# Study Protocol

Treatment of Osteogenesis Imperfecta with Parathyroid hormone and Zoledronic acid

**TOPaZ**

| Co-sponsors       | University of Edinburgh & NHS Lothian ACCORD  
The Queen’s Medical Research Institute  
47 Little France Crescent  
Edinburgh  
EH16 4TJ |
|-------------------|--------------------------------------------------|
| Funder            | National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation Programme  
Eli Lilly (supply of teriparatide only) |
| Funding Reference Number | EME 14/200/18 |
| Chief Investigator | Professor Stuart Ralston |
| EudraCT Number    | 2016-003228-22 |
| REC Number        | 16/ES/0110 |
| Protocol Number   | AC16092 |
| ISRCTN Number     | ISRCTN 15313991 |
| Version Number and Date | Version 7.0 13/02/2018 |

## COORDINATING CENTRE

<table>
<thead>
<tr>
<th>Chief Investigator</th>
<th>Co-sponsor Representative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Stuart Ralston</td>
<td>Vikki Young</td>
</tr>
<tr>
<td>Molecular Medicine Centre</td>
<td>The Queen’s Medical Research Institute</td>
</tr>
<tr>
<td>Institute of Genetics &amp; Molecular Medicine</td>
<td>47 Little France Crescent</td>
</tr>
<tr>
<td>Western General Hospital</td>
<td>Edinburgh</td>
</tr>
<tr>
<td>Edinburgh EH4 2XU</td>
<td>EH16 4TJ</td>
</tr>
<tr>
<td>Tel: 0131 651 8743</td>
<td>Tel: 0131 242 9418</td>
</tr>
<tr>
<td>Fax: 0131 651 1085</td>
<td>Fax: 0131 242 9447</td>
</tr>
</tbody>
</table>

TOPaZ, Version 7.0 13Feb2018  
IRAS 207747  
1 of 43
### GRANT HOLDERS

<table>
<thead>
<tr>
<th>Professor Stuart Ralston</th>
<th>Dr Jennifer Walsh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centre for Genomic and Experimental Medicine</td>
<td>Clinical Senior Lecturer</td>
</tr>
<tr>
<td>Institute of Genetics &amp; Molecular Medicine</td>
<td>Metabolic Bone Centre</td>
</tr>
<tr>
<td>Western General Hospital</td>
<td>Northern General Hospital</td>
</tr>
<tr>
<td>Edinburgh EH4 2XU</td>
<td>Harries Road</td>
</tr>
<tr>
<td>Tel: 0131 651 8743</td>
<td>Sheffield S5 7AU</td>
</tr>
<tr>
<td>Fax: 0131 651 1085</td>
<td>Tel: 0114 271 4705</td>
</tr>
<tr>
<td>Email: <a href="mailto:stuart.ralston@ed.ac.uk">stuart.ralston@ed.ac.uk</a></td>
<td>Email: <a href="mailto:j.walsh@sheffield.ac.uk">j.walsh@sheffield.ac.uk</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dr M Kassim Jawaid</th>
<th>Professor Christopher Weir</th>
</tr>
</thead>
<tbody>
<tr>
<td>University Lecturer in Metabolic Bone Disease</td>
<td>Centre for Population Health Sciences</td>
</tr>
<tr>
<td>Nuffield Orthopaedic Centre, Windmill Road, Headington, Oxford, OX3 7HE</td>
<td>The University of Edinburgh</td>
</tr>
<tr>
<td>Tel: 01865 227 374</td>
<td>Medical School, Teviot Place</td>
</tr>
<tr>
<td>Email: <a href="mailto:kassim.jawaid@ndorms.ox.ac.uk">kassim.jawaid@ndorms.ox.ac.uk</a></td>
<td>Edinburgh EH8 9AG</td>
</tr>
<tr>
<td></td>
<td>Tel: 0131 650 3230</td>
</tr>
<tr>
<td></td>
<td>Email: <a href="mailto:christopher.weir@ed.ac.uk">christopher.weir@ed.ac.uk</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Professor Bente Langdahl</th>
<th>Ms Patricia Osborne</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant Physician</td>
<td>Chief Executive</td>
</tr>
<tr>
<td>Department of Endocrinology</td>
<td>Brittle Bone Society</td>
</tr>
<tr>
<td>Aarhus University Hospital</td>
<td>30 Guthrie Street</td>
</tr>
<tr>
<td>DK-8000 Aarhus C</td>
<td>Dundee DD1 5BS</td>
</tr>
<tr>
<td>Denmark</td>
<td>Tel: 01382-204446</td>
</tr>
<tr>
<td>Tel +45-7846-7678</td>
<td>Email: <a href="mailto:patricia.osborne@brittlebone.org">patricia.osborne@brittlebone.org</a></td>
</tr>
<tr>
<td>Email: <a href="mailto:bente.langdahl@aarhus.rm.dk">bente.langdahl@aarhus.rm.dk</a></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dr Wayne Lam</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant Clinical Geneticist</td>
<td></td>
</tr>
<tr>
<td>South East Scotland NHS Genetics Service</td>
<td></td>
</tr>
<tr>
<td>Centre for Genomic and Experimental Medicine</td>
<td></td>
</tr>
<tr>
<td>Institute of Genetics &amp; Molecular Medicine</td>
<td></td>
</tr>
<tr>
<td>Western General Hospital</td>
<td></td>
</tr>
<tr>
<td>Edinburgh EH4 2XU</td>
<td></td>
</tr>
<tr>
<td>Tel: 0131 537 1116</td>
<td></td>
</tr>
<tr>
<td><a href="mailto:Wayne.lam@nhsofthian.scot.nhs.uk">Wayne.lam@nhsofthian.scot.nhs.uk</a></td>
<td></td>
</tr>
<tr>
<td><a href="mailto:Wayne.lam@ed.ac.uk">Wayne.lam@ed.ac.uk</a></td>
<td></td>
</tr>
</tbody>
</table>
### PARTICIPATING SITES

<table>
<thead>
<tr>
<th>NHS Lothian Health Board</th>
<th>Sheffield Teaching Hospitals NHS Trust</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>Stuart H Raiston</td>
<td>Dr Jennifer Walsh</td>
</tr>
<tr>
<td>Professor of Rheumatology</td>
<td>Clinical Senior Lecturer</td>
</tr>
<tr>
<td>Rheumatic Diseases Unit</td>
<td>Metabolic Bone Centre</td>
</tr>
<tr>
<td>Western General Hospital</td>
<td>Northern General Hospital</td>
</tr>
<tr>
<td>Edinburgh EH4 2XU</td>
<td>Herries Road</td>
</tr>
<tr>
<td>Tel: 0131 651 3427</td>
<td>Sheffield S5 7AU</td>
</tr>
<tr>
<td>Email: <a href="mailto:stuart.raiston@ed.ac.uk">stuart.raiston@ed.ac.uk</a></td>
<td>Tel: 0114 271 4705</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>North Bristol NHS Trust</th>
<th>University Hospitals Bristol NHS Trust</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>Professor Jon Tobias</td>
<td>Dr Shane Clarke</td>
</tr>
<tr>
<td>Professor of Rheumatology</td>
<td>Consultant Rheumatologist</td>
</tr>
<tr>
<td>Musculoskeletal Research Unit</td>
<td>Bristol Royal Infirmary</td>
</tr>
<tr>
<td>Southmead Hospital</td>
<td>Upper Maudlin Street</td>
</tr>
<tr>
<td>Bristol BS10 5NB</td>
<td>Bristol BS2 8HW</td>
</tr>
<tr>
<td>Tel: 0117 323 6357</td>
<td>Tel: 0117 342 7266</td>
</tr>
<tr>
<td>Email: <a href="mailto:jon.tobias@bristol.ac.uk">jon.tobias@bristol.ac.uk</a></td>
<td>Email: <a href="mailto:s.clarke@bristol.ac.uk">s.clarke@bristol.ac.uk</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The Royal Liverpool Hospital</th>
<th>The Freeman Hospital Newcastle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>Dr Fadil Hannan</td>
<td>Dr Terry Aspray</td>
</tr>
<tr>
<td>Honorary Consultant</td>
<td>Consultant Physician</td>
</tr>
<tr>
<td>Department of Clinical Chemistry and Metabolic Medicine</td>
<td>Bone Clinic</td>
</tr>
<tr>
<td>2nd Floor UCD Building</td>
<td>Freeman Hospital</td>
</tr>
<tr>
<td>Royal Liverpool University Hospital</td>
<td>Newcastle upon Tyne. NE7 7DN</td>
</tr>
<tr>
<td>Prescot Street</td>
<td>Tel: 0191 213 7975</td>
</tr>
<tr>
<td>Liverpool L7 8XP</td>
<td>Email: <a href="mailto:t.aspray@newcastle.ac.uk">t.aspray@newcastle.ac.uk</a></td>
</tr>
<tr>
<td>Tel: 0151 706 5780</td>
<td></td>
</tr>
<tr>
<td>Email: f <a href="mailto:hannan@liverpool.ac.uk">hannan@liverpool.ac.uk</a></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford</th>
<th>Queen Elizabeth Hospital Birmingham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>Dr M Kassim Javaid</td>
<td>Prof Neil Gittoes</td>
</tr>
<tr>
<td>University Lecturer in Metabolic Bone Disease</td>
<td>Department of Endocrinology</td>
</tr>
<tr>
<td>Nuffield Orthopaedic Centre, Headington, Oxford, OX3 7HE</td>
<td>Queen Elizabeth Hospital</td>
</tr>
<tr>
<td></td>
<td>Edgbaston</td>
</tr>
<tr>
<td></td>
<td>Birmingham</td>
</tr>
<tr>
<td></td>
<td>B15 2TH</td>
</tr>
<tr>
<td>Tel: 01865 227 374</td>
<td>Tel: 0121 371 6940</td>
</tr>
<tr>
<td>Email: <a href="mailto:kassim.javaid@ndorms.ox.ac.uk">kassim.javaid@ndorms.ox.ac.uk</a></td>
<td>Email: <a href="mailto:neil.gittoes@uhb.nhs.uk">neil.gittoes@uhb.nhs.uk</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cambridge University Hospitals NHS Trust</th>
<th>Aberdeen Royal Hospitals NHS Trust</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>Dr Ken Poole</td>
<td>Dr Rosemary Hollick</td>
</tr>
<tr>
<td>Consultant Rheumatologist</td>
<td>Consultant Rheumatologist</td>
</tr>
<tr>
<td>Addenbrookes Hospital</td>
<td>Aberdeen Royal Infirmary</td>
</tr>
<tr>
<td>Cambridge</td>
<td>Aberdeen AB25 2ZR</td>
</tr>
<tr>
<td>CB2 0QQ</td>
<td>Tel: 01224 438063</td>
</tr>
<tr>
<td>Tel: 0141 451 6142</td>
<td>Email: <a href="mailto:rhollick@abdn.ac.uk">rhollick@abdn.ac.uk</a></td>
</tr>
<tr>
<td>Email: <a href="mailto:kenneth.poole@nhs.net">kenneth.poole@nhs.net</a></td>
<td></td>
</tr>
<tr>
<td>Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation</td>
<td>Nottingham University Hospitals NHS Trust</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
| **Principal Investigator**  
Dr Mark Garton  
Consultant Rheumatologist  
Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation  
Oswestry AY10 7AG | **Principal Investigator**  
Dr Peter Prinsloo  
Chemical Pathology  
Nottingham City Hospital  
Nottingham NG5 1PD |
| Tel: 01691-404000  
Email: Mark.Garton@rjh.nhs.uk | Tel: 0115-969-1169  
Email: peter.prinsloo@nuh.nhs.uk |

