Clinical trial results:
Fractures and Bisphosphonates: A double-blind, randomised controlled trial on the effect of alendronic acid on healing and clinical outcomes of wrist fractures.

Summary

EudraCT number	2011-000988-28
Trial protocol	GB
Global end of trial date	02 November 2015

Results information

Result version number	v1 (current)
This version publication date	08 August 2020
First version publication date	08 August 2020

Trial information

Trial identification

Sponsor protocol code	19403

Additional study identifiers

ISRCTN number	ISRCTN62133820
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ACCORD (University of Edinburgh and NHS Lothian)
Sponsor organisation address	47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
Public contact	Edinburgh Clinical Trials Unit, University of Edinburgh, +44 01315373855, ectu@ed.ac.uk
Scientific contact	Edinburgh Clinical Trials Unit, University of Edinburgh, +44 01315373855, ectu@ed.ac.uk

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2015
Global end of trial reached?	Yes
Global end of trial date	02 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the study is to determine if alendronic acid - the drug most commonly used in the UK as treatment of osteoporosis (thinning bones) - affects fracture healing. Participants will be randomised to receive either alendronic acid or a placebo (a tablet that contains no active drug).

The main objective will be to look at the x-rays that are taken 4 weeks into the study and compare the number of healed fractures in each group (alendronic acid or placebo). We will also look at how long it takes a fracture to heal, using the x-rays taken at weeks 2, 4, 6 and 8.

One person will analyse all the x-rays in the study. The x-rays will be anonymised so that the reviewer is unaware of individual details or the treatment that the participant received.

Protection of trial subjects:

The trial was conducted in accordance with all relevant data protection, ethical and regulatory requirements to ensure the privacy and security of patient information and to ensure the rights, safety and well-being of the patients and the quality of the research data. Unblinding procedures were in place for situations where the safe management of the participant's medical condition necessitated knowledge of the study medication by the person(s) responsible for the participant's care.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 April 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 421
Worldwide total number of subjects	421
EEA total number of subjects	421

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	239
From 65 to 84 years	179
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants were randomised from 2 April 2012 to 29 September 2013 at 16 UK hospitals. Randomisation (1:1 ratio) took place following baseline assessment and prior to commencing study drug (alendronate or placebo). Randomisation was stratified by site, gender and fracture status (displaced or undisplaced).

Pre-assignment

Screening details:

8,707 patients screened. 4,913 were ineligible; 1,727 declined; 885 were missed; 739 not consented for other reasons. Of the 3,794 eligible patients, 443 consented but 11 withdrew, 8 were ineligible and 3 were withdrawn by the clinician prior to randomisation. 421 were randomised.

Pre-assignment period milestones

Number of subjects started	421
Number of subjects completed	421

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Alendronic Acid

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Alendronic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants commenced study drug (70mg tablet) within 14 days following fracture or within 7 days following randomisation, whichever come first. Ideally participants took their 1st dose the morning after randomisation. Participants took 1 tablet of alendronate once a week for 24 weeks. Alendronate was taken on the same day each week.

Alendronic acid was taken after getting up for the day and before taking any food, drink or medicine. The tablet was taken with a full glass of water only (not less than 200ml). Participants waited at least 30 minutes after taking alendronate before taking any other oral medicinal product.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants commenced placebo within 14 days following fracture or within 7 days following randomisation, whichever come first. Ideally Placebo was taken on the same day each week.

Placebo was taken after getting up for the day and before taking any food, drink or medicine. The tablet was taken with a full glass of water only (not less than 200ml). Participants waited at least 30 minutes after taking placebo before taking any other oral medicinal product.

Number of subjects in period 1	Alendronic Acid	Placebo
Started	215	206
Completed	215	206

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Alendronic Acid

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Alendronic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants commenced study drug (70mg tablet) within 14 days following fracture or within 7 days following randomisation, whichever come first. Ideally participants took their 1st dose the morning after randomisation. Participants took 1 tablet of alendronate/placebo once a week for 24 weeks. Alendronate/placebo was taken on the same day each week.

Alendronic acid was taken after getting up for the day and before taking any food, drink or medicine. The tablet was taken with a full glass of water only (not less than 200ml). Participants waited at least 30 minutes after taking alendronate before taking any other oral medicinal product.

Arm title	Placebo

Arm description: -

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants commenced placebo within 14 days following fracture or within 7 days following randomisation, whichever come first. Ideally participants took their 1st dose the morning after randomisation. Participants took 1 tablet of placebo once a week for 24 weeks. Placebo was taken on the same day each week.

Placebo was taken after getting up for the day and before taking any food, drink or medicine. The tablet was taken with a full glass of water only (not less than 200ml). Participants waited at least 30 minutes after taking placebo before taking any other oral medicinal product.

Number of subjects in period 2	Alendronic Acid	Placebo
Started	215	206
Week 4 - Primary outcome measure	202	187
Week 26 - final follow up visit	198	182
Completed	198	182
Not completed	17	24
Physician decision	2	6
Consent withdrawn by subject	13	15
Missed visit	-	3
Visit Missed	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Alendronic Acid
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Alendronic Acid	Placebo	Total
Number of subjects	215	206	421
Age categorical Units: Subjects			
Adults (18-64 years)	117	122	239
From 65-84 years	97	82	179
85 years and over	1	2	3
Age continuous Units: years			
arithmetic mean	63.9	62.8	
standard deviation	± 8.4	± 8.4	-
Gender categorical Units: Subjects			
Female	186	176	362
Male	29	30	59

Subject analysis sets	
Subject analysis set title	Intention to treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-to-treat (ITT) population will include all patients who have been randomised into the FaB study.

Subject analysis set title	Per-protocol population
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol (PP) population will comprise those members of the ITT population who completed the study without a major protocol violation and who complied adequately with the administered treatment .

Compliance will be assessed in terms of the pill counts recorded at the 4, 8 and 26 week visits. A patient will be regarded as being 'compliant' if they miss at most one dose up to the Week 4 visit. If the Week 4 pill count is missing then the patient will be classified as ‘compliant’ if the Week 8 pill count indicates that at most one dose was missed up to the Week 8 visit. If the Week 4 and Week 8 pill counts are missing then the patient will be classified as ‘compliant’ if the Week 26 pill count indicates that at most one dose was missed up to the Week 26 visit.

Reporting group values	Intention to treat population	Per-protocol population	
Number of subjects	421	359	
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years 85 years and over			

Age continuous Units: years			
arithmetic mean	63	63.4	
standard deviation	± 8.5	± 8.4	
Gender categorical Units: Subjects			
Female	362	307	
Male	59	52	

End points

End points reporting groups

Reporting group title	Alendronic Acid
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Alendronic Acid
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Intention to treat population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intention-to-treat (ITT) population will include all patients who have been randomised into the FaB study.	
Subject analysis set title	Per-protocol population
Subject analysis set type	Per protocol
Subject analysis set description:	
The per-protocol (PP) population will comprise those members of the ITT population who completed the study without a major protocol violation and who complied adequately with the administered treatment . Compliance will be assessed in terms of the pill counts recorded at the 4, 8 and 26 week visits. A patient will be regarded as being 'compliant' if they miss at most one dose up to the Week 4 visit. If the Week 4 pill count is missing then the patient will be classified as ‘compliant’ if the Week 8 pill count indicates that at most one dose was missed up to the Week 8 visit. If the Week 4 and Week 8 pill counts are missing then the patient will be classified as ‘compliant’ if the Week 26 pill count indicates that at most one dose was missed up to the Week 26 visit.	

Primary: Fracture healing at 4 weeks

End point title	Fracture healing at 4 weeks
End point description:	
X-ray assessment at visit 2, 4 weeks post-randomisation.	
End point type	Primary
End point timeframe:	
Week 4 visit.	

