Clinical trial results:
Zoledronate against fractures in children with cerebral palsy

Summary

EudraCT number	2014-002118-21
Trial protocol	DK
Global end of trial date	01 March 2022

Results information

Result version number	v1 (current)
This version publication date	11 February 2025
First version publication date	11 February 2025

Trial information

Trial identification

Sponsor protocol code	CPZOL

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Regional health research ethics application number: 1-10-72-204-14

Notes:

Sponsors

Sponsor organisation name	Randers Regional Hospital
Sponsor organisation address	Oestervangsvej 70, Randers NE, Denmark, 8930
Public contact	Research Unit, Randers Regional Hospital, 45 7842 0172, zol.mod.brud@gmail.com
Scientific contact	Research Unit, Randers Regional Hospital, 45 7842 0172, zol.mod.brud@gmail.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	01 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 March 2022
Global end of trial reached?	Yes
Global end of trial date	01 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of 12 months treatment with i.v. zoledronic acid on bone mineralization in children with non-ambulatory cerebral palsy.

Protection of trial subjects:

Local analgesia as needed for intravenous access.
Comfortable position in bed during exams and treatments.
Paracetamol and dietary supplements of vitamin D and calcium to avoid post-infusion side effects.

Background therapy:

Vitamin D and calcium supplements recommended.

Evidence for comparator:

The comparator was infusion of physiological saline solution which has no effect and is safe to infuse.

Actual start date of recruitment	01 August 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	14
Adolescents (12-17 years)	10
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were included from September 2017 to March 2020 (both inclusive).
Subjects were recruited from 5 pediatric departments in Denmark (Aalborg, Viborg, Randers, Aarhus, and Herning)

Pre-assignment

Screening details:

Exclusion criteria were having osteotomy planned between 48 hours before and 4 months after each dose of ZOL, p-25-dihydroxy-vitamin D3 below 50 nmol/L, diagnosis of a bone metabolic disease, alanine transaminase above 90 U/L, INR above 1.3, creatinine above 90 µmol/L, or any contraindication to zoledronate treatment

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

Blinding implementation details:

Numbered, sealed packages of active drug (5 mL of ZOL and 100 mL of 0.9% saline) or placebo (5 mL of 0.9% saline and 100 mL of 0.9% saline) were pre-
pared by the AUH Pharmacy and used during the first study visit in the numbered order for each consecutive, included participant.
All statistical analyses were performed before the study was unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Zoledronate

Arm description:

Subjects receiving active drug (Zoledronate)

Arm type	Experimental
Investigational medicinal product name	Zoledronate
Investigational medicinal product code	SUB00176MIG
Other name	zol, CAS number 118072-93-8
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Less than 60 minutes prior to each infusion, the study drug or placebo was mixed with saline by an unblinded nurse or
doctor (not otherwise involved in the study) and the appropriate dose per kilogram body weight was infused by a blinded nurse or doctor over 30 minutes. Doses of active medication were 0.025 mg/kg and 0.05 mg/kg ZOL (maximum 2.5 mg) for first and second doses, respectively.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	natriumchlorid in sterile water, NaCl
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Less than 60 minutes prior to each infusion, the study drug or placebo was mixed with saline by an unblinded nurse or doctor (not otherwise involved in the study) and the appropriate dose per kilogram body weight was infused by a blinded nurse or doctor over 30 minutes.

Number of subjects in period 1	Zoledronate	Placebo
Started	14	10
Completed	14	10

Baseline characteristics

Reporting groups	
Reporting group title	Zoledronate
Reporting group description:	
Subjects receiving active drug (Zoledronate)	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Zoledronate	Placebo	Total
Number of subjects	14	10	24
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Median age, years (range)			
Units: years			
median	10.9	10.7	
full range (min-max)	6.0 to 17.1	8.3 to 16.5	-
Gender categorical			
Female (%)			
Units: Subjects			
Female	7	5	12
Male	7	5	12
GMFCS level			
GMFCS level IV/V			
Units: Subjects			
GMFCS level IV	8	5	13
GMFCS level V	6	5	11
Prior fracture			
Subject with a prior fracture before inclusion			
Units: Subjects			
Yes	2	4	6
No	12	6	18
Vitamin D			
Vitamin D at entry			
Units: nmol/L			
arithmetic mean	89	87	
standard deviation	± 20.4	± 18.2	-

End points

End points reporting groups

Reporting group title	Zoledronate
Reporting group description: Subjects receiving active drug (Zoledronate)	
Reporting group title	Placebo
Reporting group description: -	

Primary: Lumbar Spine and Lateral Distal Femur BMD Z-score change

End point title	Lumbar Spine and Lateral Distal Femur BMD Z-score change
End point description: The primary end points of the trial were the LS and LDF BMD Z-score changes from the 0- to 12-month visits. DXA scans were performed at AUH Osteoporosis Clinic at visits 1 and 3 using the same Hologic DXA machine (Hologic Horizon A [S/N 100100, fan beam], software version 13.6.0.5:3) for all scans.	
End point type	Primary
End point timeframe: from the 0- to 12-month visits	

End point values	Zoledronate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	10		
Units: Z-score change				
arithmetic mean (standard deviation)				
Lumbar Spine change	0.83 (± 0.59)	0.02 (± 0.26)		
R1 of the Lateral Distal Femur change	1.55 (± 1.44)	0.85 (± 1.15)		
R2 of the Lateral Distal Femur change	0.83 (± 1.28)	-0.82 (± 1.77)		
R3 of the Lateral Distal Femur change	0.34 (± 0.46)	-0.11 (± 0.55)		

Attachments (see zip file)	barzscores.pdf

Statistical analyses

Statistical analysis title	Student t test (unpaired)
Statistical analysis description: Student t test (unpaired) after checking for Gaussian distributions	
Comparison groups	Zoledronate v Placebo

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.012 [2]
Method	t-test, 2-sided

Notes:

[1] - An intention-to-treat approach was adopted for all analyses and statistical analyses were performed using STATA statistical software (Stata/SE 17.0 for Mac (Intel 64-bit), revision 23 Aug 2022, StataCorp LLC) whereas GraphPad Prism (Prism 9 for macOS, version 9.4.1 (458), July 18, 2022) was used for graphs of bloodwork results.

[2] - R1 change 0..213
R2 change 0.014
R3 change 0.045
LS change 0.012

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From inclusion to last visit.
All subjects were included and had last visits within the period September 2017 to February 2022, both included

Adverse event reporting additional description:

Self-reporting by subjects families and care-takers.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Zoledronate

Reporting group description:

Subjects receiving active drug (Zoledronate)

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Zoledronate	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Endocrine disorders			
Hypocalcaemia	Additional description: 1 patient was admitted due to hypocalcemia with drowsiness and shivering, no further symptoms were observed and the patient was discharged.		
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 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	Zoledronate	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	0 / 10 (0.00%)	
Endocrine disorders			
Hypocalcaemia	Additional description: asymptomatic hypocalcemia		

subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Acidosis	Additional description: Asymptomatic acidosis		
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

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.

Not all primary end points were measurable in all subjects.
The planned sample size of 52 subjects total was not reached.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37235798