

# Treatment of osteogenesis imperfecta with parathyroid hormone and zoledronic acid

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| <b>Submission date</b><br>25/07/2016   | <b>Recruitment status</b><br>No longer recruiting     | <input checked="" type="checkbox"/> Prospectively registered<br><input checked="" type="checkbox"/> Protocol            |
| <b>Registration date</b><br>10/08/2016 | <b>Overall study status</b><br>Completed              | <input type="checkbox"/> Statistical analysis plan<br><input type="checkbox"/> Results                                  |
| <b>Last Edited</b><br>24/10/2024       | <b>Condition category</b><br>Musculoskeletal Diseases | <input type="checkbox"/> Individual participant data<br><input checked="" type="checkbox"/> Record updated in last year |

## Plain English summary of protocol

### Background and study aims

Osteogenesis imperfect (OI) or brittle bone disease is an inherited condition in which the bones of the skeleton break (fracture) more easily than normal, often in response to a minor injury and sometimes for no reason at all. There is no cure for OI and no treatment has been convincingly shown to reduce the risk of breaking bones. Many doctors treat OI patients with drugs called bisphosphonates, such as zoledronic acid, which are also used in osteoporosis (gradual bone loss that leads to weakened bones), but it's not clear if they are effective at preventing fractures in OI. Teriparatide (TPTD) is a form of parathyroid hormone, which works by activating bone-building cells in the body. The aim of this study is to determine if it is possible to reduce the risk of fractures occurring in OI by using a combination of treatments which will strengthen the skeleton as compared with standard care.

### Who can participate?

Men and women aged 18 years and over who have been diagnosed with OI.

### What does the study involve?

Participants are randomly allocated to one of two groups. Those in the first group are given a two-year course teriparatide (TPTD) given by daily injections and this will be followed by an infusion (through a drip) of zoledronic acid (ZA). Those in the second group receive standard care, which may involve no treatment or treatment with bisphosphonates and some other drugs used in the treatment of osteoporosis. Participants in both groups are reviewed at 12 months, 24 months and again at the end of the study. At each time point, patients have a sample of blood taken and complete a number of questionnaires. In addition, a DEXA scan (scan to measure bone density) is done at 12 and 24 months and at the end of the study. A spine x-ray is done at the start of the study and at the end of the study.

### What are the possible benefits and risks of participating?

Participants benefit from being regularly reviewed and having the chance to be treated with parathyroid hormone which cannot normally be prescribed to patients with osteogenesis imperfecta. There is a small risk of side effects with teriparatide, zoledronic acid and the other treatments that might be used as part of standard care.

Where is the study run from?

NHS Lothian and at least 21 other study centres in Scotland, Wales, England and Northern Ireland (UK) as well as four centres in Europe including Amsterdam, Paris, Dublin and Aarhus

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

November 2016 to April 2025

Who is funding the study?

Medical Research Council, Efficacy and Mechanism Evaluation Programme (UK)

Who is the main contact?

Prof. Stuart H Ralston, [topaz.trial@ed.ac.uk](mailto:topaz.trial@ed.ac.uk)

### **Study website**

<http://edin.ac/topaz-trial>

## **Contact information**

### **Type(s)**

Scientific

### **Contact name**

Prof Stuart Ralston

### **ORCID ID**

<http://orcid.org/0000-0002-2804-7586>

### **Contact details**

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EH16 4UX  
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### **Type(s)**

Public

### **Contact name**

Ms Lorna Dewar

### **Contact details**

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## **Additional identifiers**

**EudraCT/CTIS number**  
2016-003228-22

**IRAS number**

**ClinicalTrials.gov number**  
NCT03735537

**Secondary identifying numbers**  
EME 14/200/18; AC16092

## **Study information**

**Scientific Title**  
Treatment of Osteogenesis Imperfecta with Parathyroid hormone and Zoledronic acid

**Acronym**  
TOPAZ

**Study objectives**  
The aim of this study is to determine if treatment with parathyroid hormone followed by a single infusion of zoledronic acid is superior to standard care in reducing the risk of fractures in adults with osteogenesis imperfecta.

