Clinical trial results:
A multi-centre, prospective, randomised trial of short course alendronate therapy or placebo combined with vitamin D and calcium to prevent loss of bone mineral density in antiretroviral-naïve, HIV-1 infected subjects initiating antiretroviral therapy.

Summary

EudraCT number	2014-004819-37
Trial protocol	IE DK GB
Global end of trial date	07 September 2020

Results information

Result version number	v1 (current)
This version publication date	18 April 2022
First version publication date	18 April 2022

Trial information

Trial identification

Sponsor protocol code	APART_2014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02322099
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College Dublin
Sponsor organisation address	Belfield Campus, Dublin, Ireland, Dublin 4
Public contact	Prof Patrick Mallon, Centre for Experimental Pathogen Host Research, +353 17164542, cephr@ucd.ie
Scientific contact	Prof Patrick Mallon, Centre for Experimental Pathogen Host Research, +353 17164542, cephr@ucd.ie

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 September 2020
Global end of trial reached?	Yes
Global end of trial date	07 September 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

In antiretroviral-naïve, HIV1-infected adults, to compare the effect of a short (14 week) course of oral alendronate 70mg weekly versus placebo combined with calcium and vitamin D, initiated 2 weeks prior to start of antiretroviral therapy (ART) for HIV1 infection on ART-induced bone mineral density (BMD) loss over 48 weeks of follow-up post ART initiation.

Protection of trial subjects:

This trial was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. All subjects provided written informed consent before undergoing any trial related procedures. The trial was reviewed and approved by the Competent Authorities and the local Research Ethics Committees (REC).

An independent data safety monitoring board (DSMB) was established to oversee the conduct of the study. The DSMB comprised an expert in osteoporosis, two experts in HIV with clinical trial experience, and a representative of the sponsor (UCD).

All participants attended a total of 7 study visits over the 50 weeks (48 weeks post-ART initiation) follow-up period. All visits included medical/clinical review including assessments of safety and oral hygiene as well as pregnancy tests in women of childbearing potential. If pregnancy was reported during the study the woman was discontinued from the IMP but offered to remain in the study and the outcome of the pregnancy was recorded. Also, any abnormality identified on DXA scans was followed up through referral from the study team to the Rheumatology specialist in liaison with the Radiologist specialist.

In addition, a Clinical Endpoint Review Committee composed of the principal investigator and a rheumatology specialist was established to review those subjects with abnormal DXA scans at week 14 (completion of Alendronate course). Any subject with BMD<-1 at week 14 was reviewed by this committee and a decision was made as to whether calcium/vitamin D supplementation should continue for these subjects after week 14.

Background therapy:

All participants received calcium / vitamin D3 supplementation combined with either generic, oral Alendronate 70mg weekly or placebo, commenced 2 weeks prior to ART initiation and continued for a total of 14 weeks.
The ART regimen comprised tenofovir disproxil fumarate / emtricitabine and a third agent.
Randomisation was stratified by gender and use of protease inhibitors in the ART regimen.

Evidence for comparator: -

Actual start date of recruitment	01 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 53

Worldwide total number of subjects	53
EEA total number of subjects	53

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)	53
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started in Ireland in April 2016. 53 subjects were recruited, the first on 15/06/2016 and the last on 03/10/2018. A total of 50 subjects were randomised. Of the 3 subjects who withdrew before randomisation, one initiated ART before randomisation and two were lost to follow after screening.

Pre-assignment

Screening details:

Study population comprised HIV-1 positive, antiretroviral-naïve adults requiring initiation of antiretroviral therapy (ART). In order to ensure that the study population had achieved peak-bone mass, we recruited males over 25 and women over 30 years old. There were no CD4+ T-cell count or HIV RNA restrictions for study entry.

Pre-assignment period milestones

Number of subjects started	53
Number of subjects completed	50

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Lost of follow-up after screening: 2
Reason: Number of subjects	Physician decision: 1

Period 1

Period 1 title	Intention to treat (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Blinding implementation details:

A double-blind technique will be used. Alendronate and matched placebo will be packaged identically so that blind/masking is maintained. The subject, the investigator and the Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

Arms

Are arms mutually exclusive?	Yes
Arm title	Alendronate

Arm description:

Alendronate 70mg oral tablets administered once weekly for a period of 12 weeks starting 2 weeks prior to ART initiation

Arm type	Experimental
Investigational medicinal product name	Alendronate 70 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet contains 70 mg alendronic acid (as sodium alendronate trihydrate). The dosage is one 70 mg tablet once weekly for a period of 12 weeks.
Alendronate tablet must be taken at least 30 minutes before the first food, beverage or medicinal product of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate.

Arm title	Placebo

Arm description:

Placebo tablets to match sodium alendronate 70 mg. Oral tablets administered once weekly for a period of 12 weeks starting 2 weeks prior to ART initiation.

Arm type	Placebo
Investigational medicinal product name	Placebo to match Alendronate 70 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets are identical in appearance and composition apart from the active substance). The dosage is one tablet once weekly for a period of 12 weeks. Each placebo tablet contains: Cellactose 80 (lactose monohydrated and cellulose powdered), Croscarmellose sodium, Colloidal Anhydrous silica (Aerosil 200), Magnesium stearate.
Administration instructions are in line with those for alendronate in order to maintain the blinding. The IMP tablet must be taken at least 30 minutes before the first food, beverage or medicinal product of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate.

Number of subjects in period 1[1]	Alendronate	Placebo
Started	24	26
Completed	22	22
Not completed	2	4
Consent withdrawn by subject	1	-
Pregnancy	-	1
Lost to follow-up	1	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 53 subjects were enrolled in the study/signed the informed consent. Three of these subjects withdrew the study before randomisation, one initiated ART before randomisation (physician decision) and two were lost of follow-up after screening

Baseline characteristics

Reporting groups	
Reporting group title	Alendronate
Reporting group description:	
Alendronate 70mg oral tablets administered once weekly for a period of 12 weeks starting 2 weeks prior to ART initiation	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets to match sodium alendronate 70 mg. Oral tablets administered once weekly for a period of 12 weeks starting 2 weeks prior to ART initiation.	

Reporting group values	Alendronate	Placebo	Total
Number of subjects	24	26	50
Age categorical Units: Subjects			
Age continuous Units: years			
median	36	34	
inter-quartile range (Q1-Q3)	32 to 39	31 to 41	-
Gender categorical Units: Subjects			
Female	4	3	7
Male	20	23	43
Ethnicity Units: Subjects			
African	10	7	17
South American	7	3	10
Caucasian	7	16	23
HIV transmission risk group Units: Subjects			
Heterosexual contact	12	6	18
Homosexual contact	9	13	22
Injecting drug use	0	2	2
Unknown	3	5	8
Smoking status Units: Subjects			
Current smoker	7	11	18
Ex-smoker	2	6	8
Never smoked	14	8	22
Unknown	1	1	2
Prior falls Units: Subjects			
Yes	0	2	2
No	24	24	48
History of fractures Units: Subjects			
Yes	8	2	10

No	16	24	40
Type of ART regimen Units: Subjects			
PI-based ART	0	2	2
NNRTI-based ART	1	1	2
InSTI-based ART	23	23	46
BMI			
Body mass index at baseline			
Units: Kg/m2			
median	24.5	23.2	
inter-quartile range (Q1-Q3)	22.9 to 29.0	22.1 to 25.7	-
Absolute CD4+ T-cell count Units: cells/mm3			
median	348	428	
inter-quartile range (Q1-Q3)	176 to 492	256 to 598	-
Absolute CD8+ T-cell count Units: cells/mm3			
median	742	1139	
inter-quartile range (Q1-Q3)	606 to 984	726 to 1408	-
CD4+ T-cell count (%) Units: percentage			
median	24	23	
inter-quartile range (Q1-Q3)	14 to 31	14 to 29	-
CD8+ T-cell count (%) Units: percentage			
median	46	54	
inter-quartile range (Q1-Q3)	42 to 59	46 to 60	-

End points

End points reporting groups

Reporting group title	Alendronate
Reporting group description:	
Alendronate 70mg oral tablets administered once weekly for a period of 12 weeks starting 2 weeks prior to ART initiation	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets to match sodium alendronate 70 mg. Oral tablets administered once weekly for a period of 12 weeks starting 2 weeks prior to ART initiation.	

