# Clinical trial results:
# Zoledronic acid in the management of malignant pleural mesothelioma - a feasibility study

## Summary

| | |
|---|---|
| EudraCT number | 2015-004433-26 |
| Trial protocol | GB |
| Global end of trial date | 24 July 2018 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 07 August 2019 |
| First version publication date | 07 August 2019 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 3638 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | ISRCTN45536692 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | North Bristol NHS Trust |
| Sponsor organisation address | Learning and Research , Bristol, United Kingdom, |
| Public contact | Duneesha de Fonseka, North Bristol NHS Trust, 0044 1174148041, duneesha.defonseka@sth.nhs.uk |
| Scientific contact | Duneesha de Fonseka, North Bristol NHS Trust, 0044 1174148041, duneesha.defonseka@sth.nhs.uk |

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 | 24 July 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 May 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 July 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

As this is a feasibility study there are no primary or secondary objectives to the trial. The overarching question is whether it would be feasible to run a full trial to determine if the addition of Zoledronic acid to 1st line chemotherapy would confer a further benefit to patients with mesothelioma, with regards to survival.
The feasibility of this trial will be assessed along the following criteria:
1. Feasibility of randomising 50 patients in 12 months
2. Acceptability of recruitment procedures, consent and randomisation, and data collection methods
3. Acceptability of ZA in MPM patients, and the optimal timing and location for ZA administration
4. Qualitative assessment in a subgroup of 10 patients (from the randomised and non-randomised groups) to evaluate patients' experience
5. Quantification of drop-out and data completeness rates
6. Estimates of outcome event rates eg survival times, measures of mean response and outcome variance to use for calculating
full trial size

Protection of trial subjects:

Patients must be well enough to be eligible for first line chemotherapy to be considered for inclusion into the trial. Calcium levels and possible side effects are monitored regularly throughout trial participation. The Trial Steering Committee meets regularly and the Independent Data Safety Monitoring Committee report dated 05/09/2017 concluded that "neither expert clinical appraisal of adverse event details nor statistical analysis indicates a higher risk of an adverse or serious adverse event (or either) associated with one treatment group".

As well as an information sheet outlining potential side effects and an emergency contact card with details of what to do in an emergency, patients were provided with an appointments schedule to help patients manage their varying chemotherapy, trial visits and scans which occurred in different locations. This included further contact details for the various appointments.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 30 September 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 | United Kingdom: 22 |
| Worldwide total number of subjects | 22 |
| EEA total number of subjects | 22 |

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) | 2 |
| From 65 to 84 years | 18 |
| 85 years and over | 2 |

## Subject disposition

### Recruitment

Recruitment details:

The recruitment period took place 30/09/2016 to 03/11/2017 in the UK.

### Pre-assignment

Screening details:

Patients with a diagnosis of mesothelioma eligible for first line chemotherapy are potential candidates for this trial.
47 assessed for eligibility
25 excluded (15 did not meet screening criteria, 10 declined to participate)
22 consented (15 to RCT, 7 to open label arm)

### Period 1

| | |
|---|---|
| Period 1 title | Baseline |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | zoledronic acid |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | zoledronic acid |
| Investigational medicinal product code | |
| Other name | Zometa 4 mg/5 ml concentrate for solution for infusion |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

4 mg/5 ml concentrate for solution for infusion every 3 weeks alongside chemotherapy for a maximum of 6 cycles

| | |
|---|---|
| **Arm title** | Placebo |

Arm description: -

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Saline |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

100ml 0.9% Saline infusion administered every 3 weeks alongside chemotherapy

| | |
|---|---|
| **Arm title** | Open label arm |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | zoledronic acid |
| Investigational medicinal product code | |
| Other name | Zometa 4 mg/5 ml concentrate for solution for infusion |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

4 mg/5 ml concentrate for solution for infusion every 3 weeks for a maximum of 6 cycles

| Number of subjects in period 1 | zoledronic acid | Placebo | Open label arm |
|---|---|---|---|
| Started | 7 | 8 | 7 |
| Completed | 7 | 8 | 7 |

## Period 2

| | |
|---|---|
| Period 2 title | Treatment period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Patients in the zoledronic acid and placebo arms were randomised to receive either zoledronic acid or placebo alongside chemotherapy and blinding was double blind.
Patients in the Open label arm were not randomised as declined chemotherapy and chose to have open labelled zoledronic acid on its own (not blinded).

