Clinical trial results:
Randomised Trial of Genetic Testing and Targeted Zoledronic acid therapy to Prevent SQSTM1 Mediated Paget's Disease (Zoledronate in the Prevention of Paget's).

Summary

EudraCT number	2008-005667-34
Trial protocol	GB BE IT IE ES
Global end of trial date	01 April 2023

Results information

Result version number	v1 (current)
This version publication date	16 June 2023
First version publication date	16 June 2023
Summary attachment (see zip file)	ZiPP Clinical Study Report (ZiPP ACCORD Clinical Study Report V1 22May2023.pdf)

Trial information

Trial identification

Sponsor protocol code	G0701625

Additional study identifiers

ISRCTN number	ISRCTN11616770
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ACCORD
Sponsor organisation address	47 Little France Crescent, Edinburgh, United Kingdom, EH4 2XU
Public contact	Professor Stuart Ralston , University of Edinburgh, +44 1316518743, Stuart.Ralston@ed.ac.uk
Scientific contact	ACCORD, University of Edinburgh & NHS Lothian; ACCORD, +44 1316518743, enquiries@accord.scot

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	17 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether targeted intervention with Zoledronic acid can prevent the development of new focal bone lesions in carriers of SQSTM1 gene mutations.

There will be an observational group in this study who have the same risk of developing paget's disease as the general population. The primary objective of the Observational study will be to determine if genetic testing impacts on quality of life or depression in participants who do not have SQSTM1 gene mutations.

Protection of trial subjects:

The IDMC aimed to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial. To ensure safeguarding there was interim review of the trial’s progress including updated figures on recruitment, data quality, and main outcomes and safety data.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 March 2010
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	Spain: 18
Country: Number of subjects enrolled	United Kingdom: 134
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Ireland: 10
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Australia: 34
Country: Number of subjects enrolled	New Zealand: 4
Worldwide total number of subjects	222
EEA total number of subjects	50

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	204
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was randomised to the study on the 5th March 2010, and the final patient was randomised on the 16th April 2015. There was a total number of 222 participants randomised with 50% (N=111) being allocated to both treatments (Placebo, and Zoledronate 5mg). The recruitment of participants occurred at 25 sites across 7 countries.

Pre-assignment

Screening details:

The study involved an initial phase of genetic screening to identify eligible participants. Patients with PDB attending outpatient clinics underwent genetic testing for SQSTM1 mutations using Sanger sequencing of exons 7 and 8 of SQSTM1 and the intron–exon boundaries using DNA extracted from a venous blood sample according to standard techniques.

Pre-assignment period milestones

Number of subjects started	350[1]
Number of subjects completed	222

Pre-assignment subject non-completion reasons

Reason: Number of subjects	no reply: 11
Reason: Number of subjects	not interested: 83
Reason: Number of subjects	interested but not enrolled: 34

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The study involved an initial phase of genetic screening to identify eligible participants. Not all of those identified as eligible entered the full study

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The participants and investigators were blinded to treatment allocation. The ZA and placebo infusions were identical. Breaking the blind would only be performed where knowledge of the treatment is necessary for further management of the patient and was only performed by contacting the local pharmacy, which had the restricted code break details.

Arms

Are arms mutually exclusive?	Yes
Arm title	Zoledoronic Acid Treatment

Arm description:

The IMP was given by a single intravenous infusion and comprised of zoledronic acid (Aclasta®) (5mg in 100mL ready-to-infuse solution), it was given at a constant infusion rate over not less than 15min.

Arm type	Active comparator
Investigational medicinal product name	Zoledronic acid (Aclasta®) 5mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use, Infusion

Dosage and administration details:

Zoledronic acid (Aclasta®) 5mg by intravenous infusion at a constant infusion rate over not less than 15 min.

Arm title	Placebo

Arm description:

Placebo was given by a single intravenous infusion and comprised of 0.9% saline given at a constant infusion rate over not less than 15min.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

Placebo was given by a single intravenous infusion and comprised 0.9% saline. It was given at a constant infusion rate over not less than 15min.

Number of subjects in period 1	Zoledoronic Acid Treatment	Placebo
Started	111	111
Completed	90	90
Not completed	21	21
Deceased	1	4
Consent withdrawn by subject	8	9
Physician decision	1	1
Lost to follow-up	11	7

Period 2

Period 2 title	End of Study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes

Arm title	Zoledoronic Acid Treatment

Arm description:

The IMP was given by a single intravenous infusion and comprised of zoledronic acid (Aclasta®) (5mg in 100mL ready-to-infuse solution), it was given at a constant infusion rate over not less than 15min.

Arm type	Active comparator
Investigational medicinal product name	Zoledronic acid (Aclasta®) 5mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use, Infusion

Dosage and administration details:

Zoledronic acid (Aclasta®) 5mg by intravenous infusion at a constant infusion rate over not less than 15 min.

Arm title	Placebo

Arm description:

Placebo was given by a single intravenous infusion and comprised of 0.9% saline given at a constant infusion rate over not less than 15min.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

Placebo was given by a single intravenous infusion and comprised 0.9% saline. It was given at a constant infusion rate over not less than 15min.

Number of subjects in period 2	Zoledoronic Acid Treatment	Placebo
Started	90	90
Completed	90	90

Baseline characteristics

Reporting groups	
Reporting group title	Zoledoronic Acid Treatment

Reporting group description:

The IMP was given by a single intravenous infusion and comprised of zoledronic acid (Aclasta®) (5mg in 100mL ready-to-infuse solution), it was given at a constant infusion rate over not less than 15min.

Reporting group title	Placebo

Reporting group description:

Placebo was given by a single intravenous infusion and comprised of 0.9% saline given at a constant infusion rate over not less than 15min.

