Study Protocol

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

Co-sponsors	University of Edinburgh & NHS Lothian ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
Funder	Arthritis Research UK
Funding Reference Number	19403
Chief Investigator	Professor Stuart Ralston
EudraCT Number	2011-000988-28
REC Number	11/AL/0319
ISRCTN Number	ISRCTN62133820
Version Number and Date	Version 3.0 10th July 2012

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

EudraCT number: 2011-000988-28

Signatures

Professor Stuart Ralston Chief Investigator	Signature	Date
Professor Gordon Murray Trial Statistician	Signature	Date
Chris Tuck Trial Manager	Signature	Date

LIST OF ABBREVIATIONS

ACCORD	Joint office for University of Edinburgh and NHS Lothian – Academic and Clinical Central Office for Research & Development
AE	Adverse Event
AO	Arbeitsgemeinschaft für Osteosynthesefragen
AP	Anterior-Posterior
AR	Adverse Reaction
AROM	Active Range of Movement
BMD	Bone Mineral Density
CI	Chief Investigator
CRF	Case Report Form
CRPS-I	Complex Regional Pain Syndrome type I
CSG	Clinical Studies Group
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DASH	Disabilities of the Arm, Shoulder and Hand
DMC	Data Monitoring Committee
ECTU	Edinburgh Clinical Trials Unit
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated Glomerular Filtration Rate
GCP	Good Clinical Practice
IASP	International Association for the Study of Pain
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IM	Intramuscular
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IV	Intravenous
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIMP	Non Investigational Medicinal Product
NRS	Numerical Rating Scale
PI	Principal Investigator
PTH	Parathyroid Hormone
QA	Quality Assurance
R&D	Research and Development
REC	Research Ethics Committee
RSDS	Reflex Sympathetic Dystrophy Syndrome
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
WOCBP	Women of Childbearing Potential

SUMMARY

STUDY TITLE	Fractures and Bisphosphonates: A double-blind, randomised controlled trial on the effect of alendronic acid on healing and clinical outcomes of wrist fractures.
BACKGROUND	Bisphosphonates are widely used in the treatment of osteoporosis. Although fractures often occur in patients with osteoporosis who are on bisphosphonate therapy, the effects of bisphosphonates on fracture healing have not been adequately studied in humans. Sometimes bisphosphonates are withheld because of the theoretical concern about an adverse effect on fracture healing, but sometimes bisphosphonate therapy is continued. It remains unclear whether early treatment might be advantageous or deleterious to fracture healing and clinical outcome.
STUDY OBJECTIVES	Primary Objective To determine if alendronic acid affects fracture healing as assessed radiographically in men and women aged 50 years and over who have suffered a distal radial fracture. Secondary Objectives Assess upper limb function using the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire. Assess presence of Complex Regional Pain Syndrome type I (CRPS-I). Compare difference in pain between groups using a Numerical Rating Scale (NRS) and recording analgesic use. Compare the active range of movement between each group using a standard goniometer. Compare the grip strength between the groups using a JAMAR hand dynamometer. Compare the presence of malunion between both groups at 26 weeks using plain radiographs.
STUDY POPULATION	Patients (male and female) aged 50 years and over who have suffered a distal radial fracture and are not on bisphosphonate therapy. Study therapy must commence within 14 days of fracture. The sample size required for this study is 500 (not including post-randomisation exclusions).
STUDY TREAMENT	Participants will be randomised to commence either alendronic acid 70mg or placebo once weekly. Treatment will continue for 24 weeks.
STUDY ASSESSMENTS	Participants will be seen at 2, 4, 6 and 8 weeks for assessment of fracture healing and at 26 weeks to assess alignment.

1. INTRODUCTION

1.1 BACKGROUND

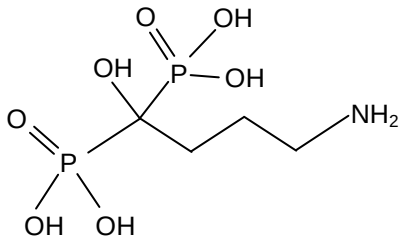
Wrist fractures are the most prevalent type of fracture in the UK[1], with incidence rates of 220 cases per 100,000 of population per year[2]. The functional outcome following wrist fracture is critically determined by the speed and adequacy of fracture healing and on whether the healing process results in a stable and well aligned skeleton[3].

Distal radial fractures have become much more common in the last 50 years[4, 5], possibly because of the increasing age of the population. Wrist fractures are especially common in postmenopausal women and some of these are associated with osteoporosis[6]. However most fractures occur in patients who do not have osteoporosis, as defined by a bone mineral density (BMD) T-score values of 2.5 or less[7].

Osteoporosis is a disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility, and a consequent increase in fracture risk[8]. It is estimated that 200 million people suffer from this disease worldwide[9], and one in two women and one in five men who are 50 years of age will have an osteoporotic fracture in their remaining lifetime[10].

In the mid 1990's several trials showed the benefit of using bisphosphonates for patients with osteoporosis[11-13]. In 2008 the bisphosphonate alendronic acid was approved by the National Institute for Health and Clinical Excellence (NICE) as first line treatment for primary prevention of osteoporotic fragility fractures in post menopausal women[14]. In 2009-2010, 5 million prescriptions were issued for alendronate[15].

Figure 1–1: Alendronic Acid



Alendronic acid is a bisphosphonate that inhibits osteoclastic bone resorption[16]. Bisphosphonates such as alendronic acid bind to calcified bone matrix and suppress bone remodelling primarily as the result of their inhibitory effects on osteoclast activity[17], although inhibitory effects on bone formation may also occur[18]. Since alendronic acid inhibits bone turnover it could theoretically affect fracture healing as restoration of the original shape and strength of a bone following fracture depends on remodelling of callus by osteoclasts and on the formation of new bone by osteoblasts. Pre-clinical studies have not shown any adverse effects in fracture healing and on the contrary have shown positive effects of bisphosphonates on the strength of fracture callus[19-23]. However, observational studies in man have raised the possibility that bisphosphonate therapy may increase the risk of fracture non-union[24].