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | zoledronic acid |

Arm description:

randomised to either zoledronic acid or placebo (double blind) every 3 weeks alongside chemotherapy for a maximum of 6 cycles

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | zoledronic acid |
| Investigational medicinal product code | |
| Other name | Zometa 4 mg/5 ml concentrate for solution for infusion |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

4 mg/5 ml concentrate for solution for infusion every 3 weeks alongside chemotherapy for a maximum of 6 cycles

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

randomised to either zoledronic acid or placebo (double blind) every 3 weeks alongside chemotherapy for a maximum of 6 cycles

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Saline |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

100ml 0.9% Saline infusion administered every 3 weeks alongside chemotherapy

| **Arm title** | Open label arm |
|---|---|

Arm description:

A non-randomised subgroup of patients who declined chemotherapy in favour of ZA open labelled on its own.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | zoledronic acid |
| Investigational medicinal product code | |
| Other name | Zometa 4 mg/5 ml concentrate for solution for infusion |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

4 mg/5 ml concentrate for solution for infusion every 3 weeks for a maximum of 6 cycles

| **Number of subjects in period 2** | zoledronic acid | Placebo | Open label arm |
|---|---|---|---|
| Started | 7 | 8 | 7 |
| Completed | 2 | 4 | 3 |
| Not completed | 5 | 4 | 4 |
| Adverse event, serious fatal | - | 1 | 1 |
| Adverse event, non-fatal | - | - | 2 |
| trial treatment stopped when chemotherapy stopped | 5 | 3 | - |
| Lost to follow-up | - | - | 1 |

| | | | |
|---|---|---|---|
| Right | 2 | 5 | 5 |
| Mode of diagnosis<br>Units: Subjects | | | |
| LA thoracoscopy | 3 | 3 | 5 |
| Image guided | 3 | 2 | 1 |
| VATS | 1 | 3 | 1 |
| Cell type<br>Units: Subjects | | | |
| Epitheliod | 6 | 5 | 5 |
| Sarcomatoid | 1 | 1 | 1 |
| Biphasic | 0 | 1 | 1 |
| Mesothelioma NOS | 0 | 1 | 0 |
| Previous pleurodesis<br>Units: Subjects | | | |
| Yes | 2 | 2 | 1 |
| No | 5 | 6 | 6 |
| Intracystic papillary carcinoma in situ<br>Units: Subjects | | | |
| Yes | 4 | 2 | 1 |
| No | 3 | 6 | 6 |
| TNM staging<br>Units: Subjects | | | |
| 000 | 0 | 1 | 0 |
| 100 | 1 | 3 | 5 |
| 110 | 1 | 1 | 0 |
| 121 | 0 | 1 | 0 |
| 210 | 1 | 0 | 0 |
| 300 | 1 | 1 | 0 |
| 320 | 1 | 0 | 0 |
| 321 | 1 | 0 | 0 |
| 400 | 1 | 0 | 1 |
| 410 | 0 | 0 | 1 |
| Not recorded | 0 | 1 | 0 |
| BMI<br>Units: m/kg | | | |
| arithmetic mean | 25.2 | 25.0 | 22.8 |
| standard deviation | ± 2.1 | ± 3.5 | ± 2.4 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 22 | | |
| Age categorical<br>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<br>Units: years<br>arithmetic mean<br>standard deviation | <br><br><br>- | | |
| Gender categorical<br>Units: Subjects | | | |
| Female<br>Male | 2<br>20 | | |
| WHO performance status<br>Units: Subjects | | | |
| PS0<br>PS1 | 6<br>16 | | |
| Previous 5-year significant medical history<br>Units: Subjects | | | |
| Yes<br>No | 15<br>7 | | |
| Length of symptoms<br>Units: Subjects | | | |
| <1 month<br>1-2 months<br>>2 months | 3<br>3<br>16 | | |
| Laterality<br>Units: Subjects | | | |
| Left<br>Right | 10<br>12 | | |
| Mode of diagnosis<br>Units: Subjects | | | |
| LA thoracoscopy<br>Image guided<br>VATS | 11<br>6<br>5 | | |
| Cell type<br>Units: Subjects | | | |
| Epitheliod<br>Sarcomatoid<br>Biphasic<br>Mesothelioma NOS | 16<br>3<br>2<br>1 | | |
| Previous pleurodesis<br>Units: Subjects | | | |
| Yes<br>No | 5<br>17 | | |
| Intracystic papillary carcinoma in situ<br>Units: Subjects | | | |
| Yes<br>No | 7<br>15 | | |
| TNM staging<br>Units: Subjects | | | |
| 000 | 1 | | |

