The ToPAZ Trial

Participant Information Sheet

The ToPAZ study

Treatment of Osteogenesis Imperfecta with Parathyroid Hormone and Zoledronic acid

We are inviting you to join a research study in which we want to study the effects of two different treatment strategies on fractures in osteogenesis imperfecta. Before you decide whether to take part, it is important that you understand the research and why it is being done. This information sheet provides an outline of what is involved. In addition to this one of the research team involved in the study will go through details of the study with you and answer any questions you may have. If you wish to discuss the study with friends or relatives please feel free to do so.

What is the purpose of the study?

We want to determine if a two year spell of treatment with a drug called teriparatide (TPTD), followed by one dose of a treatment called zoledronic acid (ZA) can reduce the risk of broken bones (fractures) occurring in osteogenesis imperfecta (brittle bone disease). Both drugs have been shown to prevent fractures in osteoporosis but it is not clear if they work in osteogenesis imperfecta. We are comparing this treatment with the usual treatment that patients with OI normally receive.

Why use the combination of TPTD and ZA?

We are using TPTD since it is the only drug currently available that can stimulate new bone formation. The idea is that we give a two year spell on TPTD to increase bone formation and follow that up with one dose of ZA which we expect to maintain the effects of TPTD on the skeleton for at least three years.

Why have I been asked to take part?

You have been asked to take part because you have been diagnosed with osteogenesis imperfecta. If you agree to take part you would be one of 380 people across the UK that will be enrolled into the trial.

Do I have to take part?

No. Participation in this study is voluntary and you don't need to take part if you don't want to. If you decline to take part this will not affect your medicalcare which will continue as normal, or your relationship with medical staff looking after you. If you do decide to take part but later wish to withdraw from the study you can do this at any time without you having to give a reason.

What will happen to me if I am interested in taking part?

We will provide you with this information sheet to read at least 24 hours before we ask you to take part in the study, If, after reading the information sheet you are happy to go ahead we will ask you to sign a consent form indicating that you agree to take part in the study and all that this involves. The consent will usually be obtained by one of the doctors in the study team but may be obtained by one of the research nurses depending on where you are enrolled.

After you have provided written consent, several tests will be performed to assess various aspects of bone health. Blood samples will be taken for genetic analysis, analysis of specialized markers of bone metabolism and routine checks such as kidney function and blood calcium. The total amount of blood will be about 25ml (or five teaspoons). We will also ask you to fill in questionnaires to assess quality of life and the presence and severity of bone pain. Each of these will take about 15 minutes to complete. You will undergo a bone density measurement (DEXA) and have a spine x-ray. You will almost certainly be familiar with these tests as part of routine care you have had in the past but if you are not sure what is involved, please speak to a member of the study team. Some of the hospitals taking part in the study have a special type of scanner that can assess the bone structure at the wrist and ankle. These are called high-resolution peripheral quantitative computed tomography scans (HRQCT). If your hospital has one of these scanners, we will ask you to have this scan too. To have the scan you sit in a chair and put your arm or leg into the scanner. Each scan takes about three minutes. Once all these tests have been completed you will be allocated to receive one of the two types of treatment we are studying.

We will provide you with a diary so that you can record any visits that you make to your own doctor or to hospitals for health problems of any type that occur during the study. We need to record these so that we can determine whether people in the two treatment group differ in the number of times they have to seek medical care for fractures or other events related to osteogenesis imperfecta or any other health problems that may occur.

What other tests and study visits are there?

Following the baseline assessment described above we will see you for review after 12 months and repeat the blood tests (20ml or four teaspoons) and repeat the questionnaires. A HRQCT scan of the wrist and ankle may be performed.

There will be a further review at 24 months when we will repeat the blood tests (20ml) and repeat the questionnaires. At this visit, we will also repeat the bone density (DEXA) scan. A HRQCT scan of the wrist and ankle may be performed.

There will be a further review at the end of the study. This is expected to be about four or five years after you commenced the trial. At this point we will repeat the blood tests (20ml), the questionnaires, the bone density (DEXA) scan and the spine x-ray. A HRQCT scan of the wrist and ankle may be performed.

Will there be any other contact with the study team?

We will aim to contact you by telephone every 6 months or so during the study. The aim of this is just to keep in touch to check how things are going and to go over any health issues that you might have recorded in your diary. If you wish, we will give you the option being sent updates about the progress of the study and birthday cards and Christmas cards as our way of thanking you for taking part in the study.

If you are randomised to receive TPTD you would also be asked to come to the hospital every 4 months to drop back your used medication pens and your pen diary, and to collect your next 4 month supply.

What does the treatment involve?

