CLINICAL STUDY PROTOCOL

Title: 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 (Acronym: the FORWARD Trial)

STUDY CODE: MEIN/14/FEB-PWV/001
EudraCT No: 2014-005567-33
Study type and design: Randomized, active-controlled, open label, evaluator blind, parallel-group, **multi-centre, multi-national Phase: IV**

Protocol Version Final n°1.4, Amendment 2: Date 30.03.2016.

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Summary of changes within Amendment 1:

1. *Exclusion criteria No. 6 (pages 16 and 30):*

"Diagnosis of, or receiving treatment for malignancy (excluding minor skin cancer) in the previous 5 years."
Replaced by:
"Diagnosis of, or receiving treatment for malignancy (excluding basalioma skin cancer) in the previous 5 years."

2. *Exclusion criteria No 17 (page 17 and 31):*

"Pregnant or breast-feeding women. Women of childbearing potential must: Have a negative urine pregnancy test at baseline (V0), Not be nursing, Be willing to use acceptable methods of contraception (e.g. IUD, spermicidal agent, oral contraceptive) throughout the study period and for 4 weeks after study completion"
Replaced by:
"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, implantable)
- 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."

3. *Text inserted on page 36:*

"Dose modification of allopurinol
In case a patient undergoes a significant renal function worsening during the study treatment period investigator has to adjust allopurinol dosage as per SmPC."

4. *Inconsistency between the info in the referrence and protocol text corrected on page, 38:*

"...colchicine 0.5-1 mg BID..."
Replaced by:
"…colchicine 0.5-1 mg QD"

Summary of changes with Amendment 2:

1. Change on page 9:

Study Medical Expert: Fabio Iachetti is replaced by *Elena Andreassi Marinelli*

Study Drug Safety Manager: Jaleh Khabirinejad is replaced by *Maria Elena Fabucci*

2. Change on page 12, 19, 28, 41,52 and 54, Secondary Endpoints:

„...sAU less than 6mg/dl...“ described more accurately „....sUA less than, or equal to 6mg/dl...“

3. Change on page 13, Secondary Endpoints :

ESR was deleted

4. Change on page 13, Number of sites and countries and Study Duration:

Croatia is added, number of sites from 30 changed to *35*.

Study duration is extended form FPI II Q2015 *to III Q 2015*, and LPLV from II Q 2016 *to III Q 2017*

5. Change on page 14-Study Procedures and Study Duration, and page 38- Randomization (sec.8.1):

Screening period is extended from 7 days to period *up to 30 days*

6. Change on page 17 and where applicable along the document (pg 31), Exclusion criteria 21:

Wording was added,to point out to the significant conditions which may result in inadequat PWV measurement . Wording added is in itallic: Inability or unwillingnes, in the Investigator's opinion, to follow study procedures*, including, but not limiting to the ability to obtain adequat PWV/PWA recordings. Special attention should be paid to any physical abnormalities which could affect quality of PWV/PWA measurements :*

- *Neck region- flexibility of the neck and accessibility of carotid artery,*
- *Upper arm and thigh region- exclude any abnormality which would prevent adequat placemet of the cuff*

7. Change on pages 22 and 23:

Flow chart is adjusted to reflect the changes within protocol

8. Change on page 27 section 5.1

Typo error in dose of Allopurinol was noticed and corrected, therefore Allopurinol dose is defined as 100-600 mg daily (previous text stated 300-600mg daily)

9. Change on page 33, sec. 7.3:

Additional wording was introduced to confirm that within IMP/NIMP starter kit treatment for flares is also included

10. Changes on page 38, sec. 8.1, screening visit:

Wording was added to emphasize significance of Physical examination, in order to confirm that PWV/PWA measurements could be performed adequately:

Physical examination should be done in detail, in order to assess if the patient presents any anatomical anomalies or other deformities which would influence the PWV measurement quality, and would disqualify patient from participation in the study. Please refer to exclusion criterion no 21.

Also, CV events collection is removed from the text throughout sec 8.1.

11. Changes on page 38, sec. 8.1, screening visit:
    Screening period is extended to up to 30 days, and possibility of re-testing of serum Uric Acid level is introduced. Text of sec. 8.1 is modified as follows:
    The screening period should last up to 1 week in case re-testing is not done. The following parameters will be checked after the patient signs the informed consent: inclusion/exclusion criteria, medical history, concomitant medications, physical examination, height, body weight, demography, vital signs, 12-lead ECG, assessment of laboratory tests (serum Uric Acid, fasting lipids, safety laboratory tests), cigarette smoking, alcohol consumption and adverse events.

    Physical examination should be done in detail, in order to assess if the patient presents any anatomical anomalies or other deformities which would influence the PWV measurement quality, and would disqualify patient from participation in the study. Please refer to exclusion criterion no 21.

    Due to variability of sUA and in case investigator is of opinion that sUA level is temporarily changed due to acute (reversible) medical condition and therefore is not in line with previous medical data, it is up to investigator's and sponsor's decision whether the patient should be re-tested for sUA. The patient may be re-tested for sUA only at one occasion and the last sUA value has to be obtained within 7 days prior to randomization.

12. Changes in sec.8.4 at page 41
    In order to avoid overlapping of analysis between central and local lab, wording has been adjusted . Trygycerides and LDL were removed from safety laboratory evaluations, as they are already analyzed within Central laboratory.
    Local laboratory evaluations : *blood assessment of fasting glucose, fasting insulinemia, serum creatinine and calculated creatinine clearance, total and fractionated bilirubin, alkaline phosphatase, sodium, chloride, calcium and potassium, albumin, Hb, Ht, RBC, WBC and differential count, platelets, AST, ALT, γGT, TSH, LDH, CPK and C-Reactive protein, coagulation (PT and/or INR), urinalysis – including blood, glucose, proteins)*
13. Changes on page 44, sec. 10.1.5
    Description of severe intensity of AE was slightly modified from „significant" to „important" abnormality:
    Severe*: makes it impossible to perform routine activities; in case of laboratory tests, when there is an important abnormality*
14. Changes on page 45, sec. 10.2
    At the beginning of the section following sentence is added to be inline with flow chart:
    All AEs occurred since signing informed consent will be collected and recorded in CRF
15. Changes on page 45, sec. 10.3

Unnecessary wording was erased regarding reporting SAEs via email. Previous wording suggested that reporting via email is accetable only if fax transmission is temporary inavaiable. Current wording suggests that both fax and email reporting are acceptable.
Name of PV officer Dominika Stelmachowska is removed, as it is no longer applicable

16. Changes on page 47, sec. 10.4
    Re-wording of the section header has been introduced. Previous wording :! „Management of non-serious adverse events (NSAEs) and/or laboratory abnormalities" has been changed to "Management of non-serious adverse events (NSAEs)"
17. Changes on page 47, addition of sec. 10.4.1-Management of laboratory abnormalities
    Following wording was added:
    During the clinical trial, abnormalities in laboratory analyses (newly occurring after IMP administration or worsening of previously known abnormalities) which are considered clinically relevant by the Principal investigator (values significantly above or under normal range or which require an intervention or diagnostic tests, or may result in the IMP discontinuation) should be reported as AEs. Concerning the laboratory parameters measured in the central laboratory (see section 8.3), these will be entered in the concerned eCRF pages and they will be assessed as secondary efficacy endpoints.
    However, all out of range values should be collected and reviewed by the CRO and Sponsor on a monthly basis.

18. Change on page 47 section 10.5
    Previous wording referred only to pregnancy of a female patient, while new wording introduced, reflects pregnancy of female patient and pregnancy of patient's partner (in case of male patients)
19. Changes on page 48, sec. 11.3
    "The *Sponsor* will perform all monitoring activities" is changed with : "The *CRO* will perform all monitoring activities "
20. Changes on page 57, sec. 14
    Following sentence was removed, as it not applicable: „Furthermore, the study will be conducted in agreement with Sponsor Standard Operating Procedures' (SOP) requirements as most appropriate."

TABLE OF CONTENTS

1. RESPONSIBILITIES

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2. STUDY SYNOPSIS	
Title	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.
Acronym	The FORWARD Trial
Sponsor Code	MEIN/14/FEB-PWV/001
Investigational Product Reference Therapy	Febuxostat: 80-120 mg/day: (ADENURIC®) is available as oral tablets. Allopurinol TEVA: 100-600 mg/day: Allopurinol is available as oral tablets.
Dose Regimen	**Starting dose and dose regimen of febuxostat** The initial daily dose is 80 mg. In case the patient has the 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. **Starting dose and dose regimen of allopurinol** The initial daily allopurinol dose is 100 mg, to be increased by 100 mg every 2 weeks in patients with serum urate concentration >6 mg/dl. **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, patients will be treated for at least 6 months with colchicine 0.5 - 1 mg QD (as per Zhang et al. EULAR guidelines, Ann Rheum Dis; 2006) or in case of colchicine intolerance, Naproxen 550 mg BID with Omeprazole (20-40 mg once daily), if indicated to be used. Gout flares will be treated in both groups with Naproxen 550 mg BID or full dosing of other NSAIDs, in case of Naproxen intolerance, as per local standards, 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
Primary Objectives	• Pulse Wave Velocity

Secondary objectives	• Pulse Wave Analysis • Brain natriuretic peptide and N-terminal prohormone of brain natriuretic peptide (BNP and NTproBNP)[60-61] • Markers of inflammation (hsCRP, TNF-α, plasma fibrinogen) • Markers of endothelial activation (sVCAM, sICAM,vWF, e-selectine) • Oxidative stress parameters: MDA, MPO, Ox-LDL, PON1 and PON2 • sUA, eGFR, Serum creatinine and urine albumin to creatinine ratio • Lipid profile • Safety and tolerability
Primary Endpoint	Comparison of the effects of febuxostat and allopurinol on Pulse Wave Velocity (PWV) after 36 weeks of treatment.
Secondary Endpoints	• Changes in BNP and NTproBNP values after 12, 24 and 36 weeks of treatment; • Changes in inflammation markers (hsCRP, TNF-α, sUA, and plasma fibrinogen) after 12, 24 and 36 weeks of treatment; • 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; • Changes in lipid profile after 12, 24 and 36 weeks of treatment; • 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. • 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 ; • Changes in eGFR with CKD-EPI formula after 12, 24 and 36 weeks of treatment; • Changes in urine albumin excretion as evaluated by first morning urine albumin/creatinine ratio (mg/g) after 12, 24 and 36 weeks of treatment; • 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; • Tender and swollen joint count; • Pulse Wave Analysis (including modifications of PWV, arterial stiffness, central blood pressure and augmentation index) after , 12, 24 and 36 weeks of treatment; • 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) • Safety and tolerability will be assessed by the following parameters evaluated at Screening (V-1), Week 2 (V1: for AEs only), Week 12 (V2) Week 24 (V3) and Week 36 (V4): o Overall incidence of adverse events (AEs). o Evidence from physical examination o Vital signs (systolic/diastolic blood pressure, pulse, body weight, axillary body temperature). o Laboratory parameters (blood chemistry, haematology, urinalysis: comprising of CRP, TBC, creatinine, alkaline phosphatase, AST, ALT, bilirubin, GGT, TSH and glucose)
Phase	IV
Study Design	Randomized, active-controlled, open label, evaluator blind, parallel-group, multi-centre, multi-national, Phase IV trial. Patients will be randomized 1:1 to receive febuxostat or allopurinol.
Number and characteristics of patients	Planned total number of randomized patients: 182 (91 per treatment arm). Patients with gout, with a history of crystal proven diagnosis (joint liquid) or anamnestic diagnosis of gout according to Wallace et al.(Preliminary criteria for the classification of the acute arthritis of primary gout; Arthritis Rheum, 1977) – please see inclusion criterion 3. All patients have to be flare free at study entry. Patients have to be either 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 the reason for ULT interruption was not due to safety concerns. Patients must have elevated serum urate level > 8 mg/dl at study entry.
No. of Sites & Countries	There will be approx. 35 sites in the following countries: Germany, the Netherlands, Italy, Poland, Serbia, Romania and Croatia

Study Duration	Study duration for individual patients will be 39 weeks. This includes a one week run-in/screening period which can be extended to max 30 days in case of re-testing, followed by a 36 weeks treatment and a 2 weeks safety follow-up (by phone call). • First Patient In (FPI) :III Q 2015 • Last Patient Last Visit (LPLV): III Q 2017
Study Procedures	The study is a randomized, active-controlled, open label, evaluator blind, parallel-group, multi-centre, multi-national, Phase IV trial and will enrol patients naïve to ULT (allopurinol, febuxostat or other treatments) or previously treated with ULT, but with no ULT treatment in the last 1 month prior to study entry and only if the reason for ULT interruption was not due to safety concerns. The study physician responsible for randomization and drug supply handling is unblinded to study medications and therefore will not be involved in the main efficacy evaluations of each patient randomized in the study. Conversely, the study physician/s responsible for the main efficacy evaluation (Pulse Wave Velocity) will be blind to study treatments. In addition, key efficacy variables will be performed by an independent core laboratory where the central reader will be blind to the treatment assigned to patients. Fasting lipid levels, NTproBNP, BNP, markers of inflammation and endothelial activation/adhesion, oxidative stress parameters, eGFR, and albumin/creatinine ratio will be also evaluated by a central laboratory. • **Screening visit (V-1):** The study will consist of up to 30 days run-in period that includes a screening visit during which patients will sign the informed consent, perform laboratory assessments and will be evaluated for eligibility to study protocol (inclusion/exclusion criteria). Potentially eligible patients will not receive any ULT treatment during the run-in period. • **Baseline/randomization visit (V0):** All the baseline instrumental and laboratory investigations (see study flow chart for details) will be performed and eligible patients will be randomized to treatment with allopurinol 100 mg or febuxostat 80 mg (1:1 ratio). • **Subsequent mandatory visits after randomization:** Will be performed at Week 2 (V1), Week 12 (V2), Week 24 (V3), and Week 36 (V4) and will consist in instrumental and laboratory investigations (see study flow chart for details). Up-titration of allopurinol or febuxostat to the maximum dose permitted in the study may be

	performed between Week 2 and Week 10. • **Follow-up safety assessment (V5):** Will be performed by a phone call 2 weeks after study termination (see study flow chart for details). • **Additional visits:** Permitted in order to assess the sUA levels (evaluation performed by the site laboratory in real time or by a portable electrochemical blood uric acid meter available on site) may be scheduled for patients not at target between Visit 1 (V1) and Visit 2 (V2), i.e.: at Week 4, 6, 8, and 10 to allow up-titration of allopurinol or febuxostat to the maximum dose permitted in the study.
Inclusion Criteria	**Patients meeting the following criteria will be eligible for entry into the study:** 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. Preliminary criteria for the classification of the acute arthritis of primary gout; Arthritis Rheum, 1977 ***To be eligible a subjects has to present at least six out of twelve clinical, laboratory, and X-ray phenomena listed below:*** 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 level >8 mg/dl.

	6. Overall CV risk based on the scoring proposed by the Joint Task Force of the European Society of Cardiology and other European Societies on cardiovascular disease prevention in clinical practice between 5 and 15-% (inclusive) as per protocol appendix 2. Patients with diabetes mellitus type 2 could be included in the study if their CV risk score is calculated as ≤7%. 7. Allowed concomitant medications should be maintained stable during the last 2 weeks before randomisation
Exclusion Criteria	**Patients will not be eligible to participate in the study if they meet ANY of the following 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 with 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, benzbromarone, pyrazinamide, captopril and enalapril (for Allopurinol), tegafur, pegloticase and tacrolimus. 13. Hypersensitivity to any one 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 of 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 (WOCBP), 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, implantable)
    - 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 arm and thigh region- exclude any abnormality which would prevent adequat placement of the cuff
22. Inability or unwillingness to issue the informed consent

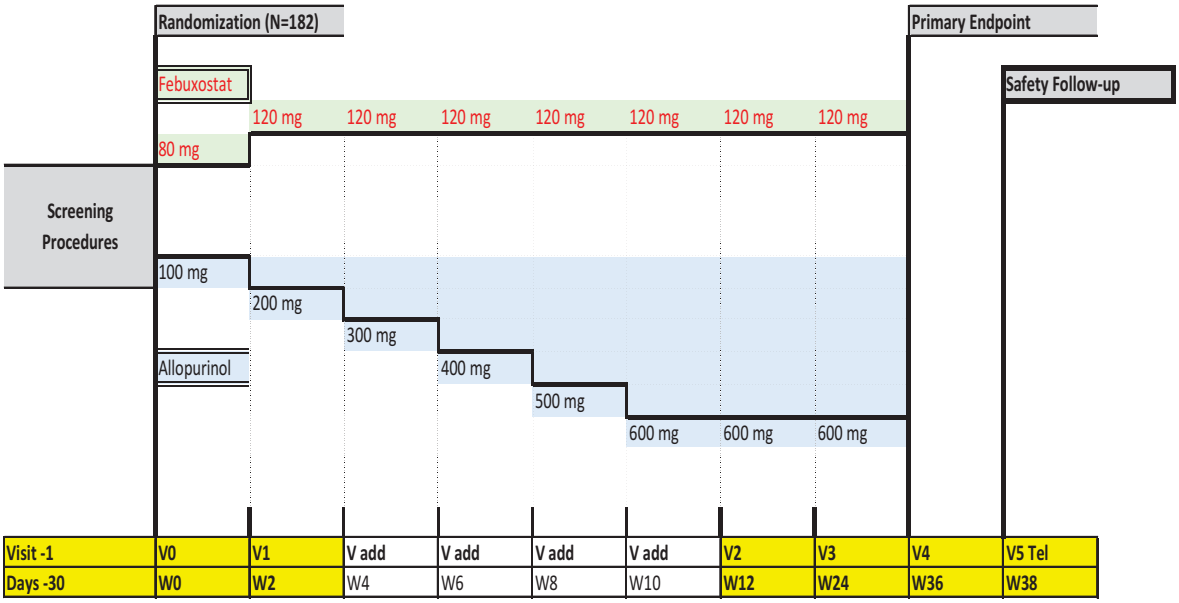
Sample Size and Statistical Analysis	For the primary efficacy endpoint (Pulse Wave Velocity), febuxostat will be tested for superiority to allopurinol. A sample size of 79 in each group will have 85% power to detect a difference in means of 1.8 m/sec at Week 36 assuming that the common standard deviation is 3.75 m/sec using a two group t-test with a 0.05 two-sided significance level. Expecting a drop-out rate of approximately 15%, the total number of subjects to be randomized in order to achieve the planned sample size will be 91 per treatment arm. <u>Primary Efficacy Analysis</u> The primary efficacy analysis will be based on the Full Analysis Set (FAS) and the primary endpoint of Pulse Wave Velocity (PWV) after 36 weeks of treatment with febuxostat or allopurinol. Analysis of covariance (ANCOVA) with the 36 weeks PWV value as dependent variable (Last Observation Carried Forward (LOCF) and/or the mean of available data within a treatment group at a given time point), treatment group as factor and age, baseline blood pressure, baseline PWV at 36 weeks as covariates, will be used to compare the efficacy of the two treatment groups. The covariates found not to be statistically significant at the 0.05 two-sided significance level, will be removed from the model; the final model will only include statistically significant covariates. The sensitivity analysis with the change from baseline to Week 36 in PWV will be performed as described above. The relationship between PWV at Week 36 (change from baseline to Week 36) and febuxostat dose will be explored using scatterplots. The efficacy evaluation will be performed in both FAS and PP Populations. The Full Analysis Set (FAS) will be the primary analysis population for the confirmatory analysis. A sensitivity analysis on the Per-Protocol (PP) Population will be performed. The number of patients who are excluded from the PP population will be presented for each specific reason, grouped by treatment. The list of patients excluded from the PP population will be determined prior to unblinding the data. <u>Secondary Efficacy Analyses</u> For the analysis of continuous secondary efficacy variables the ANCOVA model with change from baseline to respective time point as a response variable and respective baseline value and treatment group as terms in the model will be used at each time point.