**Ethics approval required**  
Ethics approval required

**Ethics approval(s)**  
Approved 15/09/2016, East of Scotland Research Ethics Service (EoSRES) (Tayside medical Science Centre, Residency Block Level 3, George Pirie Way, Ninewells Hospital and Medical School, Dundee , DD1 9SY, United Kingdom; +44 (0)1382 383878; eosres.tayside@nhs.net), ref: 16/ES/0110

**Study design**  
Prospective open-label randomised multi-centre controlled trial

**Primary study design**  
Interventional

**Secondary study design**  
Randomised controlled trial

**Study setting(s)**

Hospital

**Study type(s)**

Treatment

**Participant information sheet**

See additional files

**Health condition(s) or problem(s) studied**

Osteogenesis imperfecta

**Interventions**

Current interventions as of 14/07/2023:

Participants are randomised to one of two groups in a 1:1 ratio using minimisation to balance the groups for the following prognostic variables:

1. Clinical fracture during the two years prior to randomisation
2. Clinical subtype of OI (type I or others)
3. Gender
4. Lowest BMD T score at spine or hip (or Z-score aged 18-21)  $\leq -2.5$ ; or  $> -2.5$ .
5. Age ( $\leq 50$ ;  $> 50$ )
6. Bisphosphonate at entry or within 2 years prior to randomisation

Intervention group: Participants will receive a 2-year course of teriparatide 20mcg daily by subcutaneous injection. At the end of this period, participants will be given a single intravenous infusion of zoledronic acid 5mg.

Control group: Participants will receive standard care, which may involve no bone-specific treatment or treatment with bisphosphonates, depending on what the specialist that is normally responsible for treating participants' osteogenesis imperfecta feels is most appropriate.

Bone anabolic drugs such as teriparatide and romosozumab will be prohibited in the standard care group. In the active group, romosozumab will be prohibited. Investigational drugs will be prohibited in both groups.

This is an event-driven study which will go on until 149 clinical fractures have occurred. Based on published data, this is expected to have occurred an average of 60 months after the patient has enrolled on the study.

Participants are reviewed at 12 months, 24 months and again at the end of the study. This will on average be 60 months after enrollment but it may vary between 24 and 84 months. At each visit, the patient will get blood checked and complete questionnaires. At baseline, 24 months and the study end, a DEXA will be done. At baseline and the study end a spine-x-ray will be done.

**Previous interventions:**

Participants are randomised to one of two groups using minimisation to balance the groups for the following prognostic variables:

1. Clinical fracture during the two years prior to randomisation
2. Clinical subtype of OI (type I or others)
3. Gender
4. Lowest BMD T score at spine or hip (or Z-score aged 18-21)  $\leq -2.5$ ; or  $> -2.5$ .

5. Age ( $\leq 50$ ;  $> 50$ )

6. Bisphosphonate at entry or within 2 years prior to randomisation

**Intervention group:** Participants will receive a 2-year course of teriparatide 20mcg daily by subcutaneous injection. At the end of this period, participants will be given a single intravenous infusion of zoledronic acid 5mg.

**Control group:** Participants will receive standard care, which may involve no bone specific treatment or treatment with bisphosphonates, depending on what the specialist that is normally responsible for treating participants' osteogenesis imperfecta feels is most appropriate.

This is an event driven study which will go on until 149 clinical fractures have occurred. Based on published data, this is expected to have occurred after an average of 48 months after the patient has enrolled into the study.

Participants are reviewed at 12 months, 24 months and again at the end of study (this will on average be 48 months but it may vary between 36 and 60 months since the design is an event drive trial with a variable duration of follow up). At each visit the patient will get bloods checked and complete questionnaires. At baseline and 24 months a DEXA will be done. At baseline and 48 months (or study end) a spine-x-ray will be done.

### **Intervention Type**

Drug

### **Pharmaceutical study type(s)**

Not Applicable

### **Phase**

Phase III/IV

### **Drug/device/biological/vaccine name(s)**

Teriparatide, Zoledronic acid

### **Primary outcome measure**

Proportion of participants experiencing a clinical fracture validated by x-ray or other imaging at the final study visit (between 36-60 months).

