ISRCTN32813419 https://doi.org/10.1186/ISRCTN32813419

STAG: effect of the drug AZD4017 on bone density in post-menopausal women

Submission date
20/05/2015

Recruitment status
No longer recruiting

Registration date
20/05/2015

Overall study status
Completed

Last Edited
07/12/2022

Condition category
Musculoskeletal Diseases

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

Plain English summary of protocol

Background and study aims
As people age, their bones naturally become less dense in minerals, but for some people this can lead to osteoporosis, an advanced stage of a condition that leads to brittle bones that break (fracture) easily. It is often seen in women who have been through the menopause, or people who are at risk of osteoporosis due to various health or lifestyle factors. In older people, osteoporosis is often diagnosed following a minor fall which has led to a bone fracture. The bones most often fractured are those of the hips and spine, and these injuries cause problems for millions of people around the world (9 million every year) as a result of pain, hospital admissions, lack of independence at home or the need to move into sheltered/nursing home care. There are some similarities between the bones of older people and the bones of people taking steroid medications. This is because steroids reduce bone mineral density. A new drug called AZD4017 has been developed to reduce the level of steroids that are naturally produced by the body in local tissues; it may help to reduce the loss of bone mineral density that occurs as people age. The aim of this study is to look at the effect of AZD4017 on bones in women diagnosed with osteopaenia, a condition where some bone density has been lost but it has not yet progressed to the stage of osteoporosis.

Who can participate?
Women aged 50 and over diagnosed with osteopaenia

What does the study involve?
Participants are randomly allocated into one of two groups. Those in group 1 (intervention group) are given the drug AZD4017 to take for 90 days. Those in group 2 (control group) are given a placebo (dummy tablet with no drug in it) to take for 90 days. Participants have 5 visits to the clinic while taking the drug, and another 3 months later. Participants have blood tests and scans to check the effect of AZD4017 on bones, and urine tests to make sure that steroid production in the tissues is reduced in response to the drug. Participants also have muscle tests (walk, stand and grip tests) to see if blocking steroid production improves muscle strength.

What are the possible benefits and risks of participating?
AZD4017 has the potential to be developed into an effective treatment for patients with osteoporosis and high fracture risk. The participants involved in this study are not at high risk of fracture, and as such, are unlikely to gain any direct benefits.

Where is the study run from?
1. Northern General Hospital (UK)
2. Chapel Allerton Hospital (UK)

When is the study starting and how long is it expected to run for?
May 2015 to December 2017

Who is funding the study?
Medical Research Council (MRC) (UK)

Who is the main contact?
Dr L Flanagan

Contact information

Type(s)
Scientific

Contact name
Dr Louise Flanagan

Contact details
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds
Leeds
United Kingdom
LS2 9JT

Additional identifiers

Clinical Trials Information System (CTIS)
2013-003387-32

Protocol serial number
15665

Study information

Scientific Title
Phase II study of the impact of AZD4017, a selective 11bHSD1 inhibitor, on biochemical markers of bone turnover in post-menopausal osteopaenia

Study objectives

The drug AZD4017, which reduces steroid production in tissue, may reverse some of the bone changes that are seen with aging and improve muscle strength.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Multicentre Research Ethics Committee (MREC), 11/11/2013, ref: 13/SC/0523

Study design
Randomised interventional treatment study

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
Participants will take AZD4017, a selective 11ß-HSD1 inhibitor, for 90 days. Control group participants will take a placebo (dummy tablet with no drug in it) for 90 days.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
AZD4017

Primary outcome(s)
Change from baseline in serum osteocalcin after 90 days.

Key secondary outcome(s))
1. Change from baseline in serum ßCTx after 90 days
2. Change in bone density, microstructure and strength after 180 days
3. Change in bone remodelling after 90 days
4. Change in muscle strength after 90 days

Completion date
30/04/2016

Eligibility

Key inclusion criteria

Current inclusion criteria as of 21/06/2017:
1. Provision of informed consent prior to any study specific procedures
2. Aged >50 and post-menopausal based on amenorrhoea for >12 months
3. Documented presence of osteopenia (BMD T-score at lumbar spine and/or total hip of less than or equal to -1 and greater than -2.5) as measured by DXA
4. Placebo treatment for the duration of the study must not be considered detrimental to the study participant
5. Must be able to understand the patient information sheet and consent form and comply with study requirements

Previous inclusion criteria:
1. Provision of informed consent prior to any study specific procedures
2. Aged >50 and postmenopausal based on amenorrhoea for >12 months
3. Documented presence of osteopaenia (bone density T-score at lumbar spine or hip of less than -1 and greater than -2.5 by Dual-energy X-ray Absorptiometry (DXA) criteria)
4. Placebo treatment for the duration of the study must not be considered detrimental to the study subject
5. Must be able to understand the patient information sheet and consent form and comply with study requirements

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
Female

Total final enrolment
55

Key exclusion criteria
Current exclusion criteria as of 21/06/2017:
Bone-related exclusion criteria:
1. Clinical or biochemical evidence of secondary causes of bone loss (screening tests to include but are not restricted to: normal serum sodium, potassium, urea, creatinine (eGFR at >60 mls /min), LFTs, ALP, TFTs; free T4 and TSH), FBC and ESR (<40mm/hr))
2. Vitamin D deficiency (defined as a 25-OH vitamin D level of <20nmol/L)
3. The current or recent use (within the last 2 years) of medication likely to have an impact on bone (oestrogens, aromatase inhibitors, bisphosphonates, fluoride, denosumab, strontium ranelate, anti-convulsants; and oral, inhaled or nasal glucocorticoids). Participants already on calcium/vitamin D supplementation will be asked to continue this for the duration of the study. Those with a 25-OH vitamin D level of 20-50nmol/L at screening will be supplemented prior to inclusion. Medications will be reviewed at the screening visit
4. Bilateral fractures of the radius and/or tibia

