ISRCTN13317811 https://doi.org/10.1186/ISRCTN13317811

Losartan for older adolescents and adults with osteogenesis imperfecta

Submission date	Recruitment status	[X] Prospectively registered
27/01/2023	Recruiting	[X] Protocol
Registration date	Overall study status	[ ] Statistical analysis plan
17/08/2023	Ongoing	[ ] Results
Last Edited	Condition category	[ ] Individual participant data
09/11/2023	Musculoskeletal Diseases	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Osteogenesis imperfecta (OI) is the commonest inherited cause of bone fragility (affecting about 1 in 16,000). People with OI suffer from bone fragility causing fractures, pain and deformity; sarcopenia (loss of muscle mass) causing fatigue and poor endurance; aortic root dilatation and hearing loss. The range of severity is broad with severely affected individuals at risk of early death, e.g. from respiratory failure in infancy, or progressively deforming bone disease that leaves them permanently wheelchair-bound. Even more mildly affected individuals have an increased risk of fracture and suffer from fatigue.
No drug currently has market authorisation to treat OI. The current standard of care is multidisciplinary, with pharmacological interventions – primarily bisphosphonates - directed at increasing bone mass; however, such interventions are of equivocal effectiveness. The structural damage that can accumulate as a result of repeated fractures over time may not be reversible. The lack of a treatment with clearly defined effectiveness in terms of reducing fracture frequency or the sarcopenia that is increasingly recognised in this condition leads to the consideration of alternative treatments. Existing approaches to the treatment of OI focus on increasing bone mass as a means to address the loss of bone mass and the alteration in bone material properties that make the bones brittle. The aim of this study is to find out whether reducing circulating TGFb levels reduces bone turnover and bone loss and has a positive effect on muscle function and quality of life. This is a new approach that has not been studied previously in a clinical setting.

Who can participate?
Patients aged 16 years and above with osteogenesis imperfecta

What does the study involve?
Participants will be randomly allocated to one of three “final doses” (25, 50 or 75 mg) of losartan once daily for 24 weeks. All participants will start on the lowest dose and increase (if allocated to a higher dose) via a dose escalation pathway.

What are the possible benefits and risks of participating?
Losartan is known to cause low blood pressure (hypotension) and raise potassium levels in the blood. The study doses proposed are within the range specified for the treatment of high blood

pressure (hypertension) in adolescents and adults. In subjects without hypertension, doses within this range reduce blood pressure by 3-4 mmHg. Giving the medicine immediately before going to bed at night is likely to reduce the risk of any postural hypotension.
The researchers will be checking blood pressure and potassium levels during the dose escalation period and at several subsequent visits to ensure potassium levels are within acceptable limits and there are no symptoms of hypotension (dizziness). Should there be symptoms of intolerance, the dose will be reduced and the blood pressure and potassium will be rechecked the following week. If there are persistent symptoms or they are already taking the lowest dose they will be withdrawn from the study.
The PIS will make clear the potential risks and how we will mitigate them and the PI will discuss all aspects of the study with patients before consent is obtained. The exclusion criteria list the medications that may interact with or exaggerate the effect of losartan, and these potential participants will be ineligible. Participants allocated to either the 50 or 75 mg doses will need to attend more visits than those on the lowest dose of 25 mg. Visits will be arranged as much as possible to participant convenience to reduce the time and effort required to attend the visits.
Blood samples will be required at most visits and this may result in some discomfort for the participant, but no greater than they would usually experience when having blood tests taken.
The HRpQCTscan needs to be done in Sheffield as this is where the scanner is located. Participants recruited at non-Sheffield sites will travel to Sheffield at two timepoints in the study. The researchers will support their travel, accommodation and food costs (if required) for these visits.
Hypersensitivity to the active substance or to any of the excipients, second and third trimester of pregnancy and severe hepatic impairment are included in the exclusion criteria. Women of childbearing potential should use an effective method of contraception from the point of signing the informed consent throughout the study.

