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

Baseline characteristics

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 values	zoledronic acid	Placebo	Open label arm
Number of subjects	7	8	7
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	70.0	74.2	82.3
standard deviation	± 6.2	± 4.6	± 5.2
Gender categorical Units: Subjects			
Female	1	0	1
Male	6	8	6
WHO performance status Units: Subjects			
PS0	2	4	0
PS1	5	4	7
Previous 5-year significant medical history Units: Subjects			
Yes	6	4	5
No	1	4	2
Length of symptoms Units: Subjects			
<1 month	1	2	0
1-2 months	1	2	0
>2 months	5	4	7
Laterality Units: Subjects			
Left	5	3	2

Right	2	5	5
Mode of diagnosis Units: Subjects			
LA thoracoscopy	3	3	5
Image guided	3	2	1
VATS	1	3	1
Cell type Units: Subjects			
Epitheliod	6	5	5
Sarcomatoid	1	1	1
Biphasic	0	1	1
Mesothelioma NOS	0	1	0
Previous pleurodesis Units: Subjects			
Yes	2	2	1
No	5	6	6
Intracystic papillary carcinoma in situ Units: Subjects			
Yes	4	2	1
No	3	6	6
TNM staging 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 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 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 Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	2		
Male	20		
WHO performance status Units: Subjects			
PS0	6		
PS1	16		
Previous 5-year significant medical history Units: Subjects			
Yes	15		
No	7		
Length of symptoms Units: Subjects			
<1 month	3		
1-2 months	3		
>2 months	16		
Laterality Units: Subjects			
Left	10		
Right	12		
Mode of diagnosis Units: Subjects			
LA thoracoscopy	11		
Image guided	6		
VATS	5		
Cell type Units: Subjects			
Epitheliod	16		
Sarcomatoid	3		
Biphasic	2		
Mesothelioma NOS	1		
Previous pleurodesis Units: Subjects			
Yes	5		
No	17		
Intracystic papillary carcinoma in situ Units: Subjects			
Yes	7		
No	15		
TNM staging 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			
Units: m/kg			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	number of eligible patients
Subject analysis set type	Full analysis

Subject analysis set description:

All consented patients

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

Yes	15		
No	7		
Length of symptoms Units: Subjects			
<1 month			
1-2 months			
>2 months			
Laterality Units: Subjects			
Left			
Right			
Mode of diagnosis Units: Subjects			
LA thoracoscopy			
Image guided			
VATS			
Cell type Units: Subjects			
Epitheliod			
Sarcomatoid			
Biphasic			
Mesothelioma NOS			
Previous pleurodesis Units: Subjects			
Yes			
No			
Intracystic papillary carcinoma in situ Units: Subjects			
Yes			
No			
TNM staging Units: Subjects			
000			
100			
110			
121			
210			
300			
320			
321			
400			
410			
Not recorded			
BMI 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:	
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:	
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:	
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:	
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:	
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	4	
Units: na				
geometric mean (geometric coefficient of variation)	80.4 (± 5.8)	253.5 (± 6.1)	446.7 (± 0.3)	

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:

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: 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