Reporting group values	Zoledoronic Acid Treatment	Placebo	Total
Number of subjects	111	111	222
Age categorical Units: Subjects			
Adults (18-64 years)	102	102	204
From 65-84 years	9	9	18
Age continuous Units: years			
arithmetic mean	49.8	50.5	
standard deviation	± 8.8	± 9.3	-
Gender categorical Units: Subjects			
Female	61	60	121
Male	50	51	101
Lifestyle - Smoking			
Lifestyle characteristics of participants			
Units: Subjects			
Current Smoker	13	20	33
Previous Smoker	45	55	100
Non-smoker	53	36	89
Alkaline Phosphatase Units: Subjects			
Raised	4	4	8
Not-raised	107	107	214
Type of Mutation Units: Subjects			
Missense	101	101	202
Truncating	10	10	20
Amino Acid Change Units: Subjects			
A390X	5	3	8
E396X	0	1	1
F406V	2	0	2
G411S	7	2	9
G425R	13	11	24
Gln371X	1	1	2

Glu396	1	2	3
I424S	2	0	2
K378X	1	1	2
M404V	13	12	25
P392L	64	77	141
Thr350GinfsX28	2	1	3
Previous fractures at baseline Units: Subjects			
Tibia	6	6	12
Femur	0	2	2
Humerus	1	5	6
Wrist	12	19	31
Clavicle	3	5	8
Ribs	5	5	10
Hand	6	8	14
Foot	11	8	19
Skull	0	2	2
Lumbar Spine	2	1	3
Facial bones	3	6	9
Any other bone	15	16	31
no fractures	47	28	75
Lifestyle- Alcohol consumption Units: Subjects			
Regular Drinker	70	71	141
Non-regular drinker	41	40	81
General appearance Units: Subjects			
Normal appearance	109	109	218
Non-normal appearance	2	2	4
Skin appearance Units: Subjects			
Normal	99	104	203
Non-normal	12	7	19
Head/Neck/ENT/Eyes appearance Units: Subjects			
Normal	106	108	214
non-normal	5	3	8
Cardiovascular Units: Subjects			
Normal	103	105	208
Non-Normal	8	6	14
Musculoskeletal Units: Subjects			
Normal	101	101	202
Non-normal	10	10	20
Central Nervous System Units: Subjects			
Normal	109	108	217
Non-normal	2	3	5

Weight			
Units: Kg			
arithmetic mean	79.5	82.0	
standard deviation	± 17.7	± 19.6	-
Height			
Units: Cm			
arithmetic mean	168	169	
standard deviation	± 9.0	± 9.0	-
Body Mass Index			
Units: BMI			
arithmetic mean	27.9	28.5	
standard deviation	± 5.3	± 6.3	-
Systolic blood pressure			
Units: mmHg			
arithmetic mean	129	130	
standard deviation	± 17	± 16	-
Diastolic blood pressure			
Units: mmHg			
arithmetic mean	79.6	79	
standard deviation	± 13.4	± 12	-
Pulse Rate			
Units: bpm			
arithmetic mean	70.3	69.7	
standard deviation	± 10.3	± 11.2	-
Alkaline Phosphatase			
Units: U/L			
arithmetic mean	78.2	80.1	
standard deviation	± 41.7	± 53.1	-
Alkaline Phosphatase (adjusted)			
Adjusted results are expressed in relation to the upper limit of normal for the local reference range			
Units: adjusted			
arithmetic mean	0.44	0.47	
standard deviation	± 0.32	± 0.37	-
Albumin			
Units: g/L			
arithmetic mean	44.3	44.0	
standard deviation	± 3.6	± 3.6	-
Calcium (adjusted)			
Adjusted for albumin values.			
Units: mmol/L			
arithmetic mean	2.40	2.41	
standard deviation	± 0.11	± 0.12	-
Aspartate aminotransferase (AST)			
Units: U/L			
arithmetic mean	24.0	25.1	
standard deviation	± 8.4	± 11.7	-
Alanine Transaminase (ALT)			
Units: U/L			
arithmetic mean	28.4	27.7	
standard deviation	± 17.1	± 19.5	-
Gamma GT			
Units: U/L			

arithmetic mean	27.7	37.9	
standard deviation	± 17.3	± 50.6	-
Bilirubin			
Units: umol/L			
arithmetic mean	10.23	10.40	
standard deviation	± 5.66	± 5.86	-
Serum 25(OH) D			
Units: nmol/L			
arithmetic mean	66.7	64.9	
standard deviation	± 46.1	± 34.1	-
Serum Creatinine			
Units: µmol/L			
arithmetic mean	72	74	
standard deviation	± 13	± 13	-
eGFR			
Units: ml/min/1.73 m2			
arithmetic mean	86.1	83.3	
standard deviation	± 21.1	± 17.4	-
Urea			
Units: mmol/L)			
arithmetic mean	5.22	5.17	
standard deviation	± 1.35	± 1.55	-
Haemoglobin			
Units: g/L			
arithmetic mean	153	174	
standard deviation	± 136	± 194	-
WBC			
Units: 10^9/l			
arithmetic mean	6.36	6.21	
standard deviation	± 1.55	± 1.69	-
Platelets			
Units: 10^9/l			
arithmetic mean	243	240	
standard deviation	± 57	± 63	-

Subject analysis sets

Subject analysis set title	Zoledoronic Acid Treatment
Subject analysis set type	Intention-to-treat
Subject analysis set description: Zoledoronic Acid Treatment group.	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo Placebo was given by a single intravenous infusion and comprised of 0.9% saline given at a constant infusion rate over not less than 15min	

Reporting group values	Zoledoronic Acid Treatment	Placebo	
Number of subjects	111	111	

Age categorical Units: Subjects			
Adults (18-64 years)	102	102	
From 65-84 years	9	9	
Age continuous Units: years			
arithmetic mean	49.8	50.5	
standard deviation	± 8.8	± 9.3	
Gender categorical Units: Subjects			
Female	61	60	
Male	50	51	
Lifestyle - Smoking			
Lifestyle characteristics of participants			
Units: Subjects			
Current Smoker	13	20	
Previous Smoker	45	55	
Non-smoker	53	36	
Alkaline Phosphatase Units: Subjects			
Raised	4	4	
Not-raised	107	107	
Type of Mutation Units: Subjects			
Missense	101	101	
Truncating	10	10	
Amino Acid Change Units: Subjects			
A390X	5	3	
E396X	0	1	
F406V	2	0	
G411S	7	2	
G425R	13	11	
Gln371X	1	1	
Glu396	1	2	
I424S	2	0	
K378X	1	1	
M404V	13	12	
P392L	64	77	
Thr350GinfsX28	2	1	
Previous fractures at baseline Units: Subjects			
Tibia	6	6	
Femur	0	2	
Humerus	1	5	
Wrist	12	19	
Clavicle	3	5	
Ribs	5	5	
Hand	6	8	
Foot	11	8	
Skull	0	2	

Lumbar Spine	2	1	
Facial bones	3	6	
Any other bone	15	16	
no fractures	47	28	
Lifestyle- Alcohol consumption Units: Subjects			
Regular Drinker	70	71	
Non-regular drinker	41	40	
General appearance Units: Subjects			
Normal appearance	109	109	
Non-normal appearance	2	2	
Skin appearance Units: Subjects			
Normal	99	104	
Non-normal	12	7	
Head/Neck/ENT/Eyes appearance Units: Subjects			
Normal	106	108	
non-normal	5	3	
Cardiovascular Units: Subjects			
Normal	103	105	
Non-Normal	8	6	
Musculoskeletal Units: Subjects			
Normal	101	101	
Non-normal	10	10	
Central Nervous System Units: Subjects			
Normal	109	108	
Non-normal	2	3	
Weight Units: Kg			
arithmetic mean	79.5	82.0	
standard deviation	± 17.7	± 19.6	
Height Units: Cm			
arithmetic mean	168	169	
standard deviation	± 9.0	± 9.0	
Body Mass Index Units: BMI			
arithmetic mean	27.9	28.5	
standard deviation	± 5.3	± 6.3	
Systolic blood pressure Units: mmHg			
arithmetic mean	129	130	
standard deviation	± 17	± 16	
Diastolic blood pressure Units: mmHg			
arithmetic mean	79.6	79	

standard deviation	± 13.4	± 12	
Pulse Rate			
Units: bpm			
arithmetic mean	70.3	69.7	
standard deviation	± 10.3	± 11.2	
Alkaline Phosphatase			
Units: U/L			
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standard deviation	± 41.7	± 53.1	
Alkaline Phosphatase (adjusted)			
Adjusted results are expressed in relation to the upper limit of normal for the local reference range			
Units: adjusted			
arithmetic mean	0.44	0.47	
standard deviation	± 0.32	± 0.37	
Albumin			
Units: g/L			
arithmetic mean	44.3	44.0	
standard deviation	± 3.6	± 3.6	
Calcium (adjusted)			
Adjusted for albumin values.			
Units: mmol/L			
arithmetic mean	2.40	2.41	
standard deviation	± 0.11	± 0.12	
Aspartate aminotransferase (AST)			
Units: U/L			
arithmetic mean	24.0	25.1	
standard deviation	± 8.4	± 11.7	
Alanine Transaminase (ALT)			
Units: U/L			
arithmetic mean	28.4	27.7	
standard deviation	± 17.1	± 19.5	
Gamma GT			
Units: U/L			
arithmetic mean	27.7	37.9	
standard deviation	± 17.3	± 50.6	
Bilirubin			
Units: umol/L			
arithmetic mean	10.23	10.40	
standard deviation	± 5.66	± 5.86	
Serum 25(OH) D			
Units: nmol/L			
arithmetic mean	66.7	64.9	
standard deviation	± 46.1	± 34.1	
Serum Creatinine			
Units: µmol/L			
arithmetic mean	72	74	
standard deviation	± 13	± 13	
eGFR			
Units: ml/min/1.73 m2			
arithmetic mean	86.1	83.3	
standard deviation	± 21.1	± 17.4	
Urea			

Units: mmol/L)			
arithmetic mean	5.22	5.17	
standard deviation	± 1.35	± 1.55	
Haemoglobin			
Units: g/L			
arithmetic mean	153	174	
standard deviation	± 136	± 194	
WBC			
Units: 10^9/l			
arithmetic mean	6.36	6.21	
standard deviation	± 1.55	± 1.69	
Platelets			
Units: 10^9/l			
arithmetic mean	243	240	
standard deviation	± 57	± 63	

End points

End points reporting groups

Reporting group title	Zoledoronic Acid Treatment

Reporting group description:

The IMP was given by a single intravenous infusion and comprised of zoledronic acid (Aclasta®) (5mg in 100mL ready-to-infuse solution), it was given at a constant infusion rate over not less than 15min.

Reporting group title	Placebo

Reporting group description:

Placebo was given by a single intravenous infusion and comprised of 0.9% saline given at a constant infusion rate over not less than 15min.

Reporting group title	Zoledoronic Acid Treatment

Reporting group description:

The IMP was given by a single intravenous infusion and comprised of zoledronic acid (Aclasta®) (5mg in 100mL ready-to-infuse solution), it was given at a constant infusion rate over not less than 15min.

Reporting group title	Placebo

Reporting group description:

Placebo was given by a single intravenous infusion and comprised of 0.9% saline given at a constant infusion rate over not less than 15min.

Subject analysis set title	Zoledoronic Acid Treatment
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Zoledoronic Acid Treatment group.

Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Placebo Placebo was given by a single intravenous infusion and comprised of 0.9% saline given at a constant infusion rate over not less than 15min

Primary: Patient summary of bone lesions

End point title	Patient summary of bone lesions[1]

End point description:

At baseline, 9 (8.1%) patients in the ZA group were found to have bone lesions typical of PDB, compared with 12 (10.8%) in the placebo group. By the end of the study, only 1 (0.9%) patient had evidence of a bone lesion in the ZA group, compared with 11 (9.9%) in the Placebo group.

End point type	Primary

End point timeframe:

Bone scans were collected between Baseline and End of Study visit, the median duration between the two visits was 84.00 months for both treatment arms. Bone scans underwent a semi-quantitative analysis by imaging experts blinded to treatment.

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 this outcome was done in counts of lesion, The statistical analysis for this end point is covered in the "patients developing new bone lesions at end of study" end point. In the ZA group, none of the participants developed a new bone lesion during the study, while two patients developed new lesions in the placebo group. (p= 0.246, odds ratio: 0.406, 95% CI 0.000, 3.425).

End point values	Zoledoronic Acid Treatment	Placebo	Zoledoronic Acid Treatment	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	111	111	90	89[2]
Units: Number of participants				
Yes	9	12	1	11
No	102	99	89	78

Notes:

[2] - One participant had baseline lesions but declined to have an end of study bone scan.

Statistical analyses

No statistical analyses for this end point

Primary: patients developing new bone lesions at end of study

End point title	patients developing new bone lesions at end of study

End point description:

Two new PDB lesions developed in patients allocated to placebo compared with no new lesions in the ZA group.

End point type	Primary

End point timeframe:

Bone scans were collected between Baseline and End of Study visit, the median duration between the two visits was 84.00 months for both treatment arms. Bone scans underwent a semi-quantitative analysis by imaging experts blinded to treatment.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	90	90		
Units: number of participants	0	2		

Statistical analyses

Statistical analysis title	Primary outcome - patients developing new bone les
Comparison groups	Zoledoronic Acid Treatment v Placebo
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.246
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.406
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	3.425

Secondary: Summary of bone lesions

End point title	Summary of bone lesions

End point description:

End point type	Secondary

End point timeframe:

Bone scans were collected between Baseline and End of Study visit, the median duration between the two visits was 84.00 months for both treatment arms. Bone scans underwent a semi-quantitative analysis by imaging experts blinded to treatment.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	111	111		
Units: Number of new lesions				
Number of lesions at baseline	15	29		
Number of lesions at end of study	2	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-level change in activity of bone lesions

End point title	Patient-level change in activity of bone lesions

End point description:

End point type	Secondary

End point timeframe:

Bone scans were collected between Baseline and End of Study visit, the median duration between the two visits was 84.00 months for both treatment arms. Bone scans underwent a semi-quantitative analysis by imaging experts blinded to treatment.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	90		
Units: number of lesions				
No lesion at baseline; no lesion at follow-up	81	77		
No lesion at baseline; new lesion(s) at follow-up	0	2		

Lesion(s) at baseline; fewer lesions at follow-up	9	4		
Lesions(s) at baseline; lesions unchanged at follo	0	3		
Lesion(s) at baseline; existing lesions increased	0	3		
No end of study assessment	21	22		

Statistical analyses

No statistical analyses for this end point

Secondary: patient-level lesion outcomes at end of study

End point title	patient-level lesion outcomes at end of study

End point description:

None of the participants allocated to ZA had a poor outcome (defined as the development of new lesions, lesions remaining unchanged, or having progressed) compared with 8 in the Placebo group (OR =0.08, 95% CI 0.00-0.42, p=0.003).

End point type	Secondary

End point timeframe:

Bone scans were collected between Baseline and End of Study visit, the median duration between the two visits was 84.00 months for both treatment arms. Bone scans underwent a semi-quantitative analysis by imaging experts blinded to treatment.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	90		
Units: number of participants	0	8		

Statistical analyses

Statistical analysis title	patient-level lesion outcomes at end of study
Comparison groups	Zoledoronic Acid Treatment v Placebo
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [3]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.424
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.424

Notes:

[3] - Due to sparse and zero cell data, an unadjusted Fisher's exact test has been used, modelling the odds of a poor outcome.
A median unbiased estimate and a one-sided p-value are presented.

Secondary: Urinary N-telopeptide (uNTX) as a ratio of creatinine

End point title	Urinary N-telopeptide (uNTX) as a ratio of creatinine

End point description:

This analyte is a biochemical marker of bone resorption. Mean values at baseline and end of study are expressed as a ratio to urine creatinine - uNTX/Cr. At baseline, the uNTX/Cr was higher in the ZA treatment arm (89.7 SD 315.6) group compared to the Placebo group. (64.7 SD 56.2). When uNTX/Cr was measured at the end of the study, values had decreased in the ZA group to 56.6 (SD 65.3) but increased in the Placebo group, 88.0 (SD 174.8).

End point type	Secondary

End point timeframe:

Blood samples were collected at Baseline and End of Study Visits. The median duration of time between Baseline and End of study visit was 84.0 months for both arms.

End point values	Zoledoronic Acid Treatment	Placebo	Zoledoronic Acid Treatment	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	103	100	88	89
Units: uNTX/Cr				
arithmetic mean (standard deviation)	89.7 (± 315.6)	64.7 (± 56.2)	56.6 (± 65.3)	88.0 (± 1748)

Attachments (see zip file)	uNTX:Cr graph.png

Statistical analyses

No statistical analyses for this end point

Secondary: C-terminal telopeptide (CTX)

End point title	C-terminal telopeptide (CTX)

End point description:

Serum CTX is a marker for bone resorption. Mean baseline levels were similar in the two groups, ZA 0.33 ng/mL (SD 0.17) vs Placebo 0.35 ng/mL (SD 0.17). By the end of study CTX was slightly higher than at baseline in the placebo treatment group (0.41 ng/mL SD 0.20), but had fallen in the ZA group to 0.28 ng/mL (SD 0.14). Overall, there was a significant reduction in CTX in the ZA group (-0.09, 95% CI -0.12,-0.07, P-value <.0001).

End point type	Secondary

End point timeframe:

Samples were collected between Baseline and End of Study visit, the median duration between the two visits was 84.00 months for both treatment arms.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	101		
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline	0.33 (± 0.17)	0.35 (± 0.17)		
12 months	0.14 (± 0.12)	0.27 (± 0.13)		
24 months	0.18 (± 0.09)	0.28 (± 0.17)		
36 months	0.19 (± 0.08)	0.28 (± 0.15)		
48 months	0.20 (± 0.07)	0.27 (± 0.19)		
60 months	0.20 (± 0.07)	0.24 (± 0.09)		
End of Study	0.28 (± 0.14)	0.41 (± 0.20)		

Attachments (see zip file)	CTX.png

Statistical analyses

Statistical analysis title	C-terminal telopeptide - CTX (ng/mL)

Statistical analysis description:

Least squares mean estimates from repeated measures analysis of covariance. The estimated treatment difference (Zoledronate - Placebo) and p-value indicate the overall model-derived treatment effect (taking into account all timepoints).

Comparison groups	Zoledoronic Acid Treatment v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	-0.07

Secondary: Bone specific alkaline phosphatase - BSALP (U/L)

End point title	Bone specific alkaline phosphatase - BSALP (U/L)

End point description:

This is a marker of bone formation. At baseline, mean values were similar in the two groups, (ZA 11.0 U/L SD 7.5 vs Placebo 10.5 U/L SD 8.0). At the end of study, concentrations of BSALP increased in participants treated with ZA (14.1 U/L SD 5.9), and the Placebo group (17.2 U/L SD 10.2).). Overall, there was a significant reduction in BSALP in the ZA group (-1.68, 95% CI -2.59,-0.78, P-value 0.0003).