Where is the study run from?
University of Hull (UK)

When is the study starting and how long is it expected to run for?
January 2023 to July 2026

Who is funding the study?
UK Research and Innovation (UKRI) (UK)

Who is the main contact?
1. Prof. Nicholas Bishop, n.j.bishop@sheffield.ac.uk
2. Dr Mahboobeh Haji Sadeghi, mahboobeh.hajisadeghi@hyms.ac.uk

Study website
https://hhtu.hull.ac.uk/moi-a/

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1006449

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
SCH-2677, IRAS 1006449, CPMS 55346

Study information

Scientific Title
Matrix-directed therapy in older adolescents and adults with osteogenesis imperfecta – the MOI-A study

Acronym
MOI-A

Study objectives
The primary clinical objective is to establish the effective dose of losartan in 30 older adolescents and adults aged 16 years and above with OI, based on maximal reduction in the

bone resorption marker carboxy-terminal crosslink of type I collagen telopeptide (CTX). Reducing bone turnover may reduce fracture risk in this population. Measuring or predicting the efficacy of an anti-fracture intervention over short time periods is the subject of continuing debate. Monitoring fracture frequency over short time periods is unlikely to be an effective method unless the incident fracture rate is very high. In addition, anti-fracture medications reduce fracture risk rather than eliminate it, so an incident fracture may not reflect a lack of efficacy.
Proxy markers for the efficacy of interventions designed to increase bone strength and thus reduce fracture risk are used in both industry and investigator-led studies, with the support of regulatory authorities.

The secondary clinical objectives are to determine the changes in proxy efficacy outcomes of bone (mass, architecture and strength) using high-resolution peripheral quantitative CT (HRpQCT) and dual-energy x-ray absorptiometry (DXA) and muscle (strength) using the "Timed Up and Go" test, and determine changes in quality of life using a validated disease-specific tool (OI-QoL).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 11/08/2023, London - London Bridge Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, UK; +44 (0)2071048387, +44 (0)207 104 8140, +44 (0)207 104 8016; londonbridge.rec@hra.nhs.uk), ref: 23/LO/0158

Study design
Open randomized controlled parallel-group trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Osteogenesis imperfecta

Interventions
This is a Phase II/pilot, open-label dose-escalating study. The final dose is randomly assigned. This study aims to identify the "effective" dose for losartan in this population to inform the design of such a pivotal study.

Thirty participants will be randomized at baseline to one of three “final doses” - 25, 50 or 75 mg once daily for 24 weeks. Participants will be randomised sequentially and the responsible statistician will prepare a randomization schedule using the block randomisation with variable block sizes in a 1:1:1 ratio so that 10 participants will be randomized to each final dose arm i.e 10 randomized to the final dose of 25 mg, 10 participants to 50 mg and 10 participants to 75 mg. Randomization will be completed via the REDCap Cloud (RCC) online system provided by the HHTU. After randomisation on Day 1 all participants will start on the lowest dose and increase (if randomised to a higher dose) via a dose escalation pathway as described below.

Day 1 – Day 7
All participants will receive 25 mg of losartan on Day 1.
On Day 7, a safety assessment check will be conducted on all participants. If either the potassium level is greater than the upper limit of normal (ULN) and/or there are symptoms of persistent hypotension, the participant will be withdrawn from the study and will complete the early withdrawal visit.
If both safety assessments are within acceptable limits and the participant was randomised to either the 50 mg or 75 mg groups, the losartan dose will be increased to 50 mg on Day 8.

Day 14 – Day 21
On Day 14, a safety assessment check will be conducted on participants taking 50 mg. If both safety checks are within acceptable limits, the participant will either remain on 50 mg (if randomised to that group on Day 1), or increase to 75 mg (if randomised to that group on Day 1) on Day 15.
However, if either the potassium level is greater than ULN and/or there are symptoms of persistent hypotension, the dose will be reduced to 25 mg. A safety assessment (for those who reduced their dose from 50 mg to 25 mg) will be repeated on Day 21. If the safety assessment checks are within acceptable limits they will remain on 25 mg for the remainder of the study (Week 24), regardless of their original randomisation group on Day 1.
However, if either potassium level is greater than the ULN and/or there are symptoms of persistent hypotension, the participant will be withdrawn from the study and will compete the early withdrawal visit. They will be referred for further management of their raised serum potassium or persistent hypotension.
On Day 21, a safety assessment check will be conducted on participants taking 75 mg. If both safety assessment checks are within acceptable limits, the participant will remain on 75 mg for the remainder of the study (week 24).
However, if either the potassium level is greater than ULN and/or the participant is experiencing persistent signs of hypotension, the dose will be reduced to 50 mg. Safety checks (for those who have reduced their dose from 75 mg to 50 mg) will be repeated on Day 28.