1.2 RATIONALE FOR STUDY

Although bisphosphonates are widely used in osteoporosis currently there is no consensus as to what should be done with bisphosphonate therapy following an acute fracture. Sometimes bisphosphonates are withheld because of the theoretical concern about an adverse effect on fracture healing, but sometimes bisphosphonate therapy is continued. It remains unclear whether early treatment might be advantageous or deleterious to fracture healing and clinical outcome.

Previous studies[25,26] have investigated the effect of bisphosphonates on bone density after distal forearm fracture in patients taking bisphosphonate or placebo, but the effects of treatment on fracture healing have not been adequately assessed. A recent observational study suggested that prior bisphosphonate therapy did not substantially affect fracture healing but the study was small and included only 43 patients on bisphosphonate therapy[27].

This study will investigate the effect of alendronic acid on radiological fracture healing in the context of a randomised placebo controlled trial. Patients aged 50 and over who have fractured their wrist and are not on bisphosphonate therapy will be invited to take part in the study. Participants do not have to be osteoporotic to enter the study; the primary question is based on fracture healing in bisphosphonates and as such it is not necessary to know the BMD of participants.

The study is designed and powered to allow a definitive comparison of fracture healing rates after 4 weeks of treatment. Since previous studies have yielded conflicting results we have also ensured that the study is adequately powered to perform a non-inferiority comparison assuming that fracture healing time with alendronate will be similar to that of placebo to within four days. The difference between groups will be assessed by comparing the proportion of participants whose fracture has healed by week 4 in each treatment group. However a time to event analysis will also be performed to evaluate the trajectory of fracture healing from radiographs taken at 2, 4, 6 and 8 weeks. The study will also look at secondary endpoints linked to fracture healing, using the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire, grip strength, range of joint movement, pain scores and analgesia usage.

The study will also explore the effect of alendronic acid on Complex Regional Pain Syndrome type I (CRPS-I), which is a common complication of wrist fracture. CRPS-I, also known as Reflex Sympathetic Dystrophy Syndrome (RSDS) consists of abnormal pain, swelling, vasomotor and sudomotor dysfunction, contracture, and osteoporosis[28]. Systematic review of trials[29] suggest that there are favourable effects in using bisphosphonate therapy for established CRPS-I but the evidence is scarce. This study can assess if alendronate has any protective or prophylactic properties for the symptoms of CRPS-I in the short and long term.

The study is clinically important. If it is found that alendronic acid significantly delays fracture healing, then it may be advisable for clinicians to temporarily withdraw alendronate treatment following a fracture, or to delay starting treatment until the fracture has fully healed.

2. STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

To determine if alendronic acid affects fracture healing of men and women aged 50 years or over who have suffered a distal radial fracture.

2.1.2 Secondary Objectives

Assess upper limb function using the DASH questionnaire[30].

Assess the effect of alendronic acid on the prevalence of CRPS-I.

Compare difference in pain between groups using an NRS and recording analgesic use.

Compare the active range of movement between each group using a goniometer.

Compare the grip strength between the groups using a JAMAR hand dynamometer.

Compare the presence of malunion between both groups at 26 weeks using plain radiographs.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

Primary analysis will be measured by comparing the percentage of fractures healed in each treatment group at 4 weeks.

Assessment of fracture healing for the primary endpoint will be made centrally by a blinded observer. Assessment will be performed on anterior-posterior (AP) and lateral radiographs of the wrist using standard assessment methods[31,32]. Fractures will be defined as healed when the following features are present:

1. Bridging of three out of four cortices
2. Radiographic evidence of endosteal healing
3. Organised trabecular bridging

2.2.2 Secondary Endpoints

Upper limb function
Upper limb function will be assessed by using the DASH Outcome Measure. The DASH is a validated 30-item questionnaire which has previously been shown to detect changes of

disability over time after injury or surgery in patients with upper-extremity musculoskeletal disorders[33].

The effect of alendronate on the DASH score during the trial will be measured by comparing the change in DASH score from initial fracture to each timepoint for both treatment groups.

Complex Regional Pain Syndrome type I

CRPS-I is defined in this study using the clinical Budapest Criteria[34]. To make a diagnosis of CRPS-I, the following criteria must be met:

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in *three of the four* following categories:
   Sensory: Reports of hyperesthesia and/or allodynia
   Vasomotor: Reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
   Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry
   Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign **at time of evaluation** in *two or more* of the following categories:
   Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
   Vasomotor: Evidence of temperature asymmetry (>1°C) and/or skin colour changes and/or asymmetry
   Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
   Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

The presence of CRPS-I will be assessed at week 6 and 26 and compared between both treatment groups.

Pain assessment and analgesic use

Pain at fracture site will be assessed using an 11 point (0-10) NRS and by recording the amount of analgesia used in the 24 hours prior to questioning (except at baseline, see Section 7.2.3). Participants will be asked rank their pain from 0 (no pain) to 10 (worst pain imaginable) by circling the appropriate number on the NRS.

The difference in pain and analgesia use will be compared between both treatment groups.

Active range of movement

Active range of movement (AROM) will be measured at the wrist and distal radial-ulnar joints using a standard goniometer. The recording will be made in triplicate. The AROM of both the affected and unaffected hand will be measured.

The differences between the range of movement in each hand will be used to compare the two treatment groups.

Grip strength

Grip strength will be measured using a JAMAR hand dynamometer using the guidelines for its use issued by the American Society for Surgery of the Hand[35]. The grip strength of both the affected and unaffected hand will be measured.

The difference in grip strength between each hand will be used to compare the two treatment groups.

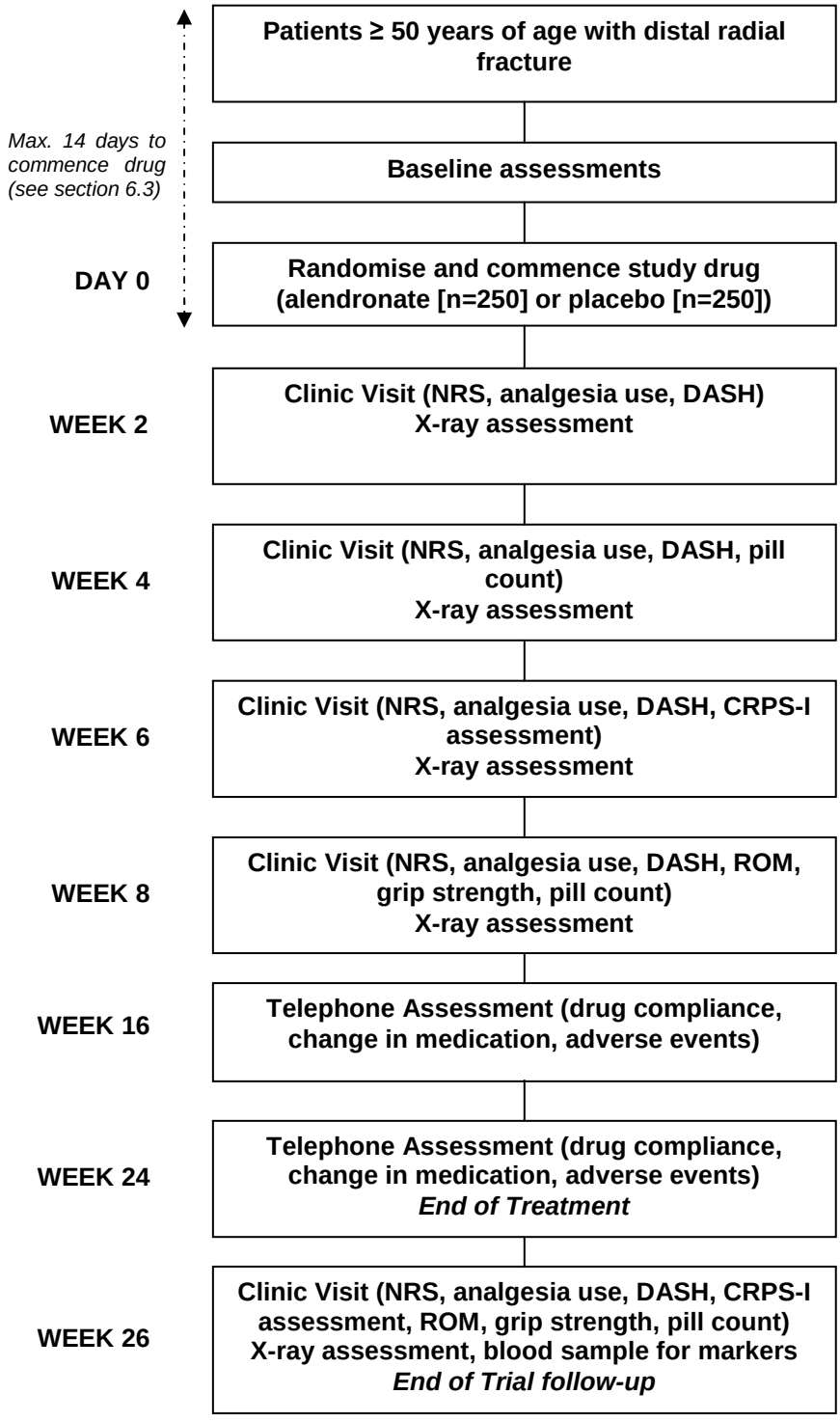
Malunion

Malunion of the fracture site will be assessed at 26 weeks using plain radiographs. The baseline radiograph will be used to classify the type of fracture using the Arbeitsgemeinschaft für Osteosynthesefragen (AO) classification[36]. Malunion will be assessed by measuring the dorsal angle, carpal alignment, and radial shortening on the radiograph taken at week 26. Malunion will be defined to be present when there is less than neutral dorsal tilt with carpal mal-alignment and more than 3mm of radial shortening[37]. Assessment of malunion will be performed centrally by a blinded observer. The presence of malunion will be compared between both treatment groups.

3. STUDY DESIGN

This study is designed as a double blind randomised controlled trial comparing the effect of a 24 week course of weekly 70mg alendronic acid on healing of distal radial fractures versus a placebo administered in a similar schedule. The study will last in total for 26 weeks, with a treatment phase of 24 weeks.

Figure 3–1 Study Design Overview



4. STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

500 participants (not including post-randomisation exclusions) aged 50 years and over who have suffered a distal radial fracture and are not on bisphosphonate therapy will be recruited into the study. The planned recruitment period is 18 months.

4.2 INCLUSION CRITERIA

1. Patients (male and female) aged 50 years and over.
2. Patients must have suffered a distal radial fracture confirmed by X-ray radiograph.
3. The distal radial fracture must be:
    i) unilateral extra-articular or minimal articular
    ii) displaced or un-displaced
    iii) treated with cast/splint, external fixation or open reduction and internal fixation.
4. Patients willing and able to consent and comply with study protocol.

4.3 EXCLUSION CRITERIA

1. Any of the following:
    i) current or previous use of zoledronic acid
    ii) current or previous use ***within the last 2 years*** of any other bisphosphonate.
    iii) current or previous use ***within the last 6 months*** of strontium ranelate, calcitonin, denosumab, parathyroid hormone (PTH) or IV, IM and oral corticosteroids (inhaled corticosteroids such as asthma inhalers are acceptable).
2. Previous distal radial fracture on affected side.
3. Bilateral distal radial fracture.
4. Contraindications to alendronic acid, including but not limited to:
    i) abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achlasia
    ii) inability to stand or sit upright for at least 30 minutes
    iii) hypersensitivity to alendronate or any of its excipients
    iv) known hypocalcaemia
    v) known renal impairment
5. Women of childbearing potential not using adequate contraception.
6. Pregnancy (see Sections 7.1 and 11).
7. The distal radial fracture is due to other pathologies e.g. Paget's Disease of Bone, metastatic bone disease etc.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Participants will be identified when presenting with an acute distal radial fracture.

5.2 CONSENTING PARTICIPANTS

Participants will be supplied the information sheet and once they have had adequate time to consider the information sheet and ask questions written consent will be sought for all eligible patients. The investigator must ensure informed consent is evidenced in writing, dated and signed, or otherwise marked, by that person so to indicate their consent. If the person is unable to sign or to mark a document so as to indicate their consent, it should be given orally in the presence of at least one impartial witness and recorded in writing.