| | | | |
|---|---|---|---|
| 100 | 9 | | |
| 110 | 2 | | |
| 121 | 1 | | |
| 210 | 1 | | |
| 300 | 2 | | |
| 320 | 1 | | |
| 321 | 1 | | |
| 400 | 2 | | |
| 410 | 1 | | |
| Not recorded | 1 | | |
| BMI<br>Units: m/kg<br>arithmetic mean<br>standard deviation | - | | |

| **Subject analysis sets** | |
|---|---|
| Subject analysis set title | number of eligible patients |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>All consented patients | |

| **Reporting group values** | number of eligible patients | | |
|---|---|---|---|
| Number of subjects | 22 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | ± | | |
| Gender categorical<br>Units: Subjects | | | |
| Female<br>Male | | | |
| WHO performance status<br>Units: Subjects | | | |
| PS0<br>PS1 | | | |
| Previous 5-year significant medical history<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Yes | 15 | | |
| No | 7 | | |
| Length of symptoms<br>Units: Subjects | | | |
| <1 month | | | |
| 1-2 months | | | |
| >2 months | | | |
| Laterality<br>Units: Subjects | | | |
| Left | | | |
| Right | | | |
| Mode of diagnosis<br>Units: Subjects | | | |
| LA thoracoscopy | | | |
| Image guided | | | |
| VATS | | | |
| Cell type<br>Units: Subjects | | | |
| Epitheliod | | | |
| Sarcomatoid | | | |
| Biphasic | | | |
| Mesothelioma NOS | | | |
| Previous pleurodesis<br>Units: Subjects | | | |
| Yes | | | |
| No | | | |
| Intracystic papillary carcinoma in situ<br>Units: Subjects | | | |
| Yes | | | |
| No | | | |
| TNM staging<br>Units: Subjects | | | |
| 000 | | | |
| 100 | | | |
| 110 | | | |
| 121 | | | |
| 210 | | | |
| 300 | | | |
| 320 | | | |
| 321 | | | |
| 400 | | | |
| 410 | | | |
| Not recorded | | | |
| BMI<br>Units: m/kg | | | |
| arithmetic mean | 24.4 | | |
| standard deviation | ± 2.8 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | zoledronic acid |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | Open label arm |
| Reporting group description: - | |
| Reporting group title | zoledronic acid |
| Reporting group description:<br>randomised to either zoledronic acid or placebo (double blind) every 3 weeks alongside chemotherapy for a maximum of 6 cycles | |
| Reporting group title | Placebo |
| Reporting group description:<br>randomised to either zoledronic acid or placebo (double blind) every 3 weeks alongside chemotherapy for a maximum of 6 cycles | |
| Reporting group title | Open label arm |
| Reporting group description:<br>A non-randomised subgroup of patients who declined chemotherapy in favour of ZA open labelled on its own. | |
| Subject analysis set title | number of eligible patients |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>All consented patients | |