<table>
<thead>
<tr>
<th>Norfolk and Norwich University Hospitals NHS Foundation Trust</th>
<th>Ninewells Hospital and Medical School</th>
</tr>
</thead>
</table>
| **Principal Investigator**  
Professor William D Fraser  
Faculty of Medicine and Health Sciences  
Bob Champion Research and Educational Building, James Watson Road, University of East Anglia  
Norwich NR4 7UQ | **Principal Investigator**  
Dr Ellen Malcolm  
Associate Specialist  
Department of Medicine  
Ninewells Hospital  
Dundee DD1 9SY. |
| Tel: 01603 597174  
Email: w.fraser@uea.ac.uk | Tel: 01382-660111  
Email: ellen.malcolm@nhs.net |

<table>
<thead>
<tr>
<th>Royal National Orthopaedic Hospital NHS Trust</th>
<th>Staffordshire &amp; Stoke on Trent Partnership NHS Trust</th>
</tr>
</thead>
</table>
| **Principal Investigator**  
Dr Richard Keen  
Consultant Rheumatologist  
RNOH Stanmore  
Brockley Hill  
Stanmore  
Middlesex HA7 4LP | **Principal Investigator**  
Dr Zoe Paskins  
Haywood Community Hospital  
Haywood Road  
Staffordshire  
ST6 7AG |
| Tel: 020 8954 2300  
Email: DrRichardKeen@aol.com | Tel: 01782-673500  
Email: z.paskins@keele.ac.uk |

<table>
<thead>
<tr>
<th>University Hospital Llandough</th>
<th>Portsmouth Hospitals NHS Trust</th>
</tr>
</thead>
</table>
| **Principal Investigator**  
Dr Mike Stone  
University Hospital Llandough  
Penlan Road, Llandough, Penarth CF64 2XX | **Principal Investigator**  
Dr Steven Young Min  
Consultant Rheumatologist  
Queen Alexandra Hospital  
Southwick Hill Road  
Cosham PO6 3LY |
| Tel: 0209 2071 1711  
Email: mikestone1959@gmail.com | Tel: 023 9228 6000  
Email: Steven.YoungMin@porthosp.nhs.uk |
<table>
<thead>
<tr>
<th>South Tees Hospitals NHS Foundation Trust</th>
<th>Manchester Royal Infirmary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Principal Investigator</strong></td>
<td></td>
</tr>
<tr>
<td>Dr Stephen Tuck</td>
<td>Professor Peter Selby</td>
</tr>
<tr>
<td>James Cook University Hospital</td>
<td>Clinical Professor of Metabolic Bone Disease</td>
</tr>
<tr>
<td>Marton Road</td>
<td>Centre for Endocrinology &amp; Diabetes</td>
</tr>
<tr>
<td>Middlesbrough</td>
<td>University of Manchester</td>
</tr>
<tr>
<td>TS4 3BW</td>
<td>Manchester Royal Infirmary</td>
</tr>
<tr>
<td>Tel: 01642 854757</td>
<td>Oxford Road, Manchester ML13 9WL</td>
</tr>
<tr>
<td>Email: <a href="mailto:stephen.tuck@stees.nhs.uk">stephen.tuck@stees.nhs.uk</a></td>
<td>Tel: 0161-276-8917</td>
</tr>
<tr>
<td></td>
<td>Email: <a href="mailto:peter.selby@manchester.ac.uk">peter.selby@manchester.ac.uk</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>University Hospital Southampton</th>
<th>Leicester Royal Infirmary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Principal Investigator</strong></td>
<td></td>
</tr>
<tr>
<td>Professor Nick Harvey</td>
<td>Dr Prashanth Patel</td>
</tr>
<tr>
<td>MRC Lifecourse Epidemiology Unit</td>
<td>Head of Service</td>
</tr>
<tr>
<td>Southampton General Hospital</td>
<td>Department of Chemical Pathology</td>
</tr>
<tr>
<td>Tremona Road</td>
<td>Sandringham Building</td>
</tr>
<tr>
<td>Southampton SO16 6YD</td>
<td>Leicester Royal Infirmary</td>
</tr>
<tr>
<td>Tel: 023 8077 7624</td>
<td>LE1 5WW</td>
</tr>
<tr>
<td>Email: <a href="mailto:nch@mrc.soton.ac.uk">nch@mrc.soton.ac.uk</a></td>
<td>Tel: 0116 258 6550</td>
</tr>
<tr>
<td></td>
<td>Email: <a href="mailto:prashanth.patel@uhl-tr.nhs.uk">prashanth.patel@uhl-tr.nhs.uk</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Guys &amp; St Thomas NHS Trust</th>
<th>Belfast Health and Social Care Trust</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Principal Investigator</strong></td>
<td></td>
</tr>
<tr>
<td>Dr Geeta Hampson</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>Consultant Physician</td>
<td>Dr John R Lindsay</td>
</tr>
<tr>
<td>Metabolic Bone Clinic</td>
<td>Royal Victoria Hospital</td>
</tr>
<tr>
<td>Guy's Hospital</td>
<td>274 Grosvenor Road</td>
</tr>
<tr>
<td>Great Maze Pond</td>
<td>Belfast BT12 6BA</td>
</tr>
<tr>
<td>London SE1 9RT</td>
<td>Tel: 028 9024 0503</td>
</tr>
<tr>
<td>Tel: 020 7188 7188</td>
<td>Email: <a href="mailto:johnrlindsay@belfasttrust.hscni.net">johnrlindsay@belfasttrust.hscni.net</a></td>
</tr>
<tr>
<td>Email: <a href="mailto:Geeta.hampson@kcl.ac.uk">Geeta.hampson@kcl.ac.uk</a></td>
<td></td>
</tr>
</tbody>
</table>

| Queen Elizabeth University Hospital    | St. Vincent’s University Hospital, Dublin |
| Glasgow                                |                                        |
| **Principal Investigator**            | **Principal Investigator**             |
| Dr Stephen Gallacher                  | Dr Rachel Crowley                      |
| Consultant Physician                  | Consultant Physician                  |
| Queen Elizabeth University Hospital    | St Vincent’s University Hospital       |
| 1345 Govan Road                        | Elm Park, Dublin 4                    |
| Glasgow G51 4TF                        | Republic of Ireland                   |
| Tel: 0141-201-1100                     | Tel: +353-1-6639822                   |
| Email: Stephen.Gallacher@ggc.scot.nhs.uk | Email: R.Crowley@st-vincents.ie       |
CONTENTS

1 INTRODUCTION ................................................................................................................13
  1.1 BACKGROUND ................................................................................................. 13
  1.2 RATIONALE FOR STUDY ............................................................................ 13

2 STUDY OBJECTIVES .................................................................................................14
  2.1 OBJECTIVES .................................................................................................. 14
    2.1.1 Primary Objective .................................................................................. 14
    2.1.2 Secondary Objectives ........................................................................... 14
  2.2 ENDPOINTS ...................................................................................................... 14
    2.2.1 Primary Endpoint .................................................................................. 14
    2.2.2 Secondary Endpoints ........................................................................... 14

3 STUDY DESIGN ........................................................................................................14

4 STUDY POPULATION ...............................................................................................15
  4.1 NUMBER OF PARTICIPANTS ........................................................................... 15
  4.2 INCLUSION CRITERIA ..................................................................................... 15
  4.3 EXCLUSION CRITERIA .................................................................................... 15
  4.4 CO-ENROLMENT .............................................................................................. 15

5 PARTICIPANT SELECTION AND ENROLMENT .......................................................16
  5.1 IDENTIFYING PARTICIPANTS ........................................................................ 16
  5.2 CONSENTING PARTICIPANTS ....................................................................... 17
  5.3 SCREENING FOR ELIGIBILITY ..................................................................... 17
  5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS .................................. 17
  5.5 RANDOMISATION ............................................................................................ 17
    5.5.1 Randomisation Procedures ..................................................................... 17
    5.5.2 Treatment Allocation ............................................................................. 17
    5.5.3 Emergency Unblinding Procedures ........................................................ 18
    5.5.4 Withdrawal of Study Participants ............................................................ 18

6 INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO ..........................18
  6.1 STUDY DRUG: IMP1 - Teriparatide ................................................................. 18
    6.1.1 Study Drug Identification ....................................................................... 18
    6.1.2 Study Drug Manufacturer ..................................................................... 18
    6.1.3 Marketing Authorisation Holder ............................................................... 18
    6.1.4 Labelling and Packaging ....................................................................... 18
    6.1.5 Storage .................................................................................................... 19
    6.1.6 Summary of Product Characteristics or Investigators Brochure .......... 19
  6.2 STUDY DRUG: IMP2 - Zoledronic acid ............................................................ 19
    6.2.1 Study Drug Identification ....................................................................... 19
    6.2.2 Study Drug Manufacturer ..................................................................... 19
    6.2.3 Marketing Authorisation Holder ............................................................... 19
    6.2.4 Labelling and Packaging ....................................................................... 19
    6.2.5 Storage .................................................................................................... 19
    6.2.6 Summary of Product Characteristics or Investigators Brochure .......... 20
  6.3 STUDY DRUG: IMP3 - Standard Care ............................................................... 20
    6.3.1 Study Drug Identification ....................................................................... 20
    6.3.2 Study Drug Manufacturer ..................................................................... 20
    6.3.3 Marketing Authorisation Holder ............................................................... 20
    6.3.4 Labelling and Packaging ....................................................................... 20
6.3.5 Storage
6.3.6 Summary of Product Characteristics or Investigators Brochure