5.3 SCREENING FOR ELIGIBILITY

Prior to any study specific screening investigations informed consent must be given by the patient. All screening investigations must be completed in time to allow a participant to commence study therapy within 14 days of their initial fracture.

For a list of screening investigations that are required prior to randomisation please see Section 7 of the protocol.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

An anonymised log will be kept for patients who were screened for the study and subsequently ineligible or not recruited. The coordinating centre (Edinburgh Clinical Trials Unit (ECTU)) may request that copies are sent to them for audit purposes.

5.5 RANDOMISATION

5.5.1 Randomisation

Participants will be randomised in a 1:1 ratio to either active drug or placebo. Randomisation will be stratified by site, gender and fracture status (displaced or undisplaced). This will be a double blind study – neither the participant nor the investigator site will be aware of the participant's treatment allocation.

Participants can be randomised before the result of the safety bloods are available but should only start their medication once it is confirmed that the participant is not hypocalcaemic and has an eGFR of ≥35ml/min. See section 7.1 for further details.

Randomisation will be performed by the ECTU. Details of the randomisation process will be available in the Investigator Site File (ISF).

Once a participant has been randomised they will be given a card to indicate they are on the trial. Participants will be instructed to show this to any healthcare professional involved in their care who is not involved in the study.

5.5.2 Treatment Allocation

Participants should ideally commence study drug the first morning after randomisation (the results of the safety bloods must also be confirmed – see section 7.1). This first dose of study drug (alendronic acid/placebo) must be within the 14 days following fracture or within the 7 days following randomisation, whichever comes first. Participants will be dispensed 26 tablets (24 + 2 spare) with instruction to take one tablet once a week for 24 weeks. For further details about the study drug please refer to Section 6 of the protocol.

5.5.3 Unblinding Procedures

Unblinding may take place in situations where the safe management of the participant's medical condition **necessitates knowledge of the study medication by the person(s) responsible for the participant's care**. In general, if time allows, the reason for unblinding should be discussed initially with the Chief Investigator.

The trial allocation will only be revealed to individuals on a "need to know" basis and should never be revealed to the Study Statistician (apart from after the final study analysis).

Each site is required to provide an emergency contact for unblinding. This contact must be available during office hours.

Unblinding will be performed on request by the Trial Manager. This service is available during office hours (09:00 – 17:00) by calling 0131 537 2573. No out of hours unblinding will be available. If it is not possible to unblind a participant investigators should treat the participant as if they were on study drug.

Each site will have an Unblinding Log which requires to be completed in the event of unblinding being performed. This is kept in the Investigator Site File.

5.5.4 Premature Withdrawal

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the investigator. If withdrawal occurs the primary reason for withdrawal should be documented in the participant's Case Report Form (CRF).

If a participant discontinues study drug this does not necessarily constitute withdrawal. In this case all attempts should be made to follow up the participant as per protocol.

If the Investigator feels that osteoporosis therapy needs to be initiated before the participant completes study treatment on clinical grounds – for example because of severe osteoporosis – then study therapy should be discontinued and the new medication should be noted in the CRF. Participants will continue to be followed up as per protocol.

6. INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG

6.1.1 Study Drug Identification

Alendronic Acid 70mg Tablets.

6.1.2 Study Drug Manufacturer

Manufacture of Alendronic Acid 70mg Tablets will be carried out by TEVA UK Limited

6.1.3 Marketing Authorisation Holder

The marketing authorisation holder of the alendronic acid tablet is:

TEVA UK Limited
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

The marketing authorisation number is PL 00289/0889.

6.1.4 Labelling and Packaging

Packaging and labelling of the Alendronic Acid 70mg Tablets will be carried out by:

Tayside Pharmaceuticals
Ninewells Hospital
Dundee
DD1 9SY
UK

6.1.5 Storage

This medicinal product should be stored at room temperature.

6.1.5 Summary of Product Characteristics

A copy of the latest version of the Summary of Product Characteristics (SmPC) is available in the ISF.

6.2 PLACEBO

A placebo will be used in this study. The placebo will be sourced from Winthrop Arzneimittel GmbH and will be packaged and labelled by Tayside Pharmaceuticals.

6.3 DOSING REGIME

Participants must commence study drug within the 14 days following fracture or within the 7 days following randomisation, whichever comes first. Ideally participants should take their 1st dose the morning after randomisation. Participants are to take 1 tablet of alendronate/placebo once a week for 24 weeks. Alendronate/placebo should be taken on the same day each week.

Alendronic acid should be taken after getting up for the day and before taking any food, drink or medicine. The tablet should be taken with a full glass of water only (not less than 200ml).

If taken at the same time, it is likely that food and beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products will interfere with absorption of alendronate. Therefore, participants must wait at least 30 minutes after taking alendronate before taking any other oral medicinal product.

Because the bioavailability of alendronic acid is very low and many side effects are caused by not following instructions on how to take alendronic acid, it is important that participants take their study medication according the guidance provided. Clear written and verbal instructions should be given to the participant before they start study treatment.

Participants will receive their study drug at the beginning of treatment. Participants should be instructed to bring their study drug to each visit and return any unused study drug at the end of the study.

6.4 DOSE CHANGES

No dose changes are necessary when taking alendronate. Participants should be instructed that if they miss a dose of study drug, they should take one tablet on the morning after they remember. They should not take two tablets on the same day but should return to taking one tablet once a week, as originally scheduled on their chosen day.

For participants requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating physician should guide the management plan of each participant based on individual benefit/risk assessment.

6.5 PARTICIPANT COMPLIANCE

Study drug compliance will be monitored during the study with the assistance of:

- Pharmacy drug returns
- Investigator questioning
- Pill counts
- Self-reported treatment diary

Pill counts will be documented on a participant's CRF. Non-compliance is not in itself a reason to withdraw a patient from the trial. Participants who stop taking study drug should still be followed up as per study protocol unless another reason prevents this.

6.6 OVERDOSE

Hypocalcaemia, hypophosphataemia and upper gastro-intestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage.