Primary: Percentage change in total hip BMD at week 50

End point title	Percentage change in total hip BMD at week 50
End point description:	
BMD determined by dual energy X-ray Absorptiometry (DXA) performed prior to and 48 weeks after ART initiation. Missing values/subjects excluded from analysis due to DXA scan not done/scan not done properly	
End point type	Primary
End point timeframe:	
Baseline to week 50	

End point values	Alendronate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: g/cm2				
median (inter-quartile range (Q1-Q3))	0.50 (-3.10 to 1.80)	-2.70 (-4.30 to -2.05)		

Attachments (see zip file)	Primary outcome analysis/Primary outcome analysis.pdf

Statistical analyses

Statistical analysis title	Difference in % change from baseline to week 50
Statistical analysis description:	
Between-group differences in percentage change in total hip BMD compared using Wilcoxon rank tests.	

Comparison groups	Placebo v Alendronate

Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	3.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	5.05

Secondary: Percentage change in lumbar spine BMD at week 50

End point title	Percentage change in lumbar spine BMD at week 50
End point description:	
Missing values/subjects excluded from analysis due to DXA scan not done/scan not done properly	
End point type	Secondary
End point timeframe:	
Baseline to week 50	

End point values	Alendronate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: g/cm2				
median (inter-quartile range (Q1-Q3))	-1.40 (-4.10 to 3.13)	-3.69 (-4.82 to -1.70)		

Statistical analyses

Statistical analysis title	Difference in % change from baseline to week 50
Statistical analysis description:	
Between-group differences in percentage change in lumbar spine BMD compared using Wilcoxon rank tests.	
Comparison groups	Alendronate v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	2.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	5.16

Secondary: Percentage change in femoral neck BMD at week 50

End point title	Percentage change in femoral neck BMD at week 50
End point description:	
Missing values/subjects excluded from analysis due to DXA scan not done/scan not done properly	
End point type	Secondary
End point timeframe:	
Baseline to week 50	

End point values	Alendronate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: g/cm2				
median (inter-quartile range (Q1-Q3))	0.62 (-3.68 to 2.10)	-4.00 (-6.75 to 0.23)		

Statistical analyses

Statistical analysis title	Difference in % change from baseline to week 50
Statistical analysis description:	
Between-group differences in percentage change in femoral neck BMD compared using Wilcoxon rank tests.	
Comparison groups	Alendronate v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	3.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	6.51

Secondary: Percentage change in total hip BMD to week 14

End point title	Percentage change in total hip BMD to week 14

End point description: Missing values/subjects excluded from analysis due to DXA scan not done/scan not done properly	
End point type	Secondary
End point timeframe: Baseline to week 14	

End point values	Alendronate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	25		
Units: g/cm2				
median (inter-quartile range (Q1-Q3))	1.88 (-0.70 to 2.81)	-0.65 (-2.65 to 1.13)		

Statistical analyses

Statistical analysis title	Difference in % change from baseline to week 14
Statistical analysis description: Between-group differences in percentage change in total hip BMD compared using Wilcoxon rank tests.	
Comparison groups	Alendronate v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	2.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	4.22

Secondary: Percentage change in total hip BMD to week 26

End point title	Percentage change in total hip BMD to week 26
End point description: Missing values/subjects excluded from analysis due to DXA scan not done/scan not done properly	
End point type	Secondary
End point timeframe: Baseline to week 26	

End point values	Alendronate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	23		
Units: g/cm2				
median (inter-quartile range (Q1-Q3))	1.05 (-2.05 to 2.23)	-2.03 (-2.97 to 0.63)		

Statistical analyses

Statistical analysis title	Difference in % change from baseline to week 26
Statistical analysis description:	
Between-group differences in percentage change in total hip BMD compared using Wilcoxon rank tests.	
Comparison groups	Alendronate v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	3.87