6.4 PLACEBO
6.5 DOSING REGIME
6.6 DOSE CHANGES
6.7 TEMPORARY AND PERMANENT TPTD STOPS
6.8 PARTICIPANT COMPLIANCE
6.9 OVERDOSE
6.10 OTHER MEDICATIONS
   6.10.1 Non-Investigational Medicinal Products
   6.10.2 Permitted Medications
   6.10.3 Prohibited Medications

7 STUDY ASSESSMENTS
   7.1 ASSESSMENT OVERVIEW
   7.2 SAFETY ASSESSMENTS
   7.3 STUDY ASSESSMENTS
   BASELINE VISIT
   REVIEW VISITS FOR PARTICIPANTS RECEIVING TPTD
   FOLLOW UP VISIT AT 12 MONTHS
   FOLLOW UP VISIT AT 24 MONTHS
   END OF STUDY VISIT
   ASSESSMENTS FOR FRACTURE
   OPTIONAL CONTACTS

8 DATA COLLECTION

9 STATISTICS AND DATA ANALYSIS
   9.1 SAMPLE SIZE CALCULATION
   9.2 PROPOSED ANALYSES

10 ADVERSE EVENTS
   10.1 DEFINITIONS
   10.2 IDENTIFYING AEs AND SAEs
   10.3 RECORDING AEs AND SAEs
   10.4 ASSESSMENT OF AEs AND SAEs
      10.4.1 Assessment of Seriousness
      10.4.2 Assessment of Causality
      10.4.3 Assessment of Expectedness
      10.4.4 Assessment of Severity
   10.5 REPORTING OF SAEs/SARs/SUSARs
   10.6 REGULATORY REPORTING REQUIREMENTS
   10.7 FOLLOW UP PROCEDURES

11 PREGNANCY

12 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS
   12.1 TRIAL MANAGEMENT GROUP
   12.2 TRIAL STEERING COMMITTEE
   12.3 DATA MONITORING COMMITTEE
   12.4 INSPECTION OF RECORDS
   12.5 RISK ASSESSMENT
13 **GOOD CLINICAL PRACTICE** ................................................................. 35
   13.1 ETHICAL CONDUCT ........................................................................ 35
   13.2 REGULATORY COMPLIANCE ......................................................... 35
   13.3 INVESTIGATOR RESPONSIBILITIES ............................................... 36
       13.3.1 Informed Consent ................................................................. 36
       13.3.2 Study Site Staff ................................................................. 36
       13.3.3 Data Recording ................................................................. 36
       13.3.4 Investigator Documentation ................................................ 36
       13.3.5 GCP Training .................................................................. 36
       13.3.6 Confidentiality ................................................................ 37
       13.3.7 Data Protection ................................................................ 37
14 **STUDY CONDUCT RESPONSIBILITIES** ........................................ 37
   14.1 PROTOCOL AMENDMENTS ......................................................... 37
   14.2 PROTOCOL VIOLATIONS AND DEVIATIONS .............................. 37
   14.3 SERIOUS BREACH REQUIREMENTS ......................................... 37
   14.4 STUDY RECORD RETENTION .................................................... 37
   14.5 END OF STUDY ...................................................................... 37
   14.6 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY ...... 37
   14.7 INSURANCE AND INDEMNITY ..................................................... 37
15 **REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS** .... 39
   15.1 AUTHORSHIP POLICY ............................................................... 39
   15.2 PUBLICATION ....................................................................... 39
   15.3 PEER REVIEW ..................................................................... 39
16 **REFERENCES** ............................................................................. 39
17 **APPENDICES** ............................................................................. 42
PROTOCOL APPROVAL

EudraCT number 2016-003228-22

Signatures

Stuart H Ralston
Chief Investigator

Signature

02 MAY 2018
Date

Christopher Weir
Trial Statistician

Signature

Date

Vikki Young
Sponsor(s) Representative

Signature

18 MAY 2018
Date

Professor Phil Conaghan
Chair, Trial Steering Committee

Signature

Date
PROTOCOL APPROVAL

EudraCT number 2016-003228-22

Signatures

Stuart H Ralston  
Chief Investigator  
Signature  
Date

Christopher Weir  
Trial Statistician  
Signature  
04 May 2018

Vikki Young  
Sponsor(s) Representative  
Signature  
Date

Professor Phil Conaghan  
Chair, Trial Steering Committee  
Signature  
Date
PROTOCOL APPROVAL

EudraCT number 2016-003228-22

Signatures

Stuart H Ralston
Chief Investigator

Signature
Date

Christopher Weir
Trial Statistician

Signature
Date

Vikki Young
Sponsor(s) Representative

Signature
Date

Professor Phil Canaghan
Chair, Trial Steering Committee

Signature
3/5/18
Date
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td>Joint office for University of Edinburgh and NHS Lothian – Academic and Clinical Central Office for Research &amp; Development</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>BBS</td>
<td>Brittle Bone Society</td>
</tr>
<tr>
<td>BMD</td>
<td>Bone Mineral Density</td>
</tr>
<tr>
<td>BPI</td>
<td>Brief Pain Inventory</td>
</tr>
<tr>
<td>CI</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>COLIA1</td>
<td>Collagen type IA1 gene</td>
</tr>
<tr>
<td>COLIA2</td>
<td>Collagen type IA2 gene</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CTA</td>
<td>Clinical Trial Agreement</td>
</tr>
<tr>
<td>CV</td>
<td>Curriculum Vitae</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>ECTU</td>
<td>Edinburgh Clinical Trials Unit</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylene diamine tetracetic acid</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated Glomerular Filtration Rate</td>
</tr>
<tr>
<td>EME</td>
<td>Efficacy and Mechanism Evaluation</td>
</tr>
<tr>
<td>EuroQol5D</td>
<td>EuroQol5D</td>
</tr>
<tr>
<td>HAQ</td>
<td>Health Assessment Questionnaire</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator Brochure</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
</tr>
<tr>
<td>ISF</td>
<td>Investigator Site File</td>
</tr>
<tr>
<td>IUD</td>
<td>Intrauterine Device</td>
</tr>
<tr>
<td>IUS</td>
<td>Intrauterine System</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NIMP</td>
<td>Non Investigational Medicinal Product</td>
</tr>
<tr>
<td>OI</td>
<td>Osteogenesis Imperfecta</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PIC</td>
<td>Patient identification centre</td>
</tr>
<tr>
<td>PQSI</td>
<td>Pittsburgh Sleep Quality Index</td>
</tr>
<tr>
<td>PTH</td>
<td>Parathyroid Hormone</td>
</tr>
<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
</tr>
<tr>
<td>RUDY</td>
<td>A study of Rare Diseases in bone, joint and vasculature</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form Health Survey</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TMF</td>
<td>Trial Master File</td>
</tr>
<tr>
<td>TPTD</td>
<td>Teriparatide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
</tr>
<tr>
<td>UAR</td>
<td>Unexpected Adverse Reaction</td>
</tr>
<tr>
<td>WOCPB</td>
<td>Women of Childbearing Potential</td>
</tr>
<tr>
<td>ZA</td>
<td>Zoledronic acid</td>
</tr>
<tr>
<td><strong>SUMMARY</strong></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td><strong>STUDY TITLE</strong></td>
<td>Randomised trial of Teriparatide followed by Zoledronic acid versus standard care to prevent fractures in adults with Osteogenesis Imperfecta (OI)</td>
</tr>
<tr>
<td><strong>SHORT TITLE AND ACRONYM</strong></td>
<td>Treatment of Osteogenesis Imperfecta with Parathyroid hormone and Zoledronic acid (TOPAZ)</td>
</tr>
<tr>
<td><strong>BACKGROUND</strong></td>
<td>Osteogenesis imperfecta is an inherited skeletal disorder characterised by increased risk of fragility fractures. Bisphosphonates are frequently prescribed for adult patients with OI with the aim of preventing fractures but the evidence base for efficacy is poor. Recent evidence suggests that the bone anabolic agent teriparatide (TPTD) increases bone mineral density (BMD) and may have the potential to prevent fractures in osteogenesis imperfecta</td>
</tr>
<tr>
<td><strong>STUDY OBJECTIVES</strong></td>
<td><strong>Primary Objective</strong></td>
</tr>
<tr>
<td></td>
<td>To investigate if a two-year course of TPTD followed by antiresorptive therapy with a single infusion of zoledronic acid (ZA) in adults with OI reduces the proportion of patients who experience a fracture as compared with standard care</td>
</tr>
<tr>
<td></td>
<td><strong>Secondary Objectives</strong></td>
</tr>
<tr>
<td></td>
<td>To investigate if a two-year course of TPTD followed by antiresorptive therapy with a single infusion of ZA in adults with OI reduces the total number of fractures, reduces the risk of vertebral fractures; or affects bone pain, quality of life and functional status as compared with standard care.</td>
</tr>
<tr>
<td></td>
<td><strong>Mechanistic Objective</strong></td>
</tr>
<tr>
<td></td>
<td>To understand which baseline characteristics of adults with OI, such as age, clinical subtype of OI, genetic diagnosis, bone turnover, BMD, and previous treatment influences the occurrence of fractures and/or the response to treatment</td>
</tr>
<tr>
<td><strong>STUDY POPULATION</strong></td>
<td>Adult patients with a clinical diagnosis of OI who are willing and able to give informed consent and who do not have contraindications to the study medications.</td>
</tr>
<tr>
<td><strong>STUDY TREATMENT</strong></td>
<td>Participants will be randomised in a 1:1 ratio to receive standard care for the duration of the study or TPTD for 2 years followed by an infusion of ZA or another antiresorptive agent in the event that ZA is contraindicated.</td>
</tr>
<tr>
<td><strong>STUDY ASSESSMENTS</strong></td>
<td>The baseline assessment will include dual energy x-ray absorptiometry (DEXA), spine x-rays, safety bloods, medical and fracture history, pain (brief pain inventory, BPI) and quality of life (SF36, HAQ, EQ5D, PSQI). Blood will be taken for genetic analysis and for analysis of biochemical markers of bone turnover. In some centres, a high resolution quantitative CT scan (HRQCT) of the wrist and tibia will be performed. Participants will be seen after 12 months when bloods, questionnaires and HRQTC will be repeated; at 24 months when bloods, questionnaires, DEXA and HRQCT will be repeated. At the end of the study participants will undergo DEXA, spine x-rays, HRQCT and bloods and questionnaires will be repeated. Information on adverse events and fractures will be collected throughout the study and participants suspected to have fractures will have x-ray or other imaging to confirm the presence of fractures.</td>
</tr>
</tbody>
</table>
1 INTRODUCTION

1.1 BACKGROUND

Osteogenesis imperfecta (OI) is an inherited skeletal disorder with a prevalence of about 11/100,000 which is characterised by an increased risk of fragility fractures (1). It is most commonly caused by mutations of the COLIA1 or COLIA2 genes which result in the production of collagen which is abnormal or present in reduced amounts although mutations in several other genes have been identified over recent years which can result in the same clinical phenotype (2).