### Primary: Number of patients randomised from those that consented

| | |
|---|---|
| End point title | Number of patients randomised from those that consented[1] |
| End point description: | |
| End point type | Primary |
| End point timeframe:<br>Number of patients who were randomised into the trial from those that were consented | |

Notes:

[1] - 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: As the study is a feasibility study, no formal comparisons will be made in any of the analyses.

| **End point values** | number of eligible patients | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 22 | | | |
| Units: participants | | | | |
| number (confidence interval 95%) | 15 (10.4 to 18.4) | | | |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Drop out rate

| | |
|---|---|
| End point title | Drop out rate |

End point description:
Number of participants who withdrew

| | |
|---|---|
| End point type | Other pre-specified |

End point timeframe:
Number of withdrawals

| **End point values** | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 8 | 7 | |
| Units: participants | 0 | 0 | 1 | |

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Overall survival rate

| | |
|---|---|
| End point title | Overall survival rate |

End point description:

| | |
|---|---|
| End point type | Other pre-specified |

End point timeframe:
Number of patients still alive at the end of the trial

| **End point values** | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 8 | 7 | |
| Units: consented participants | 7 | 7 | 4 | |

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Progression free survival rate

| | |
|---|---|
| End point title | Progression free survival rate |

End point description:
Number of participants alive or without progression at the end of the trial

| End point type | Other pre-specified |
|---|---|

End point timeframe:
progression measured by modified RECIST criteria on CT

| **End point values** | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 8 | 7 | |
| Units: consented participants | 7 | 6 | 4 | |

**Statistical analyses**

No statistical analyses for this end point

**Other pre-specified: CT scan total tumour measurement**

| End point title | CT scan total tumour measurement |
|---|---|

End point description:

| End point type | Other pre-specified |
|---|---|

End point timeframe:
Baseline

| **End point values** | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 7 | 7 | |
| Units: mm | | | | |
| geometric mean (geometric coefficient of variation) | 66.1 (± 0.8) | 44.9 (± 0.4) | 39.0 (± 0.3) | |

**Statistical analyses**

No statistical analyses for this end point

**Other pre-specified: Response on CT scan**

| End point title | Response on CT scan |
|---|---|

End point description:

| End point type | Other pre-specified |
|---|---|

End point timeframe:
After 3 cycles

| End point values | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 7 | 5 | |
| Units: participants | | | | |
| Complete response | 1 | 2 | 2 | |
| Partial response | 2 | 1 | 0 | |
| Stable disease | 3 | 0 | 0 | |
| Progressive disease | 1 | 4 | 3 | |

**Statistical analyses**

No statistical analyses for this end point

**Other pre-specified: Response on CT scan**

| End point title | Response on CT scan |
|---|---|

End point description:

| End point type | Other pre-specified |
|---|---|

End point timeframe:
6-month

| End point values | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 5 | 3 | |
| Units: participants | | | | |
| Complete response | 2 | 2 | 1 | |
| Partial response | 1 | 0 | 0 | |
| Stable disease | 2 | 0 | 0 | |
| Progressive disease | 2 | 3 | 2 | |

**Statistical analyses**

No statistical analyses for this end point

**Other pre-specified: Total Glycolytic Volume (TGV) on PET-CT scan**

| End point title | Total Glycolytic Volume (TGV) on PET-CT scan |
|---|---|

End point description:

| End point type | Other pre-specified |
|---|---|

| End point timeframe: |
|---|
| Baseline |

| End point values | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 8 | 7 | |
| Units: na | | | | |
| geometric mean (geometric coefficient of variation) | 579.5 (± 3.4) | 1062.0 (± 2.1) | 588.7 (± 1.1) | |

