



## 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 needed 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         |
| <b>Arm title</b>             | 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

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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

| <b>Number of subjects in period 1</b>                 | 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<br>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  $\leq 5\%$  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  $\leq 5\%$  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, $\Delta T_{EOS} = T_{1y} - T_{baseline}$ , 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,  $\Delta T_{EOS} = T_{1y} - T_{baseline}$ , 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 see 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 of treatment 4-6 months lumbar spine

|                        |  |
|------------------------|--|
| End point title        | T-score End of 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

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

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

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

4-6 months

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| 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           |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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

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

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

4-6 months

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| 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           |  |  |

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**Statistical analyses**

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

| <b>Non-serious adverse events</b>                     | 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

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### 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:

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### Online references

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