Study Protocol

Randomised Trial of Genetic Testing and Targeted Zoledronic acid Therapy to Prevent SQSTM1 Mediated Paget's Disease (Zoledronate in the Prevention of Paget's)

ZIPP STUDY

Co-Sponsor	University of Edinburgh NHS Lothian
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Randomised Trial of Genetic Testing and Targeted Bisphosphonate Therapy to Prevent SQSTM1 Mediated Paget's Disease: Zoledronate in the Prevention of Paget's

EudraCT number 2008-005667-34

Signatures

Professor Stuart Ralston Chief Investigator	Signature	Date
Steff Lewis Trial Statistician	Signature	Date
Dr Laura Forsyth Lead Trial Manager	Signature	Date

INVESTIGATOR STATEMENT

Randomised Trial of Genetic Testing and Targeted Zoledronic acid Therapy to Prevent SQSTM1 Mediated Paget's Disease (Zoledronate in the Prevention of Paget's)

Protocol G0701625
EudraCT number 2008-005667-34

I agree to conduct the study according to this protocol, the principles of International Conference on Harmonisation Tripartite Guidelines for Good Clinical Practice (ICH GCP) and the applicable regulatory requirements. Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of the patients.

I agree to take responsibility for the conduct of the study and ensure that all other staff involved are adequately informed about the protocol and amendments, the IMP and their study related duties and functions.

I have read and understood the information in the Summary of Product Characteristics, including the potential risk and adverse event profile of the IMP.

Signatures

Signature of Investigator Date

Name of Investigator (please print)

LIST OF ABBREVIATIONS

Academic and Clinical Central Office for Research and Development	ACCORD
Alakaline Phosphatase	ALP
Arthritis Research Campaign	ARC
Bone Specific Alkaline Phosphatase	BSAP
Brief Pain Inventory	BPI
Chief Investigator	CI
Edinburgh Clinical Trials Unit	ECTU
Hospital and Anxiety Depression Score	HADS
Medical Research Council	MRC
Paget's Disease of Bone	PDB
Principal Investigator	PI
Sequestosome 1	SQSTM1
National Association for the Relief of Paget's disease	NARPD
Urinary N-telopeptide collagen cross links	NTX

SUMMARY

Scientific

Paget's disease of bone (PDB) is characterised by increased bone turnover affecting one or multiple bones throughout the skeleton. Although some patients are asymptomatic, others develop complications such as bone deformity, pain, deafness, fracture and an increased risk of osteoarthritis.

Genetic factors play an important role in PDB and mutations of the SQSTM1 gene have recently been found to be an important cause occurring in between 20% - 50% of patients with a positive family history. Carriers of SQSTM1 mutations develop severe disease with an early age at onset and the penetrance is approximately 90% by the age of 70. Mutations of SQSTM1 are highly specific for PDB and are extremely rare in unaffected controls.

Bisphosphonates are highly effective at suppressing the elevated bone turnover which is characteristic of PDB and can help bone pain, but they are of limited benefit in patients with established disease who have already developed complications. In this study, we will test the hypothesis that genetic testing coupled with prophylactic treatment with the potent bisphosphonate Zoledronic acid can prevent the development of raised bone turnover and focal bone lesions in carriers of SQSTM1 mutations. If positive effects on these outcomes were to be demonstrated, further studies would be undertaken to determine if a programme of genetic testing and targeted intervention could prevent the development of complications associated with PDB in genetically susceptible individuals.

Subjects above the age of 30 years, who have a positive family history of PDB but who have not yet developed clinical signs of PDB, will be screened for the presence of SQSTM1 mutations. Those who are found to carry SQSTM1 mutations will be invited to take part in an intervention study in which they will be randomised to receive a single dose of either Zoledronic acid 5mg or placebo by intravenous infusion. Participants will be followed up annually until 2018-2019 and at each visit biochemical markers of bone turnover will be studied. At the end of the follow up period, the development of new bone lesions will be assessed by radionuclide bone scan. The effects of the intervention on bone pain and quality of life will also be studied.

Lay summary

Paget's disease of bone (PDB) is a serious bone disease, which causes pain, arthritis and deafness and can lead to softening of the bones causing then to enlarge and become bent.

Up to 40% of patients with PDB have inherited it from family members and mutations (inherited abnormalities) in the gene SQSTM1 is an important cause of the disease. Patients who have SQSTM1 gene abnormalities usually develop severe PDB with complications such as bone fractures and deformed bones. PDB can be treated with drugs called bisphosphonates but often the disease has caused irreversible damage to the bones before the diagnosis is made and these drugs are prescribed.

The aim of this research is to find out if better results can be obtained by giving early treatment to people who are genetically at risk of getting the disease because they have SQSTM1 gene abnormalities but who have not yet developed symptoms of the disease. We will do this by carrying out genetic tests on people with a family history of PDB to see if they carry the SQSTM1 gene abnormalities. People who are found to carry inherited abnormalities in SQSTM1 will be invited to take part in a research study in which 50% will be given an active treatment which we think might prevent the disease. The other 50% will be given a dummy treatment (also called a placebo). Participants will receive their allocated

treatment once only at the beginning of the study. Participants will be followed up annually and at the end of the trial, a test called a bone scan will be carried out to determine if the treatment has prevented development or progression of the disease. We will also study the effects of treatment on blood which can be used to detect early signs of the disease and we will look for any side effects of the treatment. Neither the patients nor their doctors will know what treatment they have received so that we can make an objective assessment of the possible risks and benefits of the treatment.

If the research shows that genetic testing combined with active treatment can prevent the development of the disease this would lead to further research to find out how best to introduce it into routine care. This could improve the outlook for people who have a family history of the disease.

1. INTRODUCTION

1.1 BACKGROUND

Paget's disease of bone (PDB) is an important cause of morbidity in older people, affecting 2-3% of British people over the age of 55. It is characterised by focal increases in osteoclastic bone resorption, coupled to increased and disorganised bone formation at one or more sites throughout the skeleton. Although some patients are asymptomatic many others develop complications such as bone deformity, pathological fracture, deafness and secondary osteoarthritis (1). These complications cause loss of mobility and independence, and adversely affect quality of life (2;3).

Genetic factors are important in PDB and the disease is inherited as an autosomal dominant trait in many families (4-6). Mutations have been identified in four genes that predispose to PDB and related conditions (7), but the most important of these is *SQSTM1* which encodes p62; a scaffold protein in the NFκB signalling pathway (8-10). Between 20-50% of patients with a family history of PDB carry *SQSTM1* mutations and the mutations also occur in between 5-20% of patients without a known family history of the disease (11-17). Individuals with mutations of the SQSTM1 gene are at high risk of developing PDB which has an early age of diagnosis and is more clinically severe than those without the mutations (18). Penetrance is about 90% by the seventh decade (11;12;14;15;17;19-22). The mutations are highly specific for PDB and are extremely rare in age and sex matched controls (14;15;17;19;23). Recently, several other genetic variants have been identified that influence susceptibility to PDB in patients without SQSTM1 mutations (24;25)

Presently, bisphosphonates are regarded as the treatment of choice for PDB. They are highly effective at suppressing biochemical markers of bone turnover and can sometimes help in the treatment of bone pain. Various bisphosphonates have been licensed for the treatment of PDB, but the most potent bisphosphonate is Zoledronic acid (26;27) which can result in a sustained biochemical remission of the disease in over 95% of subjects for up to 6.5 years following a single injection (28)

1.2 RATIONALE FOR STUDY

From a clinical standpoint, it would be attractive to intervene at an early stage in the natural history of SQSTM1 mediated PDB, since recent large scale randomised studies have shown that bisphosphonate treatment of patients with advanced PDB has limited effects on morbidity and disease complications (3) whereas patients with less advanced disease treated with potent bisphosphonates such as Zoledronic acid report slightly more favourable effects on quality of life [24]. Since a single infusion of Zoledronic acid is proven to be nearly 100% effective at normalising biochemical markers of disease activity in PDB it is an ideal treatment for the prevention of PDB in genetically susceptible individuals.

A previous MRC funded study, the GAP study [26] investigated the acceptability of genetic testing and targeted intervention in PDB. Results from this study indicated that individuals with a family history of the disease found the notion of genetic testing and targeted intervention desirable/acceptable. This indicates that recruitment into this study should be achieved and it is a research question that the consumer has considered to be important.

This study will test the hypothesis that prophylactic therapy in individuals with SQSTM1 mutations can prevent the development of bone lesions and/or elevated bone turnover. If positive effects on these outcomes were to be demonstrated, longer term follow up of the treatment groups will be carried out to determine if continued prophylactic therapy has more favourable effects than standard care in patients with SQSTM1 mutations. In the longer term

the results of this study may underpin the introduction of a programme of genetic testing and targeted intervention for familial PDB in routine clinical practice.

2. STUDY OBJECTIVES

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 PDB because they carry mutations in SQSTM1 that have previously been associated with PDB. Patients with novel mutations of SQSTM1 not so far described will be entered into the study on the basis that the mutation causes a non-conservative amino acid change affecting the ubiquitin associated domain. Participants will be screened for the presence of SQSTM1 mutations by analysis of DNA extracted from a peripheral blood sample. Participants that test positive for SQSTM1 mutations will be invited to take part in an intervention study where they will be randomised to receive either a single dose of Zoledronic acid 5mg or a matching placebo by intravenous infusion. Participants that test negative for SQSTM1 mutations will be invited to take part in an observational study to determine whether any biochemical abnormalities suggestive of PDB develop with time and to evaluate the effects that the testing process has on quality of life and anxiety

2.1 Primary Objective

The primary objective of the **Intervention study** will be to determine whether targeted intervention with Zoledronic acid can prevent the development of new focal bone lesions in carriers of SQSTM1 gene mutations.

The primary objective of the **Observational study** will be to determine if genetic testing impacts on quality of life or depression in participants who do not have SQSTM1 gene mutations.

2.2 Secondary Objectives

The secondary objective of the **Intervention study** will be to determine whether targeted intervention with Zoledronic acid can prevent increases in bone turnover in carriers of SQSTM1 gene mutations.

For the interventional study we will also investigate the effects of genetic testing and intervention on quality of life as assessed by the SF36 and the Brief Pain Inventory (BPI) questionnaire and on anxiety or depression (assessed by the HADS questionnaire) in study participants.
For the observational study, the secondary objective will be to determine if bone turnover is affected in non-gene carriers.

Blood and urine samples will be obtained from participants in both studies. These will be used to analyse specialised biochemical markers of bone turnover, analyse expression of genes relevant to the pathogenesis of Paget's disease; to test for the presence of antibodies to pathogens implicated in the pathogenesis of Paget's disease and to conduct genetic profiling for polymorphic variants relevant to the pathogenesis of Paget's disease and it's response to treatment. The purpose of these tests will be to determine if these specialised markers are of value in predicting which patients develop PDB (or complications of PDB) as compared with those who do not and if they are of value in predicting treatment response and/or the development of side effects with treatment.

2.3 Outcome measures

2.3.1 Primary outcome measures

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.

2.3.2 Secondary outcome measures

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

- the development of elevated bone turnover, as measured by ALP and other biochemical markers of bone turnover.
- 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:

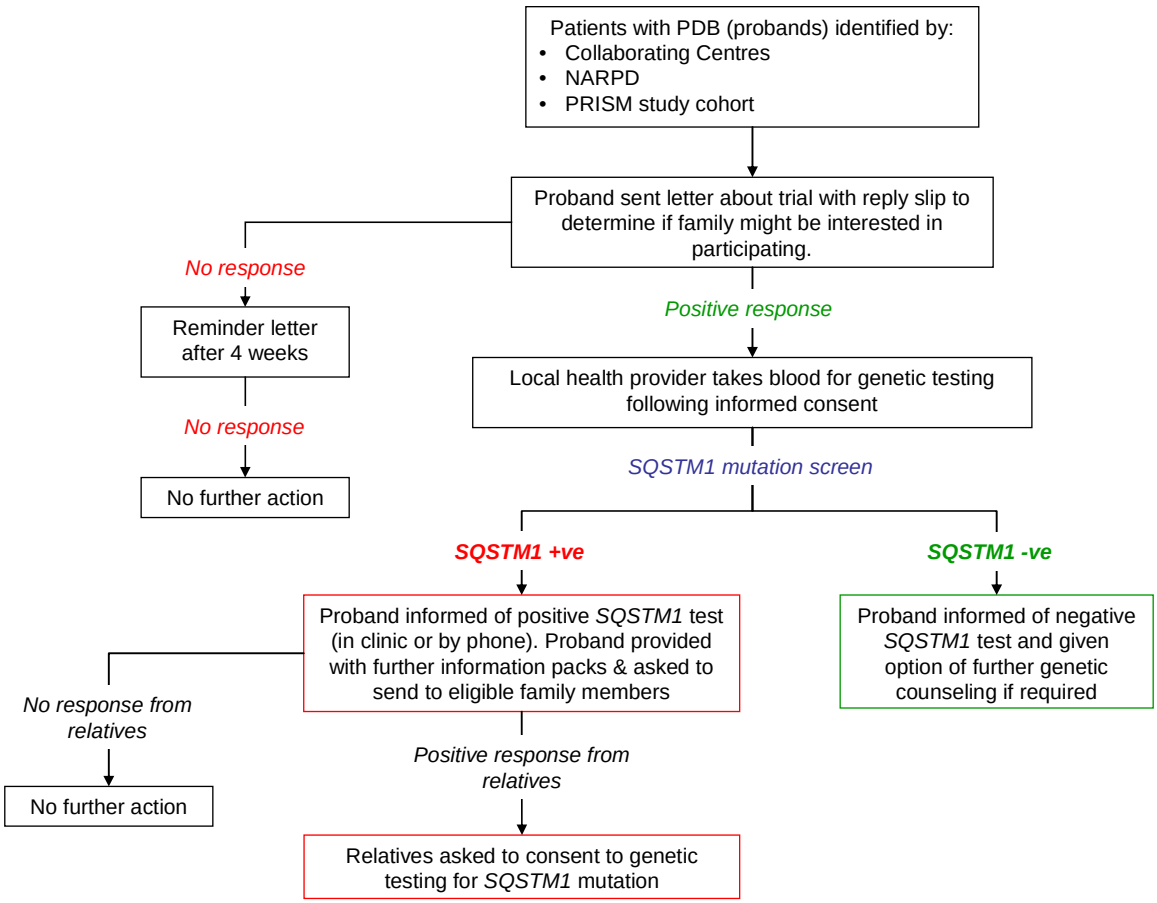
- the development of elevated bone turnover, as measured by ALP and other biochemical markers of bone turnover.
- quality of life, assessed by the SF-36 questionnaire.

The specialised markers mentioned in section 2.2 will be used to determine if it is possible to predict which patients develop PDB (or complications of PDB) as compared with those who do not and to determine if they are of value in predicting treatment response and/or the development of side effects with treatment.

3. STUDY DESIGN

This study will be a multi-centre double blind, placebo controlled, randomised trial of intravenous Zoledronic acid in SQSTM1 mutation carriers. The study involves a genetic screening phase and an intervention stage (Figure 1 and 2). Patients who are known to have PDB (probands) will be contacted by letter asking if they would like to be tested for the presence of mutations in the SQSTM1 gene. Consenting patients will be tested for the presence of SQSTM1 mutations. To do this, patients will be asked to provide a fresh blood sample or agree for an existing blood sample (given for prior research into the genetics of Paget's disease) to be tested. Those that test positively will be contacted with this result, counselled with regard to the implications and asked about their family history to determine if they have eligible relatives for the intervention phase of the study. Information packs will then be sent to probands that respond positively to pass on to their unaffected blood relatives within the desired age range.