General exclusion criteria:
1. Women of child-bearing potential (WOCBP). Note: WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea≥ 12 consecutive months or women on hormone replacement therapy with documented serum follicle stimulating hormone level >35 mIU/mL)
2. Have an estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease (GFR calculation) using theMDRD equation of <60ml/min/1.73m2
3. Have any endocrine disorder that would merit therapy according to national guidelines. The only exception to this is patients with hypothyroidism on treatment with thyroid function tests within normal parameters for a minimum of 3 months
4. Suspicion of, or known Gilbert's disease
5. CK >2 x ULN on 2 consecutive measurements
6. ALT and/or AST > 1.5*ULN
7. ALP > ULN
8. Bilirubin (total) > 1.5*ULN
9. Participant is, at the time of signing the informed consent, a user of recreational or illicit drugs (including marijuana) or has had a recent history (within the last year) of drug or alcohol abuse or dependence, on questioning or clinical history
10. Have uncontrolled systemic hypertension (BP >150/90) on 3 successive measurements on the morning of the screening visit. Note: Participants with controlled hypertension (BP of 150 /90 or better on same treatment for 3 months) may be included, and should continue on the same anti hypertensive medication for the duration of the study. Thus, if hypertension is identified at screening and the hypertension is then treated and remains controlled for 3 months, then the patient may enter screening again
11. Are receiving systemic (including vaginal/rectal) or inhaled glucocorticoid treatment at the time of the screening visit. Note: Topical (skin) application of mild, over-the-counter topical steroid containing medication to small localised areas of the skin is permitted
12. Are taking probenecid at the time of the screening visit
13. Have any screening laboratory abnormality which is outside the local reference ranges specified in the Investigator Site File that, in the investigator’s judgement, is considered to be clinically significant
14. History of any clinically significant disease or disorder which, in the opinion of the investigator, may either put the participant at risk because of participation in the study, or influence the results of the participant’s ability to participate in the study. Specifically, a diagnosis of any inflammatory disorder that might reasonably need treatment with glucocorticoids during the course of the study, should be considered for exclusion
15. History or presence of any significant gastrointestinal, hepatic, or renal disease or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs
16. Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks of the first administration of IMP as judged by the investigator
17. Have known hypersensitivity or intolerance to 11β-HSD1 antagonists or to AZD4017
18. Have been involved in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
19. Have participated in any other clinical study within 1 month prior to the screening visit
20. Previous randomisation for treatment in the present study

Previous exclusion criteria:
Bone-related exclusion criteria:
1. Clinical or biochemical evidence of secondary causes of bone loss
2. 25-OH vitamin D level <20nmol/L
3. The current or recent use (within 2 years) of medication likely to have an impact on bone

(oestrogens, aromatase inhibitors, bisphosphonates, fluoride, denosumab, strontium ranelate, anti-convulsants, teriparatide; and oral, inhaled or nasal glucocorticoids). Patients already on calcium/vitamin D supplementation will continue this for the study. Those with a 25-OH vitamin D level of 2050nmol/L at screening will be supplemented prior to inclusion

General exclusion criteria:
1. Women of child-bearing potential
2. eGFR calculated by MDRD equation <60ml/min/1.73m2
3. Any endocrine disorder, e.g. thyroid dysfunction
4. Suspicion of or known Gilbert's disease
5. CK > twice upper limit normal on 2 consecutive measurements
6. Liver transaminases > upper limit normal
7. Alkaline phosphatase > upper limit normal
8. Bilirubin (total) > upper limit normal
9. User of recreational or illicit drugs (including marijuana) or has had a recent history (within the last year) of drug or alcohol abuse or dependence
10. Uncontrolled systemic hypertension (BP >150/90); on 3 successive measurements on the morning of the screening visit
11. Systemic (including vaginal/rectal) or inhaled glucocorticoid treatment at the time of the screening visit
12. Probenicid therapy at the time of the screening visit
13. Any screening laboratory abnormality that, in the investigator’s judgement, is considered to be clinically significant
14. History of any clinically significant disease or disorder which, in the opinion of the investigator, may either put the subject at risk because of participation in the study, or influence the results of the subject’s ability to participate in the study. Specifically, a diagnosis of any inflammatory disorder that might reasonably need treatment with glucocorticoids during the course of the study
15. History of any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs
16. Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks of the first administration of
IP as judged by the investigator
17. Hypersensitivity or intolerance to 11ß-HSD1 antagonists or to AZD4017
18. Involvement in the planning and/or conduct of the study
19. Participation in any other clinical study within 1 month prior to the screening visit
20. Previous randomisation for treatment in the present study

Date of first enrolment
29/05/2015

Date of final enrolment
01/12/2017

Locations

Countries of recruitment
United Kingdom

England

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

Study participating centre
Chapel Allerton Hospital
Chapeltown Road
Leeds
United Kingdom
LS7 4SA

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study will be available upon request from ctru-stag@leeds.ac.uk dependent upon the planned usage, any trial contractual obligations, and the participant consent given.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		16/06/2022	07/12/2022	Yes	No
Abstract results		21/08/2020	23/04/2021	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes