumab

Summary

EudraCT number	2012-002887-29
Trial protocol	DE
Global end of trial date	26 January 2015

Results information

Result version number	v1 (current)
This version publication date	06 January 2021
First version publication date	06 January 2021
Summary attachment (see zip file)	OI-AK_summary (OI-AK_Ergebnisbericht_EUCTR.pdf)

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-1574

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus-Magnus-Platz, Cologne, Germany, 50923
Public contact	Klinisches Studienzentrum Pädiatrie, Children's Hospital of the University of Cologne, +49 2214784361, joerg.semler@uk-koeln.de
Scientific contact	Klinisches Studienzentrum Pädiatrie, Children's Hospital of the University of Cologne, +49 2214784361, joerg.semler@uk-koeln.de

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	26 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Pilot study to assess the safety and efficacy of a therapy with the RANKL-antibody Denosumab in children 5-10 years of age with mutation in COL1A1 or COL1A2 leading to a defect in collagen production (Osteogenesis imperfecta). Efficacy will be assessed by DXA measurements at the lumbar spine (BMD).

Protection of trial subjects:

The trial was conducted according to Good Clinical Practice guidelines, the applicable local laws, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki.
The competent authorities approved the trial as required by national regulations.
Regulatory authorities were notified of the trial and amendments as required by national regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 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	Germany: 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)	10
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

11 patients were screened into the trial (The screening period was defined as week -12 until week 0 (baseline). Patients who met all in- and exclusion criteria were enrolle (n=10) and received the investigational medicinal product

Period 1

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

Arms

Arm title	Denosumab

Arm description: -

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

Dosage and administration details:

1mg/kg body weight in 3-monthly intervals

Number of subjects in period 1	Denosumab
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			
Age continuous Units: years			
arithmetic mean	7		
full range (min-max)	5.02 to 10.96	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	7	7	

End points

End points reporting groups	
Reporting group title	Denosumab
Reporting group description: -	
Subject analysis set title	baseline-BMD (g/cm2)
Subject analysis set type	Intention-to-treat
Subject analysis set description: xxx	
Subject analysis set title	48h-BMD (g/cm2)
Subject analysis set type	Intention-to-treat
Subject analysis set description: xxx	

Primary: Changes in bone mineral density (BMD)	
End point title	Changes in bone mineral density (BMD)
End point description: Changes of bone mineral density (BMD [g/cm2]) in study week 48 of the lumbar vertebrae L2-L4 after 36 weeks of treatment with denosumab compared to baseline	
End point type	Primary
End point timeframe: 48 weeks	

End point values	Denosumab	baseline-BMD (g/cm2)	48h-BMD (g/cm2)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	10	10	
Units: g/cm²				
arithmetic mean (confidence interval 95%)	0.1 (0.06 to 0.15)	0.5070 (0.3912 to 0.6228)	0.6118 (0.4696 to 0.7540)	

Statistical analyses

Statistical analysis title	xx
Statistical analysis description: Add text from CSR	
Comparison groups	48h-BMD (g/cm2) v baseline-BMD (g/cm2)
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	96

Confidence interval	
level	95 %
sides	2-sided
lower limit	90
upper limit	99
Variability estimate	Standard deviation
Dispersion value	1

Notes:

[1] - not mandatory

[2] - xx

Primary: Changes in bone mineral density (BMD): Z-score

End point title	Changes in bone mineral density (BMD): Z-score[3]

End point description:

BMD lumbar vertebrae L2-L4 Z-score. Z-score: Age-dependent standard deviation

End point type	Primary

End point timeframe:

48 weeks after baseline

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: For the statistical analysis of the primary endpoint, please refer to the attached summary report.

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: standard deviation score				
arithmetic mean (confidence interval 95%)	0.96 (0.597 to 1.323)			

Statistical analyses

No statistical analyses for this end point

Secondary: Osteoclastic activity-DPD

End point title	Osteoclastic activity-DPD

End point description:

DPD: Deoxypyridinolin

End point type	Secondary

End point timeframe:

Week 0 (baseline) and week 48 weeks

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg/g				
arithmetic mean (standard deviation)				
baseline	189.700 (± 71.294)			
week 48	237.600 (± 95.539)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mobility of patients-Walking

End point title	Mobility of patients-Walking
End point description:	
Mobility of patients: Walking 1 and 6 minute walking test	
End point type	Secondary
End point timeframe:	
change from baseline to 48h	