Figure 1. Identification of Probands and Participants

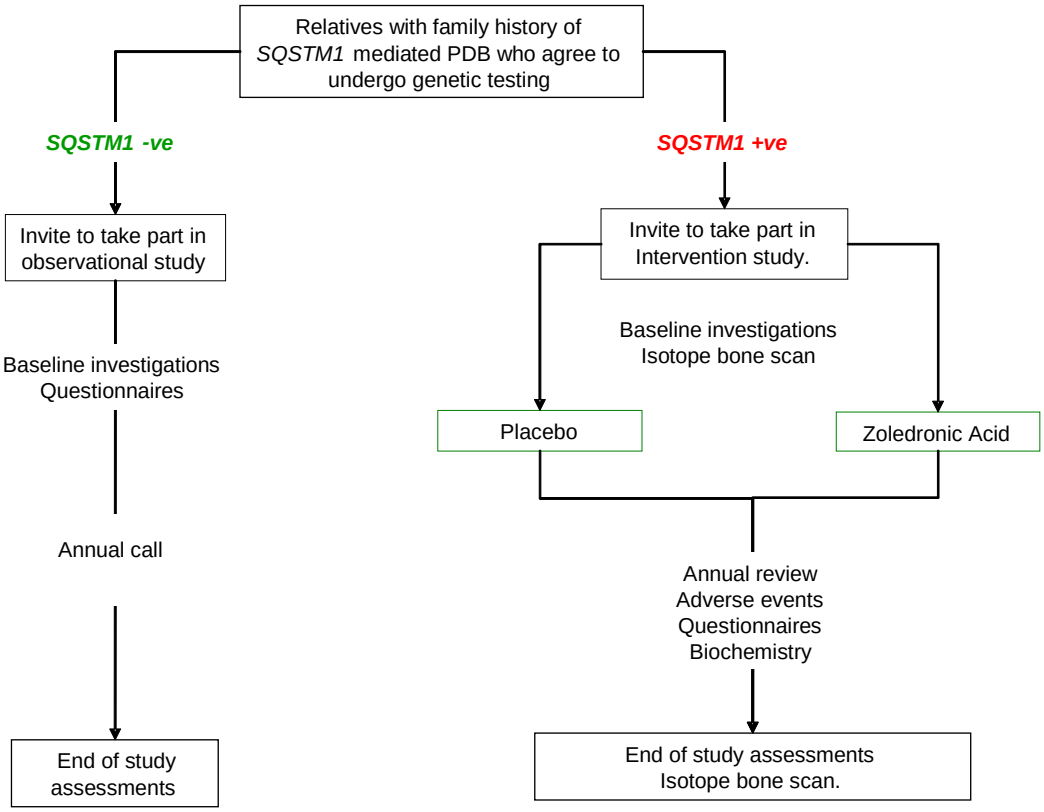


Relatives who return an "interested in study" reply slip will be contacted, and invited to undergo genetic testing. Those found to have SQSTM1 mutations will be counselled and invited to take part in the intervention study where they will be randomised to receive either Zoledronic acid 5mg or placebo by intravenous infusion.

Participants will then be followed up annually until 2018-2019. At the end of the follow up period the baseline assessments will be repeated. Details of the assessments that will be performed at each time point are shown in section 7.2.

Participants who test negative for SQSTM1 mutations will be invited to take part in the observational study. These participants will undergo blood tests to evaluate biochemical markers of bone turnover. Details of the assessments that will be performed in these subjects are shown in section 7.2.

Figure 2. Overview of Trial design



4. STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We aim to enrol a total of 260 participants into the intervention study to reach the primary endpoint (see section 9 for further details)

We aim to enrol a total of 250 participants into the observational study to reach the primary endpoint (see section 9 for further details).

The details of the participating centres in this study are listed in a separate document.

4.2 INCLUSION CRITERIA

4.2.1 Inclusion Criteria for Genetic Test - Patients with PDB (Probands)

Probands must be diagnosed with PDB.
Have at least one relative aged 30 years old or greater.

4.2.2 Inclusion criteria for a Genetic Test - Relatives

Relatives are aged 30 years old or greater.
Relatives not yet been diagnosed with PDB.

4.2.3 Inclusion Criteria for the Intervention Study

Relatives of patients with SQSTM1 mutations aged 30 years old or greater who carry SQSTM1 mutations.
Not already diagnosed with PDB at study entry.

4.2.4 Inclusion Criteria for the Observational Study

Relatives aged between 30 years old or greater.
Relatives who on screening are found **NOT** to have SQSTM1 mutations.

4.3 EXCLUSION CRITERIA

4.3.1 Exclusion Criteria for Genetic Test (Patient with PDB and Relatives)

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

4.3.2 Exclusion Criteria for the Intervention Study

Already diagnosed with PDB.
Unwilling or unable to consent.
Bisphosphonates contraindicated.
Receiving bisphosphonate therapy for another reason.
Osteonecrosis of the jaw (ONJ).
Estimated GFR (eGFR) < 35ml/min.
Hypocalcaemia .
Metastatic cancer or cancer diagnosed less than 2 years ago where treatment is still ongoing.
Active uveitis, iritis, or episcleritis.
Already taking part in another randomised controlled clinical trial.
Pregnancy [1].
Lactation.

Exclusion waivers will not be permitted.

[1] Female patients of child bearing potential should have a negative pregnancy test on the day of, or the day before, the infusion of study drug. The preferred method of testing for pregnancy is serum beta-hCG, but a urine beta-hCG is also acceptable for centres that are unable to obtain a serum beta-hCG within 1-2 days. Participants who are sexually active must receive specific advice about the possible risks associated with getting pregnant whilst on the trial and 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 IUD, a barrier method with spermicide, condoms, subdermal implant or oral contraceptives)

4.3.3 Exclusion Criteria for the Observational Study

Subjects diagnosed with PDB or SQSTM1 mutation positive

4.4 Delayed Recruitment into the Study

The following describe conditions when recruitment into the intervention study can be delayed:

4.4.1 Dental Surgery

If a potential participant in the intervention study has had invasive dental surgery (extractions, root treatment, other surgery to the mandible or maxilla) recruitment into the study will be delayed until healing has occurred. If healing has not occurred within 3 months of completion of the dental work then this would be considered a possible case of ONJ and would constitute a reason for exclusion.

If the relative has dental work planned within the first 3 months of the expected infusion date the relative should not be recruited until the dental work has been carried out and healing is complete.

Minor dental procedures such as de-scaling and fillings will not constitute a contraindication to enrolment.

4.4.2 Vitamin D Deficiency

Measurement of serum 25(OH) vitamin D levels will be carried out using the blood sample provided by relatives at the genetic testing stage of the study. Those with values below the lower limit of the local reference range and who wish to take part in the intervention study will be given vitamin D supplements according to local clinical practice..

4.4.3 Pregnancy/Breast Feeding

If a relative is pregnant and/or breastfeeding but would be interested in taking part, they can do so if the recruitment process is still ongoing when they are no longer pregnant or breastfeeding.

5. PARTICIPANT SELECTION AND ENROLMENT

Potential participants will be identified from three different sources.

1. Blood relatives of patients already known to the investigators and/or collaborators, where there is a family history of PDB.

2. Blood relatives of participants in the PRISM study who have a positive family history of PDB. (NB Only PRISM participants that have agreed to be notified of future studies will be contacted).

3. Blood relatives of potential patients with PDB attending routine outpatient clinics with or without a positive family history of PDB.

The above strategies should be sufficient to meet the target sample size. However due to the high level of consumer interest in the study it is anticipated that a large proportion of unsolicited volunteers (with PDB or a family history of PDB) will be interested in participating. These volunteers may contact the National Association for Relief of Paget's disease

(NARPD) - a UK based patient support group – or the Trial Co-ordinating Office, and every effort will be made to accommodate such volunteers.

In all cases initial contact with potential participants will be made by the local investigator or research nurse, at which point they will be offered a face to face consultation, provided with written information and an invitation to provide a blood sample for genotyping of the SQSTM1 gene. Screening is described in further detail in Section 5.2.

5.1 CONSENTING PARTICIPANTS

Consent will be taken for different purposes at different stages in this study. In all cases a designated member of the research team will fully explain the nature of the consent and the risks involved to each participant, and will also explain that the participant would be free to withdraw from the trial at any time without consequences.

Participants will have the choice in how they would like the consent process to take place, where they have the blood sample taken and how they would like the result to be given to them (for the genetic testing phase only).

If a participant would prefer to travel to the local research centre for consent and to have a blood sample taken, the local research team will co-ordinate this.