### **Secondary outcome measures**

Current secondary outcome measures:

1. Total number of clinical fractures experienced by participants validated by x-ray or other imaging at the final study visit.
2. Number of incident vertebral fractures assessed by imaging of the thoracic and lumbar spine at the final study visit.
3. Total number of fractures experienced by participants defined as the combination of validated clinical fractures and vertebral fractures and fractures reported by participants, where imaging was not performed, not feasible or where the results were inconclusive at the final study visit.
4. Bone pain is assessed by the brief pain inventory (BPI) at 12 months, 24 months and at the end of the study visit.
5. Quality of life is assessed by the SF36 questionnaire at 12 months, 24 months and at the end of the study visit.

6. Functional status is assessed by the health assessment questionnaire (HAQ) and EuroQol5D (EQ5D) assessment tools at 12 months, 24 months and at the end of the study visit.
7. Adverse events reported by participants at 12 months, 24 months and at the end of the study visit.

Previous secondary outcome measures:

1. Total number of clinical fractures experienced by participants validated by x-ray or other imaging at the final study visit (between 36-60 months)
2. Number of incident vertebral fractures assessed by imaging of the thoracic and lumbar spine at the final study visit (between 36-60 months)
3. Total number of fractures experienced by participants defined as the combination validated clinical fractures and vertebral fractures and fractures reported by participants, where imaging was not performed, not feasible or where the results were inconclusive at the final study visit (between 36-60 months)
4. Bone pain is assessed by the brief pain inventory (BPI) at 12 months, 24 months and at the end of study visit (between 36-60 months)
5. Quality of life is assessed by the SF36 questionnaire at at 12 months, 24 months and at the end of study visit (between 36-60 months)
6. Functional status is assessed by the health assessment questionnaire (HAQ) and EuroQol5D (EQ5D) assessment tools at at 12 months, 24 months and at the end of study visit(between 36-60 months)
7. Adverse events reported by participants at 12 months, 24 months and at the end of study visit (between 36-60 months)

**Overall study start date**

01/11/2016

**Completion date**

30/04/2025

## Eligibility

**Key inclusion criteria**

1. Adult patients age 18 years and over with a clinical diagnosis of osteogenesis imperfecta
2. Patients willing and able to consent and comply with the study protocol

**Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

350

**Total final enrolment**

350

**Key exclusion criteria**

Current exclusion criteria as of 07/02/2017:

1. Current or previous treatment with an investigational (non-licensed) drug with effects on bone metabolism
2. Contraindication to TPTD or ZA
3. Women of childbearing potential not using highly effective methods of contraception
4. Pregnancy
5. Women that are breastfeeding
6. Age < 18 years

Previous exclusion criteria:

1. Contraindication to TPTD or ZA
2. Current or previous treatment with an investigational drug with effects on bone metabolism
3. Women of childbearing potential not using adequate contraception
4. Pregnancy

