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Febuxostat versus allopurinol streamlined trial

Submission date
19/04/2011

Recruitment status
No longer recruiting

Registration date
28/06/2011

Overall study status
Completed

Last Edited
25/11/2020

Condition category
Musculoskeletal Diseases

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Gout is a condition in which small crystals of uric acid form inside and around the joints, causing pain and swelling. The aim of this study is to compare the safety of febuxostat and allopurinol – two drugs commonly used for gout - when taken for an average of 3 years. It will also evaluate other cardiovascular (heart) side effects of both treatments.

Who can participate?
Patients aged 60 or older who are currently taking allopurinol for gout (and other conditions involving uric acid deposition)

What does the study involve?
Participants have their blood uric acid levels measured. Participants are then randomly allocated to take either febuxostat or allopurinol, and are followed up every two months. An annual blood sample is taken for measuring patients' uric acid levels and for liver function tests. The study ends after participants have been followed up for an average of at least 3 years and once at least 456 events (heart attacks, strokes or deaths) have been recorded.

What are the possible benefits and risks of participating?
The study will improve our knowledge on the safety and effectiveness of allopurinol and febuxostat in patients with gout and will help to guide doctors to prescribe the most effective and safe medicine for their patients in the future. Participants will have their treatment reviewed and optimised if necessary to achieve good control of their uric acid levels and will have additional blood tests during the study. However, it is possible that participants may experience side effects due to the study treatments and this may include acute attacks of gout especially during the first few months if their gout treatment is changed or doses are increased.

Where is the study run from?
Trial centres are currently located in Scotland, England, Denmark and Sweden

When is the study starting and how long is it expected to run for?
September 2011 to December 2017

Who is funding the study?
Menarini Pharmaceutical (UK)

Who is the main contact?
Prof. Thomas M MacDonald
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Contact information

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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2011-001883-23

Protocol serial number
FAST V20.0 (29/06/2018) (NB original approved version V11.0)

Study information

Scientific Title
Febuxostat versus Allopurinol Streamlined Trial (FAST): a prospective, randomised, parallel group, open label, blinded endpoint study

Acronym
FAST

Study objectives
OA prospective, randomised, open-label, blinded endpoint (PROBE) clinical trial evaluating the long-term cardiovascular safety of febuxostat in comparison with allopurinol in patients with chronic symptomatic hyperuricaemia.
1. Compare the cardiovascular (CV) safety profile (in terms of Anti Platelet Trialists Collaboration [APTC] events) of febuxostat versus allopurinol when taken for an average of 3 years in patients aged 60 years or older with chronic hyperuricaemia in conditions where urate deposition has already occurred
2. Evaluate other cardiovascular adverse events for both products

Ethics approval required
Old ethics approval format

Ethics approval(s)
Scotland A Research Ethics Committee, 03/08/2011, ref: DD-08-11

Study design
Prospective randomised parallel-group open-label blinded endpoint study

Primary study design
Interventional

Study type(s)

Treatment

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

Interventions
1. All consented and screened patients potentially eligible for the study will receive allopurinol treatment prior to randomisation (allopurinol lead-in phase) according to the European League Against Rheumatism (EULAR) recommendations and the current summary of product characteristics (SmPC)
2. All patients will have their serum uric acid (sUA) levels determined
3. If the patient is below the target sUA level of 6 mg/dL, no dose escalation is required
4. Patients with a sUA level of more than or equal to 6 mg/dL will have their allopurinol dose optimised according to clinical judgement, EULAR recommendations and the current SmPC
5. This process will continue until the physician considers that the optimal allopurinol dose level has been reached for each patient, by achieving either a sUA level of < 6 mg/dL, or reaching either the maximum tolerate dose (MTD) or the maximum licensed dose (MLD) with due regard to the patients renal function
6. At the end of the allopurinol lead-in phase, patients with a sUA level of < 6 mg/dL or receiving the MTD/MLD of allopurinol will be randomised in a 1:1 ratio to receive either febuxostat or allopurinol treatment
7. Randomisation will be stratified according to whether or not the patients had a history of the following cardiovascular events: myocardial infarction (MI), stroke or previous hospitalisation due to congestive heart failure (CHF) or peripheral vascular disease (PVD)
8. After randomisation all patients will undergo a washout period of one week (window 7 to 21 days) prior to initiation of study treatment. During the washout period, they must not receive urate lowering therapy (ULT)
9. Patients who require allopurinol dose titration should continue to receive gout flare prophylaxis during the washout period. Gout flare prophylaxis will not be given during the washout period to patients who do not require allopurinol dose titration
10. All patients randomised to allopurinol will receive allopurinol treatment at the dose determined before randomisation
11. During the course of the study, the dose can be adjusted according to clinical judgement as determined by EULAR recommendations and the current SmPC
12. All patients randomised to febuxostat will initially receive febuxostat 80 mg daily
13. Patients will have their sUA level determined after 2 weeks of febuxostat treatment (9 to 24 days), and patients with a sUA level of =6 mg/dL will have their febuxostat dose increased to 120 mg daily, followed by the determination of their sUA level 2 weeks later
14. Patients will then continue to receive treatment according to clinical judgement, EULAR recommendations and the current SmPC.
15. Patients should receive prophylaxis for gout flare for 6 months from the start of the allopurinol lead-in phase, or for 6 months after starting randomised medication as appropriate, and for 6 months following any subsequent adjustment in ULT
16. Prescription of treatment medication for gout flares (preventive or curative) will be in accordance with EULAR recommendations and the current SmPC
17. Four gout flare prophylaxis regimens will be available to the trial investigator or designee:
17.1. Colchicine 0.5 mg once or twice daily
17.2. Naproxen 250 mg or 500 mg twice daily in conjunction with omeprazole 20 mg once daily or ranitidine 300 mg twice daily
17.3. Diclofenac 50 mg twice or three times daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily

17.4. Meloxicam 7.5 mg or 15 mg once daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily
18. Patients will be followed up for an average of 3 years from randomisation
19. Follow-up will be scheduled at two monthly intervals by phone, letter or visit to the patient by the study nurses or medical staff
20. The follow-up of outcomes will be done by record-linkage to hospitalisations and deaths and by direct reporting by study site coordinators
21. Each patient's sUA will be monitored at a central laboratory 1, 2 and 3 years (±1 month) after randomisation and/or as close as possible to the time of drop-out for patients who are withdrawn from the study
22. Additional laboratory assessments including sUA measurements may be undertaken at the discretion of the primary care physicians as part of the standard clinical care, EULAR recommendations and according to the current SmPC
23. The trial will be powered to demonstrate that febuxostat is not inferior to standard allopurinol therapy for the Anti-Platelet Trialists Collaboration (APTC) cardiovascular composite endpoint
24. The study will terminate after patients have been followed up for an average of at least 3 years and until at least 456 APTC events have been identified in the per-protocol (PP) population

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Febuxostat, allopurinol

Primary outcome(s)
The primary analysis will be the time from randomisation to first occurrence of any event included in the APTC composite endpoint of:
1. Hospitalisation for non-fatal MI
2. Hospitalisation for non-fatal stroke
3. Death due to a cardiovascular event

Key secondary outcome(s))
The following secondary endpoints (in rank order of importance) will be evaluated using a time to event analysis:
1. Hospitalisation for non-fatal MI
2. Hospitalisation for non-fatal stroke
3. Cardiovascular death
4. All cause mortality
5. Hospitalisation for heart failure
6. Hospitalisation for unstable, new or worsening angina
7. Hospitalisation for coronary revascularisation
8. Hospitalisation for cerebral revascularisation
9. Hospitalisation for transient ischeamic attack (TIA)
10. Hospitalisation for non-fatal cardiac arrest
11. Hospitalisation for venous and peripheral arterial vascular thrombotic event
12. Hospitalisation for arrhythmia with no evidence of ischaemia

Completion date
31/12/2019

Eligibility

Key inclusion criteria
1. Male or female patients aged 60 years or older with at least one additional cardiovascular risk factor:
1.1. Age =70 years (male) or =75 years (female)
1.2. Smoking (current or within the last 2 years)
1.3. Diabetes mellitus
1.4. Impaired glucose tolerance
1.5. Hypertension (systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg) or receiving treatment to lower blood pressure
1.6. Dyslipidaemia (investigator assessment)
1.7. Chronic kidney disease (CKD) Stage 1-3
1.8. Microalbuminuria or proteinuria
1.9 Family history of coronary heart disease or stroke in first degree relative at age < 55 years
1.10. Inflammatory arthritis (investigator assessment including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis)
1.11. Chronic non-steroidal anti-inflammatory drugs (NSAID) therapy (investigator assessment)
1.12. Previous cardiovascular (CV) event [myocardial infarction (MI), cerebrovascular accident (CVA) or transient ischaemic attack (TIA)]
1.13. Peripheral vascular disease (investigator/clinical assessment)
1.14. Chronic obstructive pulmonary disease (COPD)
1.15. Body mass index > 30 kg/m2
2. Patients who, in the opinion of the recruiting physician, require treatment for chronic hyperuricaemia where urate deposition has already occurred (including a history or presence of tophus and/or gouty arthritis) fulfilling the recommendation for treatment with urate lowering therapy
3. Patients who have received more than or equal to 60 days treatment with allopurinol, or more than or equal to two allopurinol prescriptions, within the previous 6 months
4. Patients, who in the opinion of the recruiting physician or study site coordinator, are eligible for treatment (with reference to the summary of product characteristics) with either allopurinol or febuxostat
5. Patients who are willing to give permission for their paper and electronic medical records, hospitalisation data, prescribing data, and (in the event of their death) their death certification data to be accessed and abstracted by trial investigators
6. Patients who are willing to be contacted and interviewed by trial investigators or delegates (suitably trained research nurses), should the need arise (e.g., for adverse event [AE] assessment and to determine whether an episode of acute gout has occurred)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
6128

Key exclusion criteria
1. Patients who have any contraindication to febuxostat or allopurinol (with reference to the summary of product characteristics) or any of the components of their formulations
2. Patients receiving urate lowering therapy (ULT) other than allopurinol
3. Patients with severe renal impairment [estimated glomerular filtration rate (eGFR) < 30 mL /min as defined by the Cockroft-Gault formula (http://www.nephron.com/cgi-bin/CGSI.cgi) according to creatinine, age, sex and body weight]
4. Patients with moderate or severe hepatic impairment i.e. cirrhosis with clinical and/or biological decompensation (i.e. alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x reference value, ascites, lower limb oedema, icterus or increased prothrombin time > 2x reference value).
5. Patients with a life-threatening co-morbidity or with a significant medical condition and/or conditions that would interfere with the treatment, safety or compliance with the protocol
6. Patients with a diagnosis of, or receiving treatment for malignancy (excluding minor skin cancer) in the previous 5 years
7. Patients who have experienced either a myocardial infarction or stroke within the 6 months prior to the screening visit
8. Patients with congestive heart failure, New York Heart Association (NYHA) Class III or IV
9. Patients whose behaviour or lifestyle would render them less likely to comply with study medication (i.e., abuse of alcohol, substance misuse, debilitating psychiatric conditions or inability to provide informed consent)
10. Patients with a current acute gout flare or who are within 14 days of the resolution of a gout flare
11. Patients currently participating in another clinical trial or who have participated in a clinical trial in the previous 3 months

Date of first enrolment
20/12/2011

Date of final enrolment
31/07/2017

Locations

Countries of recruitment
United Kingdom

Scotland

Denmark

Sweden

Study participating centre
University of Dundee
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Sponsor information

Organisation
University of Dundee (UK)

ROR
https://ror.org/03h2bxq36

Funder(s)

Funder type
Industry

Funder Name
Menarini Pharmaceutical (UK)

Results and Publications

Individual participant data (IPD) sharing plan
When participants consented to take part in FAST they agreed that their data could be used within the study, but that their data would not be made available outside of this. As such the researchers are not publishing any data at this level. The complete dataset is owned by the Sponsor, University of Dundee. It will also be archived according to the University's SOP. A copy of the data will also be retained by the Robertson Centre for Biostatistics, University of Dundee who were the data managers for the study.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	substudy results	30/01/2019	01/02/2019	Yes	No
Results article	results	28/11/2020	13/11/2020	Yes	No
Protocol article	protocol	10/07/2014		Yes	No

Study website	Study website	11/11/2025	11/11/2025	No	Yes