The Effect of Intensive Urate Lowering Therapy (ULT) with Febuxostat in Comparison with Allopurinol on Cardiovascular Risk in Patients with Gout Using Surrogate Markers: a Randomized, Controlled Trial.

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The primary study objective is to determine whether Febuxostat daily 80-120 mg is better than Allopurinol daily 100-600 mg in inducing positive changes in Pulse Wave Velocity (PWV) after 36 weeks of treatment.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON43921

Source
ToetsingOnline

Brief title
The FORWARD Trial

Condition

- Cardiac disorders, signs and symptoms NEC
- Joint disorders

Synonym
Gout, Hyperuricaemia

Research involving
Human

Sponsors and support

Primary sponsor: Menarini International Operations Luxembourg S.A.
Source(s) of monetary or material Support: pharmaceutical company

Intervention

Keyword: Arterial stiffness, Cardiovascular risks, Gout, Urate Lowering Therapy

Outcome measures

Primary outcome

To evaluate the effects of febuxostat and allopurinol on Pulse Wave Velocity

(PWV) after 36 weeks of treatment.

Secondary outcome

Secondary endpoints include:

1) Changes in BNP and NTproBNP values after 12, 24 and 36 weeks of treatment;

2) Changes in inflammation markers (hsCRP, TNF-*, sUA, and plasma fibrinogen)

after 12, 24 and 36 weeks of treatment;

3) Changes in oxidative stress parameters [Malondialdehyde (MDA),

Myeloperoxidase (MPO) Oxidized low-density lipoprotein (Ox-LDL), Paraoxonase 1

and 2 (PON1, PON2)] after 12, 24 and 36 weeks of treatment;

4) Changes in lipid profile after 12, 24 and 36 weeks of treatment;

5) Percentage of gout patients with a serum urate concentration of less than, or equal to 6 mg/dl after 12, 24 and 36 weeks of treatment.

6) Time to achieve sUA target levels for patients stratified for sUA levels at baseline as follows:, 8.1-8.8 mg/dl, 8.9-9.6 mg/dl, 9.7-10.3 mg/dl, 10.4-11.0 mg/dl, >11 mg/dl;

7) Changes in eGFR with CKD-EPI formula after 12, 24 and 36 weeks of treatment;

8) Changes in urine albumin excretion as evaluated by first morning urine albumin/creatinine ratio (mg/g) after 12, 24 and 36 weeks of treatment;

9) Percentage of patients above the sUA target levels at Week 12, Week 24 and week 36 after having reached the sUA target levels at Week 2;

10) Tender and swollen joint count;

11) Pulse Wave Analysis (including modifications of PWV, arterial stiffness, central blood pressure and augmentation index) after , 12, 24 and 36 weeks of treatment ;

12) Changes in endothelial activation/adhesion markers (sVCAM, sICAM, vWF, e-selectine) after 12, 24 and 36 weeks of treatment (These parameters will be evaluated in a subset of patients enrolled in selected centres only)

13) Safety and tolerability will be assessed by the following parameters

evaluated at Screening and at week 2 , 12 , 24 and 36:

* Overall incidence of adverse events (AEs).

* Evidence from physical examination

* Vital signs (systolic/diastolic blood pressure, pulse, body weight, axillary

body temperature).

* Laboratory parameters (blood chemistry, haematology and urinalysis)

Study description

Background summary

Gout is the condition in which an excess of uric acid (hyperuricemia) in the blood leads to the formation of urate crystals in various tissues of the body. These crystals can precipitate, causing kidney stones and arthritis or can accumulate in other extra-articular tissues. There is a mounting and clear association between hyperuricaemia, gout and the presence of traditional cardiovascular risk factors. Furthermore, several prospective cohort studies have demonstrated that hyperuricaemia may be an independent risk factor for cardiovascular (CV) and renal diseases in people with hypertension, diabetes, coronary heart disease, stroke, dyslipidaemia, chronic inflammation, oxidative stress and endothelial dysfunction. Gout is associated with increased risk of cardiovascular events such as myocardial infarction and cardiovascular death. However, the underlying pathophysiological links between atherosclerosis and hyperuricaemia and/or gout have not been elucidated yet.

In gout the effect of urate-lowering therapy (ULT) on cardiovascular risk is not extensively studied. ULT has been shown to reduce the formation of oxidized low-density lipoprotein autoantibodies, frequently seen in patients with gout. Inhibition of xanthine oxidase activity through allopurinol has been shown to reduce arterial wave reflection in stroke survivors and to improve endothelial function in a number of small interventional studies. Hyperuricaemic patients with chronic heart failure receiving allopurinol experienced improvements in vasodilator capacity and blood flow, whereas patients with normal urate levels had no such effects on endothelial function. In addition, significant reduction of blood pressure was observed in hyperuricaemic subject receiving allopurinol versus placebo. Finally, in a large retrospective cohort, a lower risk on both cardiovascular events and mortality was demonstrated with lower urate levels on

higher doses of allopurinol.

Febuxostat is a selective xanthine-oxidase inhibitor that safely and effectively lowers serum uric acid. Compared with a standard dose allopurinol of 300mg OD febuxostat 80 or 120mg OD is being shown to be more potent in urate lowering. In addition, febuxostat is much more potent in inhibiting endothelium-associated xanthine-oxidase and, thus, reactive oxygen species influencing vascular function. In summary, evidence from clinical trials in the field of urate, gout and CVD is limited to small trials addressing CVD risk factors. To date, no trials on the effect of ULT on hard cardiovascular outcomes have been completed in patients with gout. A valid alternative between trials addressing risk factors and clinical outcomes are trials focusing on surrogate endpoints.

Pulse Wave Velocity (PWV) is considered the golden standard to assess arterial stiffness. Increased PWV has been proven to be an independent predictor of cardiovascular events. The association between serum uric acid and arterial stiffness has been reported in several studies. Hyperuricemia has also been found to be associated with presence of subclinical renal abnormalities such as microalbuminuria and increased renal vascular resistance. Both PWV and urine albumin excretion are well known surrogate endpoints with clearly established relevance to predict CV clinical outcomes The effect of ULT treatment on this surrogate parameters would provide strong rationale for a study with CV clinical endpoints.

Study objective

The primary study objective is to determine whether Febuxostat daily 80-120 mg is better than Allopurinol daily 100-600 mg in inducing positive changes in Pulse Wave Velocity (PWV) after 36 weeks of treatment.

Study design

This is randomized, active-controlled, open label, evaluator blind , parallel;-group, multi-centre, multi-national, Phase IV trial. After the screening period (day-30 to week -1) subjects meeting inclusion criteria will be randomized 1:1 to open label treatment with either Febuxostat 80-120 mg once daily or daily Allopurinol 100-600 mg.

Intervention

Patients who are eligible for participation and have signed informed consent are randomised to either febuxostat or allopurinol treatment. The initial daily dose for febuxostat starts with 80 mg. In case the patient has a serum urate concentration > 6 mg/dl after 2 weeks of treatment the dose will be escalated to 120 mg, and if tolerated, will be maintained for the duration of the study.

The initial daily dose for allopurinol starts with 100 mg. This is to be increased by 100 mg every 2 weeks in patients with serum urate concentration > 6 mg/dl Additional visits should be scheduled on week 4, 6, 8 and 10 to allow up-titration of allopurinol to the maximum dose permitted. The maximum daily dose of allopurinol achievable in the study will depend on kidney function and tolerability, but will not exceed 600 mg.

To prevent flares in the initial stages of treatment with either febuxostat or allopurinol, patients will be treated for at least 6 months with colchicine 0.5-1 mg once daily according to the EULAR guidelines. Gout flares will be treated in both groups with full dose of Naproxen (550 mg BID) or full dosing of other NSAIDs per local standards in case of Naproxen intolerance, co-administered with GI protectors. In case of NSAIDs intolerance/contraindication or lack of efficacy, oral colchicine and/or steroids (oral or intra-articular injection) could be introduced as per local best practice.

Study burden and risks

During screening visit patients have to undergo a physical examination, vital signs, 12-lead ECG and assessment of laboratory tests. Patients who are eligible after a screening visit will enter the study and have to visit the clinic 5 times during approximately 6 months. At these visits vital signs are measured and physical examinations are performed. The efficacy parameters (pulse wave velocity, pulse wave analysis and blood sampling) are measured and, tender and swollen joints are counted. Woman of childbearing potential will have a pregnancy test at beginning and end of the study. Final study visit will be a phone call.

Most risks related to treatment with febuxostat and allopurinol as well as the medication that is used to treat and prevent flares (colchicine, NSAIDs in combination with GI protectors) are rather well known since all medications with a marketing authorisation. Most are on the market for years. Side effects of these medications are described in detail in patient leaflets which will be provided to the patients. However, like any medication, unknown side effects can occur. Patients will be closely monitored on these side effects and will be instructed what to do when any of these side effects occur.