No specific information is available on the treatment of overdosage with alendronate. If a participant overdoses (i.e. 2 or more tablets taken) calcium containing products (e.g. milk, antacids) should be given to bind alendronate. Owing to the risk of oesophageal irritation, vomiting should not be induced and the participant should remain fully upright.

6.7 OTHER MEDICATIONS

6.7.1 Prohibited Medications

Other bisphosphonates (zoledronate, risedronate, tiludronate, etidronate, pamidronate, non-study alendronate, etc.), drugs with antiresorptive activity (calcitonin, strontium ranelate), denosumab and PTH (Teriparatide/Forsteo) will be prohibited while a participant is on study treatment.

Participants who require to be treated with the above medications will be withdrawn from study treatment but should remain on study follow up schedule.

No other interactions with medicinal products of clinical significance are anticipated. Although specific interaction studies have not been performed, in clinical studies alendronate was used concomitantly with a wide range of commonly prescribed medicinal products without evidence of clinical adverse interactions.

Since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.

6.7.2 Permitted Medications

Excepting the prohibited medications listed in Section 6.7.1, participants are free to take their usual medication (including calcium and vitamin D) during the study.

Participants must wait at least 30 minutes after taking alendronate/placebo before taking any other oral medication as they may interfere with the absorption of the study drug.

Any regularly used medications that are being taken at the start of study or commenced while a participant is on study should be documented on the Concomitant Medication CRF.

7. STUDY ASSESSMENTS

7.1 SAFETY ASSESSMENTS

Prior to randomisation all participants require a baseline blood sample which must include creatinine, albumin, calcium and corrected/adjusted calcium. The results of the safety bloods are not required prior to randomisation, **but must be known and not show hypocalcaemia or poor renal function before the participant commences study therapy**. If the participant is randomised and then the safety blood sample shows that the participant is hypocalcaemic or has poor renal function (an eGFR of <35ml/min) then study medication should be stopped. These participants will be classed as post-randomisations exclusions and will continue follow-up as per protocol.

Pregnancy is contraindicated when on alendronic acid. As such, women of childbearing potential (WOCBP, defined as women who are **not** postmenopausal (12 months since last menses) or permanently sterilised) will require a negative urine pregnancy test prior to study inclusion. WOCBP will be required to use adequate contraception during the trial. Examples of adequate contraception include:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) **with** spermicidal foam/gel/film/cream/suppository.
- Male sterilisation.
- True abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

The safety assessments outlined in Table 7–1 are considered a minimum requirement. Further safety assessments may be initiated at the treating physician's discretion if medically indicated.

Safety assessments will include the monitoring of adverse events and serious adverse events by the site investigator. For more details on adverse events please refer to Section 10.

7.2 STUDY ASSESSMENTS

Ideally, follow up visits for participants should be as close to the scheduled date as possible. It is recognised that in clinical practice this is not always feasible. As such, there is a window of +/-2 days for the visits up to and including the Week 8 visit and a window of +/- 7 days thereafter. For Weeks 2 to 8, a tolerance of +/-7 days is acceptable if the trial visit is being linked to a routine follow up visit or research clinic.

7.2.1 Baseline Assessments

The following assessments and procedures should be performed at baseline. Please note that all baseline assessments must be completed in time to allow a participant to commence study therapy within 14 days of their initial fracture:

- Informed Consent
- Demographic data (including age, gender, smoking history and alcohol consumption)
- Assessment of eligibility (inclusion and exclusion criteria)
- Relevant medical history/current medical conditions
- Concomitant medication
- Biochemistry (minimum requirement is creatinine, albumin, calcium and corrected/adjusted calcium)
- Blood serum for biochemical markers (see Section 7.2.12)
- X-ray (performed at time of fracture)

- Pain assessment at fracture site using a 11 point NRS (**based on pain prior to fracture**)
- Analgesia use (**based on analgesia usage 24 hours before fracture**)
- DASH Questionnaire (**based on how the participant felt prior to fracture**)
- Urine pregnancy test (for women of child bearing potential)
- Genetic blood sample (optional – see section 7.2.11)

7.2.2 Radiological Assessment

Evaluation of fracture healing is the primary objective in this trial. Anterior-posterior (AP) and lateral radiographs of the wrist are required at **baseline** (when fracture occurs), **weeks 2, 4, 6, 8** and **26**.

Sites are required to send radiographs to the coordinating centre for central analysis. Radiographs should be anonymised and only identified by participant trial number, initials, date of birth and date of radiograph. For guidance on sending radiographs for central analysis please refer to the Investigator Site File (ISF).

7.2.3 Pain Assessment

Evaluation of pain at fracture site should be performed using an 11-point NRS. This scale ranges from 0 (no pain at all) to 10 (worst pain possible).

Pain assessment using the NRS should be done at **baseline** (this should be based on the participant's pain levels the day before fracture), **weeks 2, 4, 6, 8** and **26**.

7.2.4 Analgesic use

Assessment of analgesic use will be noted by documenting any analgesia taken by the participant in the last 24 hours prior to questioning, except at baseline when the analgesia used in the 24 hours prior to fracture should be documented.

Evaluation of a participant's analgesic use should be performed at **baseline, weeks 2, 4, 6, 8** and **26**.

7.2.5 DASH Questionnaire

The DASH Outcome Measure is a 30-item, self-report questionnaire designed to measure physical function and symptoms in patients with any or several musculoskeletal disorders of the upper limb[38].

Participants will be asked to complete the DASH at **baseline, weeks 2, 4, 6, 8** and **26**. Study staff will check to ensure that all questions have been answered prior to the participant leaving the study visit.

7.2.6 CRPS-I Assessment

CRPS-I will be assessed using an assessment tool based on the International Association for the Study of Pain's (IASP) Budapest Criteria.

CRPS-I assessment will be performed at **week 6** and **week 26**.

7.2.7 Active Range of Movement

AROM will be assessed in participants' affected and unaffected wrist and distal radio-ulnar joint using a goniometer. Range of movement will be measured for flexion/extension, radial/ulnar deviation and supination/pronation. Each individual movement will be performed and measured 3 times. Guidelines for measuring AROM are available in the ISF.