The fracture risk in OI is at least an order of magnitude above that in patients with osteoporosis. Affected individuals are at increased risk of fragility fractures throughout life but the highest rates of fracture are during childhood and above the age of 50 years (3). While affected individuals suffer tens or hundreds of fractures during their lifetime (2-4) there is relatively little information on fracture rate in prospective studies. A survey of adult patients with OI recently carried out in collaboration with the brittle bone society revealed that 79% of subjects had suffered a fracture during the previous 5 years, equivalent to an annualised fracture rate of about 16%. This is in keeping with data from randomised trials and observational studies, which on average, have reported an annualised fracture rate of about 17% (4-9).

Bone mineral density (BMD) is variable in patients with OI (10) and the increased risk of fracture is observed even in patients with normal BMD or osteopenia (3,4). However, a cohort study in Norway found that patients with BMD values in the osteoporotic range (T-score < -2.5) had a 3-fold higher rate of fractures than those with normal BMD or osteopenia (4). This is an important observation since it provides proof-of-concept that strategies aimed at increasing bone mass might reduce fracture rate in OI.

Bisphosphonates are frequently prescribed for patients with OI with the aim of preventing fractures but the evidence base for efficacy is poor. Previous Cochrane reviews and meta-analysis of trials in OI have concluded that while bisphosphonates consistently increased BMD in both children and adults the effects on fracture risk are uncertain (11-13). It remains unclear why the increase in BMD resulting from bisphosphonate treatment has not been associated with a consistent reduction in fractures. However one explanation might be that the increase in BMD that occurs with bisphosphonates is due mainly to increased mineralisation of bone, rather than an increase in the amount of bone tissue (14).

Recently a randomised placebo controlled trial with the bone anabolic agent teriparatide (TPTD) has been conducted in adults with OI with encouraging results (9). Not only did TPTD increase BMD when compared with placebo but the odds ratio of fracture was reduced in the active treatment arm, but not significantly (0.73; 95% CI 0.28-1.90). This study had a short duration of follow up however, and was not powered to detect a reduction in fracture risk. Another observational study of TPTD also showed encouraging results in OI patients previously treated with bisphosphonates but fracture data were not reported (5).

1.2 RATIONALE FOR STUDY

In view of the inconclusive results that have been obtained with bisphosphonates in the treatment of OI (12;13;15),and the encouraging preliminary results that have been obtained with TPTD (9), the aim of the present study is to determine whether TPTD, followed by antiresorptive therapy with a single infusion of zoledronic acid (ZA) to maintain the increase in bone mass reduces the risk of fracture in adults with OI as compared with standard care. The prolonged antiresorptive effect of ZA means that a single infusion is expected to maintain the increase in BMD for at least three years (16;17).
2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

The primary objective will be to investigate if a two-year course of TPTD followed by antiresorptive treatment with a single infusion of ZA in adults with OI reduces the proportion of patients who experience a fracture as compared with standard care.

2.1.2 Secondary Objectives

Secondary objectives will be to determine if treatment influences the total number of fractures, bone pain, quality of life, functional status and adverse events. In addition, the study will have a mechanistic objective which is to gain understanding of how the baseline characteristics of adults with osteogenesis imperfecta such as age, clinical subtype of OI, genetic diagnosis, BMD, and previous treatment, influence the risk of fractures; other secondary endpoints, adverse events and the response to treatment.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

The proportion of participants experiencing a clinical fracture validated by x-ray or other imaging.

2.2.2 Secondary Endpoints

The total number of clinical fractures experienced by participants validated by x-ray or other imaging.

The number of incident vertebral fractures assessed by imaging of the thoracic and lumbar spine.

The 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.

Bone pain assessed by the brief pain inventory (BPI); quality of life as assessed by the SF36 questionnaire; Pittsburgh sleep quality questionnaire (PSQI) and functional status as assessed by the health assessment questionnaire (HAQ) and EuroQol5D (EQ5D) assessment tools, and adverse events.

To evaluate the relationship between patient demographics, clinical features of OI, bone density values at baseline, type of genetic mutation and biochemical markers of bone turnover and fracture occurrence OI and the response to treatment.

3 STUDY DESIGN

Prospective, open label randomised controlled trial with centralised adjudication of the fracture endpoints by blinded assessors. Participants will be randomised in a 1:1 ratio to receive treatment with TPTD for 2 years followed by an infusion of ZA or to receive standard care for the duration of the study. All participants will be followed up for a total duration of between 2 and 5 years.
4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS
The sample size will be 380 patients, with 190 in each treatment group.

4.2 INCLUSION CRITERIA
- Adult patients age 18 years and over with a clinical diagnosis of OI
- Patients willing and able to consent and comply with the study protocol.

4.3 EXCLUSION CRITERIA
- Current or previous treatment with an investigational (non-licensed experimental) drug with effects on bone metabolism.
- Contraindication to TPTD or ZA
- Women of childbearing potential not using highly effective methods of contraception (see below)
- Pregnancy
- Women that are breastfeeding
- Age <18 years

Women of childbearing potential (WOCBP) can be enrolled into the study but will be required to use highly effective methods of contraception (as defined by the HMA Clinical Trial Facilitation Group recommendations) before, during the trial if they are being treated with TPTD or bisphosphonates. Examples of highly effective contraception include:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Bilateral tubal occlusion
- Vasectomised partner
  True abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Barrier methods of contraception (condom or occlusive cap (diaphragm or cervical/vault caps with or without spermicidal foam/gel/film/cream/suppository) are not considered to be highly effective methods of contraception.

4.4 CO-ENROLMENT
Co-enrolment will be permitted for potential participants have already been enrolled in studies that involve collection of data such as questionnaires and tissue samples such as Biobank UK and similar epidemiological studies. Participants that have consented to take part in the TOPaZ study will also be permitted to enrol in other observational studies provided that the burden of visits would not compromise the integrity of the TOPaZ study. Co-enrolment between TOPaZ and another CTIMP study may be permitted providing there is a CTIMP-CTIMP agreement in place. In this eventuality, proposals for co-enrolment between CTIMP studies will be captured in a written, authorised agreement between the sponsors and investigators of each study. At the screening visit participants will be asked if they are taking part in any other studies. During the trial, participants will also be asked to inform the study team if they have been approached to take part in any other studies.
5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS
The main route of recruitment to the study will be through the potential participants' normal NHS care providers. Potential participants will be approached directly as they attend for routine outpatient clinic visits or by telephone or letter following review of clinic lists.

Information about the trial will also be posted on the website of the Brittle Bone Society (BBS), a patient support organisation and communicated through newsletters and emails of the BBS. Information will also be provided through the RUDY project; an ongoing national cohort of patients with rare bone diseases who consent to be contacted about future ethically approved studies.

Potential participants, who become aware of the study through the BBS, RUDY or through other routes such as word of mouth from affected relatives, will be invited to contact the research team at the co-ordinating centre or their nearest study centre if they are interested in taking part. Following such contact, they will be provided with information about the trial.

We will set up several study centres spread across the UK and Republic of Ireland (summarised on pages 4-6). In addition, patient identification centres (PIC) in which patients with OI attending district general hospitals will be established. The PIC will provide potentially eligible patients attending routine clinics information about the study. Potential participants that express an interest in the study will then be offered referral to one of the main study centres.

Reasonable travel expenses (i.e. not first-class train travel) will be covered for all participants. Sites may recruit from a wide geographical area if potential participants are able and willing to comply with the study protocol by attending scheduled visits.

By prior arrangement with the TOPaZ Trial Office, sites may recruit participants who, for logistic reasons, are unable to visit study centres for TPTD resupply visits on the following conditions:

i) TPTD can be stored and dispensed from a local hospital pharmacy with GCP training

ii) local hospital pharmacies should adhere to the same procedures as recruiting site pharmacies in terms of IMP receipting, dispensing and accountability

iii) remote contact with participants by the study team via telephone interview or email is fully documented (as per a standard visit) in eCRF and in medical notes

iv) shipments of Trial TPTD from recruiting site pharmacies to local hospital pharmacies be temperature controlled with either records provided (if using system already in place) or Trial Office temperature monitors provided.

5.2 CONSENTING PARTICIPANTS
Participants will be supplied with an information sheet from a member of the study team containing details of the study aims and procedures prior to enrolment in the study. Once they have had adequate time (at least 24 hours) to consider the information sheet and ask questions written consent will be sought from trained research nurses or doctors that are involved in the study. The investigator will ensure informed consent is evidenced in writing, dated and signed, or otherwise marked, by that person so to indicate their consent. If the person is unable to sign or to mark a document so as to indicate their consent, it should be given orally in the presence of at least one impartial witness and recorded in writing. Participants will be given the option to consent separately to genetic testing and being informed of the results of the genetic tests.
Following informed consent, participants personal details including hospital numbers and NHS numbers will be held by members or the research team at study sites and by members of the study team at the co-ordinating centre to ensure that the study team can make contact with participants to feedback the results of the genetic testing, to organise study visits, to obtain radiographs of participants who are suspected to have suffered a fracture and to obtain information on adverse events.

5.3 SCREENING FOR ELIGIBILITY

Prior to any study specific screening investigations, informed consent must be given by the patient. The procedures and investigations that will be performed at the baseline visit prior to randomisation are listed in section 7.1.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

An anonymised log will be kept for patients who were screened for the study but subsequently found to be ineligible or not recruited.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

Randomisation will be performed centrally by Edinburgh Clinical Trials Unit using a secure website thus concealing the allocation sequence. Randomisation will be performed by research staff at study sites who will log onto the randomisation website with a username and password supplied by the co-ordinating centre. Participants will be randomised to receive treatment with TPTD/ZA or standard of care in a 1:1 ratio. Minimisation will be employed to balance the treatment groups for variables that might influence fracture occurrence. These include:

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

The minimisation algorithm will incorporate a computer-generated random number element to maintain unpredictability of treatment allocation.

If DEXA is not feasible for technical reasons such as in patients with metalwork in situ as the result of previous fractures or because of multiple vertebral fractures they will be assumed to have a T score of <2.5 for the purposes of minimisation.

Participants and local investigators will not be blinded to treatment allocation. However, certain members of the research team at the co-ordinating centre and the researchers responsible for adjudicating fractures will be blinded to treatment allocation. The names of the research staff at the co-ordinating centre that will not have access to the treatment allocation codes will be recorded in the trial master file.