	The Last Observation Carried Forward (LOCF) method will be used to replace missing data for any cause. 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 and 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 will be analyzed using logistic regression models at each time point to assess the difference between treatment regimens. Dependent variable is defined as a binary outcome (assessed as 1 if urate concentration ≤ 6 mg/dl, 0 otherwise). Treatment group and baseline urate concentration will be included as independent variables. Time to achieve sUA target levels will be analysed using proportional hazard model with treatment group and baseline sUA as covariates. 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 will be analysed descriptively. No correction for multiple testing will be applied to the secondary endpoints. <u>Safety Analysis</u> Evaluation of safety will be performed for "safety population" and will be based on frequency of adverse events, safety markers, laboratory parameters, vital signs. Adverse Events will be coded using the MedDRA dictionary and will be classified for each treatment group by presenting the number and percentage of patients having had an Adverse Event, both overall and by body system. Safety will be assessed by comparing differences between the two treatment groups in: • Incidence of all Adverse Events. • Serious Adverse Events/hospitalizations. • Withdrawals due to any Adverse Event. • Safety markers. • Laboratory parameters • Vital signs

	All p-values will be rounded to three decimal places. Statistical significance will be declared if the rounded p-value will be less than 0.05. Any deviation from this statistical analysis approach will be well justified and documented in the Statistical Analysis Plan (SAP). The Statistical Analysis Plan will be finalized and signed-off prior to database lock. Other analyses that could be included in the final ICH Clinical Study Report will be fully documented and justified in the analyses performed section. Statistical analyses will be performed by using SAS Software.

2.1 STUDY SCHEME:

SYNTHETIC FLOW CHART OF THE STUDY



Notes:

"V -1"=screening visit

"V0"=baseline/randomization visit

"V1,V2,V3,V4"=mandatory visits

"V5 Tel"=Telephone call for safety

"V add"=Additional visits for patients not at target with sUA

2.2 STUDY FLOW CHART	**Days -30 to Week -1*** **Visit -1**	**Day 0** **Visit 0**	**Week 2 ± 4 days** **Visit 1**	**Week 12± 4 days** **Visit 2**	**Week 24 ± 4 days** **Visit 3**	**Week 36 ±4 days** **Visit 4**	**Week 38 +3 days after** **Visit 5** **Phone call**
	Screening	**Randomisation**	**On Treatment Visit**	**On Treatment Visit**	**On Treatment Visit**	**End of Study visit**	**Safety Follow-up**
Inclusion/exclusion crit.	✓						
Informed consent	✓						
Randomization		✓					
Medical history	✓						
Concomitant medications	✓	✓	✓	✓	✓	✓	
Physical examination	✓			✓	✓	✓	
Vital signs (BP, HR body temperature) [a]	✓	✓		✓	✓	✓	
Height, Body Weight [b], demography	✓						
12-Lead ECG [c]	✓						
Pulse Wave Analysis (PWA): PWV, arterial stiffness, central blood pressure, augmentation index		✓		✓	✓	✓	
BNP, NTproBNP		✓		✓	✓	✓	
Serum Uric Acid [d]	✓		✓	✓	✓	✓	
Oxidative stress parameters: MDA, MPO, Ox-LDL, PON1 and 2		✓		✓	✓	✓	
Markers of inflammation: hsCRP, TNF-α, plasma fibrinogen		✓		✓	✓	✓	
Markers of endothelial activation/adhesion: sVCAM, sICAM, vWF, e-selectine (selected sites)		✓		✓	✓	✓	
Fasting lipid levels	✓			✓	✓	✓	
eGFR		✓		✓	✓	✓	
Urine Albumin excretion measured as Albumin to creatinine ratio[e]		✓		✓	✓	✓	
Tender and swollen joint count		✓		✓	✓	✓	

Cigarette smoking, alcohol consumption,	✓	✓	✓	✓	✓	✓	✓
Urine pregnancy test		✓				✓	
Safety Laboratory Tests [f]	✓			✓	✓	✓	
IMP dispense		✓	✓	✓	✓		
IMP accountability			✓	✓	✓	✓	
Adverse events[g]	✓g	✓	✓	✓	✓	✓	✓

NOTES:

* screening period lasts up to 7 days but can be extended to max 30 days in case of re-testing of sUA. sUA can be re-tested if current sUA level is changed due to acute (transient) condition as it is not in line previous medical data as per investigator opinion and approval from the Sponsor.

a. Blood pressure and Heart Rate will be taken with the patient in the sitting position (patient seated for 5 minutes).

b. Height without shoes and body weight will be recorded at screening and the BMI will be calculated

c. 12-lead ECGs. Patients should be lying quietly in a fully supine position for at least 10 minutes prior to do 12-lead ECG.

d. All patients randomized will monitor sUA concentrations at screening visit, and at subsequent mandatory visits scheduled for Week 2, 12, 24 and 36. Additional visits to assess the sUA levels (by the site laboratory in real time or by a portable electrochemical blood uric acid meter available on site) may be scheduled in patients not at sUA target at Week, 4, 6, 8, and 10 to allow up-titration of allopurinol or febuxostat to the maximum dose permitted in the study.

e. Albumin to Creatinine Ratio (ACR) will be evaluated in the sample collected in the same day of the visit(urine samples will be stored at -20°C and measured at a central lab)

f. Safety laboratory test – please refer to section 8.1

[g] Collection of AE to commence once patient has signed the Informed Consent.

3. ABBREVIATIONS

ACR	Albumin to Creatinine Ratio
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	Bis in Die = Twice daily
BNP	Brain Natriuretic Peptide
CA	Competent Authority
CKD	Chronic kidney disease
CRF	Case Report Form
CRP	C-reactive protein
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
GEE	Generalized estimable equations
hsCRP	High-sensitivity CRP
IRB	Independent Review Board
LOCF	Last Observation Carried Forward
MDA	Malondialdehyde Paraoxonase 1 and 2
MPO	Myeloperoxidase
NSAE	Non-Serious Adverse Event
NTproBNP	N-terminal prohormone of Brain Natriuretic Peptide
OD	Once Daily
oxLDLc	Oxidized low-density lipoprotein cholesterol
PON1	Paraoxonase 1
PON2	Paraoxonase 2
PWA	Pulse Wave Analysis
PWV	Pulse Wave Velocity
SAE	Serious Adverse Event

sICAM	Soluble intercellular cellular adhesion molecule
sUA	Serum Urate Concentration
sVCAM	Soluble vascular cell adhesion molecule-1
TNF-α	Tumour Necrosis Factor Alpha
TSH	Thyroid stimulating hormone
ULT	Urate lowering therapy
WOCBP	Women of childbearing potential
vWF	Von Willebrand Factor

4. BACKGROUND and RATIONALE

4.1 DESCRIPTION OF STUDY DISEASE

There is a mounting and clear association between hyperuricaemia, gout and the presence of traditional cardiovascular risk factors such as hypertension, lipid disorders, obesity, and CV event-equivalents conditions as chronic kidney disease, the metabolic syndrome, and diabetes.[1,2] Furthermore, several prospective cohort studies have demonstrated that hyperuricaemia may be an independent risk factor for cardiovascular and renal disease in people with hypertension, diabetes, coronary heart disease, stroke, dyslipidaemia, chronic inflammation, oxidative stress and endothelial dysfunction.[3-6] Gout is associated with increased risk of cardiovascular events such as myocardial infarction and cardiovascular death.[7-9] However, the underlying pathophysiological links between atherosclerosis and hyperuricaemia and/or gout have not been elucidated yet.

Atherosclerosis is a multi-factorial process. An atherogenic lipid profile is an important factor in the development of cardiovascular disease.[10] In patients with gout, high levels of oxidized low-density lipoprotein cholesterol (oxLDLc) antibodies are present.[11] Furthermore, hyperuricaemia is clearly associated with an increased arterial stiffness, a marker of pre-clinical atherosclerosis.[12-14] Moreover, several investigations have confirmed the important role of inflammation in initiating and accelerating atherosclerosis Indeed the ability of soluble UA to induce oxidative stress, inflammatory response such as NF-kB and mitogen-activated protein kinase activation and chemokine expression has been demonstrated “ex vivo” on human neutrophils. Furthermore UA seems to induce oxidative stress in endothelial cells, promoting scavenging of NO and induction of ECs arginase that reduces NO production and trigger the activation of the renin-angiotensin-aldosterone system axis. [15-18]. Inflammation might contributes to atherosclerosis also through the inhibition of reverse cholesterol transport from the vessel wall to the liver as well.[19] Urate is thought to behave as a pro-oxidant in vascular cells, increasing lipid oxidization, and impairing endothelium-dependent vasodilation.[10] Serum UA is also being shown to positively correlate with inflammatory markers such as WBC, neutrophil count, C-reactive protein, IL-6, IL-1ra, IL-18 and TNF-α in older people randomly selected from the general population.[20] Xanthine-oxidase mediated oxidative stress might further contribute to the development of atherosclerosis.[2] In gout the effect of urate-lowering therapy (ULT) on cardiovascular risk is less extensively studied. ULT has been shown to reduce the formation of oxidized low-density lipoprotein autoantibodies.[21] Inhibition of xanthine oxidase activity through allopurinol has been shown to reduce arterial wave reflection in stroke survivors [22] and to improve endothelial function in a number of small interventional studies. [2] 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. [23] In addition, significant reduction of blood pressure was observed in hyperuricaemic subject receiving allopurinol versus placebo. [24,25] 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.[26]

4.2 THE INVESTIGATIONAL PRODUCT

Febuxostat is a selective xanthine-oxidase inhibitor that safely and effectively lowers serum uric acid. Compared with a standard allopurinol dose of 300 mg OD febuxostat 80 or 120 mg OD is being shown to be more potent in urate lowering.[27,28] In addition, febuxostat is more potent in inhibiting endothelium-associated xanthine-oxidase and, thus, reactive oxygen species influencing vascular function.[29] However, 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.