AROM will be performed at **week 8** and **week 26**.

7.2.8 Grip Strength

Grip strength will be measured using a JAMAR hand dynamometer in both the affected and unaffected hand. Grip strength will be performed and measured 3 times at each required time point. Guidelines for measuring grip strength are available in the ISF.

Grip strength will be performed at **week 8** and **week 26**.

7.2.9 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each visit. A variety of methods will be used to ensure compliance. This information should be captured in the source document.

See Section 6.5 for further details on study drug compliance.

7.2.10 Telephone Assessments

Telephone assessment will be performed at **week 16** and **week 24**. During these calls participant compliance and adverse event information will be collected. At the week 24 assessment participants will be reminded to stop taking the study drug. Participants will also be reminded to bring in any remaining drug to their final study visit.

7.2.11 Genetic blood sample

Blood samples can be collected from participants who consent to the optional genetic sub-study. Preferably this will be collected at baseline at the same time blood is collected for biochemistry, but can be done at any point after genetic sub-study consent up until the end of the study.

9ml of blood should be taken from consenting patients and collected in EDTA tubes. No processing is required but samples should be mixed well and frozen on the day of collection. These will be marked with the patient's trial number, initials and date of birth. Samples should be stored at -80°C until shipment. If sites are unable to store samples at -80°C then samples can be stored at -20°C but must be shipped within 6 months of collection

The trial manager for the study should be notified when samples are ready to send. The trial manager will then provide a contact name and delivery address where the samples should be dispatched.

Samples should be sent in batches of approximately 50 samples and should be shipped frozen on dry ice by courier.

Full details for processing and shipment of genetic samples will be provided in the ISF.

7.2.12 Blood serum biomarker sample

At baseline participants will provide a baseline safety blood sample. At the same time blood serum samples will be collected for biomarkers of bone metabolism. They will also be collected at week 26.

7ml of blood should be collected in plain blood tubes (no gel or anticoagulant), spun and the serum should be stored in 2-3 x 1ml aliquots. Samples should be frozen at -70°C or below until ready for shipment for central analysis. Full details for processing and shipment of serum biomarker samples will be provided in the ISF.

Table 7–1: Schedule of Assessments

	Baseline[a]	Post-randomisation	Week 2	Week 4	Week 6	Week 8	Week 16	Week 24	Week 26
Informed Consent	X								
Demographics[b]	X								
Inclusion/Exclusion Criteria	X								
Relevant medical history/current medical conditions	X								
Biochemistry[c]	X								
Blood serum for biomarkers of bone metabolism	X								X
X-Rays[d]	X[e]		X	X	X	X			X
NRS Scoring	X		X	X	X	X			X
Analgesia usage	X		X	X	X	X			X
DASH Questionnaire	X		X	X	X	X			X
Urine pregnancy test[f]	X								
Pill count				X		X			X
CRPS-I assessment					X				X
Active range of movement						X			X
Grip strength assessment						X			X
Study drug administration[g]		X[h] →	→	→	→	→	→		
Concomitant medication	X →	→	→	→	→	→	→	→	→
Adverse Events[i]		X →	→	→	→	→	→	→	→
Optional genetic sub-study blood sample[j]	X →	→	→	→	→	→	→	→	→
Telephone Assessment[k]							X	X	

Notes for Table 7–1

[a] All baseline assessments must be completed in time to allow a participant to commence study therapy within 14 days of their initial fracture.
[b] Demographic information includes: age, gender, menopausal status, smoking history and alcohol consumption.
[c] Minimum biochemistry requirement includes: creatinine, albumin, calcium and corrected/adjusted calcium.
[d] X-rays must be performed +/- 2 days from scheduled visit date, except if it ties in with routine follow up/research clinic or at Week 26 X-ray where it can be +/- 7 days.
[e] This X-ray refers to X-ray at time of fracture.
[f] For women of childbearing potential
[g] Discontinuation of study drug does not constitute withdrawal from trial. Unless there is another reason participants should continue to be followed up as per protocol.
[h] Study drug administration must commence within the 14 days following initial trauma or within the 7 days following randomisation, whichever comes first.
[i] Adverse events should be documented from date of randomisation to last study visit. Any adverse events ongoing at last study visit should be followed up until resolution or no longer medically indicated.
[j] The optional genetic blood sample (9ml in EDTA tube) can be taken any time during the study. The participant must have given separate consent for this.
[k] Telephone assessment will include questions about drug compliance and adverse event information. At week 24 patients will be reminded to stop taking study drug and bring all medication with them to their final study visit (week 26).

8. DATA COLLECTION

Data will be collected from baseline to the last study visit. Data will be entered on CRFs and should be completed in accordance with the CRF completion guidelines issued for the study. All CRFs must be returned to the ECTU for data entry and ultimately, statistical analysis.

CRFs for the study will be returned and stored in line with current regulatory requirements. Other essential documents, including source data, consent forms, and regulatory documents, will be archived by or for the Investigator in an appropriate archive facility in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection.

9. STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

The proposed sample size is 250 per arm (500 in total, not including post-randomisation exclusions). The study is powered to detect a 15% difference in the proportion of patients who have evidence of fracture healing on the week 4 radiograph since this is considered to be a clinically significant difference. A total sample size of 500 patients gives at least 90% power at the 5% significance level (2-sided) to detect an absolute difference of 15% in the 4 week radiological healing rates. This holds irrespective of the actual rate in the control group. Even if the rate of non-compliance is as high as 20% then there will still be over 80% power to detect the same 15% different in 4 week radiological healing rates in a per-protocol analysis of compliant patients.