We are studying two forms of treatment; TPTD and ZA or standard care. If you are allocated to receive TPTD/ZA you will be prescribed daily injections of TPTD for a period of two years. The TPTD is supplied in a special injection device, which has been designed to allow you to administer the treatment yourself at home. The device is easy to use and you will given training in its use by a member of the study team. Typically, we will supply you with enough devices for 4months of treatment at a time and we will ask you to pick up further supplies when these run out. You will need to keep the devices in your refrigerator at home. After you complete the two years treatment with TPTD you will have one dose of ZA. This will typically involve a visit to the hospital as a day patient and having a drip set up containing the ZA. The infusion usually takes about 15min after which point you will be able to go home. After the infusion, you will be followed up for another three years without the need for any further treatment. If for any reason, it's not possible to give the ZA infusion other tablets or injections may be given instead.

If you are allocated to standard care then you will carry on with whatever treatment you are having from the doctor that you usually see for osteogenesis imperfecta. This may involve having no bone specific treatment, calcium and vitamin D supplements or one of the bisphosphonate drugs (alendronic acid, risedronate, ibandronate, pamidronate or zoledronic acid).

How long will the trial last?

If you are randomised to receive the active treatment there will be a two year treatment period and then you will be followed up for 1-3 years. If you're randomised to standard care then you may or may not have treatment depending on your local physician but the total duration of the trial will be up to 5 years. During this time you will be asked to report any new fractures to the research team.

How will my treatment be decided?

Your treatment will be decided by a process called randomisation, which will be done by computer at the study co-ordinating centre. There is a 50% chance you will be allocated to receive TPTD/ZA and a 50% chance you will be allocated to standard care, like tossing a coin.

Is it possible to get TPTD if I am randomised to standard care?

No. The only reason we are able to give treatment with TPTD is because this is a research study. Doctors in the UK are not normally permitted to give TPTD as treatment for osteogenesis imperfecta since it is an expensive treatment and it's not known whether TPTD can prevent fractures in OI. At the present time we don't know if it's better to be on TPTD or your normal treatment. That's why we have to do a comparison study. If you aren't allocated to have TPTD in this study, and we find that it works better than usual treatment, we will do all that we can to make the treatment available in the NHS for all patients with OI after the study finishes.

Do I need to take bisphosphonates if I am allocated to standard care?

No. If you are allocated to standard care the doctors that normally take care of you will fully discuss the treatment options available to you. Depending on your circumstances, the doctors may advise that no treatment is given for your bones, or that you should consider taking calcium and/or vitamin D supplements or that you consider taking bisphosphonates.

Will any genetic research be done?

Yes. As part of the study, we will perform genetic analysis on DNA extracted from a blood sample to find out more about the gene abnormalities that are responsible for the occurrence of osteogenesis imperfecta. The genetic testing is important since it will provide us with a better understanding of the factors that influence severity of osteogenesis imperfecta and its response to treatment. The genetic analysis may use a technique called whole genome sequencing since this is one of the most cost effective ways of finding out what causes osteogenesis imperfecta. Whole genome sequencing involves gathering information on all of the genetic variations that people have in their DNA. In this study however, we will only be using the whole genome sequence data to test for variants that we think might cause osteogenesis imperfecta or modify its severity. We will not be testing for variants that might cause other diseases. If you do not wish to have the genetic blood sample you can still take part in the study. If you do provide a sample for the genetic research we will also give you the opportunity of being given the results of your genetic test by a trained member of the study team.

Will any other analyses be done?

Yes. We plan to collect additional blood samples during the trial for analysis of special markers of bone metabolism that aren't usually performed in routine care. We are analysing these markers to see if they can help assess how patients with osteogenesis imperfecta respond to the treatments that are given during the study.

Are there any the side effects of TPTD?

Like all medicines, TPTD can cause side effects but most patients do not experience side effects. The most common side effects are pain in the limbs, feeling sick, headache, anaemia, depression and dizziness. You may also experience local discomfort at the injection site such as redness of the skin, pain, swelling, itching, bruising or minor bleeding around the area of the injection. This usually clears up in a few days. Some patients have experienced allergic reactions soon after injection, consisting of breathlessness, swelling of the face, rash and chest pain but this is rare. Some people can have a slight increase in blood calcium levels. Various other non-serious side effects have been reported in patients receiving TPTD and a full list is provided in the patient information leaflet which you will be given before starting the treatment.

Are there any side effects of ZA?

Like all medicines, ZA can cause side effects but most patients do not experience side effects. The most common side effect with ZA is the occurrence of fever and chills, pain in the muscles or joints, and headache usually within the first three days following the infusion. This occurs in about 1 in 5 people after treatment with ZA. The symptoms are usually mild to moderate and subside within three days. Your doctor can recommend a mild pain reliever such as ibuprofen or paracetamol to reduce

the impact of these side effects if they occur. An irregular heart rhythm (atrial fibrillation) has been reported in patients receiving ZA for the treatment of postmenopausal osteoporosis but it is rare occurring in less than 1 in 1000 cases. It is currently unclear whether ZA causes this irregular heart rhythm but if you develop palpitations you should report this to your doctor. Various other side effects have been reported with ZA and a full list is provided in the patient information leaflet which you will be given prior to the ZA infusion.