Once a participant has been randomised they will be given a card to indicate they are on the trial. Participants will be instructed to show this to any healthcare professional involved in their care who is not involved in the study

5.5.2 Treatment Allocation

Active treatment group:
TPTD 20mcg daily, given subcutaneously using a self-administered injection device for two years followed by a single intravenous infusion of ZA 5mg.

Bisphosphonates, denosumab and strontium ranelate will be stopped in the active treatment group at baseline and prohibited during treatment with TPTD since these may alter the therapeutic response to TPTD (18). Bisphosphonates will be prohibited following treatment with ZA for at least 12 months to avoid over suppression of bone turnover. If for any reason administration of ZA is not feasible, such as poor venous access, another antiresorptive agent (including - in this instance only - denosumab) may be administered as an alternative means of maintaining the increase in BMD at the end of TPTD treatment. Before commencing an alternative to ZA, local investigators should fully discuss the choice of agent and the reason for not using ZA with the co-ordinating centre.

**Standard care group:**
Participants in the standard care group may continue with existing bone modifying treatment (i.e. bisphosphonate treatment) or be given no active bone modifying treatment, according to the clinical judgement of the local investigator. Bisphosphonates may be continued, stopped or started during the study at the discretion of the local investigator. Other bone modifying drugs may also be given at the discretion of the local investigator with the exception of teriparatide and investigational (experimental) agents with effects on bone metabolism.

Calcium and vitamin D supplements and/or vitamin D supplements and hormone replacement therapy can be given in both groups if clinically indicated according to normal clinical practice and at the discretion of the local investigator. Calcium and vitamin D supplements are included within the SPC as Non-Investigational Medicinal Products (NIMPs).

### 5.5.3 Emergency Unblinding Procedures

Not applicable. The study is open label.

### 5.5.4 Withdrawal of Study Participants

Participants will be free to withdraw from the study at any point or a participant can be withdrawn by the investigator. If withdrawal occurs the primary reason for withdrawal should be documented in the participant's Case Report Form (CRF). Participants who wish to withdraw will be provided with the following options.

- Withdrawal from treatment but remaining in follow up
- Withdrawal from treatment and follow up (but with retention of data up to the time of withdrawal for use in analysis)
- Complete withdrawal with no retention of data.

Reasons for withdrawing from active treatment may include:
- Further participation is considered by the attending clinician not to be in the patient's best interest
- Development of renal impairment or other medical condition that would represent a contraindication to continued treatment with TPTD or bisphosphonates.
- Significant non-compliance with the study protocol. An exception would be in the case of a female participant who became pregnant during the study despite using contraception. If this were to occur, TPTD, ZA and other bone active treatments would be stopped for the duration of the pregnancy and breastfeeding but the participant would still be given the option of remaining in the trial.

## 6 INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

### 6.1 STUDY DRUG: IMP1 - Teriparatide

#### 6.1.1 Study Drug Identification

TOPaZ, Version 7.0 13Feb2018 IRAS 207747 18 of 43
Teriparatide (1-34 fragment of PTH) 20 micrograms daily by subcutaneous injection. Needles for Forsteo pens are not provided and compatible needles should be supplied by participating sites.

6.1.2 Study Drug Manufacturer

Teriparatide: Forsteo manufactured by Eli Lilly and Company Limited.

6.1.3 Marketing Authorisation Holder

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands,

6.1.4 Labelling and Packaging

Teriparatide: Forsteo will be supplied by Eli Lilly and Company from commercial stock to sites via PCI Pharma Services. There will be no modifications to original packaging aside from the addition of reduced labelling with regulatory approval to indicate that they are for use within the TOPaZ clinical trial only. A trial-specific dispensing label should be applied at site prior to dispensation to participants.

6.1.5 Storage

Storage and dispensing of the TPTD will be undertaken by research pharmacies in the participating centres in accordance with the Pharmacy Manual provided. TPTD must be stored in a refrigerator (2°C-8°C at all times). The pen should be returned to the refrigerator immediately after use. Do not freeze.

6.1.6 Summary of Product Characteristics or Investigators Brochure

The SPC for Forsteo is included within the trial representative set of SPC provided. The RSI can be found in section 4.8 of the Forsteo SPC.

6.2 STUDY DRUG: IMP2 – Zoledronic acid

6.2.1 Study Drug Identification

Zoledronic Acid 5 mg/100mg solution for infusion. Any licensed preparation of zoledronic acid may be employed to deliver the required dose of 5mg but vial sharing is only permitted if used by trial participants attending for infusions on the same day.

6.2.2 Study Drug Manufacturer

Any preparation ZA which has marketing authorisation in the UK and the Republic of Ireland may be employed in the active treatment group.

6.2.3 Marketing Authorisation Holder

Not applicable

6.2.4 Labelling and Packaging

A trial-specific dispensing label should be applied at site prior to dispensation of ZA.

6.2.5 Storage

TOPaZ, Version 7.0 13Feb2018 IRAS 207747
Storage and dispensing of the ZA will be undertaken by research pharmacies in the participating centres but alternative arrangements may be made for by prior arrangement with the TOPaZ trial office.

6.2.6 Summary of Product Characteristics or Investigators Brochure

A representative SmPC be provided is provided in the SPC pack. The RSI can be found in section 4.8 of the Zoledronic Acid SPC.

6.3 STUDY DRUG: Standard Care

6.3.1 Study Drug Identification

Standard care: Any licensed preparation of bisphosphonate may be employed, at doses which are normally used in routine practice for the treatment of osteogenesis imperfecta. Other bone active drugs including denosumab may also be given at the discretion of the local investigator.

6.3.2 Study Drug Manufacturer

Any bisphosphonate which has marketing authorisation in the UK and the Republic of Ireland will be permitted in the standard care group.

6.3.3 Marketing Authorisation Holder

Not applicable.

6.3.4 Labelling and Packaging

No specific arrangements are planned for labelling of the other Investigational Medicinal Products since we will use licensed medicinal products that are currently available in the UK in both treatment groups with a posology and mode of administration that is similar to the licensed indication of osteoporosis.

6.3.5 Storage

Dispensing of bisphosphonates and other medications in the standard care group will be undertaken by community pharmacies or hospital pharmacies using local internal procedures, with details recorded by site staff in the eCRF.

6.3.6 Summary of Product Characteristics or Investigators Brochure

Representative SPCs are provided in the SPC pack. The representative RSIs for standard care comparators can be found in section 4.8 of the appropriate SPC.

6.4 PLACEBO

No applicable

6.5 DOSING REGIME

The dosing regimen for TPTD will be 20mcg daily given by subcutaneous injection for 24 months. Participants randomised to TPTD will be instructed that the TPTD needs to be stored in a refrigerator and will be taught how to self-administer the injection. Participants will be supplied with needles, a coolbag and ice packs and a sharps bin to store used needles and will be instructed to return these to the research team or pharmacy team at participating centres when full or at the end of study for disposal. Participants will be asked about adherence to the medication on returning the used pens to the study centres and will be asked to keep a study-specific ‘pen diary’. The used pens will be disposed of by the
pharmacies at participating centres according to local procedures and used sharps by either the research teams or pharmacies (depending on local practices).

After completing the two years of TPTD treatment, the patients in the active treatment arm will receive an infusion of ZA 5 mg intravenously over not less than 15 minutes administered by qualified staff at the participating sites within 4 weeks of the last TPTD dose (or an alternative antiresorptive agent – including denosumab in these circumstances only - if ZA contraindicated).

In the standard care group bisphosphonates will be used at standard doses and intervals using the posology employed in routine clinical practice for osteogenesis imperfecta.

If required, calcium and vitamin D supplements will be prescribed in standard doses and intervals according to routine clinical practice.

6.6 DOSE CHANGES

If for any reason a participant discontinues TPTD before the two-year treatment period is complete, the patient will be offered ZA within 4 weeks following cessation of TPTD to maintain the increase of BMD that has accrued.

In the event that administration of ZA is not feasible an alternative antiresorptive agent may be given to maintain the increase in BMD on discussion with the co-ordinating centre.

6.7 TEMPORARY AND PERMANENT TPTD STOPS

It is permissible for participants to temporarily stop (defined as ≥ 3 consecutive days) TPTD during the treatment period for up to 6 weeks. If this occurs the duration of the interruption and reason will be logged in the trial database. An interruption of greater than 6 weeks will be considered a permanent discontinuation and the participant will be invited to attend for a ZA infusion or treatment with an alternative antiresorptive agent within 4 weeks.

If participants are going on holiday for 1-14 days they should check if facilities are available during their holiday for the pen to be stored in a refrigerator. If they are sure that refrigerator facilities are available, they should take the pen on holiday and continue the treatment as normal. If they think refrigerator facilities might not be available or are unsure they should leave the pen at home and resume treatment when they return and log the doses as having been missed. Site teams should record any such stops lasting more than 3 days on the eCRF as a temporary stop. For Trips of ≥ 14 days: if participants are planning longer trips then they should discuss with site teams, and if necessary with the TOPaZ Trial Office, to put in place arrangements to allow them to keep taking their TPTD as per schedule.

6.8 PARTICIPANT COMPLIANCE

Adherence to TPTD will be monitored during the study through monitoring of returned injection devices to pharmacies at the participating centres and by enquiring whether any injections were missed at study visits, in conjunction with a participant pen diary. This information will be recorded in the CRF. Checks for compliance with ZA will not be necessary since this drug will be administered by intravenous infusion by the research team. Adherence with standard care will be assessed by enquiring about medication taken at study visits, including an estimation of compliance from participants. Every time participants reach the end of a course of a bone-specific treatment within the standard care arm they should be asked by site teams to estimate how much of the course was taken (all, most, half the time, some or none). This information will be recorded on the CRF. No specific threshold will be defined for non-compliance since analysis of the data will be based on the intention to treat principle. For the per-protocol analysis data on actual compliance will be taken into account in the statistical analysis plan which will be agreed by the trial steering committee prior to database lock (see section 9.1).
6.9 OVERDOSE

There have been cases of medication error with TPTD where the entire contents (up to 800 mcg) of the teriparatide pen have been administered as a single dose. Events reported have included nausea, weakness/lethargy and hypotension. No fatalities associated with such overdoses have been reported. Teriparatide has also been administered in single doses of up to 100 micrograms and in repeated doses of up to 60 micrograms/day for 6 weeks. Potential adverse effects that might be expected include hypercalcaemia, orthostatic hypotension, nausea, vomiting, dizziness, and headache. In the event of overdose occurring supportive treatment will be given including intravenous fluids to reduce serum calcium levels if this proves necessary.

There is no experience of overdose 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. 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.

We are unaware of any instances of acute overdose of bisphosphonates such as alendronic acid, risedronate, pamidronate and ibandronate which may be employed in the standard care arm. If this occurs supportive care will be given according to routine practice.