Carotid-femoral pulse wave velocity (PWV), is considered the "gold standard" measurement of arterial stiffness.[30] Increased carotid-femoral PWV has been proven to be an independent predictor of cardiovascular events in patients with hypertension, impaired glucose tolerance and diabetes mellitus, end-stage renal disease, and in the elderly and general populations.[31-36] The association between serum uric acid and arterial stiffness has been reported in several studies.[37-42] For instance, in a study involving 1225 patients, newly diagnosed, never-treated hypertensive subjects, uric acid positively correlated with cf-PWV in both men and women after adjusting for confounders.[37]

Hyperuricemia has also been found to be associated with the presence of subclinical renal abnormalities such as microalbuminuria and increased renal vascular resistance [43-44]. Both Pulse Wave Analysis and urine albumin excretion are well known surrogate endpoint with clearly established relevance to predict CV clinical outcomes.[45]

The effect of ULT (febuxostat or allopurinol) treatment on these surrogate parameters would provide strong rationale for a trial with CV clinical endpoints.

5. AIM of the STUDY

5.1 PRIMARY OBJECTIVES

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. PVW is considered a valid surrogate endpoint with clearly established relevance to predict CV clinical outcome.

5.2 SECONDARY OBJECTIVES

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

- Changes in inflammation markers (hsCRP, TNF-α, sUA, and plasma fibrinogen) after 12, 24 and 36 weeks of treatment;
- 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;
- Changes in lipid profile after 12, 24 and 36 weeks of treatment;
- 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.
- 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 ;
- Changes in eGFR with CKD-EPI formula after 12, 24 and 36 weeks of treatment;
- Changes in urine albumin excretion as evaluated by first morning urine albumin/creatinine ratio (mg/g) after 12, 24 and 36 weeks of treatment;
- 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;
- Tender and swollen joint count;
- Pulse Wave Analysis (including modifications of PWV, arterial stiffness, central blood pressure and augmentation index) after , 12, 24 and 36 weeks of treatment
- 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)
- Safety and tolerability

6. INVESTIGATIONAL PLAN

6.1 OVERALL STUDY DESIGN

A randomized, active-controlled, open label, evaluator blind, parallel-group, multi-centre, multi-national, Phase IV trial. Patients will be randomized 1:1 to febuxostat or allopurinol.

6.2 SELECTION OF STUDY POPULATION

Planned total number of randomized patients: 182 (91 per treatment arm).

Patients with a history of crystal proven diagnosis (joint liquid) or anamnestic diagnosis of gout according to Wallace et al.[46]. All patients have to be flare free at study entry. Patients have to be either 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 the reason for ULT interruption was not due to safety concerns. Patients must have elevated serum urate level> 8 mg/dl at study entry

6.3 INCLUSION CRITERIA

Patients meeting the following criteria will be eligible for entry into the study:

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 et al. [46]. **To be eligible a subjects has to present at least 6 out of the twelve clinical, laboratory, and X-ray phenomena listed below**:

    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 level> 8 mg/dl.
6. Overall CV risk 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 and 15% (inclusive) [47] as per protocol appendix 2. Patients with diabetes mellitus type 2 could be included in the study if their CV risk score is calculated as ≤7%.
7. Concomitant medications should be maintained stable during the last 2 weeks before randomization

6.4 EXCLUSION CRITERIA

Patients will not be eligible to participate in the study if they meet ANY of the following 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 with 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 one of the following: azathioprine, mercaptopurine, theophylline, meclofenamate, sulfinpyrazone, trimethoprim-sulfamethoxazole, cyclophosphamide, benzbromarone, pyrazinamide, captopril and enalapril (for Allopurinol), tegafur, pegloticase and tacrolimus.
13. Hypersensitivity to any of the active substance 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 of 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, implantable)
- 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 limited to ability to obtain adequate PWV/PWA recordings. Special attention should be made to any physical abnormalities which could affect quality of PWV/PWA measurement:
    - Neck region- neck flexibility and accessibility of carotid artery
    - upper arm and thigh region- exclude any abnormalities which would prevent adequate placement of the cuff
22. Inability or unwillingness to issue the informed consent

7. INVESTIGATIONAL MEDICINAL PRODUCT

7.1 NAME AND DESCRIPTION OF THE INVESTIGATIONAL MEDICINAL PRODUCTS (IMPS), WITH A QUALITATIVE AND QUANTITATIVE DESCRIPTION

- Febuxostat 80 mg film coated tablets; each tablet is containing 76,50 mg of lactose as monohydrate. Other excipients are: microcrystalline cellulose, magnesium stearate, hydroxypropylcellulose, croscarmellose sodium, silica, colloidal hydrated, opadry II yellow 85F42129 containing: polyvinyl alcohol, titanium dioxide (E171), type macrogol 3350, talc, yellow iron oxide (E172);

- Febuxostat 120 mg film coated tablets; each tablets is containing 114,75 mg of lactose as monohydrate. Other excipients are: microcrystalline cellulose, magnesium stearate, hydroxypropylcellulose, croscarmellose sodium, silica, colloidal hydrated, opadry II yellow 85F42129 containing: polyvinyl alcohol, titanium dioxide (E171), type macrogol 3350, talc, yellow iron oxide (E172);
- Allopurinol 100 mg tablets; each tablets is containing lactose monohydrate, colloidal anhydrous silica, maize starch, powdered cellulose, sodium starch glycolate, sodium lauryl sulphate, povidone and magnesium stearate;
- Allopurinol 300 mg tablets; each tablet is containing lactose monohydrate, colloidal anhydrous silica, maize starch, powdered cellulose, sodium starch glycolate, sodium lauryl sulphate, povidone and magnesium stearate;
- Colchicine 0.5 mg tablets; each tablet is containing microcrystalline cellulose, lactose, sodium carboxy starch, magnesium stearate;
- Naproxen sodium 550 mg film coated tablets; each tablet is containing microcrystalline cellulose, povidone, talc, magnesium stearate, hypromellose, macrogol 8000, titanium dioxide, E110 (lake);
- Omeprazole 20 mg capsules; each capsule is containing disodium hydrogen phosphate dihydrate, hydroxypropylcellulose, hydroxypropylmethylcellulose, lactose anhydrous, magnesium stearate, mannitol, methacrylic acid co-polymer, microcrystalline cellulose, macrogol (polyethylene glycol), sodium laurylsulphate, iron oxide, titanium dioxide, gelatin, printing ink (containing shellac, ammonium hydroxide, potassium hydroxide and black iron oxide).

7.2 DOSAGE FORM, STRENGTH AND FORMULATION

- Febuxostat (Adenuric®) 80 mg: film coated tablets light-yellow/yellow coloured, capsule shaped and with “80” printed on a side.
- Febuxostat (Adenuric®) 120 mg: film coated tablets light-yellow/yellow coloured, capsule shaped and with “120” printed on a side.
- Allopurinol (Allopurinol-TEVA) 100 mg: white, round biconvex tablet, debossed “4K1” one side and plain on the other.
- Allopurinol (Allopurinol-TEVA) 300 mg: white, round biconvex tablet, debossed “2K1” one side and plain on the other
- Colchicine (Colchicine Sandoz) 0.5 mg: white, round tablet with “0.5” marked one side and plain on the other

- Naproxen sodium (Synflex 550)550 mg: orange colour, oval shaped, cut through bisect line on both faces, with "SYF" and "550" marked on one face, film coated tablet
- Omeprazole (Omeprazen®) 20 mg:hard gelatin capsules, with an opaque pink body and an opaque reddish-brown cap, both marked “OMEPRAZEN® 20”, and containing enteric coated pellets

These products will be supplied for the entire duration of the study.

7.3 DESCRIPTION OF PACKAGING AND LABELLING OF THE PRODUCTS

All study drugs will be administered orally. All study drug will be supplied as blistered tablets in its original marketed presentation and will be included in packs containing the adequate number of units required for each treatment period of two weeks.

At first, each clinical site will be provided with a “starter kit” (intended for a block of 4 patients) containing all study drug packs (test, comparator, prophylaxis drug and flares treatment) in amount to cover the initial treatment period of two weeks and designed to be used at each visit in order to obtain the required dosage according to study protocol. A special label will allow Clinical Investigator to assign the packs to each patient, filling in by hand with the randomisation number and the visit number.

Additional “starter kit” or single packs of each study drugs will be supply on demand by the Clinical Investigator.

Study drugs, as IMPs, will be packaged for clinical trial use only.
IMPs will be supplied all along the clinical trial in order to make sure that an appropriate amount will be delivered to each patients, according to the treatment arm they have been assigned and to the drug dosage required by Clinical Investigator.
A Certificate of Analysis (CoA) for each IMPs batch used during the study will be provided.
Labelling will be done in compliance with Good Manufacturing Practices for IMPs (cGMP; Annex 13) and the core label texts for all packaging units will be translated or adjusted, in official languages of each country involved in the clinical trial.

A description of the core text of the IMP labels is displayed below:

- *Sponsor name, address and telephone number*
- *Pharmaceutical dosage form, route of administration, quantity of dose units, product name and strength*
- *Batch number*
- *Study number*
- *Study subject identification, visit number*
- *Name of investigator*
- *Directions for use*
- *“For clinical trial use only” or similar wording*
- *Storage conditions*

- *Period of use (MM/YYYY format)*
- *"Keep out of reach and sight of children"*

The Clinical Investigator, or designee, only will administer IMPs to patients included in the clinical trial. Each patient will be provided only with the IMPs pack carrying his/her randomisation number assigned and written by hand by the Clinical Investigator.
The IMPs administration for each patient will be recorded in the electronic Case Report Form (eCRF).

7.4 STORAGE CONDITIONS

All study drugs must be stored at a temperature not above 25°C in a locked, secure and dry storage facility, with access limited to those individuals authorized to dispense the study drugs

7.5 TREATMENT COMPLIANCE

Treatment compliance will be monitored from Visit -1 to Visit 4 (end of study treatment). The Clinical Investigator must instruct subjects to return to clinical site the study drug blister packs received at the previous visit. The amount of study medication taken by the subject will be derived by counting the number of tablets returned in the blister and it will be recorded in the eCRF.

The subject compliance for study treatment period is calculated by the following formula: % compliance = number of tablets actually taken x 100 / expected number of tablets which should have been taken.

The global subject compliance will be calculated as the percentage of the number of tablets actually taken by the subject over the number of tablets expected to be taken.

The number of tablets actually taken will be calculated as the difference between the number of tablets handled out to the subject and the number of unused tablets returned or declared lost by the subject.

The expected number of tablets taken will be calculated using the difference (in days) between Visit X and Visit X-1 (i.e. V1 and V0; V2 and V1, etc.). A subject that has taken at least 60% and no more than 120% of the required study drug intake since the last visit will be considered compliant.

7.6 DRUG ACCOUNTABILITY

The Clinical Investigator of each participating institution will be responsible for the management of all the drugs to be used for the clinical trial. An inventory will be maintained by the investigator (or designee) to include a signed account of all study drugs received, dispensed to and returned by each subject at the planned visits. An explanation will be given for any discrepancies.

At the conclusion of the study, the Drug Accountability Form will be completed after a final drug supply inventory.

7.7 DRUG RETURN

All used or unused study drugs must be returned, on agreed conditions, defined by the Sponsor.

All used or unused study drugs must be accounted for and provided with relative Drug Return Form filled in as appropriate.

Any discrepancy should be investigated and satisfactorily explained.

7.8 DRUG DESTRUCTION

Destruction of all study drugs (used or unused) should be carried out after written authorisation of the Sponsor

7.9 DESCRIPTION OF DOSE, DOSING SCHEDULE, ROUTE AND MODE OF ADMINISTRATION

Starting dose and dose regimen of febuxostat

The initial daily dose is 80 mg given orally. In case a patient has serum urate level > 6 mg/dl after 2 weeks of treatment the dose will be escalated to 120 mg and if tolerated will be maintained during the study treatment period.

Starting dose and dose regimen of allopurinol

The initial daily allopurinol dose is 100 mg given orally, to be escalated of 100 mg every 2 weeks in patients with serum urate concentration >6 mg/dl.

The maximum dose of allopurinol achievable in the study will depend on kidney function and tolerability, but will not exceed 600 mg daily.

Dose modification of allopurinol

In case a patient undergoes a significant renal function worsening during the study treatment period investigator has to adjust allopurinol dosage as per SmPC.

Starting dose and dose regimen of medications used for gout flare prevention/treatment

To prevent flares in the initial stages of treatment, patients will be treated for at least 6 months with colchicine 0.5 - 1 mg QD or in case of colchicine intolerance, Naproxen 550 mg BID with Omeprazole (20-40 mg once daily), if indicated to be used.
Gout flares will be treated in both groups with Naproxen 550 mg BID or full dosing of other NSAIDs, in case of Naproxen intolerance, as per local standards, 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

7.10 TREATMENT PERIODS

Study duration for individual patients will include a one week run-in/screening period, followed by a 36-week treatment period and a 2 week safety follow-up.

7.11 RANDOMISATION AND BLINDING PROCEDURES

The study is a randomized, active-controlled, open label, evaluator blind, parallel-group, multi-centre, multi-national, Phase IV trial.

The randomization list will be based on the "RANUNI" random number generator of the SAS software (SAS Institute, Cary, NC, USA). Randomization will be in a 1:1 ratio of Febuxostat versus allopurinol and no cross-centre randomization will be performed.

The study physician responsible for randomization and drug supply handling is unblinded to study medications and therefore will not be involved in the main efficacy evaluations of each patient randomized in the study. Conversely, the study physician/s responsible for the main efficacy evaluations (pulse wave velocity, etc.) will be blinded to study treatments.

In addition, all key efficacy variables included in the pulse wave analysis (central blood pressure, augmentation index), will be rated by an independent core laboratory where the central reader will be blinded to the treatment assignment.

Fasting lipid levels, NTproBNP, BNP, markers of inflammation and endothelial activation/adhesion, oxidative stress parameters eGFR, changes in urine albumin excretion as evaluated by first morning albumin/creatinine ratio will be also measured by a central laboratory.

7.12 CONCOMITANT PERMITTED MEDICATION

Concomitant medications should be maintained stable during the last 2 weeks before randomization and during the course of the study. Any changes need to be recorded in the eCRF.

7.13 PROHIBITED CONCOMITANT MEDICATIONS

The following concomitant medications are not permitted during the study:

- azathioprine
- mercaptopurine
- didanosine theophylline
- meclofenamate
- sulfinpyrazone
- trimethoprim-sulfamethoxazole
- cyclophosphamide
- benzbromarone
- pyrazinamide
- captopril and enalapril (for Allopurinol)
- tegafur
- pegloticase
- tacrolimus

7.14 RESCUE MEDICATION

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. Oral colchicine and/or steroids (oral or intra-articular injection) could be introduced as per local best practice. Please refer to section 8.1 for detailed guidelines.

7.15 MANAGEMENT OF OVER DOSAGE

Subjects with an overdose should be managed according to symptomatic and supportive care.

8 STUDY PROCEDURES AND ASSESSMENT OF EFFICACY AND SAFETY

8.1 SYNTHESIS OF PROCEDURE

This is randomized, active-controlled, open label, evaluator blind study. After the screening period (Week -1) subjects meeting inclusion criteria will be randomized to open label treatment with either Febuxostat 80-120 mg once daily or daily Allopurinol 100-600 mg.

Gout patients, with an history of crystal proven diagnosis (joint liquid) or anamnestic diagnosis of gout according to Wallace et al.[46] have to be flare free at study entry. Patients have to be either 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 the reason for ULT interruption was not due to safety concerns. Patients must have elevated serum urate levels >8 mg/dl at study entry.

Febuxostat treatment

For patients randomized to febuxostat, the daily starting dose of febuxostat is 80 mg. In case a patient has serum urate level >6 mg/dl after 2 weeks of treatment the dose will be escalated to 120 mg and if tolerated maintained during the study treatment period.

Allopurinol treatment

For patients randomized to allopurinol, the starting daily dose is 100 mg to be escalated by 100 mg every 2 weeks in patients with serum urate concentration >6 mg/dl. The maximum daily dose of allopurinol achievable in the study will depend on kidney function and tolerability, but will not exceed 600 mg.

Flare prevention and treatment

To prevent flares in the initial stages of treatment, patients will be treated for at least 6 months with colchicine 0.5-1 mg QD according to EULAR guidelines.[48]

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. [49-50]

Visits are scheduled as follows (for study flow chart see 2.2):

Visit -1 Days -30 to Week -1 (screening visit):
The screening period should last up to 1 week in case re-testing is not done. The following parameters will be checked after the patient signs the informed consent: inclusion/exclusion criteria, medical history, concomitant medications, physical examination, height, body weight, demography, vital signs, 12-lead ECG, assessment of laboratory tests (serum Uric Acid, fasting lipids, safety laboratory tests), cigarette smoking, alcohol consumption and adverse events.
Physical examination should be done in detail, in order to assess if the patient presents any anatomical anomalies or other deformities which would influence the PWV measurement quality, and would disqualify patient from participation in the study. Please refer to exclusion criterion no 21.
Due to variability of sUA and in case investigator is of opinion that sUA level is temporarily changed due to acute (reversible) medical condition and therefore is not in line with previous medical data, it is up to investigator's and sponsor's decision whether the patient should be re-tested for sUA. The patient may be re-tested for sUA only at one occasion and the last sUA value has to be obtained within 7 days prior to randomization.

Visit 0 Day 0 :

Subjects will be randomized to receive either febuxostat or allopurinol. The following parameters will be checked: concomitant medications, vital signs, efficacy parameters (pulse wave velocity, pulse wave analysis, BNP, NTproBNP, oxidative stress parameters, markers of inflammation, endothelial activation/adhesion, eGFR with CKD-EPI formula, urine albumin excretion measured as albumin/creatinine ratio), tender and swollen joints, cigarette smoking and alcohol consumption, pregnancy test, adverse events; study medication will be dispensed according to randomization.
If deemed appropriate by the investigator and/or the clinical trial subject, PWV and PWA and remaining randomization procedures could be performed in two separate days, providing that they are performed within allowed visit window.

Visit 1 Week 2 ± 4 days:
This visit is planned to check if patients treated either with febuxostat or allopurinol starting dose have reached the sUA target or not. If patients will be at target levels of sUA they will continue with the same dose administered at randomization and will be evaluated for sUA levels at Week 12 (V2), conversely if patients will be not at target for sUA they will increase the dose of febuxostat to 120 mg/day or that of allopurinol to 200 mg/day. Patients treated with febuxostat 120 mg/day will be checked for sUA levels at Week 12 (V2). Patients treated with allopurinol not at target for sUA at subsequent visits will increase the allopurinol dose up to the maximum of 600 mg/day; if patients on allopurinol should reach the target sUA levels between the first and the last additional visit they will be checked again at Week 12 (V2).