Are there any side effects of the medications used in standard care?

The most common medications used in standard care of patients with osteogenesis imperfecta are bisphosphonates such as alendronic acid and risedronate (which are tablets); pamidronate and zoledronic acid (which are given by infusion) and ibandronate (which can be given by injection or in tablet form). The most common side effects of bisphosphonate tablets are indigestion, heartburn and stomach pain. The most common side effects of bisphosphonate injections and infusions are fever and chills, pain in the muscles or joints, and headache usually within the first three days following the infusion. The symptoms are usually mild to moderate and go away within three days. If the doctor in charge of your care decides that one of these treatments are advisable they will discuss the possible side effects and benefits with you prior to commencing treatment and issue you with a copy of the patient information leaflet which gives a more detailed description of then various side effects that can occur.

Apart from the risk of side effects, are there any other potential risks of taking part?

There are few potential risks. We will be asking you to have three DEXA scans during the study but these are normally performed at intervals of 1-5 years anyway in patients with osteogenesis imperfecta. We will also be asking you to have two spine x-rays. These wouldn't normally be performed in osteogenesis imperfecta unless symptoms of spine fractures were present. If you are in one of the hospitals that has access to HRQCT, up to four scans will be performed during the study. Although these x-rays involve slightly more exposure to radiation than would be usual in routine practice, the total radiation dose from this study is approximately the same as 14 months background radiation, and is classed as a very low risk (less than one in 7,700) for any long-term effects on health. You might experience some mild discomfort as the blood sample is taken.

What are the possible benefits of taking part?

You may not gain direct benefit from taking part in this study but the knowledge gained probably will be beneficial to you and to other patients with osteogenesis imperfecta in the longer term since it will help us to understand what the best way is to treat osteogenesis imperfecta to prevent fractures.

What happens if I suffer a fracture?

As you know, fractures occur commonly in people with osteogenesis imperfecta. If you think you may have suffered a fracture of any bone during the trial we would like you to attend your nearest study centre or local hospital for an x-ray to confirm whether or not a fracture has occurred. If you do have an x-ray for a suspected fracture a copy of this will be retrieved by a member of the study team from the hospital where the x-ray was performed. An anonymised copy of the x-ray (a copy in which your name has been removed) will then be uploaded onto the study database where it will be looked at by an imaging expert. If you do suffer a fracture you should continue your treatment as normal unless you are advised otherwise by your own doctor or member of the study team.

What about pregnancy and breastfeeding?

You should not take part in this study if you are pregnant or breast-feeding. If there is a possibility that you could become pregnant, you must agree to use a reliable form of contraception during the trial, (for example, oral contraceptive, intra-uterine device (IUD)). If you do become pregnant during the course of the study, we would ask you to tell your study doctor immediately so we can help decide appropriate action.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time. If you decide to withdraw you don't have to give us a reason why, and your decision to withdraw will not affect the standard of any future care that you might require. If you choose to withdraw from the study you will be given three options. One would be for you to allow us to use the samples and data collected from you up until the time you withdraw but not to continue with any further study visits. The second would be for you to stop the treatment but to continue with the study visits. The third would be for you to ask us to delete any data that we hold about you and destroy the samples we have collected during the study.

What if something goes wrong?

If you have a concern about any aspect of this study, you should speak to a member of the research team who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through your local NHS Complaints Procedure. Details can be obtained from <<insert local contact details>>. In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against University of Edinburgh/NHS Lothian but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

What happens when the study is finished?

At the end of the study you will be followed up in the normal way by your local healthcare provider. It is our intention to let all participants know about the results of the study when the analysis is complete and this will most probably be done within 6-12 months of the study finishing. If the study shows that TPTD/ZA is better than standard care we very much hope that the treatment might be adopted within the NHS for the treatment of osteogenesis imperfecta.

Will my taking part in the study be kept confidential?

All the information we collect during the course of the research will be kept confidential and there are strict laws that safeguard your privacy at every stage. Your medical records will only be available to your normal care team, the study research team, the study sponsor and the regulatory authorities. Any information stored on computers will be securely stored and access granted to the research team only. Your name will not appear on any report or publication. In accordance with normal practice, we will store your information for at least 15 years.

What will happen to the blood samples that I provide?