End point type	Secondary

End point timeframe:

Samples were collected between Baseline and End of Study visit, the median duration between the two visits was 84.00 months for both treatment arms.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	100		
Units: U/L				
arithmetic mean (standard deviation)				
Baseline	11.0 (± 7.5)	10.5 (± 8.0)		
12 months	8.7 (± 3.0)	11.0 (± 3.9)		
24 months	10.0 (± 4.3)	12.5 (± 7.0)		
36 months	11.0 (± 4.7)	11.4 (± 3.5)		
48 months	11.0 (± 5.4)	12.3 (± 3.8)		
60 months	11.2 (± 3.5)	11.3 (± 3.8)		
End of Study	14.1 (± 5.9)	17.2 (± 10.2)		

Attachments (see zip file)	Bone specific alkaline phosphatase (BSALP)/BSALP.png

Statistical analyses

Statistical analysis title	Bone specific alkaline phosphatase - BSALP (U/L)
Comparison groups	Zoledoronic Acid Treatment v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0003
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.59
upper limit	-0.78

Notes:

[4] - Least squares mean estimates from repeated measures analysis of covariance.
The estimated treatment difference (Zoledronate - Placebo) and p-value indicate the overall model-derived treatment effect (taking into account all timepoints).

Secondary: Procollagen type 1 N-terminal Propeptide - P1NP (ng/mL)

End point title	Procollagen type 1 N-terminal Propeptide - P1NP (ng/mL)

End point description:

This is a marker of bone formation. Mean (SD) baseline P1NP levels were similar in the two groups (ZA 55.0 ng/mL SD 27.0 vs Placebo 59.5 ng/mL SD 40.8). At the end of study, P1NP had fallen in the ZA group (44.0 ng/mL SD 17.4), but increased in the placebo group (63.9 ng/mL SD 67.0). Overall, there was a significant reduction in PINP in the ZA group (-16.32 (-22.05,-10.59), P-value <.0001).

End point type	Secondary

End point timeframe:

Samples were collected between Baseline and End of Study visit, the median duration between the two

visits was 84.00 months for both treatment arms.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	101		
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline	55 (± 27)	59.5 (± 40.8)		
12 month	29.3 (± 11.0)	53.7 (± 22.8)		
24 month	37.8 (± 16.7)	59.9 (± 48.1)		
36 month	40.4 (± 13.6)	59.3 (± 42.5)		
48 month	44.3 (± 13.6)	61.5 (± 56.0)		
60 month	42.9 (± 12.6)	52.3 (± 15.3)		
End of study	44.0 (± 17.4)	63.9 (± 67.0)		

Attachments (see zip file)	Plasma Procollagen type 1 N-terminal Propeptide (P/P1NP.png

Statistical analyses

Statistical analysis title	Procollagen type 1 N-terminal Propeptide - P1NP

Statistical analysis description:

Results of each biomarker sample was modelled using a repeated measures analysis of covariance (ANCOVA) adjusting for the relevant baseline measure and the minimisation variables.

Comparison groups	Placebo v Zoledoronic Acid Treatment
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-16.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.05
upper limit	-10.59

Secondary: Brief Pain Inventory - Interference Score

End point title	Brief Pain Inventory - Interference Score

End point description:

Scores range between 0 – 10. Higher scores indicate greater pain
At baseline the mean interference score was higher in the ZA group (1.00 SD 1.71) compared to the Placebo group (0.82 SD 1.49). During the study interference scores increased with a trend for a lesser increase in the ZA group. Overall there was no significant difference between the groups (-0.37, 95% CI

-0.78,0.03, P-value 0.070).

End point type	Secondary

End point timeframe:

Scores were collected between Baseline and End of Study visit and at annual review visits. The median duration between the two visits was 84.00 months for both treatment arms.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	111	111		
Units: Interference Score				
arithmetic mean (standard deviation)				
Baseline	1.00 (± 1.71)	0.82 (± 1.49)		
12 month	1.14 (± 1.94)	1.17 (± 2.03)		
24 month	1.19 (± 1.93)	1.27 (± 2.22)		
36 month	1.25 (± 2.08)	1.43 (± 2.30)		
48 month	1.29 (± 2.14)	1.19 (± 2.05)		
60 month	1.40 (± 2.17)	1.55 (± 2.39)		
End of Study	1.26 (± 2.13)	1.47 (± 2.26)		

Attachments (see zip file)	Pain interference score/BPI interference.png

Statistical analyses

Statistical analysis title	Brief Pain Inventory - Interference score

Statistical analysis description:

Formal analyses of these scores was undertaken, modelled using a repeated measures analysis of covariance (ANCOVA) adjusting for the relevant baseline QoL measure and the minimisation variables. The estimated treatment effect and 95% confidence interval will be presented for each outcome.

Comparison groups	Zoledoronic Acid Treatment v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	-0.03

Secondary: Brief Pain Inventory - Severity Score

End point title	Brief Pain Inventory - Severity Score

End point description:

Brief Pain Inventory questions are scored within a range of 0 to 10 where higher scores indicate greater pain
At baseline the mean BPI severity scores were similar in the two groups; ZA 1.34 SD 1.68 vs 1.24 SD 1.53. During the study scores in both groups increased but there was no significant difference between the (-0.28 95% CI 0.70, 0.13, P-value 0.175)

End point type	Secondary

End point timeframe:

Scores were collected between Baseline and End of Study visit and at annual review visits. The median duration between the two visits was 84.00 months for both treatment arms.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	110	111		
Units: Score				
arithmetic mean (standard deviation)				
Baseline	1.34 (± 1.68)	1.29 (± 1.61)		
12 month	1.50 (± 1.99)	1.46 (± 1.92)		
24 month	1.64 (± 2.08)	1.62 (± 2.03)		
36 month	1.58 (± 1.95)	1.68 (± 2.02)		
48 month	1.74 (± 2.16)	1.72 (± 2.10)		
60 month	1.80 (± 2.22)	1.92 (± 2.28)		
End of Visit	1.66 (± 1.94)	1.86 (± 2.04)		

Attachments (see zip file)	Pain severity score /BPI severity.png

Statistical analyses

Statistical analysis title	Brief Pain Inventory - Severity score

Statistical analysis description:

Formal analyses of these scores was modelled using a repeated measures analysis of covariance (ANCOVA) adjusting for the relevant baseline QoL measure and the minimisation variables.

Comparison groups	Zoledoronic Acid Treatment v Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.175
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.13

Secondary: SF-36 - Physical Component Score

End point title	SF-36 - Physical Component Score

End point description:

Each sub-scale of the SF-36 questionnaire has been normalised with a mean of 50 and a standard deviation of 10. A score less than 50 indicates health status below average and vice versa.
At baseline the mean physical component summary scores were similar in the ZA arm 51.4 (SD 8.1) and placebo arm 51.9 (SD 8.6). By the end of the study, values had fallen slightly in both arms but there was no significant difference between the groups (mean difference, 95% CI) 1.60 (-0.24, 3.43, P- value 0.086).

End point type	Secondary

End point timeframe:

Scores were collected between Baseline and End of Study visit and at annual review visits. The median duration between the two visits was 84.00 months for both treatment arms.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	111	111		
Units: Score				
arithmetic mean (standard deviation)				
Baseline	51.4 (± 8.1)	51.9 (± 8.6)		
12 month	51.0 (± 8.4)	50.9 (± 9.1)		
24 month	50.9 (± 9.3)	50.5 (± 8.4)		
36 month	50.7 (± 9.0)	49.4 (± 9.8)		
48 month	49.5 (± 8.8)	49.9 (± 9.6)		
60 month	49.6 (± 9.0)	48.9 (± 10.6)		
End of Study	50.3 (± 9.1)	48.6 (± 9.9)		

Attachments (see zip file)	Changes in SF36 physical component summary during/SF36

Statistical analyses

Statistical analysis title	SF-36 - Physical Component Score

Statistical analysis description:

Formal analyses of these scores was modelled using a repeated measures analysis of covariance (ANCOVA) adjusting for the relevant baseline QoL measure and the minimisation variables.

Comparison groups	Zoledoronic Acid Treatment v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.086
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	3.43

Secondary: SF-36 - Mental Component Score

End point title	SF-36 - Mental Component Score

End point description:

Each sub-scale of the SF-36 questionnaire has been normalised with a mean of 50 and a standard deviation of 10. A score less than 50 indicates health status below average and vice versa.
Values for the SF-36 - Mental Component Summary Score were identical at baseline with a mean value of 52.5 (SD 8.5). During the study scores tended to increase in the ZA arm but had decreased slightly in the placebo arm. Overall, there was no difference between the groups (mean difference 0.51, 95% CI-1.31, 2.32, P-value 0.584)

End point type	Secondary

End point timeframe:

Scores were collected between Baseline and End of Study visit and at annual review visits. The median duration between the two visits was 84.00 months for both treatment arms.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	111	111		
Units: Score				
arithmetic mean (standard deviation)				
Baseline	52.5 (± 8.5)	52.5 (± 8.8)		
12 month	51.9 (± 8.0)	51.3 (± 10.2)		
24 month	52.5 (± 8.2)	50.9 (± 9.2)		
36 month	52.7 (± 8.6)	50.6 (± 9.2)		
48 month	51.7 (± 10.3)	52.1 (± 8.7)		
60 month	52.7 (± 8.6)	49.7 (± 10.5)		
End of Study	53.1 (± 8.2)	50.9 (± 11.7)		

Attachments (see zip file)	Changes in SF36 mental component summary /SF36 mental.

Statistical analyses

Statistical analysis title	SF-36 - Mental Component Score

Statistical analysis description:

Formal analyses of these scores was modelled using a repeated measures analysis of covariance (ANCOVA) adjusting for the relevant baseline QoL measure and the minimisation variables.

Comparison groups	Zoledoronic Acid Treatment v Placebo

Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.584
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	2.32

Secondary: Health Anxiety and Depression Scale (HADS) - Anxiety Score

End point title	Health Anxiety and Depression Scale (HADS) - Anxiety Score

End point description:

Anxiety scores range between 0 and 21. Higher scores indicate greater anxiety levels.
At baseline there was no significant difference between the groups in levels of anxiety and no difference between groups during the study

End point type	Secondary

End point timeframe:

Scores were collected between Baseline and End of Study visit and at annual review visits. The median duration between the two visits was 84.00 months for both treatment arms.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	111	111		
Units: Score				
arithmetic mean (standard deviation)				
Baseline	3.5 (± 2.7)	3.7 (± 3.2)		
12 month	3.5 (± 3.2)	3.9 (± 3.7)		
24 month	3.4 (± 3.3)	3.7 (± 3.1)		
36 month	3.7 (± 3.2)	4.2 (± 3.8)		
48 month	3.9 (± 3.7)	3.9 (± 3.5)		
60 month	3.3 (± 3.3)	4.1 (± 3.5)		
End of Study	3.3 (± 3.0)	4.1 (± 3.9)		

Attachments (see zip file)	. Changes in anxiety scores /HADS anxiety.png

Statistical analyses

Statistical analysis title	Health Anxiety and Depression Scale (HADS) - Anxie

Statistical analysis description:

Formal analyses of these scores was modelled using a repeated measures analysis of covariance (ANCOVA) adjusting for the relevant baseline QoL measure and the minimisation variables.

Comparison groups	Zoledoronic Acid Treatment v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.574
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	0.49

Secondary: Health Anxiety and Depression Scale (HADS) - Depression Score

End point title	Health Anxiety and Depression Scale (HADS) - Depression Score

End point description:

Depression scores range between 0 and 21. Higher scores indicate greater depression levels.
At baseline, mean depression scores were marginally lower in the ZA group compared to the placebo group (3.3 (SD 3.0) vs 3.5 (SD 2.8)). As the trial progressed, the ZA treatment group depression score tended to decrease but increased in the placebo group. However, there was no significant difference between the two treatments; mean difference (95% CI) = -0.29 (-0.90, 0.31), P-value 0.340.

End point type	Secondary

End point timeframe:

Scores were collected between Baseline and End of Study visit and at annual review visits. The median duration between the two visits was 84.00 months for both treatment arms.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	111	111		
Units: Score				
arithmetic mean (standard deviation)				
Baseline	3.3 (± 3.0)	3.5 (± 2.8)		
12 month	3.2 (± 2.7)	3.8 (± 3.4)		
24 month	3.2 (± 2.9)	3.4 (± 3.0)		
36 month	3.3 (± 2.8)	3.7 (± 3.4)		
48 month	3.7 (± 3.5)	3.6 (± 3.2)		
60 month	3.0 (± 2.7)	3.8 (± 3.4)		
End of Study	3.1 (± 2.9)	3.9 (± 3.7)		

Attachments (see zip file)	Changes in depression scores /HADS depression.png

Statistical analyses

Statistical analysis title	Health Anxiety and Depression Scale (HADS) - Depr

Statistical analysis description:

Formal analyses of these scores was modelled using a repeated measures analysis of covariance (ANCOVA) adjusting for the relevant baseline QoL measure and the minimisation variables.

Comparison groups	Zoledoronic Acid Treatment v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.31

Secondary: Health Anxiety and Depression Scale (HADS) - Total Score

End point title	Health Anxiety and Depression Scale (HADS) - Total Score

End point description:

Total scores range from 0 to 42. Higher scores indicate greater anxiety and depression levels.
There was no significant difference between the two treatments in terms of combined scores for anxiety and depression at baseline or during the study as shown in Figure 13. Mean difference = -0.48 (95% CI -1.71,0.74) P-value 0.437.

End point type	Secondary

End point timeframe:

Scores were collected between Baseline and End of Study visit and at annual review visits. The median duration between the two visits was 84.00 months for both treatment arms.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	111	111		
Units: Score				
arithmetic mean (standard deviation)				
Baseline	6.9 (± 5.4)	7.3 (± 5.6)		
12 month	6.6 (± 5.5)	7.7 (± 6.9)		
24 month	6.6 (± 6.0)	7.2 (± 5.9)		
36 month	7.0 (± 5.8)	7.6 (± 6.9)		
48 month	7.6 (± 7.0)	7.5 (± 6.5)		
60 month	6.3 (± 5.8)	7.9 (± 6.7)		
End of Study	6.4 (± 5.7)	8.0 (± 7.3)		

Attachments (see zip file)	Changes in combined anxiety and depression score d/HADS

Statistical analyses

Statistical analysis title	Health Anxiety and Depression Scale (HADS) - Total

Statistical analysis description:

Formal analyses of these scores was modelled using a repeated measures analysis of covariance (ANCOVA) adjusting for the relevant baseline QoL measure and the minimisation variables.

Comparison groups	Zoledoronic Acid Treatment v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.437
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.71
upper limit	0.74

Secondary: Number of new lesions at end of study

End point title	Number of new lesions at end of study

End point description:

End point type	Secondary

End point timeframe:

Bone scans were collected between Baseline and End of Study visit, the median duration between the two visits was 84.00 months for both treatment arms. Bone scans underwent a semi-quantitative analysis by imaging experts blinded to treatment.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	90		
Units: number of lesions	0	2		

Statistical analyses

Statistical analysis title	Number of NEW lesions at end of study
Statistical analysis description:	
A rate ratio of <1 indicates a treatment effect in favour of Zoledronate	
Comparison groups	Zoledoronic Acid Treatment v Placebo
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.247
Method	Poisson regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	3.434

Secondary: Change in activity of existing lesions

End point title	Change in activity of existing lesions

End point description:

In the ZA group 13/15 lesions had disappeared (86.7%), 2/15 had decreased (13.3%) and none remained stable or had progressed. In the Placebo group, 1 had disappeared (3.4%), 12 were thought to have decreased in intensity (41.4%), 8 were thought to be unchanged (27.6%) and 4 had increased in intensity and/or extent (13.8%).

End point type	Secondary

End point timeframe:

Bone scans were collected between Baseline and End of Study visit, the median duration between the two visits was 84.00 months for both treatment arms. Bone scans underwent a semi-quantitative analysis by imaging experts blinded to treatment.

End point values	Zoledoronic Acid Treatment	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	111	111		
Units: number of lesions				
Disappeared	13	1		
Decreased	2	12		

No change	0	8		
Increased	0	4		
No end of study assessment	0	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Zoledronate 5mg

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Zoledronate 5mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 110 (16.36%)	25 / 111 (22.52%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	1	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
missing	Additional description: missing		
subjects affected / exposed	2 / 110 (1.82%)	3 / 111 (2.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Vascular disorders			
missing	Additional description: missing		
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
missing	Additional description: missing		
subjects affected / exposed	4 / 110 (3.64%)	8 / 111 (7.21%)	
occurrences causally related to treatment / all	0 / 4	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			

missing	Additional description: missing		
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
missing	Additional description: missing		
subjects affected / exposed	1 / 110 (0.91%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
missing	Additional description: missing		
subjects affected / exposed	1 / 110 (0.91%)	3 / 111 (2.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Congenital, familial and genetic disorders			
missing	Additional description: missing		
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
missing	Additional description: missing		
subjects affected / exposed	3 / 110 (2.73%)	3 / 111 (2.70%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
missing	Additional description: missing		
subjects affected / exposed	6 / 110 (5.45%)	3 / 111 (2.70%)	
occurrences causally related to treatment / all	2 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
missing	Additional description: missing		
subjects affected / exposed	1 / 110 (0.91%)	3 / 111 (2.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
missing	Additional description: missing		
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
missing	Additional description: missing		
subjects affected / exposed	1 / 110 (0.91%)	3 / 111 (2.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
missing	Additional description: missing		
subjects affected / exposed	4 / 110 (3.64%)	3 / 111 (2.70%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
missing	Additional description: missing		
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Zoledronate 5mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 110 (75.45%)	82 / 111 (73.87%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
missing	Additional description: missing		
subjects affected / exposed	9 / 110 (8.18%)	4 / 111 (3.60%)	
occurrences (all)	10	4	
Vascular disorders			
missing	Additional description: missing		
subjects affected / exposed	5 / 110 (4.55%)	9 / 111 (8.11%)	
occurrences (all)	5	9	
Surgical and medical procedures			

missing	Additional description: missing		
subjects affected / exposed	28 / 110 (25.45%)	36 / 111 (32.43%)	
occurrences (all)	82	59	
General disorders and administration site conditions			
missing	Additional description: missing		
subjects affected / exposed	8 / 110 (7.27%)	15 / 111 (13.51%)	
occurrences (all)	10	21	
Immune system disorders			
missing	Additional description: missing		
subjects affected / exposed	2 / 110 (1.82%)	1 / 111 (0.90%)	
occurrences (all)	2	1	
Social circumstances			
missing	Additional description: missing		
subjects affected / exposed	0 / 110 (0.00%)	2 / 111 (1.80%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
missing	Additional description: missing		
subjects affected / exposed	11 / 110 (10.00%)	13 / 111 (11.71%)	
occurrences (all)	13	13	
Respiratory, thoracic and mediastinal disorders			
missing	Additional description: missing		
subjects affected / exposed	9 / 110 (8.18%)	10 / 111 (9.01%)	
occurrences (all)	10	18	
Psychiatric disorders			
missing	Additional description: missing		
subjects affected / exposed	9 / 110 (8.18%)	13 / 111 (11.71%)	
occurrences (all)	10	17	
Investigations			
missing	Additional description: missing		
subjects affected / exposed	26 / 110 (23.64%)	35 / 111 (31.53%)	
occurrences (all)	45	57	
Injury, poisoning and procedural complications			
missing	Additional description: missing		
subjects affected / exposed	27 / 110 (24.55%)	28 / 111 (25.23%)	
occurrences (all)	37	47	
Cardiac disorders			

missing	Additional description: missing		
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Nervous system disorders			
missing	Additional description: missing		
subjects affected / exposed	23 / 110 (20.91%)	20 / 111 (18.02%)	
occurrences (all)	30	27	
Blood and lymphatic system disorders			
missing	Additional description: missing		
subjects affected / exposed	0 / 110 (0.00%)	3 / 111 (2.70%)	
occurrences (all)	0	3	
Ear and labyrinth disorders			
missing	Additional description: missing		
subjects affected / exposed	5 / 110 (4.55%)	8 / 111 (7.21%)	
occurrences (all)	6	9	
Eye disorders			
missing	Additional description: missing		
subjects affected / exposed	5 / 110 (4.55%)	6 / 111 (5.41%)	
occurrences (all)	5	6	
Gastrointestinal disorders			
missing	Additional description: missing		
subjects affected / exposed	19 / 110 (17.27%)	24 / 111 (21.62%)	
occurrences (all)	29	43	
Hepatobiliary disorders			
missing	Additional description: missing		
subjects affected / exposed	0 / 110 (0.00%)	4 / 111 (3.60%)	
occurrences (all)	0	5	
Skin and subcutaneous tissue disorders			
missing	Additional description: missing		
subjects affected / exposed	6 / 110 (5.45%)	13 / 111 (11.71%)	
occurrences (all)	9	17	
Renal and urinary disorders			
missing	Additional description: missing		
subjects affected / exposed	4 / 110 (3.64%)	5 / 111 (4.50%)	
occurrences (all)	4	10	
Endocrine disorders			
missing	Additional description: missing		

subjects affected / exposed	4 / 110 (3.64%)	3 / 111 (2.70%)	
occurrences (all)	4	3	
Musculoskeletal and connective tissue disorders			
missing	Additional description: missing		
subjects affected / exposed	46 / 110 (41.82%)	56 / 111 (50.45%)	
occurrences (all)	96	106	
Infections and infestations			
missing	Additional description: missing		
subjects affected / exposed	50 / 110 (45.45%)	48 / 111 (43.24%)	
occurrences (all)	145	111	
Metabolism and nutrition disorders			
missing	Additional description: missing		
subjects affected / exposed	6 / 110 (5.45%)	9 / 111 (8.11%)	
occurrences (all)	8	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2009	1. Protocol Change- Genetic test on previous samples. 2. Cover letters for participants updated. 3. Consents updated - "GP will be informed". 4. Minor protocol amendments- telephone consent.
07 April 2009	1. Routine bloods added. 2. Hypocalcaemia has been added as an exclusion criterion. PIL and consent updated. 3. Addition of new study letters (Protocol appendix 9-12).
29 June 2009	1. Relative info gathered - gender, age, initials and the town/country in which they live. 2. Other minor protocol clarifications.
29 September 2009	1. Addition of Sites - Salford and Nottingham 2. Addition of PICS - Glasgow and Newcastle 3. Minor protocol clarifiactions. 4. Update of PILs - 40ml blood sample not 20ml. Patients should be fasted.
11 November 2009	1. Addition of Sites - London Kings College, Oswestry 2. Non-sub amendments to Documents
30 March 2010	1. Removal of physical exam, BPI from Observational Study. 2. Collection of the specialised biomarkers optional for Observational Study. 3. Pregnancy test to be taken on at baseline, not screening. Urine test now allowed but serum preferred. 4. No repeat Vitamin D at baseline or 30mths. 5. Protocol changed to specify tests carried out on blood/urine samples in "future research" PILs updated to reflect this. 6. Clarification - SAE data collected from Interventional only. 7. Site list removed from protocol - as separate doc. 8. Consents updated to have correct PIL dates on them. 9. Minor amendments to QOL Qs. 10. Addition of Site- Brussels, Barcelona
27 March 2012	1. Extension to duration of study - 2020 2. Reduction in sample size - 260 from 400. 3. Removal of second infusion at 30 months. 4. Changes in exclusion criteria-removed abnormalities of liver function, hypocalcaemia remainsbut cut-off of <2.2mmol/l removed. 5. Collecting contact information about relatives of probands 6. Biochemical marker and bone lesion sub-studies - references removed as now one group. 7. Assessing causality of adverse events and serious adverse events. 8. Establishing twitter and Facebook pages for the ZIPP trial
09 June 2014	1. To request approval to send out a birthday card, Christmas card and newsletter to all intervention and observational participants each year
10 December 2015	Update protocol to v7 modify RSI
14 December 2016	Update to RSI
19 December 2017	Update to RSI

07 June 2018	1. clarifications of the technical details around how the primary outcome will be assessed by the imaging expert(s) 2. addition of secondary outcomes, which principally concern semi-quantitative analysis of bone lesions found on imaging as well as the addition of clinical endpoints that might be due to progression of Paget's disease.
29 October 2019	Change of trial timelines. EU Sponsor Representative. Clean-up of historic SmPC amendments for international sites
18 December 2020	Allow visits to continue beyond 2020

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.

We did not anticipate that ~10% of participants would already show bone scan evidence of PDB at baseline. The proportion of participants developing new lesions was very small; only 2 participants developed new lesions compared to the predicted 15%

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32176830

http://www.ncbi.nlm.nih.gov/pubmed/31488492