The following parameters will be checked: concomitant medications, sUA, cigarette smoking and alcohol consumption, adverse events, dispensing study medication according to febuxostat or allopurinol dose reached, drug supply accountability.

Visit 2 Week 12 ± 4 days:
The following parameters will be checked: concomitant medications, physical examination, vital signs, efficacy parameters (Pulse wave velocity, pulse wave analysis , BNP, NTproBNP, oxidative stress parameters, markers of inflammation, endothelial activation/adhesion , fasting lipid levels, eGFR with CKD-EPI formula, urine albumin excretion measured as albumin/creatinine ratio), assessment of laboratory tests (serum Uric Acid, safety laboratory tests), tender and swollen joints, cigarette smoking and alcohol consumption, adverse events, dispensing study medication according to febuxostat or allopurinol dose reached, drug supply accountability.

Visit 3 Week 24 ± 4 days:
The following parameters will be checked: concomitant medications, physical examination, vital signs, efficacy parameters (Pulse wave velocity, pulse wave analysis, BNP, NTproBNP, oxidative stress parameters, markers of inflammation, endothelial activation/adhesion , fasting lipid levels, eGFR with CKD-EPI formula, urine albumin excretion measured as albumin/creatinine ratio), assessment of laboratory tests (serum Uric Acid, safety laboratory tests), tender and swollen joints, cigarette smoking and alcohol consumption, adverse events, dispensing study medication according to febuxostat or allopurinol dose reached , drug supply accountability.

Visit 4 Week 36 ± 4 days (End of Study Visit):
The following parameters will be checked: concomitant medications, physical examination, vital signs, efficacy parameters (Pulse wave velocity, pulse wave analysis, BNP, NTproBNP, Oxidative stress parameters, markers of inflammation, endothelial activation/adhesion , fasting lipid levels, eGFR with CKD-EPI formula, urine albumin excretion measured as albumin/creatinine ratio), assessment of laboratory tests (serum Uric Acid, pregnancy test, safety laboratory tests), Tender and swollen joints, cigarette smoking and alcohol consumption, adverse events, drug supply accountability.

Visit 5 Safety follow-up Visit (occurs 38 Weeks after randomization + 3 days after):
The following parameters will be checked: assessment of cigarette smoking and alcohol consumption and adverse events by a telephone call to the patient.

Additional visits:
Permitted in order to assess the sUA levels (evaluation performed by the site laboratory in real time or by a portable electrochemical blood uric acid meter available on site) may be scheduled for patients not at target (serum urate level >6 mg/dl) between Week 2 (V1) and Week 12 (V2), i.e.: at Week 4, 6, 8, and 10 to allow up-titration of allopurinol to the maximum dose permitted in the study. Adverse events and changes in concomitant medications will also be checked during additional visits.

Early Withdrawal Visit:
At the time of early withdrawal (if applicable), assessment of laboratory tests, pregnancy test, physical examination, vital signs, etc., as described for the End of Study Visit (ESV)

8.2 PRIMARY (EFFICACY) ENDPOINT

- Pulse Wave Velocity [51-59]

Subjects will rest in a supine position for at least 10 min after which blood pressure will be measured in triplicate using an automated blood pressure monitor (Omron705 CPII). Pulse wave velocity, i.e. the gold standard parameter to asses arterial stiffness will be assessed noninvasively using the validated SphygmoCor pulse waveform analysis system (AtCor Medical, Gloucestershire, UK). With the SphygmoCor instrument, PWV is calculated as the velocity of the wave from the heart to the femoral artery, measuring distance between femoral artery and carotid artery in agreement with indications of recent guide-lines and task force on the argument, i.e. by a rigid ruler using 80% of the distance to calculate PWV. A transformation formula will be employed to analyse PWV data obtained with the two different devices. Assessments and data analyses are carried out by individuals who are blinded to the study treatment administered to the patients. Detailed instruction on PWV conduction and preservation of blindness will be provided in a separate document – PWV Working Instructions.

8.3 SECONDARY EFFICACY ENDPOINTS

- Changes in BNP and NTproBNP values after 12, 24 and 36 weeks of treatment;
- Changes in inflammation markers (hsCRP, TNF-α, sUA, and plasma fibrinogen) after 12, 24 and 36 weeks of treatment;
- 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;
- Changes in lipid profile after 12, 24 and 36 weeks of treatment;
- 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.
- 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.
- Changes in eGFR with CKD-EPI formula after 12, 24 and 36 weeks of treatment;
- Changes in urine albumin excretion as evaluated by first morning urine albumin/creatinine ratio (mg/g) after 12, 24 and 36 weeks of treatment;

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

Detailed instruction on PWA conduction will be provided in a separate document – PWA Working Instructions.

The following laboratory parameters will be performed in ***central lab:***

- BNP, NTproBNP
- Markers of inflammation: hsCRP, TNF-α, plasma fibrinogen
- Oxidative stress parameters: MDA, MPO, Ox-LDL, PON1, PON2
- Markers of endothelial activation/adhesion: sVCAM, sICAM, vWF, e-selectine
- sUA, eGF, Serum creatinine and urine albumin to creatinine ratio
- Lipid profile

Details on all central laboratory analyses including reference ranges will be provided in Central Laboratory Manual.

8.4 SAFETY ASSESSMENT

Safety and tolerability will be assessed by the following parameters evaluated at screening (V-1), and at Week 2 (V1: for AEs only), 12 (V2) and 24 (V3) and 36 (V4):

- Collection and assessment of adverse events (AEs).
- Physical examination (Complete examination, including assessments of the skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, lymph nodes, extremities and body weight)
- Vital signs (systolic/diastolic blood pressure, pulse, body weight, axillary body temperature)
- ***Local laboratory evaluations*** :blood assessment of fasting glucose, fasting insulinemia, serum creatinine and calculated creatinine clearance, total and fractionated bilirubin, alkaline phosphatase, sodium, chloride, calcium and potassium, albumin, Hb, Ht, RBC,

WBC and differential count, platelets, AST, ALT, γGT, TSH, LDH, CPK and C-Reactive protein, coagulation (PT and/or INR), urinalysis – including blood, glucose, proteins)

- Pregnancy test (urine dipstick pregnancy test (for females of child-bearing potential or within two years to the menopause)

9. WITHDRAWAL OF PATIENTS AND DEVIATION FROM THE PROTOCOL

Specification on criteria for withdrawal of patients: patient and investigator criteria

The patient may withdraw from the study at any time without explanation, without losing the right to future medical care. The participation of the patient may, at any moment, be terminated by the investigator, if considered appropriate.

Patients who discontinue from the study early will complete an early termination visit that will correspond in terms of examinations and testing to the end of study visit (See: ESV in paragraph 8.1 study Procedures.

Study drug treatment must be terminated during the study for any of the following reasons:

- Patient becomes pregnant during the study
- Request of the patient
- Investigator deems it to be in the best interest of the patient to discontinue
- Failure to comply adequately with the dosing, evaluations, or other requirements of the study

The investigator must immediately notify the Sponsor or Sponsor designee by telephone or fax when a patient has been discontinued/withdrawn due to an AE.

The reason for the withdrawal must be well documented in the eCRF.

Any deviation from the protocol (to be classified as major or minor) will be accepted only in case of emergency and/or after a written agreement with the Sponsor.

10. ADVERSE EVENTS

10.1 DEFINITIONS

10.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

10.1.2 Drug Relationship

The relationship between an AE and study drugs will be judged according to the following categories:

1. **Certain**: The AE occurs in a plausible time relation to the administration of the drug and cannot be explained by a concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
2. **Probable**: The AE occurs in a reasonable time relation to the administration of the drug, it is unlikely to be attributed to a concurrent disease or other drugs or chemicals and it follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information (AE reappearance after drug reintroduction) is not required to fulfil this definition.
3. **Possible**: The AE occurs with a reasonable time relation to the administration of the drug, but it could also be explained by a concurrent disease or other drugs or chemicals. Information on drug withdrawal (dechallenge) may be lacking or unclear.
4. **Un-assessable**: The relationship cannot be judged, because of the information is insufficient or contradictory and cannot be supplemented or verified.
5. **Unlikely**: A causal relationship cannot be definitively ruled out, but
   - other drugs, chemicals, or underlying disease provide plausible explanations and/or
   - the temporal relation to the administration of the drug makes a causal relation improbable.
6. **Not Related**: Any of the following are present:
   - existence of a clear alternative explanation, and/or
   - unreasonable temporal relationship between Drug and Event, and/or
   - non-plausibility.

10.1.3 Adverse Drug Reactions (ADRs)

ADRs are all untoward and unintended responses to an investigational medicinal product related to any dose administered.

The definition implies a reasonable possibility of a causal relationship between the event and the Investigational Medicinal Product (IMP). This means that there are facts (evidence) or arguments to suggest a causal relationship.

ADRs are considered all AEs for which the relationship is considered as:

1. Certain
2. Probable
3. Possible

4. Un-assessable

AEs are **not** considered as ADRs when the relationship is judged as:

5. Unlikely
6. Not related

10.1.4 Seriousness

An AE/ADR is considered **Serious** when:

- results in death;
- is life-threatening;

Note: Life-threatening is considered any AE in which the patient 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.

- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is another medically important condition that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Any suspected transmission of an infectious agent via a medicinal product is considered serious and should be assessed under the category of medically important events in the absence of other seriousness criteria.

An AE/ADR is considered **Non-serious** when it does not fulfil the conditions for the definition of Serious AE/ADR.

10.1.5 Adverse Event (AE)/Adverse Drug Reaction (ADR) Intensity

The intensity level of a Serious or a Non-serious AE or ADR is attributed according to the following definitions:

- **Mild**: does not interfere with routine activities; in case of laboratory tests, when there is a mild abnormality
- **Moderate**: interferes with the routine activities; in case of laboratory tests when there is a moderate abnormality.
- **Severe**: makes it impossible to perform routine activities; in case of laboratory tests when there is an important abnormality.

