Clinical trial results:
Randomised trial of Teriparatide followed by Zoledronic acid versus standard care to prevent fractures in adults with Osteogenesis Imperfecta (OI)

Summary

EudraCT number	2016-003228-22
Trial protocol	GB IE DK FR NL
Global end of trial date	16 February 2025

Results information

Result version number	v1 (current)
This version publication date	26 March 2026
First version publication date	26 March 2026

Trial information

Trial identification

Sponsor protocol code	AC16092

Additional study identifiers

ISRCTN number	ISRCTN15313991
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Edinburgh and NHS Lothian
Sponsor organisation address	Usher Building The University of Edinburgh Edinburgh BioQuarter 5-7 Little France Road, Edinburgh, United Kingdom, EH16 4UX
Public contact	Prof. Stuart Ralston, Institute of Genetics and Cancer, University of Edinburgh , 44 131-651-8743 , stuart.ralston@ed.ac.uk
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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	20 August 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2025
Global end of trial reached?	Yes
Global end of trial date	16 February 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective
To investigate if a two-year course of TPTD followed by antiresorptive therapy with a single infusion of zoledronic acid (ZA) in adults with OI reduces the proportion of patients who experience a fracture as compared with standard care

Secondary Objectives
To investigate if a two-year course of TPTD followed by antiresorptive therapy with a single infusion of ZA in adults with OI reduces the total number of fractures, reduces the risk of vertebral fractures; or affects bone pain, quality of life and functional status as compared with standard care.

Mechanistic Objective
To understand which baseline characteristics of adults with OI, such as age, clinical subtype of OI, genetic diagnosis, bone turnover, BMD, and previous treatment influences the occurrence of fractures and/or the response to treatment

Protection of trial subjects:

Specific measures were implemented to protect trial participants and minimise potential risk, pain, and distress. Participants randomised to the interventional arm received structured training by appropriately qualified healthcare professionals on the correct use of the investigational medicinal product (IMP) injection pen, including clear written and verbal instructions on administration and correct storage, including refrigeration requirements. Participant-completed injection pen diaries were used to support adherence and facilitate early identification of potential issues. A predefined safety monitoring plan was implemented and overseen by the study sponsor, with independent oversight provided by a Data Monitoring Committee (DMC). Prior to initiation of study medication, safety blood tests were performed to assess serum creatinine, serum calcium, albumin, serum total alkaline phosphatase (ALP), and estimated glomerular filtration rate (eGFR), with serum 25-hydroxyvitamin D measured where clinically indicated, to ensure there were no contraindications to teriparatide or bisphosphonate therapy. Participants were monitored for adverse events throughout the study and were free to withdraw at any time without impact on their standard clinical care.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	26 June 2017
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	Netherlands: 8

Country: Number of subjects enrolled	United Kingdom: 303
Country: Number of subjects enrolled	Denmark: 18
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Ireland: 10
Worldwide total number of subjects	349
EEA total number of subjects	46

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)	319
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From 26th June 2017 to 16th February 2023 we recruited adults with a clinical diagnosis of osteogenesis imperfecta to the trial from 27 referral centres for bone disease located in five different countries. The distribution was UK (n=303, 87%), Republic of Ireland (n=10, 3%), Holland (n=9, 3%), France (n=10, 3%), and Denmark (n=18, 5%).

Pre-assignment

Screening details:

A total of 792 subjects with osteogenesis imperfecta were identified. Of these, 361 (45.5%) consented and entered screening; 11 were not eligible due to failed or incomplete eligibility assessment, entry in error, or low body weight. Overall, 350 subjects were randomised (176 TPTD/ZA; 174 standard care). Study population reflects protocol criteria.