Day 28 – Day 35
The researchers will re-evaluate tolerance specifically and all participants will have a safety assessment on Day 28.
Participants taking 75 mg at Day 28: If the safety assessment is acceptable, the participant will continue on 75 mg to the end of the study (week 24). If the potassium level is greater than ULN and/or the participant is experiencing persistent signs of hypotension, the dose will be reduced to 50 mg. Safety assessments will be conducted the following week to check if 50 mg of losartan potassium and hypotension symptoms are within acceptable limits. If acceptable, the participants will continue on 50 mg to the end of the study (week 24). However, if safety assessments are unacceptable, the participant may be further reduced to 25 mg followed by a safety assessment check one week later. If safety assessments remain unacceptable, the participant will be withdrawn from the study and referred for further management to either

their GP or their normal clinical support team.
Participants taking 50 mg at Day 28: If the safety assessment is acceptable, the participant will continue on 50 mg to the end of the study (week 24) regardless of their original randomisation group on Day 1. However, if safety assessments are unacceptable, the participant will be further reduced to 25 mg followed by a safety assessment check 1 week later. If safety assessments remain unacceptable, the participant will be withdrawn from the study and referred for further management to either their GP or their normal clinical support team.
Participants taking 25 mg at Day 28: If the safety assessment is acceptable, the participant will continue on 25 mg to the end of the study (week 24) regardless of their original randomisation group on Day 1. However, participants who have persistently elevated potassium or hypotension despite a dose reduction to 25 mg will be withdrawn from the study and referred for further management to either their GP or their normal clinical support team.

Day 56
The researchers will re-evaluate tolerance specifically and all participants will have a safety assessment on Day 56.
Based on existing evidence for the general use of losartan, if serum potassium has not risen within a week of either starting or escalating the dose it is unlikely to do so. However, if at any stage there are problems with symptoms likely to be attributable to losartan, the patient is reviewed in their local centre and if necessary the dose is reduced to a lower dose and the patient is reassessed after 1 week - and if they are on 25 mg that they are withdrawn at that stage.

Day 112 & Day 168
There will be further blood tests on Day 112 and at the end of the study on day 168. The final visit on Day 168 will be in Sheffield so that the specialised scans can be repeated.

Day 84 - Day 140
These visits are simply to check physical well-being so no blood tests are done. Will be either at home, or in the local centre.

Early withdrawal visit
Participants who decide to leave the study or who are withdrawn will be asked to attend an unscheduled early withdrawal visit to assess patient safety and collect surplus drug supplies. Scheduled 1 to 3 days after the last dose (ALD). If a participant decided to withdraw in or after week 12 would be optional to do HRpQCT scan radius and tibia, DXA LS and Hip and a “timed up and go” test. For earlier withdrawal don’t need to repeat these tests.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Losartan potassium

Primary outcome measure
Percentage change in CTX over the 24-week period of the study, measured by a fasting blood test on Day 1 and Weeks 1, 4, 8, and 24

Secondary outcome measures
1. Percentage change in TGFβ, measured by a fasting blood test on Day 1, Weeks 1, 4, 8, 24 and early withdrawal visit
2. Change in dual x-ray absorptiometry (DXA) lumbar spine and hip measured by DXA lumbar spine areal bone mineral density (LSaBMD) scans on Day 1, Week 24 and early withdrawal visit (after week 12)
3. Change in radial and tibial total vBMD measured by HRpQCT at Day 1, Week 24 and early withdrawal visit (after week 12)
4. Change in Timed Up and Go test measured by a "Timed up and go" test on Day 1, Week 8, 24 and early withdrawal visits
5. Change in osteogenesis imperfecta (OI) QoL measured by a OI quality of life questionnaire at Day 1, Week 8, 16, 24 and early withdrawal visits