**Statistical analyses**

No statistical analyses for this end point

**Other pre-specified: CT scan total tumour measurement**

| End point title | CT scan total tumour measurement |
|---|---|
| End point description: | |
| End point type | Other pre-specified |
| End point timeframe: After 3 cycles | |

| End point values | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 7 | 5 | |
| Units: mm | | | | |
| geometric mean (geometric coefficient of variation) | 45.0 (± 0.9) | 33.7 (± 1.0) | 78.7 (± 0.1) | |

**Statistical analyses**

No statistical analyses for this end point

**Other pre-specified: CT scan total tumour measurement**

| End point title | CT scan total tumour measurement |
|---|---|
| End point description: | |
| End point type | Other pre-specified |
| End point timeframe: 6-month follow up | |

| End point values | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 5 | 3 | |
| Units: mm | | | | |
| geometric mean (geometric coefficient of variation) | 48.6 (± 0.6) | 71.3 (± 0.2) | 69.0 (± 0.9) | |

**Statistical analyses**

No statistical analyses for this end point

**Other pre-specified: Total Glycolytic Volume (TGV) on PET-CT scan**

| | |
|---|---|
| End point title | Total Glycolytic Volume (TGV) on PET-CT scan |

End point description:

| | |
|---|---|
| End point type | Other pre-specified |

End point timeframe:

After 3 cycles

| End point values | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 6 | | |

| End point values | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 8 | 7 | |
| Units: score | | | | |
| arithmetic mean (confidence interval 95%) | 0.636 (0.357 to 0.916) | 0.727 (0.559 to 0.895) | 0.694 (0.503 to 0.884) | |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Quality of Life index score

| End point title | Quality of Life index score |
|---|---|

End point description:

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Pre-cycle 2

| End point values | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 6 | 6 | 7 | |
| Units: index score | | | | |
| arithmetic mean (confidence interval 95%) | 0.576 (0.39 to 0.762) | 0.582 (0.231 to 0.933) | 0.611 (0.411 to 0.81) | |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Quality of Life index score

| End point title | Quality of Life index score |
|---|---|

End point description:

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Pre-cycle 3

| End point values | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 4 | 5 | |
| Units: index score | | | | |
| arithmetic mean (confidence interval 95%) | 0.575 (0.336 to 0.817) | 0.798 (0.542 to 1.054) | 0.644 (0.422 to 0.866) | |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Quality of Life index score

| End point title | Quality of Life index score |
|---|---|

End point description:

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Pre-cycle 4

| End point values | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 6 | 4 | |
| Units: index score | | | | |
| arithmetic mean (confidence interval 95%) | 0.718 (0.587 to 0.85) | 0.866 (0.696 to 1.036) | 0.578 (0.068 to 1.087) | |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Quality of Life index score

| End point title | Quality of Life index score |
|---|---|

End point description:

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Pre-cycle 5

| End point values | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 5 | 4 | 4 | |
| Units: index score | | | | |
| arithmetic mean (confidence interval 95%) | 0.673 (0.582 to 0.764) | 0.88 (0.753 to 1.007) | 0.514 (0.184 to 0.844) | |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Quality of Life index score

| End point title | Quality of Life index score |
|---|---|

End point description:

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Pre-cycle 6

| End point values | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 3 | 3 | |
| Units: index score | | | | |
| arithmetic mean (confidence interval 95%) | 0.722 (0.599 to 0.845) | 0.846 (0.708 to 0.984) | 0.496 (-0.144 to 1.135) | |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Quality of Life index score

| End point title | Quality of Life index score |
|---|---|

End point description:

| End point type | Other pre-specified |
|---|---|

End point timeframe:

End of Treatment follow up

| End point values | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 6 | 4 | 1 | |
| Units: index score | | | | |
| arithmetic mean (confidence interval 95%) | 0.625 (0.506 to 0.744) | 0.867 (0.713 to 1.021) | 0.221 (0.221 to 0.221) | |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Quality of Life index score

| End point title | Quality of Life index score |
|---|---|

End point description:

| End point type | Other pre-specified |
|---|---|

End point timeframe:

6 month follow up

| End point values | zoledronic acid | Placebo | Open label arm | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 3 | 3 | |
| Units: index score | | | | |
| arithmetic mean (confidence interval 95%) | 0.655 (0.54 to 0.77) | 0.55 (-0.554 to 1.653) | 0.439 (-0.375 to 1.253) | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| From randomisation until final trial follow up completed (6 months post randomisation) | |
| Adverse event reporting additional description: | |
| Adverse events are assessed at every follow up visit or triggered by information provided by participants/participant's families | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 1 |

| Reporting groups | |
|---|---|
| Reporting group title | Zoledronic Acid |
| Reporting group description: | |
| Participants randomised to receive Zoledronic Acid alongside chemotherapy | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants randomised to receive Placebo alongside chemotherapy | |
| Reporting group title | Open label ZA |
| Reporting group description: | |
| Participants who declined to receive chemotherapy and received open label Zoledronic Acid alone | |

| Serious adverse events | Zoledronic Acid | Placebo | Open label ZA |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 8 (62.50%) | 3 / 7 (42.86%) | 3 / 7 (42.86%) |
| number of deaths (all causes) | 0 | 0 | 3 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 7 (0.00%) | 2 / 7 (28.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 7 (14.29%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Neutrophil count decreased | Additional description: also low platelets and white cell count, as well as an elevated ALT and generally feeling unwell | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 7 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory tract infection | Additional description: drug reaction to penicillin antibiotic | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 7 (14.29%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 7 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 7 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Zoledronic Acid | Placebo | Open label ZA |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 8 (100.00%) | 7 / 7 (100.00%) | 7 / 7 (100.00%) |
| General disorders and administration site conditions | | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 7 (28.57%) | 1 / 7 (14.29%) |
| occurrences (all) | 3 | 3 | 1 |
| Appetite disorder | Additional description: poor appetite | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 7 (14.29%) | 1 / 7 (14.29%) |
| occurrences (all) | 1 | 1 | 1 |
| Fatigue | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 8 (37.50%) | 4 / 7 (57.14%) | 2 / 7 (28.57%) |
| occurrences (all) | 3 | 7 | 2 |
| Dizziness | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 7 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 2 | 0 | 1 |
| Weight decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 7 (0.00%) | 2 / 7 (28.57%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 7 (28.57%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 8 (50.00%) | 2 / 7 (28.57%) | 2 / 7 (28.57%) |
| occurrences (all) | 5 | 3 | 3 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 7 (28.57%) | 1 / 7 (14.29%) |
| occurrences (all) | 2 | 3 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 7 (14.29%) | 2 / 7 (28.57%) |
| occurrences (all) | 0 | 1 | 2 |
| breathlessness | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 7 (28.57%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 2 | 1 |
| infection | Additional description: chest infection | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 7 (28.57%) | 3 / 7 (42.86%) |
| occurrences (all) | 1 | 2 | 3 |

| | | | |
|---|---|---|---|
| Upper respiratory tract infection | Additional description: common cold | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 7 (14.29%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 3 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 3 / 7 (42.86%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 22 September 2016 | Removed the need for 'measurable disease on CT' to be measured by modified RECIST criteria |
| 16 February 2017 | Removed inclusion criteria 'measurable disease on CT (tumour thickness > 5mm)' |
| 15 September 2017 | Added option to invite patients who declined to participate to be interviewed |
| 26 September 2017 | Extended recruitment period by one month |

Notes:

### 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.

As the study is a feasibility study, no formal comparisons are made in any of the analyses.

Notes:

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/30157910