Pre-assignment period milestones

Number of subjects started	349
Number of subjects completed	349

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard Care

Arm description:

Participants in the standard care group were permitted to continue with existing bone modifying treatment (i.e., bisphosphonate treatment) or be given no active bone modifying treatment, according to the clinical judgement of the local investigator. Bisphosphonates could be continued, stopped or started during the study at the discretion of the local investigator. Other bone modifying drugs could also be given at the discretion of the local investigator with the exception of teriparatide and investigational (experimental) agents with effects on bone metabolism

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Active treatment group

Arm description:

TPTD 20mcg daily, given subcutaneously using a self-administered injection device for two years followed by a single intravenous infusion of ZA 5mg. If TPTD given for < 12 months no ZA infusion is required.
Bisphosphonates, denosumab and strontium ranelate were stopped in the active treatment group at baseline and prohibited during treatment with TPTD since these may alter the therapeutic response to TPTD (18). Bisphosphonates were prohibited following treatment with ZA for at least 12 months to avoid over suppression of bone turnover.

Arm type	Experimental

Investigational medicinal product name	Teriparatide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Injection

Dosage and administration details:

20mcg daily, given subcutaneously using a self-administered injection device in participants ≥30Kg
20mcg given twice weekly, given subcutaneously using a self-administered injection device in participants <30kg

Investigational medicinal product name	Zoledronic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Zoledronic Acid 5 mg/100ml solution for single infusion

Number of subjects in period 1	Standard Care	Active treatment group
Started	173	176
Completed	152	150
Not completed	21	26
Adverse event, serious fatal	6	4
Physician decision	7	9
Consent withdrawn by subject	8	13

Baseline characteristics

Reporting groups	
Reporting group title	Standard Care
Reporting group description:	
Participants in the standard care group were permitted to continue with existing bone modifying treatment (i.e., bisphosphonate treatment) or be given no active bone modifying treatment, according to the clinical judgement of the local investigator. Bisphosphonates could be continued, stopped or started during the study at the discretion of the local investigator. Other bone modifying drugs could also be given at the discretion of the local investigator with the exception of teriparatide and investigational (experimental) agents with effects on bone metabolism	
Reporting group title	Active treatment group
Reporting group description:	
TPTD 20mcg daily, given subcutaneously using a self-administered injection device for two years followed by a single intravenous infusion of ZA 5mg. If TPTD given for < 12 months no ZA infusion is required. Bisphosphonates, denosumab and strontium ranelate were stopped in the active treatment group at baseline and prohibited during treatment with TPTD since these may alter the therapeutic response to TPTD (18). Bisphosphonates were prohibited following treatment with ZA for at least 12 months to avoid over suppression of bone turnover.	

Reporting group values	Standard Care	Active treatment group	Total
Number of subjects	173	176	349
Age categorical			
The fracture risk in OI is at least an order of magnitude above that in patients with osteoporosis. Affected individuals are at increased risk of fragility fractures throughout life but the highest rates of fracture are during childhood and above the age of 50 years.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	159	160	319
From 65-84 years	14	16	30
85 years and over	0	0	0
Age continuous			
The fracture risk in OI is at least an order of magnitude above that in patients with osteoporosis. Affected individuals are at increased risk of fragility fractures throughout life but the highest rates of fracture are during childhood and above the age of 50 years.			
Units: years			
arithmetic mean	43.8	43.6	
standard deviation	± 13.9	± 14.1	-
Gender categorical			
Units: Subjects			
Female	93	95	188
Male	80	81	161
Female Reproduction			
Units: Subjects			
Childbearing potential (yes)	51	57	108