The samples that you give will be for research purposes and will be considered as a gift. Some of the samples will be tested straight away by your local hospital, and some will be sent to the study centre in Edinburgh to have more specialist tests done. We will keep some of your samples in the freezer, in case we need to double-check results, or new tests become available that might help with the results of the study. Any sample remaining after the study has ended will be stored for future research into osteogenesis imperfecta and other bone diseases. The reason for storing these samples is that new tests to monitor bone metabolism might be developed in the future which could provide better insights into the causes of osteogenesis imperfecta and its response to treatment than the tests we have at present. You will be asked to provide consent for us to use your stored samples in the future for this purpose. If you decide that you don't want to do this you can still take part in the study. Your samples may be sent for testing to other laboratories some of which may be outside the United Kingdom. All of these samples will be anonymized, which means that the person analysing your sample will not be able to identify you.

What happens at the end of the study?

At the end of the study your medical care will be undertaken by your GP and usual hospital specialist. In order to evaluate the long-term effects of treatment we will ask for your permission for us to contact the Information Services Division (Scotland), the NHS Central Register and other NHS organisations to enquire about your long term health status and collect additional information relevant to the study through 'data linkage'. This is when medical information from two or more sources are brought together. The CHI number or NHS or hospital number is the information that we use for this data linkage. This can provide valuable information about the possible long term effects of treatment. If you consent to this it will not involve any further study visits.

What will happen to the results of the research study?

The results of this research will be presented at scientific meetings in the UK and overseas and published in medical journals. We may also combine information from this trial with that of other completed and ongoing trials (a meta-analysis) to further explore the effects of these treatments. It will not be possible to identify you in any report or publication. The results of this study may lead to the development of patents and/or to commercial benefits for sponsors and researchers. You would not be entitled to receive any financial benefit. We will contact all the participants after the study has finished to let them know the outcomes from the study.

Will my GP be informed?

With your permission, we would like to inform your General Practitioner of your participation in this study. We will notify your General Practitioner should any clinically relevant information comes to light during the study.

Will my travel expenses be reimbursed?

Yes. We will be able to refund any reasonable expenses for travel that you incur as the result of taking part in the study.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment being studied. If this does happen and it is thought to influence conduct of the trial, a member of the research team will tell you about it and discuss you whether you want to carry on in the study. If you decide to carry on you will be asked to sign an updated consent form.

Who is organising and funding the research?

The study is being led by Professor Stuart Ralston, Professor of Rheumatology at Edinburgh University and is being co-sponsored by NHS Lothian and the University of Edinburgh. The study is being funded by the Efficacy of Medicines Evaluation Board (EME) which supports clinical research on behalf of the Medical Research Council.

Who has reviewed the study?

The study has been reviewed by the Efficacy and Mechanism Evaluation Programme (EME). The study has also been reviewed by the Medicines and Healthcare Regulatory Products Agency in the UK and by a NHS Research Ethics Committee, which has responsibility for scrutinising proposals for medical research in humans. In this case, the reviewing committee was the East of Scotland Research Ethics Service REC 2, who have raised no objections from the point of view of medical ethics. NHS management approval has also been obtained in each hospital that is involved in the study.

Thank you for reading this. If you have any further questions about the study please contact:

Professor Stuart H Ralston
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Western General Hospital
Edinburgh EH4 2XU
Email: stuart.ralston@ed.ac.uk

If you would like to discuss this study with someone *independent* of the study team please contact

Dr Philip Riches
Rheumatic Diseases Unit
Western General Hospital
Edinburgh EH4 2XU
Email: Philip.riches@nhslothian.scot,nhs,uk

If you wish to make a complaint about the study please contact NHS Lothian:

Patient Experience team
NHS Lothian, 2nd Floor

Waverley Gate, 2-4 Waterloo Place
Edinburgh EH1 3EG
Tel: 0131-536-3370

Email: feedback@nhslothian.scot.nhs.uk

The study visit schedule at a glance

Visit no.	What will happen?
Baseline (Week 0)	• Questions about you and your lifestyle. • Questions about your pain. • Questions about quality of life • A brief physical examination • Blood samples • Pregnancy test (if needed) • Bone density (DEXA) • Spine x-ray • HRQCT scan of wrist and ankle
Randomisation (this may be done at the baseline visit)	• You will be allocated to one or other treatment group • Treatment will be commenced
• Visit 1 • (12 months)	• Questions about your pain. • Questions about quality of life • Blood samples • Questions about how you are feeling and managing with medication • Questions about any fractures that may have occurred • HRQCT scan of wrist and ankle
• Visit 2 • (24 months)	• Questions about your pain. • Questions about quality of life • Blood samples • Questions about how you are feeling and managing with medication • Questions about any fractures that may have occurred • Treatment with TPTD stopped and ZA infusion given (TPTD/ZA group only) • Bone density (DEXA) • HRQCT scan of wrist and ankle
• End of study • (48-60 months)	• Questions about your pain. • Questions about quality of life • Blood samples • Questions about how you are feeling and managing with medication • Questions about any fractures that may have occurred • Bone density (DEXA) • Spine x-ray • HRQCT scan of wrist and ankle