6.10 OTHER MEDICATIONS

6.10.1 Non-Investigational Medicinal Products

Medicinal products that are already being prescribed to participants as part of routine care will be continued during the trial. Calcium and vitamin D supplements may be prescribed in both groups according to standard practice unless the attending clinician feels that dietary intake of calcium and vitamin D and/or sunlight exposure are adequate to meet the recommended intake of both nutrients. Representative reference safety information for calcium (Calcichew D3) and vitamin D (Futium-D3) are included within the trial SPC pack as Non-Investigational Medicinal Products (NIMPs).

6.10.2 Permitted Medications

Participants will therefore be free to take all their usual medication during the study including HRT with the exception of the prohibited medications listed in Section 6.7.3

Any regularly used medications that are being taken at the start of study or commenced while a participant is on study will be documented on the CRF.

6.7.3. Prohibited Medications

Active treatment: During the phase of treatment with TPTD, the following drugs will be prohibited; bisphosphonates, denosumab, strontium ranelate, calcitriol and investigational (experimental) drugs with effects on bone metabolism. These drugs will also be prohibited within 12 months of receiving ZA to avoid over suppression of bone turnover. An exception would be if for any reason ZA cannot be given to maintain the increase in BMD following TPTD. In this case an alternative antiresorptive agent (including denosumab within this context only) may be given on discussion with the co-ordinating centre.

Standard care group: Teriparatide and investigational (experimental) drugs with effects on bone metabolism will be prohibited.

If a prohibited medication is taken in error during the study this will be noted as a protocol deviation and the prohibited medication will be stopped. Patients who receive prohibited medications will remain in the study. If the local investigator feels on clinical grounds that the
prohibited medication requires to be continued the participant will be withdrawn from the study.

7 STUDY ASSESSMENTS

7.1 OVERVIEW

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Screening / Baseline &amp; Randomisation Visit(s)</th>
<th>TPTD Resupply Visits See page 23 for further details</th>
<th>6 &amp; 18 month telephone call</th>
<th>12 month Visit (52 weeks)</th>
<th>24 month Visit (104 weeks)</th>
<th>Follow-up 6 monthly telephone call</th>
<th>End of Study Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/exclusion</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic data</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEXA</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine x-ray</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRQCT</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety bloods</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDTA blood sample</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum blood sample</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urine pregnancy test</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant Questionnaire Pack</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Training on treatment</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Issue of diary</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diary data entry</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>TPTD accountability</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medications check</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZA infusion</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrieval of incident fracture x-rays*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

* Retrieval of x-rays may occur at any point throughout the trial as and when Incident fractures are reported. Sites are encouraged to retrieve and upload images as soon as possible after the report of an incident fracture.

7.2 SAFETY ASSESSMENTS

Blood will be taken and analysed in local laboratories for assessment of serum creatinine, serum calcium, albumin, serum total alkaline phosphatase (ALP) and eGFR and (if clinically indicated) serum 25(OH)D prior to starting the study to ensure there is no contraindication to TPTD or bisphosphonate therapy. Blood results from ≤ 3 months prior to the date of consent will be accepted as being valid for the Baseline Visit unless there has been an intercurrent illness which in the opinion of the local investigator necessitates that the bloods be repeated. Creatinine clearance will also be calculated within the trial database at Baseline, 12 and 24 month and end of trial visits based on age, serum creatinine and body weight using the Cockcroft-Gault formula (20). Safety bloods must be checked prior to the ZA infusion (on the same day where possible or within the previous 7 days) at the 24 month visit (or before if TPTD stopped earlier) to ensure that there is no contraindication to ZA. Elevated serum
calcium and ALP occur commonly in patients treated with TPTD and no action is required if this is indicated by the safety bloods collected at study visits or intervening periods. In the event of the development of impaired renal function with an eGFR ≤ 35 or moderate to severe hypercalcaemia (serum adjusted calcium >3.2mmol/l), study sites should contact the central coordinating centre for advice.

Investigators at site may choose to carry out more frequent safety blood tests. These tests will not be recorded within the eCRF but if they are performed, the results should be filed in the participant's medical records. Any abnormal blood test results that are considered clinically significant by the local Investigator should be reported as Adverse Events.

Pregnancy tests will be performed at the baseline visit in women of childbearing potential. Additionally, a pregnancy test will be performed at 24 months prior to the infusion of ZA. Further pregnancy tests may be performed at any time at the discretion of the local investigator if they have reason to believe that a female participant has become pregnant despite taking adequate contraceptive measures.

7.3 STUDY ASSESSMENTS

BASELINE VISIT

At the baseline visit, participants will be provided with information about the study and invited to take part by providing written informed consent. Following provision of the information about the study participants will be advised that they can take as much time (and at least 24 hours) as they need to decide whether or not to take part in the study. Following completion of the baseline investigations there will be a window of 14 days during which randomisation should be completed and treatment commenced.

- **Demographics**: After consent has been obtained, information will be collected on demographics including date of birth, gender, smoking, alcohol intake, dietary calcium intake estimated by food frequency questionnaire, past medical history, family history of osteogenesis imperfecta, previous fractures, use of a hearing aid, current medications and current and previous bone active medications. In women, information will be collected on age at menarche, menopausal status and age at menopause.

- **Clinical examination**: Participants will undergo a clinical examination recording height and weight. The presence of bone deformity will be noted. Deformity will be recorded on the basis of the region involved; right and left lower limbs; pelvis, spine, rib cage, right and left upper limbs and skull. For each region the local investigator will be asked to grade deformity a 4-point scale at each site assessed: 0 = no deformity; 1=mild deformity; 2 = moderate deformity; 3=severe deformity. The presence or absence of blue sclerae and dentinogenesis imperfecta as assessed clinically will be noted.

- **DEXA**: Participants will undergo a bone mineral density scan using dual x-ray absorptiometry of the spine and hip by DEXA according to standard techniques, unless the local investigator feels that DEXA would not be feasible or informative (for example in patients with severe OI and multiple skeletal deformities or those with metalwork in situ that would preclude DEXA). If a DEXA scan has been performed within ≤ 6 months from the baseline visit this will be accepted as valid for the baseline assessment unless the patient has received bone active treatment during the intervening period.

- **Spine x-ray**: Lateral radiographs will be performed of the thoracic and lumbar spine to detect prevalent vertebral fractures. If a spine radiograph has been performed within ≤ 6 months from the baseline visit this will be accepted as valid for the baseline
assessment unless the patient has received bone active treatment during the intervening period.

- **HRQCT:** Patients who are attending centres with access to high resolution CT equipment will have the option of having a high resolution quantitative CT (HRQCT) scan of the wrist and tibia.

- **Research bloods:** A sample of venous blood (2 x 5ml) will be collected into EDTA tubes for DNA extraction and genetic analysis. These will be sent immediately by first class post at ambient temperature to the University of Edinburgh Bone Research Laboratory. Another sample of up to 10ml will be collected and allowed to clot. Serum will be separated on site and 2 x 1ml aliquots prepared. These will be stored frozen at -70°C or below at the study site and shipped on dry ice to the University of Edinburgh Bone Research Laboratory where they will be stored at -70°C or below until they are used for analysis of biochemical markers of bone turnover. The date and time of taking the blood samples will be recorded on the CRF.

- **Safety bloods:** As described in Section 7.2, a sample of venous blood will be collected and analysed locally by laboratories at participating centres for serum creatinine, calculation of eGFR, serum calcium, albumin, serum total alkaline phosphatase (ALP) and (if clinically indicated) serum 25(OH)D.

- **Urine pregnancy test:** All women of childbearing potential (WOCBP) defined as women who are premenopausal who have not been sterilised will require a negative urine pregnancy test prior to study inclusion.

- **Participant Questionnaire Pack:** Questionnaires will be completed for SF36, HAQ, EQ5D, PSQI and the brief pain inventory (BPI).

- **Participant training:** Participants allocated to the active treatment group (TPTD/ZA) will be trained in use of the injection device and given instructions on how to store the device.

- **Issue of Diary:** Participants will be issued with a diary to record visits made to their general practitioner, outpatient visits to hospital and in-patient hospital admissions. The date of the event and reason for seeking healthcare advice will be recorded. The occurrence of suspected fractures will also be recorded in the patient diary. The date and site of the suspected fracture will be recorded. Participants will be instructed to seek medical advice and undergo x-ray examination if they suspect they have suffered a fracture, in keeping with normal clinical practice.

**REVIEW VISITS FOR PARTICIPANTS RECEIVING TPTD**

Participants randomised to the active arm and receiving TPTD will be asked to attend the study centre at set intervals as set out in Table 2 below in order to collect new supplies of drug and to return used injection devices and sharps. During this visit, a member of the research team will review the patient and ask about any general health issues, missed doses, issues with the injection device and check the participant’s pen diary and events diary for AEs. Full sharps bins will be returned to research teams for disposal and new bins provided. Research pharmacies will then issue new pens and collect in previously issued pens for basic accountability checks (unused pens or multiple missed doses).

Table 2 sets out the schedule of visits for participants allocated to the active treatment arm. Visits are scheduled for the final week of treatment to ensure that there are no gaps in supplies (i.e. participants issued with 16 weeks drug at baseline but attend site to collect their next supplies at 15 weeks).

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Baseline</th>
<th>15 weeks</th>
<th>31 weeks</th>
<th>52 weeks</th>
<th>67 weeks</th>
<th>83 weeks</th>
<th>104 weeks</th>
</tr>
</thead>
</table>

TOPaZ, Version 7.0 13Feb2018  IRAS 207747  25 of 43
### FOLLOW UP VISIT AT 12 MONTHS (52 WEEKS)

The time window for this visit will be plus or minus 14 days from the date of randomisation.

- **Safety bloods:** A sample of venous blood will be collected and analysed locally by the laboratories at participating centres for serum creatinine, calculation of eGFR, serum calcium, albumin and serum total alkaline phosphatase (ALP).

- **Research bloods:** Another sample of up to 10ml will be collected and allowed to clot. Serum will be separated on site and 2 x 1ml aliquots prepared. These will be stored frozen at -70°C or below at the study site and shipped on dry ice to the University of Edinburgh Bone Research Laboratory where they will be stored at -70°C or below until they are used for analysis of biochemical markers of bone turnover. The date and time of taking the blood samples will be noted on the CRF.

- **Clinical examination:** Recording of weight and height

- **HRQCT:** Patients who are attending centres with access to high resolution CT equipment will have the option of having a HRQCT scan of the wrist and tibia.

- **Participant Questionnaire Pack:** Questionnaires will be completed for SF36, HAQ, EQ5D, PSQI and the brief pain inventory (BPI).