If a participant lives a substantial distance away from a local research centre but are still willing to provide a blood sample for screening of the SQSTM1 gene and routine blood tests, then a consent form and blood pack will be posted to the participant.

If participants wish to have an existing blood sample tested (provided in prior research studies in PDB), they will have the option of consenting to this by post or attending a local clinic.

A member of the research team will contact all participants who have been posted a consent form (at an agreed time, a few days later). They will answer any questions about the study and ask the participant to sign and date the consent form. A designated member of the research team will also sign and date a copy of the consent form at the same time. The participant will be asked to send their signed version of the consent form back to the local coordinating site where the 2 different signed consent forms will be collated. A copy of the collated signed consent form (signatures from both research team member and the participant) will be sent back to the participant for their records.

The consent forms will be printed on carbonless copy paper, with 4 sheets. The top original signed form will be retained by the participant. The other 3 layers will be filed in the site file, hospital notes and Central Trial Office file. In the case of postal consent, a copy will not be filed in the hospital notes.

The different consent forms are detailed below;

1. Patients with PDB who wish to have a blood sample taken for SQSTM1 genotyping will be asked to sign the **“Genetic Testing for People with PDB consent form”.**

2. Relatives who wish to have a blood sample taken for SQSTM1 genotyping (after mutation has been identified in family) will be asked to sign the **“Genetic Testing for Relatives consent form”.**

3. Relatives who test positive for the SQSTM1 mutation and who wish to take part in the intervention study will be asked to sign the "**Participation in Intervention study consent form".**

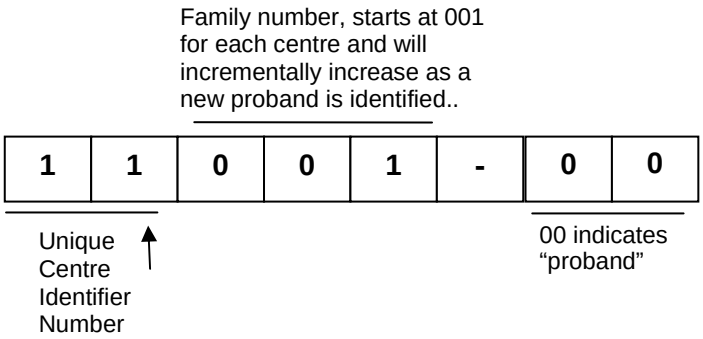
4. Relatives who **do not** have the SQSTM1 mutation and who wish to take part in the observational study will be asked to sign the **"Participation in the observational study".**

5.2 IDENTIFYING AND SCREENING FOR ELIGIBILITY

5.2.1 Identifying and Screening Patients with PDB

Patients known to have PDB will be contacted by letter and given a patient information leaflet detailing why we would like to test for the SQSTM1 mutation. This will be co-ordinated locally by each collaborating centre. All patients contacted will be allocated a family number (e.g. as detailed in Figure 4) to enable completion of the consort diagram.

Figure 4: Patient with PDB family identifier.



Patients with PDB will be asked to return a reply slip if they are interested in receiving a genetic test, or would like more information.

A designated member of the research team will contact the patient with PDB who return a reply slip indicating an interest in receiving more information or participating. Each patient will be given the opportunity to ask questions and discuss the study.

Interested patients with PDB will be offered the option of consenting by post and having their blood taken at their local primary care surgery, or they can come into a hospital-based clinic to provide consent and a blood sample.

If the patient prefers to attend a hospital-based clinic at the collaborating centre, an appointment will be made where they will be asked to sign a "**Genetic Testing for People with PDB consent form**" and a blood sample will be taken for genotype screening.

If the participant wishes to have a blood sample taken by their local general practitioner, (GP), a blood pack will be sent to the participant with the "**Genetic Testing for People with PDB consent form**". After going through the consent form on the phone with a member of the research team (see Section 5.1), the participant will make an appointment with their GP who will arrange for the blood sample to be taken.

The blood pack will be returned by routine mail to Edinburgh (for UK centres), or other appointed laboratories (for sites outside the UK) for analysis.

If patients with PDB have previously provided a blood sample, they will have the option of having their existing sample tested. If they agree to this, they will have the option of consenting by post or coming into a local clinic (see Section 5.1).

In some of the collaborating international centres, people with PDB may have already had a genetic test for the SQSTM1 gene and have been informed of the result. In this case, the subjects who have been identified as having the SQSTM1 mutations **will not** be asked to provide another blood sample but they will be asked to discuss their family history and to supply their eligible relatives with information packs for the study if they consent to do so.

5.2.2 Notifying Patients with PDB of the Results of the Genetic Test

All patients with PDB will have the result of the genetic test explained by a member of the research team at each centre by their preferred method (phone or clinic). All staff involved in this study will be trained in genetic counselling, so that the genetic test results can be delivered effectively, and the information needs of the participating patient are addressed. Those who do not have the SQSTM1 gene will be informed of the result and will not have any more involvement in the study. If they require any more information about any aspect of genetics or their Paget's disease, they will be given contact details of relevant advice sources (e.g. contact details for a local genetic counselling centre, or Paget's disease specialist).

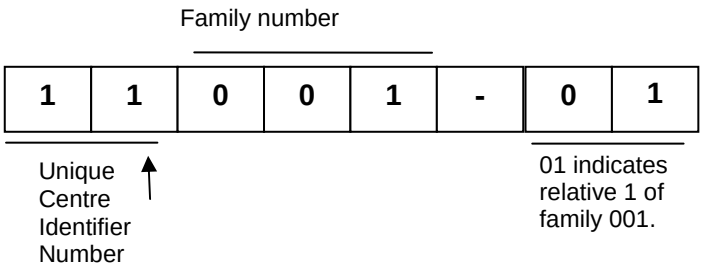
Patients with PDB who test positive for a SQSTM1 mutation will have the result explained to them and will be given the opportunity to discuss any concerns they may have.

5.2.3 Identifying and Screening Relatives

The research team will ask the proband if they have any family members above the age of 30 who might be eligible for the study and ascertain if the proband has had the opportunity to discuss the study with their relatives. For families in which the proband has indicated that their relatives are interested in the study, the names and contact details of the relatives will be recorded. For families where the probands has not indicated that their relatives are interested in the study, we will collect anonymised details only including initials, gender, age and town/city of residence until the relative affirms that they are interested in the study by sending back a reply slip. .

From the family history discussion a relative information pack (patient information leaflets, "reply if interested slip", pre-paid envelope) will be produced for eligible relatives (aged greater than 30 years old, and who have not been diagnosed with PDB). For families where the proband has indicated that their relatives are interested in the study the packs will be sent directly to the relative. For families where the proband has not been able to contact relatives to check if they are interested or not, we will send the packs to the proband, who will then be asked to pass the packs on to their relatives. Relatives will be allocated a study number to correspond to the proband family number (e.g. 11001-01, 11001-02 etc as detailed in **Figure 5**. A log of despatched relative information packs will be recorded (see Section 5.4) (detailing relation to patient with PDB, including the patient with PDB screening code). This log will allow completion of a CONSORT diagram.

Figure 5: Relative study number.



Relatives who return the "reply if interested slip" will be contacted by the research team and will be given the opportunity to ask questions and discuss any concerns they may have about the concept of genetic testing. Relatives will be offered the option of consenting by post and having their blood taken at their local primary care surgery, or they can attend a clinic appointment to provide consent and a blood sample. The reply slip will detail their preferred option.

If the relative prefers to attend clinic, an appointment will be made where they will be asked to sign a **"Genetic Testing for Relatives consent form**". Blood samples will be taken to test for the presence of SQSTM1 mutations and for analysis of routine biochemistry and 25(OH) vitamin D levels to test if they are eligible to take part in the intervention study.

If the relative wishes to have the blood samples taken by their local GP, a blood pack will be sent to the participant with the "**Genetic Testing for Relatives consent form**". After going through the consent form on the phone with a member of the research team (see Section 5.1), the relative will make an appointment with their local GP who will arrange for the blood sample to be taken.

The blood pack will be returned by routine mail to Edinburgh (for UK centres), or other appointed laboratories (for sites outside the UK) for analysis.

5.2.4 Notifying Relatives of the Results of the Genetic Test – SQSTM1 mutation carriers

All relatives will have the result of the genetic blood test explained by a member of the research team at each centre by their preferred method (phone or clinic). If they test positive for a SQSTM1 mutation they will be counselled on the implications of this and given information about the intervention study. The relative will be given the option of coming into the clinic for a further discussion. Relatives who have the SQSTM1 mutation in whom clinically significant abnormalities are discovered on routine bloods tests that preclude inclusion in the study will have this explained to them and will be referred to their GP. The GP will be given full details of the test results.

Relatives who test positive for SQSTM1, in whom routine blood tests are satisfactory will be invited to participate in the intervention study. If they want to take part, an appointment will be made where they will be invited to sign the **"Participation in Intervention Study consent form".** Detailed information about the assessments that are performed in the intervention study are provided in Section 7.2.

5.2.5 Notifying Relatives of the Results of the Genetic Test – No SQSTM1 Mutation

All relatives will have the result of the genetic test explained by a member of the research team by their preferred method (phone or clinic). Relatives who do not have SQSTM1 mutations will be counselled on the implications of this, and told that this does not completely exclude the possibility of them developing PDB but it means that their risk is low and no greater than in the general population. If significant abnormalities are discovered on routine blood tests the patient will be informed and advised to consult with their GP. Their GP will be fully informed of the test results. They will be invited to take part in an observational study, and if agreeable they will be asked to sign a **"Participation in Observational Study consent form"**.

5.3 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

For ineligible relatives and eligible relatives who are not subsequently randomised, the reason for non-recruitment will be recorded and entered onto the database. Local research nurses will keep a local log of all relatives to whom information packs have been sent. This local log will hold identifiable information to facilitate participant contact. At the end of the recruitment phase this log will be anonymised. This anonymised log will allow completion of a CONSORT diagram.

5.4 RANDOMISATION

Following completion of the "**Participation in Intervention study consent form**" subjects will complete the baseline assessments including an isotope bone scan, unless an isotope bone scan had already been performed for another reason within the previous 2 years.

Participants will then be randomised to receive either a single dose of Zoledronic acid 5mg or placebo by intravenous infusion. The study database will inform the research nurse/Investigator which label code the participant has been randomised to. Local Pharmacies will be given this code and they will dispense the correct infusion (either placebo or Zoledronic acid). This code will not give away any information about the actual treatment, thus allocation will be concealed, so that the participant and the research nurse/Investigator will remain blind to the treatment that has been given. From the moment of randomisation, the patient will be included in the final analysis regardless of treatment received (intention-to-treat).

Allocation will be minimised according to the type of mutation (missense versus truncating or frameshift), by gender (male /female); on the basis of whether or not bone lesions suggestive of PDB are present on the baseline bone scan, whether ALP levels are elevated at baseline (yes/no) and by age in increments as follows: 30-40, 41-50, 51-60, 61-70, 71+

5.4.1 Administration of study Medication

Participants will be randomised in a double blind manner to receive Zoledronic acid, 5mg or placebo by intravenous infusion over a period of at least 15 minutes.

5.4.2 Emergency Unblinding Procedures

The study will be performed double blind, so neither the participant nor the Investigator will know which treatment has been allocated.

Breaking of the study blind should only be performed where knowledge of the treatment is absolutely necessary for further management of the patient. Breaking of the blind can only be performed by contacting the local pharmacy, who will have restricted code break details.

Unless there is a clinical requirement, the blind will not be broken until after data entry is complete, the validity of the data is checked, all queries resolved and the trial steering committee has agreed.

5.4.3 Premature Withdrawal

Participation in the study is voluntary. Participants will have the right to withdraw from the study at any time for any reason. The Investigator will have the right to withdraw a participant at any time if it is deemed to be in the participant's best interest. This would occur if serious adverse effects develop, considered by the investigator to be due to the study medication or if complications of PDB develop (progressive lytic lesions, uncontrolled symptoms, bone deformity, pathological fracture) in a participant assigned to the placebo group. The reason and circumstances for premature withdrawal from treatment will be documented in a Participant Withdrawal form. However, wherever possible, data will continue to be collected on participants regardless of treatment received, unless they specifically request not to be followed up.

Female participants who become pregnant during the course of the study will not undergo isotope bone scanning while they are pregnant or whilst breastfeeding (see Section 11).

6. INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG

6.1.1 Study Drug Identification

Zoledronic acid (Aclasta®) 5mg solution for infusion.

6.1.2 Study Drug Manufacturer

Novartis Pharmaceuticals UK Limited
Frimley Business Park
Camberley
Surrey
GU16 7SR

6.1.3 Marketing Authorisation Holder

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex,
RH12 5AB

6.1.4 Labelling and Packaging

Labelling and Packaging will be carried out by;
Novartis Pharmaceuticals Corp.
Drug Supply Management
One Health Plaza
East Hanover,
NJ 07936
USA

Label text will be in accordance with the Medicines for Human Use (Clinical Trials) regulations 2004.

The allocation of Zoledronic acid /placebo will be double blinded.

6.1.5 Storage

The unopened bottle of Aclasta® does not require any special storage conditions. Each bottle is for single use only. Any unused solution should be discarded. Only clear solution free from particles and discoloration should be used.

If refrigerated, solution should be allowed to reach room temperature before administration. Aseptic techniques must be followed during the preparation of the infusion.

6.1.6 Summary of Product Characteristics

An online link to the latest version of the Summary of Product Characteristics (SmPC) is given in Appendix 1.

The most common side effects of Zoledronic acid are flu like symptoms. The incidence of post-dose symptoms occurring within the first three days after administration of Zoledronic acid can be reduced with the administration of paracetamol or ibuprofen shortly following administration.

Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥ 1/10,000, <1/1,000) adverse drug reactions are described in Appendix 1 but are also shown in Figure 8. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

6.2 PLACEBO

0.9% saline (containing mannitol) will be used as a placebo. This will be bottled and labelled to match the active drug by Novartis.

6.3 DOSING REGIME

Participants in the intervention study will receive either a single infusion of Zoledronic acid 5mg or placebo by intravenous infusion following completion of the baseline investigations and randomisation. Zoledronic acid (5 mg in 100 ml ready-to-infuse solution) and placebo (0.9% saline, containing mannitol) will be administered via a vented infusion line and given at a constant infusion rate over not less than 15 minutes.

Table 1

Cardiac disorders	*Common*	Atrial fibrillation
Nervous system disorders	*Common*	Headache, dizziness
	Uncommon	Lethargy, paraesthesia, somnolence, tremor, syncope, dysgeusia
Eye disorders	*Uncommon*	Conjunctivitis, eye pain, uveitis
	Rare	Episcleritis, iritis
Ear and labyrinth disorders	*Uncommon*	Vertigo
Gastrointestinal disorders	*Common*	Nausea, vomiting, diarrhoea
	Uncommon	Dyspepsia, abdominal pain, dry mouth, oesophagitis
Renal and urinary disorders	*Uncommon*	Blood creatinine increased
Skin and subcutaneous tissue disorders	*Uncommon*	Rash
Musculoskeletal and connective tissue disorders	*Common*	Myalgia, arthralgia, bone pain, back pain, pain in extremity
	Uncommon	Joint swelling, shoulder pain, muscle spasms, muscular weakness, joint stiffness
Metabolism and nutrition disorders	*Common*	Hypocalcaemia†
	Uncommon	Anorexia
General disorders and administration site conditions	*Very common*	Fever
	Common	Flu-like symptoms, chills, fatigue, asthenia, pain, malaise, rigors†
	Uncommon	Peripheral oedema, thirst
Psychiatric disorders	*Uncommon*	Insomnia
† Common in Paget's disease only. For hypocalcaemia, see also text below.		

6.4 DOSE/TREATMENT CHANGES

Dose changes at baseline are not permitted within the protocol.

6.5 PARTICIPANT COMPLIANCE

Participants in the intervention study will receive a single infusion of study medication. As the infusion will be administered in the clinic, it is expected that compliance with the medication will be 100%. In this study a 10% drop out rate has been factored into the sample size for participants that no longer wish to continue after randomisation or are lost to follow up.

6.6 OVERDOSE

There is no experience of acute intoxication with Zoledronic acid. The SmPC states that people who have received doses higher than those recommended should be carefully monitored. In the event of overdose leading to clinically significant hypocalcaemia, reversal may be achieved with supplemental oral calcium and/or an intravenous infusion of calcium gluconate. See Appendix 1.

It is highly unlikely that any participant in this study will be given an overdose of Zoledronic acid since the infusions will be administered under controlled conditions by experienced staff.

6.7 OTHER MEDICATIONS

6.7.1 Permitted Medications

Patients will be advised to check with the Investigator or their primary care practitioner before they take any new medication. The incidence of post-dose symptoms occurring within the first three days after administration of Zoledronic acid can be reduced with the administration of paracetamol or ibuprofen shortly following the infusion. Participants will be informed of this and details of any medication taken will be recorded by the study nurse in the 1 week follow up phone call.

Details of any permitted medications taken will also be recorded on the electronic CRF during the annual clinical reviews and participants will also be given a study diary in which they can detail any medication taken between the annual clinical reviews.

6.7.2 Prohibited Medications

Other bisphosphonates (alendronate, risedronate, tiludronate, etidronate, pamidronate), drugs with antiresorptive activity (calcitonin, strontium ranelate) and Denosumab and PTH (Teriparatide/Forsteo).

Participants who require to be treated with the above medications will be withdrawn from the study.

7. STUDY ASSESSMENTS

7.1 SAFETY ASSESSMENTS

For participants in the interventional study, baseline blood samples will include a full blood count, liver function tests, calcium, albumin, alkaline phosphatase, creatinine and urea and electrolytes. At each annual review, blood samples will be taken for liver function tests, calcium, alkaline phosphatase, albumin, creatinine and urea and electrolytes.

Serum 25-(OH) vitamin D levels will be taken prior to the baseline visit and if values are below the lower limit of the local reference range, vitamin D supplements will be given according to local clinical practice.

A food frequency questionnaire will be completed to assess dietary calcium intake at the baseline visit (intervention study only). If the estimated daily calcium intake is below the RDA (700mg), the participant will be advised on dietary modification or given calcium supplements to ensure that the calcium intake is above the RDA (as would be performed in routine clinical care).

Blood samples taken for routine biochemistry will be sent to standard laboratories at each site. The results for serum adjusted calcium, liver function tests, alkaline phosphatase, creatinine, eGFR and 25-(OH) vitamin D will be recorded according to local practice and SOPs at each site and also recorded on the eCRF. The eCRF will be set up to alert the central office in ECTU of when results are abnormal and the Trial Manager will follow up with the centre that the correct course of action is being followed.

7.1.1 Renal Safety

If the estimated creatinine clearance (eGFR) is < 35 ml/min, Zoledronic acid is not recommended so this would constitute an exclusion from the study. The eGFR will be calculated on the basis of age, gender, race and serum creatinine

7.1.2 Abnormal Liver Function

Patients with abnormalities of liver function can be included in the study since the SmPC indicates that liver disease is not a contraindication to Zoledronic acid and no adjustment of dose is needed.

7.1.3 Adverse Effects Immediately Post Infusion

One week (±2 days) after participants have received the infusion of study drug, the study nurse or investigator at each site will telephone the participant and go through a questionnaire to determine if any symptoms or side effects have occurred following the infusion.

7.1.4 Adverse Event Recording

Participants will also be given an event diary for them to record details of primary care visits, medication taken, hospitalisations and any other side effects/ health problems reported. If they have been hospitalised then the patient will be asked to contact the Principal Investigator at their relevant study centre. The PI will then complete an SAE monitoring form, assess causality and inform ECTU as detailed in Sections 10.3 and 10.4. Contact details will also be included in the event diary so they can call and discuss any concerns about their health in relation to their involvement in the study.

7.2 STUDY ASSESSMENTS

7.2.1 Genetic Screening

Patients with PDB and relatives who consent to give a fresh blood sample for genetic testing will have consent and a blood sample taken (10ml for patients with PDB and 20ml for relatives) by their preferred method (postal consent and local health care provider to take the blood sample or clinic appointment where a research nurse will take consent and a blood sample). This sample will be used for SQSTM1 genotyping carried out by DNA sequencing at the central laboratory in Edinburgh (for UK centres) or other appointed laboratories (for centres out with the UK) and for analysis of routine biochemistry, and 25(OH) vitamin D levels (relatives only). All participants who take part in the intervention study will have the genetic diagnosis confirmed by the Edinburgh Laboratory.

7.2.3 Baseline Information gathered

Once a relative has given informed consent to join the intervention or the observational study the investigator / research nurse will record on standard forms the information stated below at the baseline clinic visit. Information will then be entered onto the study database by members of the local research team using a web-based eCRF.

Identifying and contact information of relatives consented to the intervention or observational studies (Participant Details Forms)

- Full name, address, telephone number
- Date of birth, gender
- NHS, hospital number and CHI number (where relevant)
- Marital status, woman's maiden name
- General Practitioner's contact details

For the **intervention study**, descriptive information (detailed below) will be gathered using the Baseline Clinical Review Form;

- Medical history, current medication and physical examination (including pulse, blood pressure, weight, & height)
- Routine biochemistry
    - total serum alkaline phosphatase (ALP)
    - serum calcium
    - albumin
    - liver function (AST and/or ALT, γGT, bilirubin)
    - serum creatinine, urea and electrolytes
    - haematology (Full Blood count)
- serum 25-OH Vitamin D
- pregnancy test (in females of child-bearing potential)
- Specialised markers of bone turnover:
    - Blood samples for bone specific alkaline phosphatase (BSAP) and other relevant biomarkers of bone metabolism
    - Urine sample for deoxypyridinoline / creatinine ratio (DPD) and N-telopeptide collagen cross links (NTX) and other relevant biomarkers of bone metabolism.
- Isotope bone scan to determine if lesions are present
- Presence/absence of bone pain as assessed by Brief Pain Inventory (BPI)
- Quality of Life Questionnaires:
    - The Short Form (36) Health Survey (SF-36)
- Anxiety & Depression Index (as measured by)
    - Hospital Anxiety and Depression Scale (HADS)
- Food frequency questionnaire to assess dietary calcium intake

For the **observational study**, descriptive information (detailed below) will be gathered using the Baseline Clinical Review Form;

- Routine biochemistry
    - total serum alkaline phosphatase (ALP)
    - serum calcium
    - albumin
    - liver function (AST and/or ALT, γGT, bilirubin)
    -
    - serum creatinine, urea and electrolytes
- Specialised markers of bone turnover
    - Blood samples for bone specific alkaline phosphatase (BSAP) and other relevant biomarkers of bone metabolism
- Quality of Life Questionnaires:
    - The Short Form (36) Health Survey (SF-36)
- Anxiety & Depression Index (as measured by)
    - Hospital Anxiety and Depression Scale (HADS)

7.2.4 Baseline Clinical Measurements

7.2.4.1 Isotope Bone Scans

Prior to or during the baseline clinic review, participants in the intervention study will have a radionuclide bone scan to screen for the presence of bone lesions.

These will be uploaded on to the database and analysed centrally by Professor Ignac Fogelman or a qualified member of the study team (who will be blinded to the treatment allocation). The presence of PDB-like bone lesions (yes/no) will be enter ed into the study database. Participants who are noted to have bone lesions of uncertain significance will have further imaging (for example, X-ray, CT scan or MRI scan) at the local centre if this is thought to be clinically indicated to clarify whether early PDB bone lesions are present. At the end of the trial a repeat bone scan will be carried out and further imaging carried out if necessary, as described for the baseline visit.

Participants in the observational study will not undergo bone scanning.

7.2.4.2 Routine Biochemistry

All participants will have routine biochemistry including renal function, serum total alkaline phosphatase and liver function tests.

7.2.4.3 Specialised Biomarkers of Bone Metabolism

Samples will be collected for the assessment of specialised biomarkers of bone metabolism relevant to the pathogenesis of PDB. These will include bone-specific alkaline phosphatase (BSAP), urinary N-telopeptide collagen cross links (NTX) and urinary deoxypyridinoline / creatinine (uDPD/Cr). In order to assess treatment response and to provide further information on participants risk of developing PDB-like bone lesions or complications of PDB, we may also measure other biochemical markers of bone formation and bone resorption (e.g. PINP, CTX, Osteocalcin, TRAP); antibodies to viruses that have been implicated in the pathogenesis of PBD (e.g. measles or distemper); expression of genes relevant to the pathogenesis of PDB (e.g. TNALP, SQSTM1, RANK, RANKL, OPG) and other genetic markers that have been implicated in the pathogenesis of PDB or related bone diseases. The urine samples will be second-voided “spot” samples collected in the morning. The baseline and end of study samples for specialised biomarkers will be collected between 09.00-12.00 (fasted) and the time of sample collection recorded. Samples for specialised biomarkers collected at all other timepoints do not need to be taken in a fasted state. Other biomarkers may also be analysed on stored samples if it is thought that additional information on the course or complications of Paget’s disease may be provided.

The serum, plasma and urine samples will be aliquoted and stored at -80℃, until ready for shipment to the relevant central laboratory for analysis.

7.2.4.4 Baseline Infusions

The infusion will be performed within 6 months of the eligibility bloods having been taken (i.e routine biochemistry, and 25 (OH) vitamin D). The infusion visit will be carried out as long as all baseline screening and safety assessments are satisfactory and the participant has been randomised. If for any reason the infusion cannot be given within 6 months of the eligibility

bloods, 25(OH) will be repeated in subjects not taking vitamin D supplements. The routine biochemistry will be rechecked as part of the baseline bloods.

7.2.5 Follow up visits

Participants in the intervention study will be reviewed on an annual basis. At these visits data will be collected on any adverse events and significant health events that required a visit to their primary care physician or to hospital. Current medication use will be recorded. In addition the following samples and information will be obtained:

- Routine biochemistry
  - total serum alkaline phosphatase (ALP)
  - serum calcium
  - albumin
  - liver function (AST and/or ALT, γGT, bilirubin)
  - serum creatinine, urea and electrolytes
- Specialised markers of bone turnover
  - Blood samples for bone specific alkaline phosphatase (BSAP) and other relevant biomarkers of bone metabolism
- Presence/absence of bone pain as assessed by Brief Pain Inventory (BPI)
- Quality of Life Questionnaires:
  - The Short Form (36) Health Survey (SF-36)
- Anxiety & Depression Index (as measured by)
  - Hospital Anxiety and Depression Scale (HADS)

Participants in the observational study will be contacted annually to check their contact details remain the same. No other procedures will be performed between the baseline and end of trial assessments.

7.2.6 Duration of Follow up

Participants in both the interventional and observational study will have a final follow up visit between 2018 and 2019. The duration of follow up for individual participants will vary between 5 and 8 years depending on when participants were enrolled into the trial.

7.2.7 End of Trial Assessments

For the **intervention study**, the following information will be collected;

- Medical history and current medication (including pulse, blood pressure, weight, & height)
- Routine biochemistry
    - total serum alkaline phosphatase (ALP)
    - serum calcium
    - albumin
    - liver function (AST and/or ALT, γGT, bilirubin)
    - serum creatinine, urea and electrolytes
    - haematology (Full Blood count)
- Specialised markers of bone turnover:
    - Blood samples for bone specific alkaline phosphatase (BSAP) and other relevant biomarkers of bone metabolism
    - Urine sample for deoxypyridinoline / creatinine ratio (DPD) and N-telopeptide collagen cross links (NTX) and other relevant biomarkers of bone metabolism.
- Isotope bone scan to determine if lesions are present
- Presence/absence of bone pain as assessed by Brief Pain Inventory (BPI)
- Quality of Life Questionnaires:
    - The Short Form (36) Health Survey (SF-36)
- Anxiety & Depression Index (as measured by)
    - Hospital Anxiety and Depression Scale (HADS)

For the **observational study,** the following information will be collected

- Routine biochemistry
    - total serum alkaline phosphatase (ALP)
    - serum calcium
    - albumin
    - liver function (AST and/or ALT, γGT, bilirubin)
    - serum creatinine, urea and electrolytes,
- Specialised markers of bone turnover *
    - Blood samples for bone specific alkaline phosphatase (BSAP) and other relevant biomarkers of bone metabolism
- Quality of Life Questionnaires:
    - The Short Form (36) Health Survey (SF-36)
- Anxiety & Depression Index (as measured by)
    - Hospital Anxiety and Depression Scale (HADS)

Table 3. Summary of assessments for the intervention study.

	Screening	Baseline visit	+1 week	Annual Review	End of study
Medical History		√		√	√
Current medication		√		√	√
Physical Examination		√			
Height, weight, blood pressure		√			√
Routine Biochemistry[1]	√	√		√	√
Haematology[2]		√			√
Blood for Biomarkers[3]		√		√	√
Urine for Biomarkers[4]		√			√
SQSTM1 genotyping	√				
25(OH) vitamin D	√				
Pregnancy Test[5] (in women of child-bearing potential)		√			
Isotope Bone Scan		√			√
Radiographs[6]		√			√
Infusion		√			
Telephone Questionnaire			√		
Food Frequency Questionnaire		√			
SF36, HADS, & BPI questionnaires		√		√	√

1. – Calcium, albumin/total protein, alkaline phosphatase, liver function (AST, ALT, GGT, bilirubin), urea and electrolytes & creatinine (U&E),. 2 – Full blood count . 3 - Blood samples for measurement of bone specific alkaline phosphatase (BSAP), and other specialised markers of bone metabolism. 4 – Second-voided morning urine to be taken and stored for measurement of N-telopeptide collagen cross links (NTX), deoxypyridinoline/creatinine ratio (DPD) and other specialised markers of bone metabolism. 5 - A negative pregnancy test must be obtained on the day of, or the day before, infusion of the study drug. The preferred method of is serum beta-hCG, but a urine beta-hCG is acceptable for centres that are unable to obtain a serum beta-hCG. 6 – To be taken of relevant areas in subjects suspected to have PDB-like bone lesions on bone scan.

Table 4. Summary of assessments performed in observational study.

	Screening	Baseline visit	End of study
Routine Biochemistry[1]		√	√
Blood for Biomarkers[2]		√	√
SQSTM1 genotyping	√		
SF36, HADS questionnaires		√	√

1. – Calcium, albumin/total protein, alkaline phosphatase, liver function (AST, ALT, GGT, bilirubin), urea and electrolytes & creatinine (U&E),. 2 - Blood samples for measurement of bone specific alkaline phosphatase (BSAP), and other specialised markers of bone metabolism.

8. DATA COLLECTION

Data that is collected at baseline at the follow up visits and at the end of trial will be entered on the eCRF.

9. STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

Sample Size for the Intervention Study

Assuming that 15% of patients in the placebo group and 1.5% of patients in the active treatment group will develop new lesions over a six year period, we will need to follow 85 subjects in each group to have 89% power to detect a treatment effect at an alpha of 0.05. This assumes that Zoledronic acid can prevent the development of PDB lesions in 90% of treated patients. There is no information on the likely effectiveness of Zoledronic acid in preventing PDB lesions, but we feel this level of efficacy is conservative given that this treatment can normalise biochemical markers of bone turnover in 90% of patients with established PDB.

However, because more than one affected subject per family will be enrolled in some cases there may be a clustering effect in the outcome measures. To account for this we calculated the mean squared alkaline phosphatase values in patients within families who carried the same mutation (271.3) and the mean squared alkaline phosphatase values between families (619.7) and combined this with the average number of subjects per family with SQSTM1 mutations likely to be enrolled in the study (2) to obtain a design effect factor of 1.391.

To account for clustering as calculated above and to allow for a 10% dropout rate we need to enrol about 130 subjects per group (85+33+12) into the study.

Sample Size for Observational Study

A sample size of 110 placebo treated SQSTM1 mutation carriers and 250 subjects who do not carry SQSTM1 mutations would provide 80% power to detect a difference between the groups of 0.43 standard deviations (alpha=0.05, and allowing for clustering and dropout as above).

9.2 PROPOSED ANALYSES

The principal analysis will be based on intention-to-treat (based on all randomised participants, regardless of treatment received).

All analyses will allow for clustering by family, and all primary analyses will be adjusted for the minimisation variables. Precise details of the analyses will be included a separate Statistical Analysis Plan (SAP). Comparisons will be performed using an appropriate linear modelling procedure, taking into account repeated measures where these are available. Patients with completely missing data for a particular outcome will be removed from the analysis of that particular outcome. The effect of this will be examined using sensitivity analysis. Other sensitivity analyses will look at unadjusted analyses, and the effect of adjusting for centre.

10. ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below. NOTE: the safety reporting procedures described below apply only to participants in the intervention group.

Full details of contraindications and side effects that have been reported following administration of the trial drug can be found by following the link to the latest version of the Summary of Product Characteristics (SmPC) in Appendix 1.

Details of AE's, SAE's and SUSAR's will be recorded. Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AEs) that occur after joining the trial must be reported in detail in the CRF. In the case of an AE, the Investigator will 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 subject who is administered an investigational medicinal product (IMP), which does not necessarily have a causal relationship with the IMP.

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

An **unexpected adverse reaction** (UAR) is an adverse reaction that is not consistent with the product information in the SmPC.

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 is 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.

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE. Complications occurring during such hospitalisation will be AEs.

10.2 DETECTING AEs AND SAEs

All AEs and SAEs must be recorded from the time a participant consents to join the study until the last study visit.

The Investigator will ask 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.

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 will 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 EVALUATION OF AEs AND SAEs

Seriousness, causality, severity and expectedness will be evaluated as though the participant is taking active IMP. Cases that are considered serious, possibly, probably or definitely related to the IMP (i.e. serious adverse reactions, SARs) and unexpected (i.e. SUSARs) should be unblinded. (NOTE: not all serious adverse events are SARs).

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 will 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 related or unrelated) 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 study IMP.

Possibly Related The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug.

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 Serious Adverse Event (SAE) 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 will be made based on knowledge of the reaction and the relevant product information documented in the SmPC/IB.

The event may be classed as either:

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

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

10.5 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, they must report the information to the ACCORD Clinical Research Governance & QA Office within 24 hours. The SAE form must be completed as thoroughly as possible with all available details of the event, signed by the Investigator or designee. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying the ACCORD Clinical Research Governance & QA Office. The form can be updated when the additional information is received.

The SAE report must provide an assessment of causality and expectedness at the time of the initial report to the ACCORD Clinical Research Governance & QA Office according to Sections 10.4.2, Assessment of Causality and 10.4.4, Assessment of Expectedness.

The SAE form should be transmitted by fax to the ACCORD Clinical Research Governance & QA Office on 0131 242 9447 or may be transmitted by hand to the office.

10.6 REGULATORY REPORTING REQUIREMENTS

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

The ACCORD Clinical Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and the relevant ethics committee (main 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 the ACCORD Clinical Research Governance & QA Office is first aware of the reaction.

The ACCORD Clinical Research Governance & QA Office will also report SAEs to Novartis Pharmaceuticals within 15 days of first becoming aware of the event. Novartis Pharmaceuticals will provide an updated Investigator's Brochure or updated locally approved product information as appropriate.

An Annual Safety Report will be submitted to the regulatory competent authority and the 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. Follow up information on an SAE should be reported to the ACCORD Clinical Research Governance & QA 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

A pregnancy test will be carried out for female patients of childbearing potential prior to the infusion of study medication at baseline. A negative pregnancy test must be obtained before the study medication is infused.

Female participants will be informed that they should avoid pregnancy for at least the first 12 months post infusion. If they do become pregnant the Investigator should record the information on a Pregnancy Notification Form and submit this to the ACCORD Clinical Research Governance & QA 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 following the birth or otherwise (i.e. spontaneous termination) to allow information on the status of the mother and child to be reported to the ACCORD Clinical Research Governance & QA Office.

12. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 PROJECT MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grantholders (Chief Investigator and Principal Investigator in Edinburgh), trial statistician, Data Management Systems Officer, Trial Manager(s) and coordinating nurse. There will also be an international Advisory Board which includes all grantholders and all collaborators in the study.

12.2 TRIAL MANAGEMENT

A 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.

12.3 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.

12.4 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 are detailed in a separate document.

12.5 DATA MONITORING COMMITTEE

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

12.6 INSPECTION OF RECORDS

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

12.7 STUDY MONITORING

The ACCORD (joint office for University of Edinburgh and Lothian Health Board) Clinical Trials Monitor or an appointed local monitor will visit the Edinburgh study site prior to the start of the study and during the course of the study.

12.8 RISK ASSESSMENT

An independent risk assessment carried out by the ACCORD Clinical Trials Monitor is given in a separate document.

12.8.1 Potential Risks

Patient safety – low to medium risk: This trial is a regulated CTIMP, using a licensed drug in a new indication/ population. The drug in question has common side effects that are not severe and are detailed in the SmPC which can be found by following the link in Appendix 1. Severe side effects (e.g. osteonecrosis of the jaw) can occur but are extremely rare.

The greatest risk to participants (screened and in the trial) is causation of anxiety due to the introduction of genetic risk. However, due to the experience of the team who will provide training and advice to Investigators and nurses, it is anticipated that this risk will be minimised. In addition, local genetic centres will be involved to provide genetic counselling if it is required.

Risk of non-completion of trial – low risk: A combination of an experienced team of Investigators who have successfully delivered trials in the past, involvement of the NARPD and patients, the positive response to the GaP study, the interest of patients with PDB, the large pool of potential participants, and the involvement of a Clinical Trials Unit, the risk of non-completion of the trial is low.

Governance and legislative risk – low risk: The trial will be run from the Edinburgh Clinical Trials Unit by an experienced Trial Manager. ACCORD Clinical Research Governance and QA staff will provide governance oversight and will ensure all regulatory requirements are met, and clinical trials agreements and insurance are in place as appropriate.

13. GOOD CLINICAL PRACTICE MODULE

13.1 ETHICAL CONDUCT OF THE STUDY

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 OF THE STUDY

The study will not commence until a Clinical Trial Authorisation (CTA) (or equivalent authorisations) 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. All appropriate approvals (including ethics and health provider approvals), and contracts and site agreements must be in place for each site before that site commences the study.

ARSAC approval (or equivalent) will be obtained before the study commences.

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.

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

13.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training or undergo 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, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, or the REC. 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 (and equivalent national legislation outwith the UK) 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 research team (local centres will see their own blinded participant data, the Central Office will have access to all data). Pharmacists and laboratory staff will have access only to their own designated section.

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

The Investigator 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 5 years after publication of the results.

14.4 END OF STUDY

The end of the study in terms of the participant's involvement is the last participant's final clinical follow up. The end of study is defined as the end of the funding period.

The Investigators and/or the trial steering committee have the right at any time to terminate the study for clinical or administrative reasons. The trial may be stopped prematurely on the basis of a recommendation by the data safety monitoring board if it is felt that patients in one or other of the treatment arms may be disadvantaged as the result of the study continuing. This may either occur because of the occurrence of serious adverse effects in the active treatment or because of the development of progressive Paget's disease and associated complications in the placebo arm.

The end of the study will also be defined as the end of the funding period. At this point, all data will be entered into the database, the database locked and the data analysed.

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.

14.5 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

This study is a proof of concept study. Longer term follow up of all participants will be considered depending on the results at the end of the study and if feasible participants may be enrolled into a longer term study, and thus may continue with Zoledronic acid. However this will depend on both the positive results of the study and further secured funding. At the end of the study, and if no further follow up is planned, participants will be informed of the treatment they have received and the results of the study. If they want to continue having Zoledronic acid infusions they will need to discuss this with their local Clinician/ doctor.

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 good practice 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 Campaign (ARC) and the Medical Research Council (MRC) as part of the funding application process.

Investigators at each site, the Trial Steering Committee, Ethical Review Boards, MHRA, and local R&D departments have reviewed 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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APPENDIX 1: SUMMARY OF PRODUCT CHARACTERISTICS

The online version of the SoPC can be found at the following address:
http:emc.medicines.org.uk/document.aspx?documentId=18171