The blood samples that will be taken during the study may cause discomfort and can leave bruises.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Male or female patients 18 years and older;;2) History of gout, flare free in the 4 weeks prior to study entry;;3) History of crystal (joint liquid) proven diagnosis or anamnestic diagnosis of gout according to Wallace at el. At least six out of twelve clinical, laboratory and X-ray phenomena listed below are present:
1. Maximum inflammation developed within 1 day;
2. More than one attack of acute arthritis;
3. Monoarticular arthritis attack;
4. Redness observed over joints;
5. First metatarsophalangeal (MTP) pain or swelling;
6. Unilateral first MTP joint attack;
7. Unilateral tarsal joint attack;
8. Suspected or proven tophus;
9. Hyperuricemia;
10. Asymmetric swelling within a joint on a X-ray;
11. Subcortical cysts without erosions on X-ray;
12. Negative organisms on culture of joint fluid.;4) Naive to ULT or previously treated with

ULT, but with no ULT treatment in the last 1 month prior to study entry and only if reason for ULT interruption was not due to safety concerns;;5) Patients at study entry have elevated serum urate levels >8 mg/dl;;6) Overall CV risk factors based on the scoring proposed by the Joint Task Force of the European Society of Cardiology and other Societies on cardiovascular disease prevention in clinical practice between 5-15% (inclusive), as per protocol appendix 2. Patient with diabetes mellitus type 2 could be included in the study if their CV risk factor is calculated as *7%;;7) Concomitant medications should be maintained stable during the last 2 weeks before randomisation.

Exclusion criteria

1) Severe chronic renal failure (creatinine clearance < 30 ml/min); ;2) Hepatic failure;;3) Active liver disease or hepatic dysfunction, defined as both ALT and AST >2 times the upper limit of normal;;4) Diabetes mellitus type1; ;5) Life-threatening co-morbidity or a significant medical condition and/or conditions that would interfere with the treatment, the safety or the compliance with the protocol;;6) Diagnosis of, or receiving treatment for malignancy (excluding basalioma skin cancer) in the previous 5 years;;7) Patients who have experienced either myocardial infarction or stroke; ;8) Patients with inflammatory based arthritis (e.g.: rheumatoid arthritis, etc.);;9) Patients with congestive heart failure, New York Heart Association (NYHA) Class III or IV;;10) Patients with untreated/uncontrolled thyroid function;;11) Patients with clinically severe peripheral arterial disease; ;12) Concomitant administration of any of the following: azathioprine, mercaptopurine, theophylline, meclofenamate, sulfinpyrazone, trimethoprim-sulfamethoxazole, cyclophosphamide, benzobromarone, pyrazinamide, captopril and enalapril (for Allopurinol), tegafur, pegloticase and tacrolimus;;13) Hypersensitivity to any of the active substances or to any of the excipients;;14) Any contraindication to febuxostat or allopurinol (with reference to the summary of product characteristics);;15) Subject is unable to take either the protocol-required gout flare prophylactic medications (NSAID or colchicine) due to contraindications or intolerance, e.g. hypersensitivity, active gastric ulcer disease, renal impairment and/or changes in liver enzymes;;16) Participation in another trial of an investigational drug or device within 30 days prior to screening, or prior treatment with investigational product(s);;17) Women of childbearing potential, including peri-menopausal women who have had a menstrual period within 1 year, not willing to use highly effective method of birth control throughout the study period and for 4 weeks after study completion (defined as a method which results in a failure rate of less than 1% per year) such as:
* combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal);
* progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, impantable);
* intrauterine device (IUD);
* intrauterine hormone-releasing system (IUS);
* bilateral tubal occlusion;
* vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success);

* sexual abstinence.
In each case of delayed menstrual period (over one month between menstruations) absence of pregnancy has to be confirmed. This also applies to WOCBP with infrequent or irregular menstrual cycles.;18) Severe psychiatric disorders/neurological disorders;;19) Severe concurrent pathology, including terminal illness (cancer, AIDS, etc);;20) Abuse of alcohol, analgesics, or psychotropic drugs;;21) Inability or unwillingness, in the investigator*s opinion, to follow study procedures, including, but not limiting to ability to obtain adequate PWV/PWA recordings. Special attention should be paid to any physical abnormalities which could affect quality of PWV/PWA measurement:
* neck region- flexibility of the neck and accessibility of carotid artery;
* upper arem and thigh region- exclude any abnormality whihc would prevent adequate placement of cuff.;22) Inability or unwillingness to issue the informed consent.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-11-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Adenuric
Generic name:	Febuxostat
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	Allopurinol Teva
Generic name:	Allopurinol
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-03-2015
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	11-09-2015
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	16-06-2016
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	15-05-2017
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	06-06-2017
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-005567-33-NL
CCMO	NL52310.048.15

Study results

Date completed: 29-07-2016

Actual enrolment: 1

Summary results
Trial is onging in other countries