- **Participant Diary, AE and medications check:** Data recorded on patient diaries (GP visits, hospital visits, hospital admissions and fractures) will be reviewed by research staff at the study sites and entered onto the study database.

### FOLLOW UP VISIT AT 24 MONTHS (104 WEEKS)

The time window for this visit will be within 28 days from the date of randomisation in the standard care group and within 28 days of completing the 24 month course of TPTF in the active group.

- **Safety bloods:** A sample of venous blood will be collected and analysed locally by laboratories at participating centres for serum creatinine, calculation of eGFR, serum calcium, albumin, and serum total alkaline phosphatase (ALP).

- **Research bloods:** Another sample of up to 10ml will be collected and allowed to clot. Serum will be separated on site and 2 x 1ml aliquots prepared. These will be stored frozen at -70°C or below at the study site and shipped on dry ice to the University of Edinburgh Bone Research Laboratory where they will be stored at -70°C or below until they are used for analysis of biochemical markers of bone turnover. The date and time of taking the blood samples will be noted on the CRF.

- **Clinical examination:** Recording of weight and height.
• **DEXA:** Participants will undergo a bone mineral density scan using dual x-ray absorptiometry of the spine and hip by DEXA according to standard techniques, unless the local investigator feels that DEXA would not be feasible or informative (for example in patients with severe OI and multiple skeletal deformities or those with metalwork in situ that would preclude DEXA). This should be performed, as far as possible, on the same machine used for the baseline assessment.

• **HRQCT:** Patients who are attending centres with access to high resolution CT equipment will have the option of having a HRQCT scan of the wrist and tibia.

• **Participant Questionnaire Pack:** Questionnaires will be completed for SF36, HAQ, EQ5D, PSQI and the brief pain inventory (BPI).

• **Participant Diary, AE and medications check:** Data recorded on patient diaries (GP visits, hospital visits, hospital admissions and fractures) will be reviewed and entered onto the study database by research staff.

• **ZA infusion:** Participants allocated to the active treatment group (TPTD/ZA) will undergo an infusion of zoledronic acid 5mg intravenously following completion of TPTD therapy. This may either be performed on the same day at the 24 month visit or depending on logistical issues and patient convenience at a subsequent visit. Whenever possible the ZA infusion should be administered within 4 weeks of finishing TPTD.

• **Urine pregnancy test:** Women of childbearing potential (WOCBP), defined as women who are premenopausal who have not been sterilised and who have not been using a robust form of contraception (4.3.1) will require a negative urine pregnancy test prior to the infusion of ZA (or ZA alternative).

**END OF STUDY VISIT**

The timing of the end of study visit will be dependent on accrual of fractures during the study since this is an event driven trial (section 9). It is expected that the end of study visit will on average, occur after participants have been on the study for 48 months but depending on the rate of fracture accrual it may occur at any time between 36 to 60 months after enrolment into the study.

• **Safety bloods:** A sample of venous blood will be collected and analysed locally by laboratories at participating centres for serum creatinine, calculation of eGFR, serum calcium, albumin and serum total alkaline phosphatase (ALP).

• **Research bloods:** Another sample of up to 10ml will be collected and allowed to clot. Serum will be separated on site and 2 x 1ml aliquots prepared. These will be stored frozen at -70°C or below at the study site and shipped on dry ice to the University of Edinburgh Bone Research Laboratory where they will be stored at -70°C or below until they are used for analysis of biochemical markers of bone turnover. The date and time of taking the blood samples will be noted on the CRF.

• **Clinical examination:** Recording of weight and height.

• **DEXA:** Participants will undergo a bone mineral density scan using dual x-ray absorptiometry of the spine and hip by DEXA according to standard techniques, unless the local investigator feels that DEXA would not be feasible or informative (for example in patients with severe OI and multiple skeletal deformities or those with metalwork in situ that would preclude DEXA). This should be performed, as far as possible, on the same machine used for the baseline and 24 month assessment.

• **Spine x-ray:** Lateral radiographs will be performed of the thoracic and lumbar spine to detect vertebral fractures.
• **HRQCT:** Patients who are attending centres with access to high resolution CT equipment will have the option of having a HRQCT scan of the wrist and tibia.

• **Participant Questionnaire Pack:** Questionnaires will be completed for SF36, HAQ, EQ5D, PSQI and the brief pain inventory (BPI).

• **Participant Diary, AE and medications check:** Data recorded on patient diaries (GP visits, hospital visits, hospital admissions and fractures) will be reviewed and entered onto the study database by research staff.

**ASSESSMENTS FOR FRACTURE**

Participants who think they have experienced a fracture during the trial will be advised to seek medical advice and if clinically indicated undergo x-ray or other imaging as appropriate to confirm or exclude the presence of a fracture. Participants will be advised to contact the local study centre with details of the hospital where the imaging had been performed. Sites are also asked to collect information on fractures including whether it resulted in hospitalisation and in any surgical or medical procedures (i.e. pinning) as per Section 10.1. Relevant x-ray images will be identified and retrieved by members of the study team. The de-identified images will be uploaded onto the study database or images copied onto CD and shipped to the co-ordinating centre for review.

The electronic images will be reviewed on an ongoing basis by an imaging expert based at the co-ordinating centre who is blinded to treatment allocation. The imaging expert will adjudicate if a fracture is present or not and will record within the database the site of the fracture.

Ascertainment of incident vertebral fractures will be achieved by comparing the appearances of spine radiographs at baseline and the end of study an imaging expert blinded to treatment allocation and recorded within the database. The images will be uploaded onto the study database after removing patient identifiable information, as described for the images performed for investigation of suspected clinical fractures.

**TELEPHONE CONTACTS**

Telephone contacts will be made every 6 months during the study (with a window of 14 days either side of the target date) to check if the participant is having any problems with the medication; to check on compliance; to gather information on adverse events and to gather information on fractures.

**OPTIONAL CONTACTS**

To promote retention in the trial participants will be offered the opportunity to sign up to receive regular updates about the progress of the trial and other communications such as Christmas cards and birthday cards.

**8 DATA COLLECTION**

It is anticipated that paper forms will be used for patient diaries and quality of life questionnaires which will be completed at the study visits or by sending the questionnaires to participants in advance. Standard tools will be used including SF36, HAQ, PSQI, EQ5D and the brief pain inventory (BPI). Electronic media may also be used to collect this data if suitable technology becomes available during the study.

The information collected will be transferred on an electronic CRF (eCRF) by research staff at study sites. The eCRF will be developed by data programmers at Edinburgh Clinical Trials
Unit which will be the co-ordinating centre. The eCRF will include range checks to enhance data quality and tools to check for completeness of data. Other essential documents, including source data, consent forms, and regulatory documents, will be archived by or for the Investigator in an appropriate archive facility in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection.

Completeness of data will be assessed during the study and local study centres alerted if there is a need to contact participants who have not completed questionnaires.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION
The proposed sample size is 380 subjects (190 per treatment group).

The sample size has been arrived at based on the following assumptions.
(a) The proportion of patients experiencing a first fracture during each year of the trial will be 16%.
(b) The active treatment will reduce the proportion of patients who experience a first fracture by relative reduction of 25% as compared with standard care.
(c) The primary outcome will be time to first fracture analysed by the log-rank test taking into account baseline characteristics.
(d) The statistical power calculation is based on the cumulative risk difference at the 48 month time point.

Based on analysis of previous clinical trials and observational studies of adult OL patients (5-9) we expect the annual rate of participants experiencing a first fracture to be about 16% in the standard care group. If this assumption is correct and active treatment reduces the proportion of patients who experience a fracture by 25%, this equates to an absolute risk reduction over 4 years of 16% (from 64% to 48%) and a hazard ratio of 0.608.

With these assumptions, a sample size of 176 patients per group would be expected to result in 149 patients with new clinical fractures after an average of 48 months follow up. If the active treatment reduces the proportion of patients that experience a fracture by 25% we would expect that in the standard care group there would be 90 patients with at least one fracture by 48 months as compared with 67 in the TPTD/ZA group.

The sample size will be inflated to 190 per group to account for missing data and the possibility that patients may be lost to follow up, giving a total sample size of 380. This assumes that up to 15% of patients may discontinue the intervention early or be lost to follow up, and that these drop-outs are evenly spread throughout follow-up. With these assumptions we have 85% power in analysis of the primary endpoint.

In the final analysis, statistical power will be further enhanced by stratifying the log-rank test for the prognostic factors being used in the minimisation procedure of the trial randomisation.

9.2 PROPOSED ANALYSES
A detailed statistical analysis plan (SAP) will be developed and finalised prior to the locking of the trial database in consultation with the trial steering committee. Here we outline the main principles to be followed. Throughout, a 5% two-sided significance level will be used. The intention to treat principle will be followed in the primary analysis. A per-protocol analysis will be performed as a sensitivity analysis: the per-protocol population will be identified and agreed by the trial steering committee (TSC) prior to database lock and analysis of the data.

There will be no formal interim analysis for early stopping due to efficacy or futility.

Primary outcome
The primary outcome will be the proportion of participants experiencing a clinical fracture validated by x-ray or other imaging. The main analysis of the primary outcome will summarise time to first fracture by treatment group using Kaplan-Meier survival curves, the groups being compared using the log-rank test stratified by the minimisation variables.

We will review accumulation of fractures during the study and review the situation at 48 months or when 149 patients have suffered a clinical fracture. This will be done by the blinded trial statistician and the DMC will then be asked to make a recommendation to the TSC on continuation (or termination) of the trial.

A secondary analysis will use binary logistic regression, with treatment group (active vs. standard care) and the minimisation variables (fracture in last 2 years, OI clinical subtype, gender, age, BMD group and bisphosphonate use at baseline or in 2 years prior to randomisation) as the independent variables. The effect of randomised treatment will be measured by the odds ratio (and 95% confidence interval) for TPTD/ZA vs. standard care. While every effort will be made to obtain complete follow-up data on all patients, it is recognised that in the OI population some study participants will be lost to follow-up. A sensitivity analysis in which missing data are imputed will be developed according to the principles outlined in (20), namely to develop an understanding for the reasons for loss to follow-up, define the primary set of assumptions about the missing data mechanism on this basis, conduct a statistically valid analysis under these assumptions and explore the robustness of the conclusions in further sensitivity analyses that capture departures from the primary missing data assumptions.

Secondary outcomes
The number of fractures (patient reported and imaging validated) will be analysed using a Poisson regression model, adjusting for the minimisation variables and, if required, including an overdispersion parameter.

