

Zoledronate in the Prevention of Paget's: the ZiPP study

Submission date 16/09/2008	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 17/10/2008	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
Last Edited 21/12/2023	Condition category Musculoskeletal Diseases	<input type="checkbox"/> Individual participant data

Plain English summary of protocol

Background and study aims

Paget's disease is caused by a problem with bone regeneration that causes bone to be replaced at a faster rate than usual, leading to enlarged bones that are weak and brittle. People who inherit a mutation in a gene called SQSTM1 have an increased chance of developing Paget's disease. The aim of this study is to determine whether the drug zoledronic acid can prevent Paget's disease in people with SQSTM1 mutations. We also wish to find out whether having a genetic test increases anxiety and depression even if the patient is found not to have the SQSTM1 mutation, and whether there any differences in the markers of Paget's disease in people with and without the mutation.

Who can participate?

Patients diagnosed with Paget's disease and their relatives who have not yet been diagnosed with Paget's disease.

What does the study involve?

Genetic tests are carried out to identify patients with the SQSTM1 mutation, who are then randomly allocated to be treated with either zoledronic acid or placebo (salt solution) via intravenous infusion (i.e., delivered into a vein). All participants (with and without the SQSTM1 mutation) are asked to give blood samples and complete health questionnaires.

What are the possible benefits and risks of participating?

Not provided at time of registration

Where is the study run from?

Edinburgh Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?

January 2009 to May 2022

Who is funding the study?

1. Medical Research Council (MRC) (UK)
2. Arthritis Research Council (ARC) (UK)

Who is the main contact?
ZiPP Trial Office
zipptri1@exseed.ed.ac.uk

Study website

<http://www.clinicaltrials.ed.ac.uk/trials/zipp/default.asp>

Contact information

Type(s)

Scientific

Contact name

Dr ZiPP Trial Office

Contact details

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Additional identifiers

EudraCT/CTIS number

2008-005667-34

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

MRC ref: G0701625

Study information

Scientific Title

Randomised trial of genetic testing and targeted zoledronic acid therapy to prevent SQSTM1-mediated Paget's disease

Acronym

ZiPP

Study objectives

Main aim of the interventional component of the trial:

To determine if targeted intervention with zoledronic acid can prevent the development of raised bone turnover and/or focal bone lesions in subjects who are genetically predisposed to develop Paget's disease of bone (PDB) because they carry mutations in SQSTM1 that have previously been associated with PDB.

An observational sub-study will be carried out in participants who have the same risk of developing Paget's disease as the general population. The sub-study will aim to answer the following two questions:

1. Does having a genetic test cause increased anxiety and depression, even if found not to have the SQSTM1 gene mutation?
2. Is there any difference in the biochemical makers which are predictive of the disease in this group compared to the group who have the mutation?

Genetic tests will be carried out to identify patients with a mutation in the SQSTM1 gene as part of the screening of potential participants.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Fife and Forth Valley Research Ethics Committee, 22/12/2008, ref: 08/S0501/84

Study design

Multi-site double-blind placebo-controlled randomised trial

Primary study design

Interventional

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

Not available in web format, please contact zipptri1@exseed.ed.ac.uk to request a patient information sheet.

Health condition(s) or problem(s) studied

Paget's disease of the bone (PDB)

Interventions

Current interventions as of 26/06/2012:

Participants will be randomised to either infusions of zoledronic acid (Aclasta®) 5 mg by intravenous infusion over 15 minutes or placebo (0.9% saline) at baseline.

In the observational study participants will have blood samples taken at a baseline and end of study visit and will be asked to complete health questionnaires.

Previous interventions:

Participants will be randomised to either infusions of zoledronic acid (Aclasta®) 5 mg by intravenous infusion over 15 minutes or placebo (0.9% saline) at baseline. Repeat infusions will be given after 30 months in both treatment arms. Patients in the placebo arm will receive a further placebo infusion at 30 months.