End point values	Alendronic Acid	Placebo	Intention to treat population	Per-protocol population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	184	174	421	356
Units: Number of subjects				
Fracture healed = yes	42	49	100	91
Fracture healed = no	140	125	289	265
Fracture healed = missing	2	1	32	3

Statistical analyses

Statistical analysis title	Primary Outcome analysis
Comparison groups	Placebo v Alendronic Acid v Intention to treat population v Per-protocol population
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	12.8

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were documented from date of randomisation to last study visit. Any adverse events ongoing at last study visit were followed up until resolution or no longer medically indicated.

Assessment type	Systematic

Dictionary used

Dictionary name	Study bespoke
Dictionary version	n/a

Reporting groups

Reporting group title	Alendronic Acid
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Alendronic Acid	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 184 (3.26%)	4 / 175 (2.29%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Other			
subjects affected / exposed	6 / 184 (3.26%)	4 / 175 (2.29%)	
occurrences causally related to treatment / all	0 / 10	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Alendronic Acid	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	100 / 184 (54.35%)	101 / 175 (57.71%)	
Vascular disorders			
Cardiovascular			
subjects affected / exposed	7 / 184 (3.80%)	7 / 175 (4.00%)	
occurrences (all)	14	14	
Nervous system disorders			

Nervous System (central or peripheral) subjects affected / exposed occurrences (all)	13 / 184 (7.07%) 32	19 / 175 (10.86%) 32	
General disorders and administration site conditions Dental subjects affected / exposed occurrences (all) Other subjects affected / exposed occurrences (all)	8 / 184 (4.35%) 14 35 / 184 (19.02%) 84	6 / 175 (3.43%) 14 49 / 175 (28.00%) 84	
Blood and lymphatic system disorders Haematological subjects affected / exposed occurrences (all)	3 / 184 (1.63%) 6	3 / 175 (1.71%) 6	
Eye disorders Opthalmic subjects affected / exposed occurrences (all)	3 / 184 (1.63%) 4	1 / 175 (0.57%) 4	
Gastrointestinal disorders Gastrointestinal subjects affected / exposed occurrences (all)	19 / 184 (10.33%) 27	8 / 175 (4.57%) 27	
Renal and urinary disorders Renal subjects affected / exposed occurrences (all)	2 / 184 (1.09%) 2	0 / 175 (0.00%) 2	
Musculoskeletal and connective tissue disorders Musculoskeletal subjects affected / exposed occurrences (all)	62 / 184 (33.70%) 119	57 / 175 (32.57%) 119	
Infections and infestations Infection subjects affected / exposed occurrences (all)	25 / 184 (13.59%) 53	28 / 175 (16.00%) 53	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2012	Change to Protocol: change to the manufacture of the IMP and placebo because of the size of the tablet made which was considered too large so could potentially be a major barrier to recruitment. Two other changes to the protocol in the "Exclusion Criteria" section: 1. Removal of the adjusted serum calcium value of 2.2mmol/L from the hypocalcaemia exclusion to take account of the fact that different laboratories have different lower limits of normal and different algorithms for adjusting serum calcium for albumin. Also, the normal reference range for serum calcium differs with age (Gardner & Scott J Clin Path 1980;33:380-385). Therefore, "Hypocalcaemia" listed in the revised protocol (v2) as the exclusion criterion which brought the study in line with the wording in the Summary of Product Characteristics (SmPC) for Alendronic acid. It allowed for variations between institutions without impacting on safety. 2. Removal of the MDRD formula as the method for calculating GFR since in routine clinical practice it is usual to calculate GFR values on the basis of age, gender and serum creatinine. Patients who had a GFR below 35ml/min were excluded from the study. This also brought the wording in line with the SmPC for alendronic acid which does not stipulate a specific method of calculating GFR.
13 July 2012	Change to protocol: change in the process so participants could be randomised before the results of their safety bloods. This gave sites flexibility to complete all baseline procedures and dispense medication in one day, reducing the number of extra visits a participant needed to make. Participants were instructed not to commence study medication until the blood results were back and showed no contraindication to take alendronic acid. The change affected the exclusion criteria to only exclude known hypocalcaemia and renal impairment at the time of randomisation. If blood tests showed renal impairment the participant would not start therapy but would still have the opportunity to be followed up within the trial if they wished. Any post-randomisation exclusions would be replaced.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30845365