Changes in BMD, bone pain, EQ5D, HAQ, SF36, PSQI will be analysed using analysis of covariance (ANCOVA). In each case the model will adjust for the baseline value and the minimisation variables.

Mechanistic Study
The mechanistic objective will be addressed in two stages. First, descriptive statistics of fracture rate will be summarised by treatment group for clinical subtype of OI, baseline BMD, gender and molecular diagnosis. This will be used to inform a subsequent individual patient data meta-analysis combining the data from this trial and the TPTD and standard care groups from the trial led by co-applicant Professor Bente Langdahl which has started recruitment in Scandinavia (EudraCT 2011-002811-27) and by sourcing data from the trial previously reported by Orrill in which TPTD was compared with placebo in patients with OI (9). These analyses will include a fixed effect for trial and will formally test, in a separate model for each baseline variable, for an interaction between the baseline variable and the effect of TPTD (versus standard care) on fracture rate. In further pooled analyses data from the standard care groups in both trials will be combined to estimate the association between each baseline variable and fracture risk in patients receiving standard care.

10 ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SmPC)

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after joining the trial must be reported in detail in the Case Report Form (CRF) or AE form. In the case of an AE,
the Investigator should 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 participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An adverse reaction (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A serious adverse event (SAE), serious adverse reaction (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consisit of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was 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.

^Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be caused by the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SmPC) or Investigators Brochure.

10.2 IDENTIFYING AEs AND SAEs

All AEs and SAEs will be recorded from the time a participant signs the consent form to take part in the study until the final study visit. Participants with adverse events will be followed up until they have resolved.

Participants will be asked 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.

AEs and SAEs may also be identified via information from support departments such as abnormal results occurring as the result of routine laboratory safety testing performed during the study.

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 ASSESSMENT OF AEs AND SAEs

Seriousness, causality, severity and expectedness will be assessed by the Principal Investigator. For randomised double-blind studies, AEs will be assessed as though the participant is taking active IMP. Cases that are considered serious, possibly, probably or definitely related to IMP and unexpected (i.e. SUSARs) will be unblinded.

The Investigator is responsible for assessing each AE but this may be delegated to other members of the study team.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

10.4.1 Assessment of Seriousness

The Investigator will 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.

- **Unrelated**: where an event is not considered to be related to the 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. The assessment of causality will be made against the reference safety information (RSI) found in the representative Summary of Product Characteristics. Investigators may use different brands of the drugs than those listed in the representative SPC but should continue to make assessments of causality against the RSI in the representative SPC.

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. 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 Expectedness

If an event is judged to be an AR, the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SmPC.

The event may be classed as either:

**Expected**: the AR is consistent with known adverse events associated with the IMP listed in the SmPC.

**Unexpected**: the AR is not consistent with known adverse events associated with the IMP as listed in the SmPC.

10.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the CRF or 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.

10.5 REPORTING OF SAEs/SARs/SUSARs

ADVERSE EVENTS THAT DO NOT REQUIRE TO BE REPORTED TO THE SPONSOR (EVEN IF MEETING SERIOUSNESS CRITERIA)

Fractures are an expected occurrence in OI and are the trial endpoint. Incident fractures that occur during the trial will be recorded (using the New Fracture Report) but not reported to the Sponsor. If an incident fracture requires hospitalisation or a medical or surgical procedure (i.e. pinning) then this information should be added to the fracture report and it will not be reported as a Serious Adverse Event.

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office immediately or within 24 hours. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.3, Assessment of Expectedness.

The SAE form will be transmitted by fax to ACCORD on +44 (0)131 242 9447 or may be transmitted by hand to the office or submitted via email to Safety.Accord@ed.ac.uk. Only forms in a pdf format will be accepted by ACCORD via email.

ACCORD will onward report SARs/SUSARs to Eli Lilly within 24 hours of notification via email to UK_Team_Gbmail-GPS@lilly.com

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

10.6 REGULATORY REPORTING REQUIREMENTS

The ACCORD Research Governance & QA Office is responsible for pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

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

ACCORD will inform Investigators at participating sites of all SUSARs and any other arising safety information.

An Annual Safety Report/Development Safety Update Report (DSUR) will be submitted, by ACCORD, to the regulatory authorities and RECs listing all SARs and SUSARs. ACCORD will also submit a copy of the DSUR to Eli Lilly via email to UK_Team_Gbmail-GPS@lilly.com
10.7 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the CRF or AE log or additional information section of SAE form.

11 PREGNANCY

Pregnancy tests will be performed at the baseline visit in women of childbearing potential. Additionally, a pregnancy test will be performed at 24 months prior to the infusion of ZA. Further pregnancy tests may be performed at any time at the discretion of the local investigator if they have reason to believe that a female participant has become pregnant despite taking adequate contraceptive measures.

During the study pregnancy information will be collected for any female participants or female partners of male participants who become pregnant while participating in the study. The Investigator will record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy. Pregnancy will not be considered an AE or SAE. If a woman that is being currently treated with bisphosphonates or TPTD becomes pregnant during the study, these treatments will be stopped for the duration of the pregnancy. No specific action is required with regard to pregnancy in female partners of males that are being treated with TPTD or bisphosphonates during the study.

12 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), A Trial Manager and the trial statistician.

The 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.

12.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The TSC will consist of an independent chair with clinical experience in rheumatology or bone disease, an independent statistician, an independent clinician with experience in rheumatology or bone disease, an independent individual representing the stakeholder group of patients with OI, a patient representative; a representative from the sponsor, the principal investigator and one of the grant holders. The terms of reference and operation of the TSC will conform to the research governance guidelines in operation at the EME.


The names and contact details of the TSC will be detailed in a separate document.
12.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The DMC will consist of an independent chair with clinical experience in rheumatology or bone disease, an independent statistician, and a second independent clinician with experience in rheumatology or bone disease.

The terms of reference operation of the DMC will conform to the research governance guidelines in operation at the EME.


The names and contact details of the DMC will be detailed in a separate document.

12.4 INSPECTION OF RECORDS

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

12.5 RISK ASSESSMENT

An independent risk assessment will be performed by an ACCORD Clinical Trials Monitor to determine if monitoring is required and if so, at what level. An independent risk assessment will also be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and if so, at what locations and at what frequency.

12.6 STUDY MONITORING AND AUDIT

An ACCORD Clinical Trials Monitor or an appointed monitor will visit the Investigator site prior to the start of the study and during the course of the study if required, in accordance with the monitoring plan if required. Risk assessment will determine if audit, by the ACCORD QA group, is required. Details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

13 GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT

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 favorable 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

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.
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.

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 will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

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 will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed outside the hospital.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant’s medical notes.

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 Principle Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site. The source data plan identifies which source data correspond to CRF data and states which data are recorded directly into 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 Research Governance & 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 Research Governance & QA Office will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF), where required, and that appropriate documentation is available in local ISFs.

13.3.5 GCP Training
All study staff must hold evidence of appropriate GCP training.

The exception to this will be radiology staff performing DEXA scanning and HR-pQCT. These personnel will document training on the study-specific scanning protocol, GxP guidance and the scanning database.

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. 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 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 those clinicians treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

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 in the case of a urgent safety measure, 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 anc to Eli Lilly for information prior to participants being enrolled into an amended protocol. Amended protocols and approvals will also be sent to Eli Lilly via email to UK_Team_Gbmail-GPS@lilly.com

14.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. 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.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within three days of becoming aware of the violation.

14.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) must be notified within 24 hours. It is the responsibility of the cc-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

14.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

14.5 END OF STUDY

The end of study is defined as the last participant’s last visit.

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, Regulatory Authority, R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow-up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to researchgovernance@ed.ac.uk.

In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Sponsor (QA@accord.scot) and REC within 1 year of the end of the study. A study report and manuscript (including summary results for the primary and secondary objectives) will be submitted to Eli Lilly within 90 days of completion of the study.

Upon completion of the study, the investigator will upload clinical trial results onto the EudraCT database on behalf of the Sponsor.

The Investigator will submit a short confirmatory email to the MHRA (CT.Submission@mhra.gsi.gov.uk) and HPRA (clinicaltrials@hpра.in) once the result-related information has been uploaded to EudraCT, with ‘End of trial: result-related information: EudraCT 2016-003228-22’ as the subject line. The Sponsor(s) will be copied in this email (QA@accord.scot). It should be noted that an acknowledgment email or letter will not be supplied by the MHRA.

14.6 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Individual sites will assess participants according to standard clinical practice to determine what therapy (if any) should be continued following cessation of the study. The continuation of study therapy following the end of the study rests with the judgement of the treating physician.

14.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors’ responsibilities:

• The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

• Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care.
owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.

- Sites which are part of the United Kingdom’s Nation Health Service will have the benefit of NHS Indemnity.

- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

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 ICH guidelines.

15.2 PUBLICATION

The clinical study report will be used as the basis for publications and presentations of the results of the trial as abstracts scientific meetings. Authorship of abstracts and publications arising from the trial will include the grant holders and investigators at participating sites subject to the individuals fulfilling the criteria for authorship as recommended by the International Committee of Medical Journal Editors. A separate document outlining the publication policy and authorship for publications arising from the study will be prepared and implemented subject to the approval of the TSC.

Summaries of results will also be made available to investigators for dissemination within their clinics where appropriate and according to their discretion and to members of the brittle bone society and general public through the BBS and RUDY websites

15.3 PEER REVIEW

The study concept and design has been reviewed by the EME as part of the funding application process.

Investigators at each site, the Trial Steering Committee, Ethical Review Boards, MHRA, and local R&D departments will review 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.

16 REFERENCES

(2) Cundy T. Recent advances in osteogenesis imperfecta. Calcif Tissue Int ;90:439-49.


(14) Boivin GY, Chavassieux PM, Santora AC, Yates J, Meunier PJ. Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. Bone ;27:687-94.


APPENDIX 1

Contributors to protocol

The study was conceived and designed by Prof Stuart H Ralston and Prof Bente Langdahl. Professor Chris Weir provided statistical expertise and contributed to the study design. Dr Kassim Javaid, Jenny Walsh, Wayne Lam and Ms Patricia Osborne contributed to refinement of the protocol. All investigators reviewed and approved the protocol.

Role of Sponsor and Funders

The sponsors and funders had no role in the design of the study or its execution, analysis, interpretation of the data or decision to submit results for publication.
APPENDIX 2

Standard operating procedures

The study will be performed according to the relevant standard operating procedures in operation published by the ACCORD office.

http://www.accord.scot/research-access/resources-researchers/sop

Note: When study sites are initiated, hard copies of the relevant SOP on serious breaches of GCP (SOP CR003) and on identifying and reporting AEs, SAEs (SOP CR005) and on Deviations and Violations (SOP CR010) will be placed in the investigator site file.