**Date of first enrolment**

01/02/2017

**Date of final enrolment**

30/11/2022

**Locations****Countries of recruitment**

Denmark

England

France

Ireland

Netherlands

Northern Ireland

Scotland

United Kingdom

Wales

**Study participating centre**

NHS Lothian

Western General Hospital

Edinburgh  
United Kingdom  
EH4 2XU

**Study participating centre**  
**St Vincent's Hospital**  
Dublin  
Ireland  
4

**Study participating centre**  
**Aberdeen Royal Infirmary**  
Aberdeen  
United Kingdom  
AB25 2ZR

**Study participating centre**  
**Royal Victoria Hospital**  
Belfast  
United Kingdom  
BT12 6BA

**Study participating centre**  
**Queen Elizabeth Hospital**  
Birmingham  
United Kingdom  
B15 2TH

**Study participating centre**  
**Bristol Royal Infirmary**  
Bristol  
United Kingdom  
BS2 8HW

**Study participating centre**  
**Addenbrooke's Hospital**  
Cambridge  
United Kingdom  
CB2 0QQ



**Study participating centre**

**Ninewells Hospital**

Dundee

United Kingdom

DD1 9SY

**Study participating centre**

**Queen Elizabeth University Hospital**

Glasgow

United Kingdom

G51 4TF

**Study participating centre**

**Leicester Royal Infirmary**

Leicester

United Kingdom

LE1 5WW

**Study participating centre**

**Royal Liverpool Hospital**

Liverpool

United Kingdom

L7 8XP

**Study participating centre**

**Llandough University Hospital**

Llandough

United Kingdom

CF64 2XX

**Study participating centre**

**Guy's and St Thomas' Hospital**

London

United Kingdom

SE1 9RT

**Study participating centre**  
**Manchester Royal Infirmary**  
Manchester  
United Kingdom  
M13 9WL

**Study participating centre**  
**James Cook University Hospital**  
Middlesbrough  
United Kingdom  
PS4 3BW

**Study participating centre**  
**Freeman Hospital**  
Newcastle Upon Tyne  
United Kingdom  
NE7 7DN

**Study participating centre**  
**Norfolk and Norwich University Hospital**  
Norwich  
United Kingdom  
NR4 7UQ

**Study participating centre**  
**Nottingham City Hospital**  
Nottingham  
United Kingdom  
NG5 1PD

**Study participating centre**  
**Nuffield Orthopaedic Centre**  
Oxford  
United Kingdom  
OX3 7HE

**Study participating centre**  
**Queen Alexandra Hospital**  
Portsmouth

United Kingdom  
P06 3LY

**Study participating centre**  
**Northern General Hospital**  
Sheffield  
United Kingdom  
S5 7AU

**Study participating centre**  
**University Hospital Southampton**  
Southampton  
United Kingdom  
S016 6YD

**Study participating centre**  
**Royal National Orthopaedic Hospital**  
Stanmore  
United Kingdom  
HA7 4LP

**Study participating centre**  
**Haywood Community Hospital**  
Stoke-on-Trent  
United Kingdom  
ST6 7AG

**Study participating centre**  
**Wishaw General Hospital**  
Wishaw  
United Kingdom  
ML2 0DP

**Study participating centre**  
**Aarhus University Hospital**  
Tage-Hansens Gade 2  
Aarhus  
Denmark  
800 Aarhus C

**Study participating centre**  
**Amsterdam University Medical Centre**  
Dr Boelelaan 1117  
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1081 HV Amsterdam

**Study participating centre**  
**Hôpital Lariboisière**  
Department of Rheumatology  
2 Rue Ambroise Paré  
Paris  
France  
75010 Paris

## **Sponsor information**

**Organisation**  
University of Edinburgh

**Sponsor details**  
The Queen's Medical Research Institute  
47 Little France Crescent  
Edinburgh  
Edinburgh  
Scotland  
United Kingdom  
EH16 4TJ  
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Fiach.o'mahoney@ed.ac.uk

**Sponsor type**  
University/education

**Website**  
[www.ed.ac.uk](http://www.ed.ac.uk)

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

## **Funder(s)**

**Funder type**

Government

**Funder Name**

Efficacy and Mechanism Evaluation Programme

**Alternative Name(s)**

NIHR Efficacy and Mechanism Evaluation Programme, EME

**Funding Body Type**

Government organisation

**Funding Body Subtype**

National government

**Location**

United Kingdom

## Results and Publications

**Publication and dissemination plan**

The results of the trial will be published in peer reviewed scientific journals

**Intention to publish date**

01/04/2026

**Individual participant data (IPD) sharing plan**

The current data sharing plans for the current study are unknown and will be made available at a later date

**IPD sharing plan summary**

Data sharing statement to be made available at a later date

**Study outputs**

| Output type                                   | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---------|--------------|------------|----------------|-----------------|
| <a href="#">Participant information sheet</a> |         | 18/04/2018   | 18/04/2018 | No             | Yes             |
| <a href="#">HRA research summary</a>          |         |              | 28/06/2023 | No             | No              |
| <a href="#">Protocol article</a>              |         | 22/11/2023   | 23/11/2023 | Yes            | No              |