Secondary: Percentage change in lumbar spine BMD to week 14

End point title	Percentage change in lumbar spine BMD to week 14
End point description:	
Missing values/subjects excluded from analysis due to DXA scan not done/scan not done properly	
End point type	Secondary
End point timeframe:	
Baseline to week 14	

End point values	Alendronate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	25		
Units: g/cm2				
median (inter-quartile range (Q1-Q3))	1.24 (-0.04 to 3.02)	-0.96 (-3.10 to 0.78)		

Statistical analyses

Statistical analysis title	Difference in % change from baseline to week 14
Statistical analysis description:	
Between-group differences in percentage change in lumbar spine BMD compared using Wilcoxon rank tests.	
Comparison groups	Alendronate v Placebo
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	4.97

Secondary: Percentage change in lumbar spine BMD to week 26	
End point title	Percentage change in lumbar spine BMD to week 26
End point description:	
Missing values/subjects excluded from analysis due to DXA scan not done/scan not done properly	
End point type	Secondary
End point timeframe:	
Baseline to week 26	

End point values	Alendronate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	23		
Units: g/cm2				
median (inter-quartile range (Q1-Q3))	0.05 (-3.04 to 3.30)	-2.48 (-4.65 to -0.24)		

Statistical analyses

Statistical analysis title	Difference in % change from baseline to week 26
Statistical analysis description:	
Between-group differences in percentage change in lumbar spine BMD compared using Wilcoxon rank tests.	
Comparison groups	Alendronate v Placebo

Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	3.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	6.17

Secondary: Percentage change in femoral neck BMD to week 14

End point title	Percentage change in femoral neck BMD to week 14
End point description:	
Missing values/subjects excluded from analysis due to DXA scan not done/scan not done properly	
End point type	Secondary
End point timeframe:	
Baseline to week 14	

End point values	Alendronate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	25		
Units: g/cm2				
median (inter-quartile range (Q1-Q3))	-0.48 (-2.77 to 4.26)	0.07 (-4.27 to 2.90)		

Statistical analyses

Statistical analysis title	Difference in % change from baseline to week 14
Statistical analysis description:	
Between-group differences in percentage change in femoral neck BMD compared using Wilcoxon rank tests.	
Comparison groups	Alendronate v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.08
upper limit	4.94

Secondary: Percentage change in femoral neck BMD to week 26	
End point title	Percentage change in femoral neck BMD to week 26
End point description: Missing values/subjects excluded from analysis due to DXA scan not done/scan not done properly	
End point type	Secondary
End point timeframe: Baseline to week 26	

End point values	Alendronate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	23		
Units: g/cm2				
median (inter-quartile range (Q1-Q3))	-1.94 (-3.36 to 2.42)	-0.86 (-4.48 to 0.13)		

Statistical analyses

Statistical analysis title	Difference in % change from baseline to week 26
Statistical analysis description: Between-group differences in percentage change in femoral neck BMD compared using Wilcoxon rank tests.	
Comparison groups	Alendronate v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.62
upper limit	4.16

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Signing of Informed Consent through End of Study (Up to 50 weeks)

Adverse event reporting additional description:

Safety population included all randomized subjects who either received study treatment Alendronate or placebo. Subjects were analyzed according to their actual treatment received

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Alendronate

Reporting group description:

Alendronate 70mg oral tablets administered once weekly for a period of 12 weeks starting 2 weeks prior to ART initiation

Reporting group title	Placebo

Reporting group description:

Placebo tablets to match sodium alendronate 70 mg. Oral tablets administered once weekly for a period of 12 weeks starting 2 weeks prior to ART initiation.