10.1.6 Adverse Event (AE)/Adverse Drug Reaction (ADR) Expectedness

An AE/ADR is considered **unexpected** when the nature, severity, or outcome of the AE/ADR is not consistent with the information provided in the Reference Safety Document *(Summary of Product Characteristics).*

10.1.7 Serious Unexpected Adverse Drug Reaction (SUSAR)

Any serious adverse event judged by the Investigator or the Sponsor as drug-related (see Section 10.1.3), and considered as unexpected qualifies as a serious unexpected ADR (SUSAR).

SUSARs are subject to expedited reporting, as specified in Section 10.3.2, as having a "Reasonable Possibility" of relationship with the IMP.

10.2 MONITORING AND RECORDING OF ADVERSE EVENTS

All AEs occurred since signing informed consent will be collected and recorded in CRF.

At each visit the Investigator will assess any occurred subjective or objective AE.

AEs communicated by the patient or by the patient's relatives or delegates through phone calls, letters or emails will also be recorded. In these cases the Investigator will try to obtain medical confirmation and assessment of the occurred AE.

When an AE has occurred the **Investigator shall record within the concerned paper AE form any case, both serious and non-serious, whether or not thought to be drug-related**, observed in or reported by the patient (or relatives/delegates), specifying the judgement on the causal relationship with the study treatment.

Any available information and diagnostic measure (laboratory and instrumental tests, procedures, etc.) shall be recorded in and/or attached to the CRF.

The Investigator is expected to record also any AE occurring during the study follow-up period (of two weeks) after the administration of the last treatment dose.

The Investigator is expected to follow up any AE occurred during the study, including the follow-up period, until the outcome of the AE has been determined.

10.3 Management of Serious Adverse Events

10.3.1 Reporting Duties of the Investigator

The Investigator must report all the collected information on any Serious AE (SAE, whether or not thought to be related to the investigational drug) sending by fax /email the concerned paper AE form **no later than 24 hours** after the first knowledge of the occurrence of the event, according to the following contact details:

CRO Pharmacovigilance Officer: Ewelina Kijak or Szymon Sajdak
Fax: +48 12 622 44 60
Email: safety@ergomedplc.com
Tel: +48 12 622 44 62
Mobile: +48 691 90 35 44

The investigators will receive detailed instruction regarding means of reporting, before start of enrolment phase of the study.

In case of serious cutaneous/hypersensitivity reactions and/or hepatic events, the Investigator is required to perform any attempt for collecting all the available additional clinical information, by filling in the specific FU forms as in Appendix 6a and Appendix 6b.

The mentioned FU forms duly filled will be sent by the Investigators to the CRO by fax, while for the possible photographic documentation the Investigator will contact the CRO for receiving adequate instruction for sending.

When relevant, also the ~~e~~-CRF pages concerning medical history, concomitant medication, and laboratory tests will be retrieved and forwarded by the CRO to the Sponsor

Any further information and supporting documentation that becomes available (copies of laboratory reports, tests, procedures, autopsy evidence of the cause of death, etc.) shall be provided no later than 24 hours after the knowledge, by the Investigator to the CRO by fax or email

The Investigator must also comply with the local applicable obligation(s) on the reporting of ADRs to the local concerned Regulatory Authority/Ethics Committee.

10.3.2 Reporting Duties of the Sponsor

The Sponsor shall ensure that all relevant information about any suspected serious and unexpected adverse drug reaction (SUSAR), will be expeditiously reported to the competent Authorities (including EudraVigilance Clinical Trial Module for clinical trials for which a EudraCT number has been assigned) and Ethics Committees (following general and local rules and procedures), with these deadlines after the first knowledge, intended as the day when the CRO receives the notification of the SUSAR:

- Fatal and life threatening suspected unexpected adverse reactions , no later than 7 days;
- Other suspected unexpected serious adverse reactions, no later than 15 days.

The Sponsor shall ensure that all relevant information and supporting documentation that subsequently become available will be also expeditiously reported as follow-up information according to the above mentioned deadlines.The following safety issues will be subjected to expedited management for the identification of possible necessary actions:

- SAEs associated with the trial procedures
- Potential clinically significant findings emerging from non-clinical studies

- An anticipated end or suspension for safety reasons of another trial with the same study drug.

When appropriate and applicable the Sponsor will arrange the adequate information also to the Investigators.

10.4 Management of non-serious adverse events (NSAEs)

The Investigator will record all the available information on each occurred NSAE in the concerned paper AE form and will forward them to the CRO by fax (see section 10.3.1) within 10 calendar days after the knowledge.

The CRO will forward to the Sponsor the above mentioned AE form, until all the cases occurred during the study and follow-up period have been collected.

When relevant, also the ~~e-~~CRF pages concerning medical history, concomitant medication, and laboratory test will be retrieved and forwarded by the CRO to the Sponsor.

Any further information and supporting documentation that become available (copies of laboratory, tests, procedures etc...) shall be provided by the Investigator trough additional written reports to the CRO officer for forwarding to the Sponsor.

At Sponsor level the collected cases will be finally assessed for the eventual identification of potential safety concerns and eventual consequent actions including the collection of the all the available additional clinical information on significant cutaneous/hypersensitivity reactions and/or hepatic events by filling the above mentioned FU forms.

10.4.1 Management of laboratory abnormalities

During the clinical trial, abnormalities in laboratory analyses (newly occurring after IMP administration or worsening of previously known abnormalities) which are considered clinically relevant by the Principal investigator (values significantly above or under normal range or which require an intervention or diagnostic tests, or may result in the IMP discontinuation) should be reported as AEs. Concerning the laboratory parameters measured in the central laboratory (see section 8.3), these will be entered in the concerned eCRF pages and they will be assessed as secondary efficacy endpoints.

However, all “out of range” values should be collected and reviewed by the CRO and the Sponsor on a monthly basis.

10.5 Management of Pregnancy Exposure Cases

The Investigator is expected to record in a specific provided form any case of pregnancy exposure occurring in a female patient or in a patient’s partner during the treatment and follow-up periods, sending it by fax or email to the CRO within 5 days after being made aware of the pregnancy.

The CRO will forward the mentioned form to the Sponsor within 24 hours.

The Investigator is requested to follow each case of pregnancy exposure until the outcome.

If the pregnancy results in an abnormal outcome, this will be recorded in the CRF as a SAE and managed as above described.

11. DATA QUALITY MANAGEMENT

11.1 Study Documentation/Data Collection

11.1.1 Case Report Forms

Data collected during the study will be recorded in an electronic CRF (eCRF), which is confidential. Data reported on the CRF have to be consistent with the source documents. The Investigator must ensure the accuracy, the completeness and the consistency of the data entered in the CRF.
On the CRF, patients will be identified by the patient number, assigned at the Screening Visit. The patient number will be a number composed of combination of site and patient number assigned at screening.
During the conduct of the clinical part of the study, the CRF must be available and up-to-date, so that it always reflects the latest observations on the respective patient.

The Investigator will be responsible for entering study data into the CRF in accordance to the CRF user guidelines.

Entries in the CRF must be made in English language. The study monitor will review the CRFs and in case of inconsistency or missing data the Investigator will be asked for correction or completion. Corrections must be made in line with eCRF completion guideline.

11.2 Patient Records/Source Data Documentation

For each patient participating in the study, the Investigator must keep a written or electronic patient record, separate from the electronic CRF. These patient records are considered as source documents, contain all data raised in the study to be transferred into the CRF.
(Patient records shall also contain the complete 12-Lead ECG tracing report, when defined data/values are reported into the CRF).

11.3 Data Quality Control/Study Monitoring

The Investigator will be contacted by the study monitor on a regular basis. The monitor will have the responsibility of reviewing the ongoing study with the Investigator to verify adherence to the protocol and to deal with any problems. CRFs will be checked for completeness and consistency with the source data and special attention should be dedicated to the following items: patient enrolment, obtaining of the signed informed consent, occurrence of AEs, drug accountability, and accurate recording of efficacy and safety variables. At all times, the confidentiality of study related documents will be maintained. The

Investigator agrees to allow access to all study materials needed for the proper review of study conduct. The Investigator agrees to assist the monitor in resolving any problem that may be detected during the monitoring visit or data cleaning process. The CRO will perform all monitoring activities.

Direct Access to Primary Patient Data:
Clinical monitor(s) and any further party allowed should be given direct access to primary patient data (i.e. source data) which supports the data on the CRFs for the study, i.e., general practice charts, hospital notes, appointment books, original laboratory records etc. Direct access is defined as the permission to examine, analyse, verify and reproduce any records and reports that are important for evaluation of a clinical study. Any party allowed direct access to study source data and documents should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and Sponsor proprietary.

11.4 Quality Assurance

An independent quality audit/inspection at the study site may take place at any time during or after the study. The independent audit/inspection can be carried by the Sponsor independent Quality Assurance (QA), by a CA, or an IRB/EC.

12. STATISTICS

12.1 STUDY DESIGN (BLINDING AND RANDOMISATION)

The study is a randomized, active-controlled, open label, evaluator blind, parallel-group, multi-centre, multi-national, Phase IV trial.

The randomization list will be based on the “RANUNI” random number generator of the SAS software (SAS Institute, Cary, NC, USA), randomization will be in a 1:1 ratio of Febuxostat versus allopurinol, no cross-centre randomization will be performed.

The study personnel responsible for randomization and drug supply handling is unblinded to study medications and therefore will not be involved in the main efficacy evaluations of each patient randomized in the study. Conversely, the study physician/s responsible for the main efficacy evaluations (pulse wave velocity, etc.) will be blinded to study treatments.