The sample size calculation given above is based on a conventional superiority comparison. The primary question being addressed in the trial can be viewed as a non-inferiority comparison, and so the implications of using the proposed sample for a non-inferiority analysis was also explored. In a recent study, funded by the Chief Scientist's Office of the Scottish Government which investigated the effects of vitamin C and placebo on wrist fracture healing, it was found that the average time to radiological healing in undisplaced wrist fractures was 42 days (SD 13) and in displaced fractures 48 days (SD 13). (Ekrol, Court-Brown, Ralston & McQueen, unpublished data). From a clinical point of view we feel that a 10% non-inferiority margin in time to radiological healing (i.e. less than 4 days) would not be clinically significant. Conversely, if the intervention delayed healing by more than 10% this would be clinically significant given that resolution of symptoms such as pain and restoration of function correlate closely with fracture healing. As is apparent from Table 9–1, the current sample size provides good power to demonstrate non-inferiority with a 10% margin if the true mean delay in healing is up to one day, and reasonable power for a true mean delay of up to 2 days. With the more stringent 7.5% margin there is good power to demonstrate non-inferiority if the treatments are equivalent, and reasonable power for a true mean delay of up to one day. Another way to look at this same issue is to note that with the planned sample size the resulting 95% confidence interval for the mean delay in healing will be the observed mean difference plus/minus approximately 2.5 days.

Table 9–1: Power to demonstrate non-inferiority at 5% significance level (one-sided)

True mean delay in healing (days)	Non-inferiority Margin 10%	7.5%
0	97%	85%
1	86%	57%
2	59%	24%

It is anticipated that enrolment for the study will last 18 months. During that time it is estimated that 4500 eligible patients will be seen at the centres taking part in the trial which should be an adequate number to achieve a target of 500 patients.

9.2 PROPOSED ANALYSES

A detailed Statistical Analysis Plan will be developed and finalised prior to database lock and the trial being unblinded. This section sets out the basic principles which will be followed for the analysis.

The response of the primary outcome variable (fracture healing at 4 weeks) in the two randomised groups will be analysed using logistic regression with adjustment for the variables used in the randomisation algorithm (study site, gender, fracture status) and other variables known to influence fracture outcome (including age, the presence of comminution and ulnar variance at presentation on X-ray)[39]. The results will be presented as an adjusted odds ratio with the corresponding 95% confidence interval and p-value. In addition a simple unadjusted comparison of the two 4 week healing rates will be made, and the result presented as a difference in healing rates along with the corresponding 95% confidence interval. The primary analysis will be conducted on an intention-to-treat basis, but given the interest in the non-inferiority comparison the per-protocol analysis will be an important secondary analysis. A similar approach will be used for other categorical outcome variables. The identification of the per-protocol population will be agreed with the Trial Steering Committee (TSC) and finalised before the data are analysed.

The analysis of the time to fracture healing will not be straightforward as there is heavy interval censoring of these data (since the 'time of healing' cannot be observed directly, and rather all that is known is whether healing has occurred by Week 2, 4, 6 or 8 (or 26)). The analysis of interval censored data is an area of active statistical research and the precise approach to be used for this analysis will be chosen nearer the end of the trial. It is likely that a parametric survival analysis will be performed, using the same covariates as for the analysis of the fracture healing rates at 4 weeks. There are libraries of statistical code available which can be used with the package "R" to perform such analyses.

Analysis of covariance will be used to compare treatment effects on continuous variables such as the DASH score, with the corresponding baseline value and the covariates identified above being included in the models. The results will be presented as adjusted mean differences along with the corresponding 95% confidence intervals and p-values.

When outcomes variables are measured on several study visits then each visit will be analysed separately. In general in terms of interpretation the Week 4 visit will be prioritised. No formal adjustments will be made to p-values to adjust for multiplicity, but the interpretation of the p-values resulting from secondary analyses will be interpreted very conservatively.

Every effort will be made to minimise missing data, especially for the key outcome measures. If more than 5% of values are missing then the primary analysis will use imputation and a complete cases analysis will be performed as a sensitivity analysis.

There is no intention to perform any formal interim analyses of the efficacy measures which might lead to a recommendation to stop the trial early on the basis of evidence of efficacy or futility. The only grounds on which the Data Monitoring Committee (DMC) could potentially recommend stopping the trial prematurely would be on the basis of a safety issue.

10. ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below. This responsibility may be delegated to a member of the research team. Assessment of events may be delegated to other suitably qualified physicians in the research team who are trained in recording and reporting adverse events (AEs).

Investigational Medicinal Product (IMP) is defined as any active substance or placebo being studied or used as a reference in the trial. This section also applies to medicinal products that are not the active substance or placebo, but are used as a concomitant medication to the IMP or as a rescue/escape medicine for preventative, diagnostic or therapeutic reasons. These are referred to as non Investigational Medicinal Products (NIMPs).

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant SmPC in the ISF.

Participants should be instructed to contact their Investigator (or member of the study team) at any time after consenting to join the trial if any symptoms develop. All AEs that occur after joining the trial and result in interaction with a healthcare professional must be reported in detail in the CRF or AE form. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment. Participants with AEs present at the last visit must be followed up until resolution of the event.

10.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward or unintended response to an IMP which is related to any dose administered to that participant.

An **unexpected adverse reaction** (UAR) is an adverse reaction that is not consistent with the applicable product information for the IMP, e.g. the Investigator Brochure (IB) for a non licensed IMP or the SmPC for a licensed product.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR) or **suspected unexpected serious adverse reaction** (SUSAR) is any AE, AR or UAR that at any dose:

- results in death;
- is life threatening* (i.e. the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect.

* Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

^Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation, will meet the SAE criteria. The only exception to this is the **elective** admission for surgery relating to the participants wrist fracture. This **does not** require to be reported as an SAE.

10.2 DETECTING AEs AND SAEs

All AEs and SAEs must be recorded from the time a participant commences study drug until the last study visit.

Participants will be asked about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified by support departments e.g. laboratories. Abnormal laboratory values and test results should only be noted as adverse events if they are symptomatic or require treatment (e.g. blood transfusion for low haemoglobin).

10.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator should then record all relevant information in the CRF and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

10.4 ASSESSMENT OF AEs AND SAEs

Seriousness, causality, severity and expectedness should be assessed as though the participant is taking active IMP. Cases that are considered serious, possibly, probably or definitely related to IMP and unexpected (i.e. SUSARs) should be unblinded.

The Investigator is responsible for assessing each AE. This may be delegated to other suitably qualified physicians in the research team who are trained in recording and reporting AEs.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

10.4.1 Assessment of Seriousness

The Investigator should make an assessment of seriousness as defined in Section 10.1.