Overall study start date
24/01/2023

Completion date
31/07/2026

Eligibility

Key inclusion criteria
1. Age 16 years and above
2. Diagnosed with osteogenesis imperfecta (any type)
3. Prior treatment with up to and including 6 weeks of oral bisphosphonate therapy is allowed provided there has been a 6-month washout period since the last dose of treatment
4. Prior treatment with a single dose of an intravenous bisphosphonate is allowed provided there has been a 6-month washout period since the treatment was given
5. Prior treatment with a single dose of denosumab is allowed provided there has been a 6-month washout period since the treatment was given
6. A woman of childbearing potential (WOCBP) who agrees to use an effective method of contraception from point of signing the informed consent throughout the study
7. Agreed not to participate in another interventional research project during their involvement in this study
8. Not taking prohibited concomitant medications, listed in exclusion criteria
9. Any other contraindication that makes the patient unsuitable to take part in the study in the opinion of the investigator

Participant type(s)
Patient

Age group
Mixed

Lower age limit
16 Years

Sex
Both

Target number of participants
30

Key exclusion criteria
1. Current use of losartan
2. Prior use of losartan within the preceding 6 months to enrolment
3. Presence of other chronic illnesses including renal failure likely to affect bone metabolism or structure
4. Known severe hypotension resulting in dizziness, fainting or headaches
5. Hyperkalaemia
6. Current medication that increases potassium retention, or may increase potassium levels, such as potassium-retaining diuretics
7. Current medication with lithium
8. Current medication with other substances which may induce hypotension
9. Currently taking oral bisphosphonates or intravenous bisphosphonates
10. Prior treatment with more than 6 weeks oral bisphosphonates treatment
11. Prior treatment with more than a single dose of intravenous bisphosphonate
12. Prior treatment with more than one dose of denosumab
13. Recent (last 12 months) or current treatment likely to affect bone – this does not include inhaled or intermittent oral therapy with steroids for asthma (no more than 3 months of oral steroids in previous 12 months)
14. Severe hepatic impairment
15. Renal impairment (glomerular filtration rate [GFR] <60 ml/min/m^2) if treated with aliskiren-containing products
16. Diabetes mellitus if treated with aliskiren-containing products
17. Cardiac failure treated with diuretics
18. Pregnancy or lactation
19. Known hypersensitivity to losartan or any of the excipients

Date of first enrolment
01/11/2023

Date of final enrolment
31/10/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Sheffield Children's Hospital
Western Bank
Sheffield
United Kingdom
S10 2TH

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

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

Sponsor information

Organisation
Sheffield Children's NHS Foundation Trust

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Sponsor type
University/education

Website
http://www2.hull.ac.uk/

ROR
https://ror.org/02md8hv62

Funder(s)

Funder type

Government

Funder Name
UK Research and Innovation

Alternative Name(s)
UKRI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on website

All data will be completely anonymised for purposes of analysis and any subsequent reports or publications. Data analysis will be undertaken with University of Hull.

Public and patient involvement
The study OI PPI Group informed this study and support the value to patients of quantifying the net effects (benefits and side-effects) of losartan in OI. The PPI group felt that the intervention and assessments were acceptable. The researchers are committed to active patient involvement at all stages of the study to ensure the research is grounded and relevant to the experiences of patients, family members and the wider public. A study team PPI lead will coordinate and facilitate PPIs activity as PPI members will provide feedback as Trial Management Group and Trial Steering Committee members. As members of the Trial Management Group, patients will be involved in all practical and strategic decisions about study conduct and management. PPI members will also be involved in the interpretation of analysed findings and dissemination. They will be mentored and supported by the PPI facilitator and OI PPI group throughout the study.

Intention to publish date
31/07/2027

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication

IPD sharing plan summary

Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 2.0	08/08/2023	09/11/2023	No	No