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	7[4]			
Units: meters				
arithmetic mean (confidence interval 95%)				
1 minute walking	11 (-3.633 to 25.63)			
6 minutes walking	48.7 (18.561 to 78.773)			

Notes:

[4] - 7 for 1 minute and 6 for 6 minutes

Statistical analyses

No statistical analyses for this end point

Secondary: Morphometry of spine-anterior-posterior index

End point title	Morphometry of spine-anterior-posterior index
End point description:	
Morphometry of spine anterior-posterior index	
End point type	Secondary
End point timeframe:	
baseline and 48 weeks	

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: (1-ah/ph)*100				
arithmetic mean (standard deviation)				
Baseline	-16.18 (± 41.46)			
Week 48	-4.475 (± 14.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Morphometry of spine-concavity index

End point title	Morphometry of spine-concavity index
End point description: Morphometry of spine-concavity index	
End point type	Secondary
End point timeframe: baseline and week 48	

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: (1-mh/ah)*100				
arithmetic mean (standard deviation)				
Baseline	5.436 (± 25.7)			
Week 48	7.332 (± 23.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mobility of patients-GMFM88

End point title	Mobility of patients-GMFM88
End point description: GMFM= Gross Motor Function Measure	
End point type	Secondary

End point timeframe:
changes from baseline to 48 hours

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percent				
arithmetic mean (confidence interval 95%)	2.722 (0.8253 to 6.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes of bone mineral density (BMD)-total without head

End point title	Changes of bone mineral density (BMD)-total without head

End point description:

End point type	Secondary

End point timeframe:
change in value between week 48 and baseline

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: g/cm²				
arithmetic mean (confidence interval 95%)	0.049 (-0.0005 to 0.099)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes of bone mineral density (BMD)-total without head

End point title	Changes of bone mineral density (BMD)-total without head

End point description:

End point type	Secondary

End point timeframe:
change in value 48 weeks after baseline

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Z-score				
arithmetic mean (confidence interval 95%)	0.566 (0.30738 to 0.8259)			

Statistical analyses

No statistical analyses for this end point

Secondary: BMC total body withour head

End point title	BMC total body withour head
End point description: BMC: bone mineral content	
End point type	Secondary
End point timeframe: change in value 48 weeks after baseline	

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: gram(s)				
arithmetic mean (confidence interval 95%)	85 (36 to 134)			

Statistical analyses

No statistical analyses for this end point

Secondary: Osteoclastic activity-Calcium

End point title	Osteoclastic activity-Calcium
End point description:	
End point type	Secondary
End point timeframe: baseline (week 0) and 48 weeks	

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mmol/l				
arithmetic mean (standard deviation)				
baseline	2.440 (± 0.080)			
week 48	2.568 (± 0.124)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were reported from inclusion of patients into the study (signature of informed consent).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Denosumab

Reporting group description: -

Serious adverse events	Denosumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Interne Fixatur einer Fraktur			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Denosumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
Investigations			
Kalzium im Blut erniedrigt	Additional description: Calcium ionised decreased		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Fraktur des Schluesselbeins	Additional description: Clavicle fracture		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Obeschenkelfraktur			

subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	4		
Sturz	Additional description: fall		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Tibiafraktur	Additional description: Tibia fracture		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Surgical and medical procedures			
Operation am Penis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Husten			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Nervous system disorders			
Erniedrigter Muskeltonus			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fieber			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Lymphadenopathie			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominalschmerz			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Diarrhoe			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Erbrechen			

subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	5		
Funktionsstoerung des Gastrointestinaltrakts			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gaumenerkrankung			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Nasenverstopfung			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Schmerzen im Oropharynx			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Symptom einer allergischen Erkrankung			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Ausschlag mit Juckreiz			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgie			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	7		
Brustschmerzen die Skelettmuskulatur betreffend			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gelenkschwellung			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gliederbeschwerden	Additional description: Limb discomfort		

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Muskelspasmen	Additional description: Muscle spasms		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rückenschmerzen	Additional description: Back pain		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Schmerz in einer Extremitaet			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	4		
Wachstumsschmerzen	Additional description: Growing pains		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hand-Fuß-Mund Krankheit			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Infektion			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Infektion der oberen Atemwege			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	5		
Nasopharyngitis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Streptokokken-Infektion			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Virusinfektion			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

Metabolism and nutrition disorders			
Appetit vermindert	Additional description: Decreased appetite		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	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

None reported