10.4.2 Assessment of Causality

The Investigator must make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably, definitely) to the IMP will be considered as related to the IMP (ARs/SARs).

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR/SAR.

Unrelated: where an event is not considered to be related to the IMP.

Possibly: although a relationship to the IMP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

Probably: the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP.

Definitely: The known effects of the IMP or its therapeutic class, or based on challenge testing, suggest that the IMP is the most likely cause.

Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

10.4.3 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the CRF or AE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

10.4.4 Assessment of Expectedness

If an event is judged to be an AR/SAR, the evaluation of expectedness should be made based on knowledge of the reaction and the relevant product information documented in the SmPC.

The event should be classed as either:

Expected: the AR is consistent with the toxicity of the IMP listed in the SmPC or IB.

Unexpected: the AR is not consistent with the toxicity in the SmPC or the IB.

10.5 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office **immediately or within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.4, Assessment of Expectedness.

The SAE form will be transmitted by fax to ACCORD on **+44 (0)131 242 9447** or may be transmitted by hand to the office.

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information until this is supplied.

All SAE, SAR and SUSAR reports faxed to ACCORD and any follow up information will be retained in the ISF.

10.6 REGULATORY REPORTING REQUIREMENTS

The ACCORD Research Governance & QA Office is responsible for Pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and Lothian Health Board).

The ACCORD Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD will inform Investigators at participating sites of all SUSARs and any other arising safety information.

An Annual Safety Report will be submitted to the regulatory competent authority and main REC listing all SARs and SUSARs.

10.7 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator is required to follow each participant until resolution or death of the participant. Follow up information on an SAE should be reported to the ACCORD office.

AEs still present in participants at the last study visit should be monitored until resolution of the event or until no longer medically indicated.

11. PREGNANCY

Pregnancy is not considered an AE or SAE, however, the Investigator must collect pregnancy information for any female participants or female partners of male participants who become pregnant while participating in the study. The Investigator should record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy.

All pregnant female participants and partners of male participants should be followed up until the outcome of the pregnancy.

12. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grantholders (Chief Investigator and Principal Investigator (PI) in Edinburgh), a Trial Manager and coordinating nurse.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial. If any changes are made to the Delegation Log during the study an updated copy should be sent to the Clinical Trial Manager at the Central Trial Office.

12.2 CENTRAL TRIAL OFFICE

The Central Trial Office is based in the Edinburgh Clinical Trials Unit (ECTU) and will provide support to each site. The office will be responsible for randomisation, collection of data in collaboration with the research nurses, data processing and analysis.

Publication and dissemination of the study results will be coordinated by ECTU in collaboration with the Chief Investigator and Investigators.

12.3 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the Trial Steering Committee, the draft template for reporting and the names and contact details will be detailed in a separate document.

12.4 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The terms of reference of the Data Monitoring Committee and the names and contact details will be detailed in a separate document.

12.5 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

12.6 RISK ASSESSMENT

An independent risk assessment will be performed by an ACCORD Clinical Trials Monitor to determine if monitoring is required and if so, at what level. An independent risk assessment will also be carried out by the ACCORD Quality Assurance (QA) Group to determine if an audit should be performed before/during/after the study and if so, at what locations and at what frequency.

12.7 STUDY MONITORING

An ACCORD Clinical Trials Monitor or an appointed monitor will visit the Investigator site prior to the start of the study and during the course of the study if required, in accordance with the monitoring plan if required. Investigator sites will be risk assessed by the ACCORD QA Manager, or designee, in order to determine if audit, by the ACCORD QA group, is required.

13. GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

A favourable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

13.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, and any relevant amendments.

13.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list.

13.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant should be performed by the Investigator or designated person, and must cover all the elements specified in the Participant Information Sheet/Informed Consent Form(s).

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant should be informed and agree to their medical records being inspected by regulatory authorities but understand that their name will not be disclosed outside the hospital.

The Investigator or delegated member of the trial team and the participant should sign and date the Informed Consent Form(s) to confirm that consent has been obtained. If the person is unable to sign or to mark a document so as to indicate their consent, it should be given orally in the presence of at least one impartial witness and recorded in writing. The participant should receive a copy of this document and a copy filed in the Investigator Site File (ISF).

13.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

13.3.3 Data Recording

The Investigator is responsible for the quality of the data recorded in the CRF.

13.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV), signed and dated by the Investigator indicating that it is accurate and current.

The ACCORD Research Governance & QA Office will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) and that appropriate documentation is available in local ISFs.

13.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

13.3.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

14. STUDY CONDUCT RESPONSIBILITIES

14.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the Chief Investigator.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to participants being enrolled into an amended protocol.

14.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Investigators should not implement any deviation from the protocol without agreement from the Chief Investigator and appropriate REC, Regulatory Authority and R&D approval except where necessary to eliminate an immediate hazard to trial participants.

In the event that an Investigator needs to deviate from the protocol, the nature of and reasons for the deviation should be recorded in the CRF. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

14.3 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point.

14.4 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and take the appropriate action.

Not every violation from the protocol needs to be reported to the regulatory authority as a serious breach. If the sponsor(s) deem the incident to be a violation that does not constitute a serious breach from the protocol when identified, corrective and preventative actions will be taken where appropriate and they will be recorded in file notes, held within the TMF or ISF.

14.5 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators and/or the trial steering committee and/or the Sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved.

A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

14.6 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Individual sites will assess participants and bone mineral density measurements will be taken according to standard clinical practice to determine if bisphosphonate therapy should be continued following cessation of the study. The continuation of study therapy following the end of the study rests with the judgement of the treating physician.

14.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the Sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's Nation Health Service (NHS) will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

15. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

15.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

15.3 PEER REVIEW

The study concept and design has been reviewed by the Arthritis Research UK and the Metabolic bone Disease Clinical Studies Group (CSG) as part of the funding application process.

Investigators at each site, the Trial Steering Committee, Ethical Review Boards, MHRA, and local R&D departments will review the protocol as part of the study approval process.

The results of the study will be disseminated by peer review publication and presentation at national and international meetings.

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