In the zoledronic acid group, a second 5 mg infusion will be given only if the serum bone specific alkaline phosphatase value taken at the routine review visit at 24 months lies above the reference range or has risen by 30% of the bone specific alkaline phosphatase (BSAP) level at baseline. If values lie below this a placebo infusion will be given to maintain blinding of the study.

In the observational sub-study participants will have blood and urine samples taken annually and will be asked to complete health questionnaires.

Intervention Type

Drug

Phase

Not Applicable

Drug/device/biological/vaccine name(s)

Zoledronic acid

Primary outcome measure

Current primary outcome measure (s):

In the intervention study, the primary outcome will be the total number of subjects who develop new bone lesions between the baseline visit and the final follow up visit.

In the observational study, the primary outcome measure will be anxiety / depression, measured using the HADS scale.

Previous primary outcome measure (s):

1. Bone-lesion sub-study: total number of subjects who develop new bone lesions after 5 years
2. Biochemical marker sub-study: the development of elevated bone turnover over 3 years, as measured by alkaline phosphatase (ALP)
3. Observational study: anxiety/depression over 3 years, measured using the Hospital Anxiety and Depression Scale (HADS)

Secondary outcome measures

Current secondary outcome measure (s):

In the interventional study, the secondary outcome measures will be:

1. The development of elevated bone turnover, as measured by ALP and other biochemical markers of bone turnover.
2. Quality of life, and anxiety and depression assessed by the SF-36, BPI and HADS questionnaires.

In the observational study, the secondary outcomes will be:

1. The development of elevated bone turnover, as measured by ALP and other biochemical markers of bone turnover.
2. Quality of life, assessed by the SF-36 questionnaire.

Previous secondary outcome measure (s):

1. Biochemical marker study:

1.1. Patients will be followed up for 5 years and investigated for the development of bone lesions. At the end of study, we will perform a pooled analysis of data from the bone lesion sub-study and biochemical markers sub-study to determine if there is an overall effect of treatment on bone lesions

2. Biochemical and bone-lesion sub-study:

2.1. Quality of life, anxiety and depression assessed by the 36-item short form health survey (SF-36), Brief Pain Inventory (BPI) and HADS questionnaires at baseline and annually for 5 years

3. Observational sub-study:

3.1. Development of elevated bone turnover, as measured by ALP (blood sample) at baseline and once a year for 5 years

3.2. Quality of life, assessed by the SF-36 questionnaire at baseline and annually for 5 years

Overall study start date

12/01/2009

Completion date

31/05/2022

Eligibility

Key inclusion criteria

Both males and females are eligible for participation in this study.

Genetic test:

1. Patients with PDB (probands):

1.1. Diagnosed with PDB

1.2. Have relatives older than 30 years who have not yet been diagnosed with PDB

2. Relatives:

2.1. Relatives are aged 30 years old or greater

2.2. Relatives not yet been diagnosed with PDB

Intervention study:

1. Relatives of patients with SQSTM1 mutations

2. Aged 30 years old or greater

3. Carry SQSTM1 mutations

4. Not already diagnosed with PDB at study entry

Observational study:

1. Relatives aged between 30 years old or greater

2. Relatives who on screening are found NOT to have SQSTM1 mutations

Participant type(s)

Mixed

Age group

Adult

Sex

Both

Target number of participants

510 in total (260 participants in the interventional study; 250 participants in the observational study)

Total final enrolment

222

Key exclusion criteria

Current exclusion criteria as of 26/06/2012:

Genetic test:

For patients with PDB and relatives:

1. Subjects not willing to have a blood sample taken
2. Subjects who are unwilling or unable to consent.

Intervention study:

1. Already diagnosed with PDB
2. Unwilling or unable to consent
3. Bisphosphonates contraindicated
4. Receiving bisphosphonate therapy for another reason
5. Severe liver or renal disease
6. Osteonecrosis of the jaw (ONJ)
7. If creatine clearance levels are less than 35 ml/min
8. Metastatic cancer or cancer diagnosed less than 2 years ago where treatment is still ongoing
9. Active history of uveitis, iritis, or episcleritis
10. Already taking part in another randomised controlled clinical trial
11. Female patients of child bearing potential are eligible only if they are:
 - 11.1. Not pregnant - negative pregnancy test on the day of or the day prior to the infusion
 - 11.2. Consent to a pregnancy test prior to the infusion
 - 11.3. Non-lactating
 - 11.4. Are sexually abstinent or are surgically sterile (tubal ligation or hysterectomy)
 - 11.5. If sexually active:
 - 11.5.1. Must receive specific advice from their consultant about possible risks associated with getting pregnant whilst on the trial, and
 - 11.5.2. Must agree to practice a medically acceptable form of birth control for at least 12 months post infusion (acceptable birth control defined as the use of an intrauterine device [IUD], a barrier method with spermicide, condoms, subdermal implant or oral contraceptives)

Previous exclusion criteria

Genetic test:

For patients with PDB and relatives:

1. Subjects not willing to have a blood sample taken
2. Subjects who are unwilling or unable to consent.

Intervention study:

1. Already diagnosed with PDB
2. Unwilling or unable to consent
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9. Active history of uveitis, iritis, or episcleritis
10. Already taking part in another randomised controlled clinical trial
11. Female patients of child bearing potential are eligible only if they are:
 - 11.1. Not pregnant - negative serum beta-human chorionic gonadotropin (b-hCG) pregnancy test done on the day, with results available, prior to infusion
 - 11.2. Consent to a pregnancy test prior to every dose administration
 - 11.3. Non-lactating
 - 11.4. Are sexually abstinent or are surgically sterile (tubal ligation or hysterectomy)
 - 11.5. If sexually active:
 - 11.5.1. Must receive specific advice from their consultant about possible risks associated with getting pregnant whilst on the trial, and
 - 11.5.2. Must agree to practice a medically acceptable form of birth control for at least 12 months post infusion (acceptable birth control defined as the use of an intrauterine device [IUD], a barrier method with spermicide, condoms, subdermal implant or oral contraceptives)

Date of first enrolment

12/01/2009

Date of final enrolment

16/04/2015

Locations

Countries of recruitment

Australia

Belgium

Ireland

Italy

New Zealand

Scotland

Spain

United Kingdom

Study participating centre

Edinburgh Clinical Trials Unit

Edinburgh

United Kingdom

EH4 2XU

Sponsor information

Organisation

University of Edinburgh

Sponsor details

The Queen's Medical Research Institute
47 Little France Crescent
Edinburgh
Scotland
United Kingdom
EH16 4TJ

Sponsor type

University/education

Website

<http://www.clinicaltrials.ed.ac.uk>

ROR

<https://ror.org/01nrxf90>

Organisation

Lothian NHS Board (UK)

Sponsor details

Deaconess House
148 Pleasance
Edinburgh
Scotland
United Kingdom
EH8 9RS

Sponsor type

Hospital/treatment centre

Website

www.nhsllothian.scot.nhs.uk

Funder(s)

Funder type

Research organisation

Funder Name

Medical Research Council (MRC) (UK) (ref: G0701625; 85281)

Alternative Name(s)

Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United Kingdom

Funder Name

Arthritis Research Council (ARC) (UK) (ref: 18163)

Results and Publications

Publication and dissemination plan

The researchers intend to publish the results of this trial in a high-impact, peer-reviewed, open-access journal. A detailed publication and dissemination plan is currently in development.

Intention to publish date

31/05/2023

Individual participant data (IPD) sharing plan

Access to the datasets generated and/or analysed during the current study can be requested in writing from the Edinburgh Clinical Trials Unit (ECTUdatashare@ed.ac.uk) following publication. All proposals will be considered by a review panel, which will decide whether and what type of data can be made available. This will depend on various factors, including the risk of re-identification and the scientific merit of proposed data use. The review panel will also consider the method of access and whether any additional agreements will be required prior to the access being granted.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	04/09/2019	28/01/2020	Yes	No
HRA research summary			28/06/2023	No	No
Results article		20/12/2023	21/12/2023	Yes	No