Childbearing potential (No)	42	38	80
N/A i.e Male participants	80	81	161
Disease characteristics - Blue Sclerae Units: Subjects			
Blue sclerae (No)	40	27	67
Blue sclerae (Yes)	133	149	282
Fracture history - Last 2 years Units: Subjects			
Yes	80	83	163
No	93	93	186
Clinical examination - bone deformities Units: Subjects			
Bone Deformity - Yes	105	115	220
Bone Deformity - No	68	61	129
Baseline spine x-ray - Vertebral Units: Subjects			
Confirmed vertebral fracture - Yes	83	94	177
Confirmed vertebral fracture - No	88	82	170
confirmed vertebral fracture missing	2	0	2
Genetic biomarkers - Molecular diagnosis Units: Subjects			
Qualitative	54	55	109
Quantitative	69	77	146
Splice site	29	26	55
Variant of uncertain significance	3	4	7
No pathogenic variant	17	14	31
No result	1	0	1
Genetic biomarkers - Pathogenic variant Units: Subjects			
COL1A1	104	114	218
COL1A2	44	39	83
FKBP10	2	0	2
IFITM5	1	2	3
P3H1	1	0	1
PLS3	0	1	1
SERPINF1	0	1	1
Variant of uncertain significance	3	4	7
No pathogenic variant	17	14	31
Other [1]	0	1	1
Missing	1	0	1
Bone targeted medications at, or within 2 years prior to, randomisation - Bisphosphonates			
Other = Non-Bisphosphonates/None			
Units: Subjects			
Bisphosphonates	50	48	98
Other	123	128	251
Bone targeted medications at, or any time prior to, randomisation - Bisphosphonates			
Other = Non-bisphosphonates/None			

Units: Subjects			
Targeted Meds - Bisphosphonates	117	128	245
Other	56	48	104
Baseline spine xray - Lumbar			
Those participants that did not report a potential fracture, are categorised as 'N/A'			
Units: Subjects			
Confirmed lumbar fracture - Yes	38	44	82
Confirmed lumbar fracture - No	45	50	95
N/A	90	82	172
Baseline spine xray - thoracic			
Those participants that did not report a potential fracture, are categorised as 'N/A'			
Units: Subjects			
Confirmed thoracic fracture - Yes	76	80	156
Confirmed thoracic fracture - No	7	14	21
N/A	90	82	172
Bone targeted medications at, or any time prior to, randomisation - NonBisphosphonates			
Other = Bisphosphonates/None			
Units: Subjects			
Non-Bisphosphonates	97	93	190
Other	76	83	159
Bone targeted medications at, or within 2 years prior to, randomisation - NonBisphosphonates			
Other = Bisphosphonates/None			
Units: Subjects			
Non-Bisphosphonates	87	86	173
Other	86	90	176
Disease characteristics - Dentinogenesis			
Units: Subjects			
Yes	61	64	125
No	112	112	224
Age of menarche			
Units: years			
arithmetic mean	13	13	
standard deviation	± 2	± 2	-
Age of menopause			
Units: years			
arithmetic mean	48	49	
standard deviation	± 7	± 6	-
Total dietary calcium			
Units: mg/day			
arithmetic mean	809	827	
standard deviation	± 412	± 376	-
Clinical examination - Height			
Height			
Units: cm			
arithmetic mean	155	156	
standard deviation	± 18	± 17	-
Clinical examination - Weight			
Units: kg			

arithmetic mean	70.9	68.5	
standard deviation	± 18.8	± 19.9	-
Clinical exam - BMI			
Units: kg/m²			
arithmetic mean	29.6	27.8	
standard deviation	± 7.6	± 6.4	-
DEXA scan results - Spine			
Units: BMD (g/cm 2)			
arithmetic mean	0.849	0.862	
standard deviation	± 0.201	± 0.172	-
DEXA scan results - Total hip			
Units: BMD (g/cm 2)			
arithmetic mean	0.83	0.824	
standard deviation	± 0.149	± 0.142	-
DEXA scan results - Femoral neck			
Units: BMD (g/cm 2)			
arithmetic mean	0.740	0.741	
standard deviation	± 0.151	± 0.144	-
DEXA scan results - T-score - Spine			
Units: SD			
arithmetic mean	-2.11	-2.18	
standard deviation	± 1.92	± 1.57	-
DEXA scan results - T-score -Total hip			
Units: SD			
arithmetic mean	-1.12	-1.33	
standard deviation	± 1.26	± 1.21	-
DEXA scan results - T-score -Femoral neck			
Units: SD			
arithmetic mean	-1.41	-1.55	
standard deviation	± 1.3	± 1.22	-
Biochemical biomarkers of bone turnover - C-terminal telopeptide of type I collagen (CTX)			
Units: µg/L			
arithmetic mean	0.2	0.21	
standard deviation	± 0.12	± 0.13	-
Biochemical biomarkers of bone turnover - Procollagen type I amino-terminal propeptide			
Units: µg/L			
arithmetic mean	37.5	39.7	
standard deviation	± 23.1	± 30.5	-
Per-patient number of fractures - last 2 years			
Units: Subject			
median	0	0	
full range (min-max)	0 to 8	0 to 5	-
Per-patient number of fractures (>2years)			
Units: subjects			
median	10	11	
full range (min-max)	0 to 257	0 to 257	-

End points

End points reporting groups

Reporting group title	Standard Care

Reporting group description:

Participants in the standard care group were permitted to continue with existing bone modifying treatment (i.e., bisphosphonate treatment) or be given no active bone modifying treatment, according to the clinical judgement of the local investigator. Bisphosphonates could be continued, stopped or started during the study at the discretion of the local investigator. Other bone modifying drugs could also be given at the discretion of the local investigator with the exception of teriparatide and investigational (experimental) agents with effects on bone metabolism

Reporting group title	Active treatment group

Reporting group description:

TPTD 20mcg daily, given subcutaneously using a self-administered injection device for two years followed by a single intravenous infusion of ZA 5mg. If TPTD given for < 12 months no ZA infusion is required.
Bisphosphonates, denosumab and strontium ranelate were stopped in the active treatment group at baseline and prohibited during treatment with TPTD since these may alter the therapeutic response to TPTD (18). Bisphosphonates were prohibited following treatment with ZA for at least 12 months to avoid over suppression of bone turnover.

Subject analysis set title	Intent-to-Treat (ITT) Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population is all randomised patients, analysed according to randomised treatment. 176 TPTD and 173 standard care.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population will include all patients who were randomised. Patients were summarised according to treatment received. For TPTD safety has 177 participants and standard care has 172.

Primary: The proportion of participants experiencing a clinical fracture validated by x-ray or other imaging.

End point title	The proportion of participants experiencing a clinical fracture validated by x-ray or other imaging.

End point description:

End point type	Primary

End point timeframe:

From randomisation until final study visit.

End point values	Standard Care	Active treatment group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	176		
Units: Participants	63	65		

Statistical analyses

Statistical analysis title	Primary analysis – Cox proportional hazard
Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.872
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.38
Variability estimate	Standard error of the mean

Statistical analysis title	secondary analysis - BinaryLogisticRegression
Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.937
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.59
Variability estimate	Standard error of the mean

Statistical analysis title	Sensitivity analysis - interval censoring

Statistical analysis description:

Interval censoring takes account of fractures identified at the end of study x-ray where the exact time of fracture is unknown. Fractures are known to have occurred at some point between baseline x-ray (or the last incidental x-ray date for those patients where the x-ray didn't result in a confirmed non-vertebral fracture) and end of study x-rays.

Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8561
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.46
Variability estimate	Standard error of the mean

Statistical analysis title	sensitivity analysis - Dept.Rand Trt.
Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.854 [1]
Method	CACE
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.38
Variability estimate	Standard error of the mean

Notes:

[1] - Complier-average causal effect (CACE)

Secondary: Adjudicated incident fractures	
End point title	Adjudicated incident fractures

End point description:

End point type	Secondary

End point timeframe:

Randomisation to final visit.

End point values	Standard Care	Active treatment group	Intent-to-Treat (ITT) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	173	176	349	
Units: Fracture number	88	70	158	

Statistical analyses

Statistical analysis title	Poisson regression
Comparison groups	Active treatment group v Standard Care
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.911
Method	Poisson regression
Parameter estimate	Incidence rate ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.65
Variability estimate	Standard error of the mean

Secondary: Brief pain inventory (BPI) interference score	
End point title	Brief pain inventory (BPI) interference score
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to End of study visit.	

End point values	Standard Care	Active treatment group	Intent-to-Treat (ITT) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	173	176	349	
Units: BPI pain interference score (0–10)				
arithmetic mean (standard deviation)	4.34 (± 2.87)	3.28 (± 2.65)	3.82 (± 2.81)	

Statistical analyses

Statistical analysis title	Repeated measures linear mixed model estimates
Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	-0.29
Variability estimate	Standard error of the mean

Notes:

[2] - Overall p-value

Secondary: SF-36 - physical component score

End point title	SF-36 - physical component score

End point description:

End point type	Secondary

End point timeframe:

Baseline to final study visit

End point values	Standard Care	Active treatment group	Intent-to-Treat (ITT) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	173	176	349	
Units: SF-36 Physical Component Score (PCS)				
arithmetic mean (standard deviation)	33.5 (± 12.3)	36.7 (± 13.6)	35.1 (± 13)	

Statistical analyses

Statistical analysis title	Repeated measures linear mixed model estimates
Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.083 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	3.06
Variability estimate	Standard error of the mean

Notes:

[3] - Overall

Secondary: Pittsburgh sleep quality questionnaire (PSQI)

End point title	Pittsburgh sleep quality questionnaire (PSQI)

End point description:

End point type	Secondary

End point timeframe:

Baseline to Final study visit

End point values	Standard Care	Active treatment group	Intent-to-Treat (ITT) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	173	176	289	
Units: PSQI score				
arithmetic mean (standard deviation)	10.5 (± 3.9)	9.8 (± 3.5)	10.1 (± 3.7)	

Statistical analyses

Statistical analysis title	Repeated measures linear mixed model estimates
Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0279 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.06
Variability estimate	Standard error of the mean

Notes:

[4] - Overall

Secondary: Health Assessment Questionnaire - disability index

End point title	Health Assessment Questionnaire - disability index

End point description:

End point type	Secondary

End point timeframe:

Baseline to final study visit

End point values	Standard Care	Active treatment group	Intent-to-Treat (ITT) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	173	176	349	
Units: HAQ-DI score				
arithmetic mean (standard deviation)	1.13 (± 0.79)	0.97 (± 0.81)	1.05 (± 0.8)	

Statistical analyses

Statistical analysis title	Stage 1 – Modelling Probability zero score
Statistical analysis description:	
Stage 1 – Modelling the Probability of a zero (no difficulty) score	
Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9495 [5]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.72
Variability estimate	Standard error of the mean

Notes:
[5] - overall

Statistical analysis title	Stage 2 – ModellingDistribution positive scores
Statistical analysis description:	
Stage 2 – Modelling the distribution of positive (non-zero) scores	
Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0975 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.01
Variability estimate	Standard error of the mean

Notes:
[6] - overall

Secondary: DEXA scan - femoral neck BMD

End point title	DEXA scan - femoral neck BMD

End point description:

End point type	Secondary

End point timeframe:
baseline to final study visit

End point values	Standard Care	Active treatment group	Intent-to-Treat (ITT) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	173	176	349	
Units: Bone Mineral Density (BMD)				
arithmetic mean (standard deviation)	0.724 (± 0.159)	0.726 (± 0.155)	0.743 (± 0.158)	

Statistical analyses

Statistical analysis title	Repeated measures linear mixed model estimates
Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8862 [7]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.027
upper limit	0.032
Variability estimate	Standard error of the mean

Notes:
[7] - Overall

Secondary: DEXA scan - total hip BMD

End point title	DEXA scan - total hip BMD

End point description:

End point type	Secondary

End point timeframe:

Baseline to final study visit

End point values	Standard Care	Active treatment group	Intent-to-Treat (ITT) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	173	176	349	
Units: Bone Mineral Density (BMD)				
arithmetic mean (standard deviation)	0.836 (± 0.154)	0.872 (± 0.164)	0.854 (± 0.160)	

Statistical analyses

Statistical analysis title	Repeated measures linear mixed model estimates
Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0156 [8]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.038
Variability estimate	Standard error of the mean

Notes:

[8] - Overall

Secondary: DEXA scan - spine BMD

End point title	DEXA scan - spine BMD

End point description:

End point type	Secondary

End point timeframe:

Baseline to final study visit

End point values	Standard Care	Active treatment group	Intent-to-Treat (ITT) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	173	176	349	
Units: Bone Mineral Density (BMD)				
arithmetic mean (standard deviation)	0.879 (± 0.209)	0.927 (± 0.183)	0.903 (± 0.197)	

Statistical analyses

Statistical analysis title	Repeated measures linear mixed model estimates
Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.018
upper limit	0.045
Variability estimate	Standard error of the mean

Notes:

[9] - Overall

Secondary: Brief pain inventory (BPI) Severity score

End point title	Brief pain inventory (BPI) Severity score

End point description:

End point type	Secondary

End point timeframe:

Randomisation to final study visit

End point values	Standard Care	Active treatment group	Intent-to-Treat (ITT) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	173	176	349	
Units: BPI pain severity score (0-10)				
arithmetic mean (standard deviation)	4.07 (± 2.42)	3.24 (± 2.14)	3.67 (± 2.32)	

Statistical analyses

Statistical analysis title	Repeated measures linear mixed model estimates
Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0134
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	-0.08
Variability estimate	Standard error of the mean

Secondary: Adjudicated fractures at end of study

End point title	Adjudicated fractures at end of study

End point description:

End point type	Secondary

End point timeframe:

Baseline to Final study visit

End point values	Standard Care	Active treatment group	Intent-to-Treat (ITT) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	173	176	349	
Units: Fractures	85	125	210	

Statistical analyses

Statistical analysis title	Poisson regression
Comparison groups	Active treatment group v Standard Care
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28
Method	Poisson regression
Parameter estimate	Incidence rate ratio
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	2.36
Variability estimate	Standard error of the mean

Secondary: SF-36 -mental component score	
End point title	SF-36 -mental component score
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to Final study visit	

End point values	Standard Care	Active treatment group	Intent-to-Treat (ITT) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	173	176	349	
Units: SF-36 Mental Component Score (MCS)				
arithmetic mean (standard deviation)	44 (± 14.5)	46.7 (± 14)	45.4 (± 14.3)	

Statistical analyses

Statistical analysis title	Repeated measures linear mixed model estimates
Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1768 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	3.33
Variability estimate	Standard error of the mean

Notes:
[10] - Overall

Secondary: EQ5D-3L index score

End point title	EQ5D-3L index score

End point description:

End point type	Secondary

End point timeframe:
Baseline to final study visit

End point values	Standard Care	Active treatment group	Intent-to-Treat (ITT) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	173	176	349	
Units: EQ5D-3L index score				
arithmetic mean (standard deviation)	0.62 (± 0.21)	0.68 (± 0.21)	0.65 (± 0.21)	

Statistical analyses

Statistical analysis title	Repeated measures linear mixed model estimates
Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.214 [11]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.06
Variability estimate	Standard error of the mean

Notes:
[11] - Overall

Secondary: EQ5D-3L Visual Analogue Scale (VAS)

End point title	EQ5D-3L Visual Analogue Scale (VAS)

End point description:

End point type	Secondary

End point timeframe:

Baseline to final study visit

End point values	Standard Care	Active treatment group	Intent-to-Treat (ITT) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	173	176	349	
Units: EQ5D-3L Visual Analogue Scale (VAS)				
arithmetic mean (standard deviation)	60.2 (± 22.5)	64.6 (± 23.1)	62.4 (± 22.9)	

Statistical analyses

Statistical analysis title	Repeated measures linear mixed model estimates
Comparison groups	Standard Care v Active treatment group
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0023 [12]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	4.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.74
upper limit	7.94
Variability estimate	Standard error of the mean

Notes:

[12] - Overall

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	TPTD
Reporting group description: -	
Reporting group title	Standard care
Reporting group description: -	

Serious adverse events	TPTD	Standard care	
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 172 (22.67%)	41 / 177 (23.16%)	
number of deaths (all causes)	3	7	
number of deaths resulting from adverse events	3	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
missing	Additional description: missing		
subjects affected / exposed	4 / 172 (2.33%)	6 / 177 (3.39%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
missing	Additional description: missing		
subjects affected / exposed	0 / 172 (0.00%)	3 / 177 (1.69%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
missing	Additional description: missing		
subjects affected / exposed	8 / 172 (4.65%)	8 / 177 (4.52%)	
occurrences causally related to treatment / all	0 / 10	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

missing	Additional description: missing		
subjects affected / exposed	2 / 172 (1.16%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
missing	Additional description: missing		
subjects affected / exposed	4 / 172 (2.33%)	5 / 177 (2.82%)	
occurrences causally related to treatment / all	1 / 5	0 / 5	
deaths causally related to treatment / all	1 / 2	0 / 1	
Psychiatric disorders			
missing	Additional description: missing		
subjects affected / exposed	4 / 172 (2.33%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
missing	Additional description: missing		
subjects affected / exposed	1 / 172 (0.58%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
missing	Additional description: missing		
subjects affected / exposed	6 / 172 (3.49%)	4 / 177 (2.26%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
missing	Additional description: missing		
subjects affected / exposed	2 / 172 (1.16%)	3 / 177 (1.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nervous system disorders			
missing	Additional description: missing		
subjects affected / exposed	3 / 172 (1.74%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

missing	Additional description: missing		
subjects affected / exposed	1 / 172 (0.58%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
missing	Additional description: missing		
subjects affected / exposed	4 / 172 (2.33%)	4 / 177 (2.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
missing	Additional description: missing		
subjects affected / exposed	0 / 172 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
missing	Additional description: missing		
subjects affected / exposed	1 / 172 (0.58%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
missing	Additional description: missing		
subjects affected / exposed	2 / 172 (1.16%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
missing	Additional description: missing		
subjects affected / exposed	0 / 172 (0.00%)	1 / 177 (0.56%)	
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	5 / 172 (2.91%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			

missing	Additional description: missing		
subjects affected / exposed	8 / 172 (4.65%)	5 / 177 (2.82%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	TPTD	Standard care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	137 / 172 (79.65%)	135 / 177 (76.27%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
missing	Additional description: missing		
subjects affected / exposed	6 / 172 (3.49%)	7 / 177 (3.95%)	
occurrences (all)	6	11	
Vascular disorders			
missing	Additional description: missing		
subjects affected / exposed	6 / 172 (3.49%)	9 / 177 (5.08%)	
occurrences (all)	21	10	
Surgical and medical procedures			
missing	Additional description: missing		
subjects affected / exposed	22 / 172 (12.79%)	22 / 177 (12.43%)	
occurrences (all)	28	30	
Pregnancy, puerperium and perinatal conditions			
missing	Additional description: missing		
subjects affected / exposed	1 / 172 (0.58%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
missing	Additional description: missing		
subjects affected / exposed	3 / 172 (1.74%)	1 / 177 (0.56%)	
occurrences (all)	3	1	
Reproductive system and breast disorders			
missing	Additional description: missing		
subjects affected / exposed	9 / 172 (5.23%)	8 / 177 (4.52%)	
occurrences (all)	10	11	
Respiratory, thoracic and mediastinal disorders			

missing	Additional description: missing		
subjects affected / exposed	20 / 172 (11.63%)	19 / 177 (10.73%)	
occurrences (all)	27	24	
Psychiatric disorders			
missing	Additional description: missing		
subjects affected / exposed	10 / 172 (5.81%)	11 / 177 (6.21%)	
occurrences (all)	13	15	
Product issues			
missing	Additional description: missing		
subjects affected / exposed	1 / 172 (0.58%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Investigations			
missing	Additional description: missing		
subjects affected / exposed	28 / 172 (16.28%)	15 / 177 (8.47%)	
occurrences (all)	39	23	
Injury, poisoning and procedural complications			
missing	Additional description: missing		
subjects affected / exposed	48 / 172 (27.91%)	51 / 177 (28.81%)	
occurrences (all)	82	98	
Congenital, familial and genetic disorders			
missing	Additional description: missing		
subjects affected / exposed	2 / 172 (1.16%)	1 / 177 (0.56%)	
occurrences (all)	2	1	
Cardiac disorders			
missing	Additional description: missing		
subjects affected / exposed	11 / 172 (6.40%)	8 / 177 (4.52%)	
occurrences (all)	13	10	
Nervous system disorders			
missing	Additional description: missing		
subjects affected / exposed	42 / 172 (24.42%)	16 / 177 (9.04%)	
occurrences (all)	57	20	
Blood and lymphatic system disorders			
missing	Additional description: missing		
subjects affected / exposed	4 / 172 (2.33%)	1 / 177 (0.56%)	
occurrences (all)	4	1	
Ear and labyrinth disorders			

missing	Additional description: missing		
subjects affected / exposed	10 / 172 (5.81%)	8 / 177 (4.52%)	
occurrences (all)	11	8	
Eye disorders			
missing	Additional description: missing		
subjects affected / exposed	10 / 172 (5.81%)	7 / 177 (3.95%)	
occurrences (all)	11	9	
Gastrointestinal disorders			
missing	Additional description: missing		
subjects affected / exposed	29 / 172 (16.86%)	20 / 177 (11.30%)	
occurrences (all)	60	31	
Hepatobiliary disorders			
missing	Additional description: missing		
subjects affected / exposed	2 / 172 (1.16%)	2 / 177 (1.13%)	
occurrences (all)	2	2	
Skin and subcutaneous tissue disorders			
missing	Additional description: missing		
subjects affected / exposed	15 / 172 (8.72%)	13 / 177 (7.34%)	
occurrences (all)	18	17	
Renal and urinary disorders			
missing	Additional description: missing		
subjects affected / exposed	7 / 172 (4.07%)	5 / 177 (2.82%)	
occurrences (all)	7	5	
Musculoskeletal and connective tissue disorders			
missing	Additional description: missing		
subjects affected / exposed	94 / 172 (54.65%)	86 / 177 (48.59%)	
occurrences (all)	259	193	
Infections and infestations			
missing	Additional description: missing		
subjects affected / exposed	69 / 172 (40.12%)	58 / 177 (32.77%)	
occurrences (all)	134	119	
Metabolism and nutrition disorders			
missing	Additional description: missing		
subjects affected / exposed	5 / 172 (2.91%)	10 / 177 (5.65%)	
occurrences (all)	11	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2024	1. The participating sites section and funder details are updated. Correction of typos and grammatical errors. The details of the SWAT study have been removed. Provided an additional rationale for reducing the sample size. 2. Introduction of the option to locally purchase teriparatide and labelling updates 3. The primary and secondary mechanistic objectives of the protocol have been updated and added. There is clarification around onward reporting of SARs/SUSARs when using generic TPTD. The method of ascertaining adherence for both arms of the study has been changed. 4. The Clinical study site agreement will have to be amended for sites with patients who require IMP beyond 31 October 2024. 5. Biochemical markers will be analysed at the University of East Anglia. 6. Update to the following representative SPC's for the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 March 2020	1 Recruitment, screening and randomisation has been temporarily halted following a Sponsor communication on 17th March 2020. 2 Study visits will be conducted remotely by telephone or videocall wherever possible to reduce patient travel to hospitals during the Covid19 emergency. Any study procedure that cannot be performed remotely will be carried out a later date and marked in the interim as a protocol deviation. 3 IMP shipments will be transported from site pharmacies to participant homes via courier service to reduce patient travel to hospital.	16 September 2020

Notes:

Limitations and caveats

None reported