Clinical trial results:
A randomized controlled trial of alendronate as preventive treatment against the development of gluco-corticoid-induced osteoporosis in patients being treated for malignant lymphoma

Summary

EudraCT number	2015-005688-18
Trial protocol	DK
Global end of trial date	28 February 2021

Results information

Result version number	v1 (current)
This version publication date	26 June 2022
First version publication date	26 June 2022

Trial information

Trial identification

Sponsor protocol code	Paw1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aalborg University Hospital
Sponsor organisation address	Moelleparkvej 4, Aalborg, Denmark, 9000
Public contact	Paw Jensen, Department of Hematology, 0045 97663860, paje@rn.dk
Scientific contact	Paw Jensen, Department of Hematology, 0045 97663860, paje@rn.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	29 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 February 2021
Global end of trial reached?	Yes
Global end of trial date	28 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study has as main purpose to investigate whether bisphosphonate treatment alendronate can prevent the development of osteoporosis expressed as low T-score by DXA and / or the identity of the spine in patients Glucocortikoidholdig chemotherapy treatment for malignant lymphoma

Protection of trial subjects:

Subjects were fully informed of all aspects of the clinical trial as well as the possibility to discontinue at any time appropriate for the subject.
At the end of the trial all subjects received the results of the last DEXA scan including a recommendation regarding the action neded to be taken according the result (ex. if T-score<2,5 the recommendation was start medication for osteoporosis)

Background therapy:

calcium and vitamin-D

Evidence for comparator: -

Actual start date of recruitment	05 December 2016
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	Denmark: 59
Worldwide total number of subjects	59
EEA total number of subjects	59

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)	18
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 59 (30 in the ALN arm and 29 in the placebo arm) patients were enrolled in the study during the preplanned recruitment period (December 2016 until February 2020)

Pre-assignment

Screening details:

Additional glucocorticoid treatment for a maximum of four weeks at the time of screening was allowed.

Period 1

Period 1 title	Interventional (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:

Randomization in blocks of 2-8 patients was performed by the hospital pharmacy. Only the pharmacy had access to the randomization key. Unblinding was performed after the last patient had last study visit and all DXA scan results had been reported. All analyses were pre-specified in the statistical analysis plan with final version signed prior to study unblinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Alendronate

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Alendronate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

70 mg once weekly for 12 months

Arm title	placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

one tablet once weekly for 12 months

Number of subjects in period 1	Alendronate	placebo
Started	30	29
Completed	22	23
Not completed	8	6
Consent withdrawn by subject	5	1
Adverse event, non-fatal	1	1
Lost to follow-up	1	-
discontinuing glucocorticoid containing chemothera	1	3
lack of compliance	-	1

Baseline characteristics

Reporting groups

Reporting group title	Interventional

Reporting group description: -

Reporting group values	Interventional	Total	
Number of subjects	59	59	
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)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	18	18	
From 65-84 years	41	41	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	66		
full range (min-max)	40 to 80	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	44	44	

Subject analysis sets

Subject analysis set title	Analysis
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The efficacy population for primary and secondary endpoints was patients with baseline BMD assessment and at least one follow-up BMD assessment. The safety population was all patients who received at least one dose of study medication. All P-values ≤5% were considered statistically significant.

Reporting group values	Analysis		
Number of subjects	47		
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)	15		
From 65-84 years	32		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	66		
full range (min-max)	40 to 80		
Gender categorical			
Units: Subjects			
Female	12		
Male	35		

End points

End points reporting groups

Reporting group title	Alendronate
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	
Subject analysis set title	Analysis
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The efficacy population for primary and secondary endpoints was patients with baseline BMD assessment and at least one follow-up BMD assessment. The safety population was all patients who received at least one dose of study medication. All P-values ≤5% were considered statistically significant.

Primary: T-score lumbar spine 12 months

End point title	T-score lumbar spine 12 months

End point description:

Primary endpoint of the study was change in T-score from baseline to EOS after 12 months, ΔT_EOS=T_1y-T_baseline, measured by dual-energy X-ray absorptiometry scan (DXA) at lumbar spine L3 level.

End point type	Primary

End point timeframe:

Primary endpoint of the study was change in T-score from baseline to EOS after 12 months, ΔT_EOS=T_1y-T_baseline, measured by dual-energy X-ray absorptiometry scan (DXA) at lumbar spine L3 level.

End point values	Alendronate	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: T-score				
number (not applicable)	0.15	-0.12		

Statistical analyses

Statistical analysis title	2-sided t-test

Statistical analysis description:

Differences in delta T(eos) and delta T(eot) between treatment groups were tested using a 2-sided t test assuming equal variance. For details se article.

Comparison groups	placebo v Alendronate
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	0.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.51

Secondary: Number of fractures

End point title	Number of fractures

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Alendronate	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	29		
Units: numbers	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: T-score End ot treatment 4-6 months lumbar spine

End point title	T-score End ot treatment 4-6 months lumbar spine

End point description:

End point type	Secondary

End point timeframe:

4 to 6 months

End point values	Alendronate	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: T-score				
number (not applicable)	0.01	0.00		

Statistical analyses

No statistical analyses for this end point

Secondary: T-score Total hip 12 months

End point title	T-score Total hip 12 months

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Alendronate	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: T-score				
number (not applicable)	-0.05	-0.10		

Statistical analyses

No statistical analyses for this end point

Secondary: T-score femoral neck 12 months

End point title	T-score femoral neck 12 months

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Alendronate	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: T-score				
number (not applicable)	-0.07	-0.10		

Statistical analyses

No statistical analyses for this end point

Secondary: T-score EOT 4-6 months total hip

End point title	T-score EOT 4-6 months total hip

End point description:

End point type	Secondary

End point timeframe:

4-6 months

End point values	Alendronate	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: T-score				
number (not applicable)	-0.05	-0.05		

Statistical analyses

No statistical analyses for this end point

Secondary: T-score ETO 4-6 months femoral neck

End point title	T-score ETO 4-6 months femoral neck

End point description:

End point type	Secondary

End point timeframe:

4-6 months

End point values	Alendronate	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: T-score				
number (not applicable)	-0.11	-0.02		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 months

Adverse event reporting additional description:

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Grade 1-4 AEs were registered for the gastrointestinal canal, as these were of special interest, and registrations for other AEs were limited to Grade 3 and 4. A potential relationship of AE`s to study med

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Alendronate arm
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Alendronate arm	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 30 (50.00%)	14 / 29 (48.28%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
venous tromboembolism			
subjects affected / exposed	2 / 30 (6.67%)	2 / 29 (6.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
anemia			
subjects affected / exposed	2 / 30 (6.67%)	3 / 29 (10.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
retinal rupture			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Social circumstances			
low performance			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
upper GI			
subjects affected / exposed	3 / 30 (10.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lower GI			
subjects affected / exposed	3 / 30 (10.00%)	4 / 29 (13.79%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
hematuria			
subjects affected / exposed	1 / 30 (3.33%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Diabetes mellitus			
subjects affected / exposed	3 / 30 (10.00%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain			
subjects affected / exposed	1 / 30 (3.33%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

neutropene febrile			
subjects affected / exposed	5 / 30 (16.67%)	8 / 29 (27.59%)	
occurrences causally related to treatment / all	0 / 9	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Alendronate arm	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 30 (33.33%)	3 / 29 (10.34%)	
Vascular disorders			
venous embolism			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
upper			
subjects affected / exposed	8 / 30 (26.67%)	1 / 29 (3.45%)	
occurrences (all)	8	1	
Musculoskeletal and connective tissue disorders			
Pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
infektion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	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

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

no

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35045567