ISRCTN15313991 https://doi.org/10.1186/ISRCTN15313991

# Treatment of osteogenesis imperfecta with parathyroid hormone and zoledronic acid

**Submission date**
25/07/2016

**Recruitment status**
No longer recruiting

**Registration date**
10/08/2016

**Overall study status**
Completed

**Last Edited**
24/10/2024

**Condition category**
Musculoskeletal Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] 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

# Contact information

### Type(s)
Scientific

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Public

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# Additional identifiers

### Clinical Trials Information System (CTIS)
2016-003228-22

### ClinicalTrials.gov (NCT)
NCT03735537

### Protocol serial number
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

### Study type(s)
Treatment

### 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) ≤-2.5; or >-2.5.
5. Age (≤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) ≤-2.5; or >-2.5.
5. Age (≤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

## Phase
Phase III/IV

## Drug/device/biological/vaccine name(s)
Teriparatide, Zoledronic acid

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

## Key secondary outcome(s))
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)

### 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

### Healthy volunteers allowed
No

### Age group
Adult

### Lower age limit
18 years

### Sex
All

### 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**
United Kingdom

England

Northern Ireland

Scotland

Wales

Denmark

France

Ireland

Netherlands

**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**
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NR4 7UQ

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

**Study participating centre**
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OX3 7HE

**Study participating centre**
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P06 3LY

**Study participating centre**
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**Study participating centre**
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# Sponsor information

**Organisation**
University of Edinburgh

**ROR**
https://ror.org/01nrxwf90

# Funder(s)

**Funder type**
Government

**Funder Name**
Efficacy and Mechanism Evaluation Programme

**Alternative Name(s)**
NIHR Efficacy and Mechanism Evaluation Programme, Efficacy and Mechanism Evaluation (EME), EME

**Funding Body Type**
Government organisation

**Funding Body Subtype**
National government

**Location**
United Kingdom

# Results and Publications

**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? |
|---|---|---|---|---|---|
| Protocol article | | 22/11/2023 | 23/11/2023 | Yes | No |

| | | | | | |
|---|---|---|---|---|---|
| HRA research summary | | | 28/06/2023 | No | No |
| Participant information sheet | | 18/04/2018 | 18/04/2018 | No | Yes |
| Participant information sheet | Participant information sheet | 11/11/2025 | 11/11/2025 | No | Yes |
| Study website | Study website | 11/11/2025 | 11/11/2025 | No | Yes |