Serious adverse events	Alendronate	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 23 (8.70%)	5 / 26 (19.23%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Post herpetic neuralgia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Eosinophilic folliculitis			

subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cachexia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Folliculitis			
subjects affected / exposed	2 / 23 (8.70%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Pyelonephritis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
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			
Folliculitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Incorrect self-administration of IMP			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bilateral epididymorchitys			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
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: 5 %

Non-serious adverse events	Alendronate	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 23 (78.26%)	18 / 26 (69.23%)	
Vascular disorders			
Syncope			
subjects affected / exposed	1 / 23 (4.35%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Incorrect self-administration of IMP			
subjects affected / exposed	0 / 23 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Fatigue			
subjects affected / exposed	1 / 23 (4.35%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Immune system disorders			
Psoriasis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Allergic reactions to antibiotics			
subjects affected / exposed	1 / 23 (4.35%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Genital rash			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Pharyngeal hyperaemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Sinusitis			

subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Nightmares			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Investigations			
Bone density decreased			
subjects affected / exposed	2 / 23 (8.70%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Elevated creatinine			
subjects affected / exposed	2 / 23 (8.70%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Elevated ALT			
subjects affected / exposed	0 / 23 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Elevated GGT			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Elevated Glucose			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Elevated creatinine kinase			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Elevated liver enzymes			
subjects affected / exposed	1 / 23 (4.35%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Congenital, familial and genetic disorders			
Dry cough			
subjects affected / exposed	0 / 23 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 23 (4.35%)	1 / 26 (3.85%)	
occurrences (all)	1	1	

Headache			
subjects affected / exposed	1 / 23 (4.35%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Pain in arm			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	2 / 23 (8.70%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Lymphogramuloma venereum			
subjects affected / exposed	1 / 23 (4.35%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea and vomiting			
subjects affected / exposed	4 / 23 (17.39%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Abdominal pain			
subjects affected / exposed	3 / 23 (13.04%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Diarrhoea			
subjects affected / exposed	2 / 23 (8.70%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Abdominal cramps			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Dental pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Heartburn			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Oral candidiasis			

subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Gum Bleeding			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Itching			
subjects affected / exposed	2 / 23 (8.70%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Facial rash			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 23 (4.35%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Seborreheic dermatitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Skin changes			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 23 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	3	
Back pain			
subjects affected / exposed	2 / 23 (8.70%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Arthralgia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Joint pain			

subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Muscle pain			
subjects affected / exposed	1 / 23 (4.35%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Knee pain			
subjects affected / exposed	1 / 23 (4.35%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Ankle pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Chlamydial infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Pustular blisters			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Leg ulcer			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Appetite lost			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2019	Extension of placebo shelf-life (manufactured in January 2015) to match the shelf life of a new batch of active alendronate acquired in Nov 2018 (expiry date June 2020). The competent authorities had no objection to the proposal that the placebo shelf life matched the test product shelf life but advised that the sponsor remained fully responsible for quality of the placebo, including absence of microbial contamination, i.e. compliance with Ph. Eur. requirements. In order to comply with this requirement, an analytical testing on the placebo to confirm absence of contamination was performed in April 2019. This report was submitted to the HPRA and the MHRA. The MHRA required that the proposed placebo shelf life extension was submitted as a substantial amendment for assessment – submitted 18th July 2019. Notice of acceptance of amendment received in July 2019.
20 October 2019	Reduction on study sample size. The original sample size of 80 subjects had to be reduced to 64 due to lack of sufficient placebo that raised as a result of unplanned extra tests associated with packaging of new study drug in July 2019. A reduced sample size of 32 subjects per arm was the maxium possible target. With 32 subjects per arm, the study provides 80% power to detect slightly larger but clinically meaningful between-group differences in change in femoral neck BMD of 2.58% (assuming SD is 3.63%) at 48 weeks. Approval was obtained in Nov 2019.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 March 2020	As of 13 March 2020, due to the COVID-19 pandemic, a directive was issued to halt all non-essential research activity at the participating sites. At this time, there were 53 subjects (49 randomised) recruited in Ireland and on follow-up. For participants already enrolled in the clinical trial all the visits were completed by 7th Sept 2020. The Sponsor notified the Regulatory Authorities that the study had been terminated prematurely in Nov 2020.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

- Reduction in sample size might affect the power of the study to detect differences between arms
- Limited female representation
- Third ART agent was almost exclusively INSTIs, unable to detect potential differential effects of alternative agents