In addition, all key efficacy variables included in the pulse wave analysis (i.e.: modifications of PWV, arterial stiffness, central blood pressure, augmentation index), will be performed by an independent core laboratory where the central reader will be blinded to the treatment assigned to patients.

Fasting lipid levels, NTproBNP, BNP, markers of inflammation and endothelial activation/adhesion, oxidative stress parameters, eGFR, changes in urine albumin excretion as evaluated by first morning albumin/creatinine ratio will be also measured by a central laboratory.

12.2 DETERMINATION OF SAMPLE SIZE

For the primary efficacy endpoint (Pulse Wave Velocity), febuxostat will be tested for superiority to allopurinol.
A sample size of 79 in each group will have 85% power to detect a difference in means of 1.8 m/sec at Week 36 assuming that the common standard deviation is 3.75 m/sec using a two group t-test with a 0.05 two-sided significance level. Expecting a drop-out rate of approximately 15%, the total number of subjects to be randomized in order to achieve the planned sample size will be 91 per treatment arm.

12.3 ANALYSIS POPULATIONS

The following analysis population will be defined:

- Full Analysis Set (FAS): All randomised patients who have taken at least one dose of IMP specified by treatment group and performed at least one primary efficacy assessment (PWV) after randomisation.
- Per-protocol (PP): All patients randomised to either of the two treatment groups and having completed the study without any major protocol violation as per blinded data review meeting.
- Safety: All patients randomised to any of the two treatment groups and having taken at least one dose of IMP.

The PP will consist of the randomized patients who:

- did not have major deviations from inclusion and exclusion criteria as per blinded data review meeting;
- have received at least 80% of the expected amount of the treatment assigned at the end of the randomization procedure;
- have completed all the planned study visits and have been evaluated for the primary endpoint of the study at the final visit.
- The list of patients excluded from the PP population will be determined prior to data unblinding.

Based on the definitions above, the subjects and data will be classified into analysis sets at a data review meeting held after all the data have been entered into the study database and verified.
The numbers of patients who will be excluded from the Per-protocol Population will be presented for each specific reason, grouped by treatment. A frequency table representing the occurrence of each of the major and minor protocol deviations in each treatment group will be created.

12.4 ANALYSIS VARIABLES

Primary efficacy variable

The primary efficacy objective is to evaluate the effects of febuxostat and allopurinol on Pulse Wave Velocity (PWV) after 36 weeks of treatment. The primary efficacy variable will be the 36 weeks PWV value.

Secondary variables

The following variables of interest will be considered for the secondary endpoints:

- Changes in BNP and NTproBNP values after 12, 24 and 36 weeks of treatment;
- Changes in inflammation markers (hsCRP, TNF-α, sUA, and plasma fibrinogen) after 12, 24 and 36 weeks of treatment;
- 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;
- Changes in lipid profile after 12, 24 and 36 weeks of treatment;
- Percentage of gout patients with a serum urate concentration below or equal to 6 mg/dl after 12, 24 and 36 weeks of treatment.
- 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
- Changes in eGFR with CKD-EPI formula after 12, 24 and 36 weeks of treatment;
- Changes in urine albumin excretion as evaluated by first morning urine albumin/creatinine ratio (mg/g) after 12, 24 and 36 weeks of treatment;
- 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;
- Tender and swollen joint count;
- Pulse Wave Analysis (including modifications of PWV, arterial stiffness, central blood pressure and augmentation index) after 12, 24 and 36 weeks of treatment (in selected sites only);
- 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)
- Safety and tolerability

12.5 STATISTICAL ANALYSIS

All p-values will be rounded to three decimal places. Statistical significance will be declared if the rounded p-value will be less than 0.050. If a p-value is less than 0.001 it will be reported as “<0.001.” If a p-value is greater than 0.999 it will be reported as “>0.999.”

Statistical analyses will be performed by using SAS Software.

The primary efficacy analysis will be based on the Full Analysis Set (FAS); it will include all patients randomized and treated. The primary endpoint is Pulse Wave Velocity (PWV) after 36 weeks of treatment with febuxostat or allopurinol. The missing data will be imputed using the Last Observation Carried Forward (LOCF) approach; the sensitivity analysis using with imputations based on the means of available data within a treatment group at a given time point will be conducted if feasible.

Analysis of covariance (ANCOVA) with the 36 weeks PWV value as dependent variable, treatment group as factor and age, baseline blood pressure, baseline PWV at 36 weeks as covariates, will be used to compare the efficacy of the two treatment groups. The covariates found not to be statistically significant at the 0.05 two-sided significance level, will be removed from the model; the final model will only include statistically significant covariates. For covariates found to be significant, the treatment by covariate interaction will be evaluated using ANCOVA model with the terms for treatment, covariate and treatment by covariate interaction. If interaction is statistically significant at the 0.1 two-sided significance level, additional analyses will be performed to explore the interaction.

The sensitivity analysis with the change from baseline to Week 36 in as response variable will be performed similarly to the primary analysis.

The relationship between PVW at Week 36 (change from baseline to Week 36) and febuxostat dose will be explored using scatterplots.

The efficacy evaluation will be performed in both FAS and PP Populations. The Full Analysis Set (FAS) will be the primary analysis population. A sensitivity analysis based on the Per-Protocol (PP) Population will be performed. The number of patients excluded from the PP population will be summarized by treatment. The list of patients excluded from the PP population will be determined prior to unblinding the data.

Secondary Efficacy Analyses

For the analysis of continuous secondary efficacy variables the ANCOVA model with change from baseline to respective time point as a response variable and respective baseline value and treatment group as the terms in the model will be used at each time point.

The Last Observation Carried Forward (LOCF) method will be utilized for missing data imputations.
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 and 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 will be analyzed using logistic regression model at each time point to assess the difference between treatment regimens. Dependent

variable is defined as a binary outcome (assessed as 1 if urate concentration ≤ 6 mg/dl, 0 otherwise). Treatment group and baseline urate concentration will be included as independent variables.

Time to achieve sUA target levels will be analysed using proportional hazards model with treatment group and baseline sUA as covariates.

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 will be analysed descriptively.

No correction for multiple testing will be applied to the secondary endpoints.

Safety Analysis

Evaluation of safety will be performed on the "safety population" and will be based on frequency of adverse events, safety markers, laboratory parameters, vital signs.

Safety will be assessed by comparing differences between the two treatment groups in:

- Incidence of all Adverse Events.
- Serious Adverse Events/hospitalizations.
- Withdrawals due to any Adverse Event.
- Safety markers.
- Laboratory evaluations
- Vital signs (systolic/diastolic blood pressure, pulse, body weight, axillary body temperature).

Adverse Events will be coded using the MedDRA dictionary and will be classified for each treatment group by presenting the number and percentage of patients having had an Adverse Event, both overall and by body system.

For quantitative laboratory parameters, mean changes from baseline to the different study visits as well as to the final value will be summarized. Laboratory data values will be categorized as low, normal, or high based on normal ranges of the laboratories used in this study. Shift tables from baseline to final values will be created for each variable. The shift tables cross tabulate the frequency of patients with baseline values below/within/above the normal range versus final values below/within/above the normal range.

Physical examination will be presented in the data listing by subject and treatment group.

For systolic and diastolic blood pressure, mean changes from baseline to the different study visits as well as to the final value will be summarized.

12.6 PROTOCOL VIOLATIONS AND BLIND REVIEW

The full list of protocol deviations for the study report, those assessed either prior to randomization or after randomization, will be compiled prior to database closure, following the evaluation of the Data Review Committee.

12.7 STATISTICAL ANALYSIS PLAN

Any deviation from this statistical analysis approach will be well justified and documented in the Statistical Analysis Plan (SAP). The Statistical Analysis Plan will be finalized and signed-off prior to database lock. Other analyses that could be included in the final ICH Clinical Study Report will be fully documented and justified in the analyses performed section.

13. MONITORING/AUDITS/REGULATORY INSPECTIONS

13.1 Monitoring

Ergomed representatives (and/or designee) and regulatory authority inspectors are responsible for contacting and visiting the clinical sites for the purpose of inspecting the facilities, to inspect the various records of the trial (e.g. CRFs and other pertinent data), provided that subject confidentiality is respected. Ergomed's monitor or representative will notify the investigator before conducting any clinical site visit.

The sponsor's monitor (or designee) is responsible for inspecting the CRFs at regular intervals throughout the trial to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subjects' medical records and any other trial-related records needed to verify the entries in the CRFs. It is important that the investigator and other trial personnel are available during the monitoring visits and that sufficient time is devoted to the process. The investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

13.2 Audits

In accordance with ICH GCP and Ergomed's and/or its designee's or Sponsor's audit plans, this trial may be selected for an audit. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories) and review of trial-related records will occur in order to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

The investigator will permit an independent audit by an auditor mandated by the sponsor, after reasonable notice. An audit or a regulatory inspection is intended to determine if the trial was conducted as per protocol, GCP, and applicable regulatory requirements; if the rights and well-being of the subjects were protected; and if the data relevant for the evaluation of the IMP were captured, processed and reported in compliance with the planned arrangements.

13.3 Regulatory Inspections

Regulatory authorities may perform an inspection of the trial until several years after its completion. As for an audit, the investigator will permit a direct access to all trial documents, IMP accountability records, source records, and source data. If an inspection is announced, the sponsor will be informed without delay.

The investigator/institution guarantees access to source documents by the Sponsor, Ergomed and/or its designee, the FDA, the EMA, other regulatory bodies, and the IRB/IEC.

14. ETHICS ASPECTS

This study will be carried out in compliance with the study protocol, the recommendations on biomedical research on human subjects of the Declaration of Helsinki, International Conference of Harmonisation – Good Clinical Practice (ICH-GCP) Guidelines, EU-Directive 2001/20 of April 4, 2001, and national requirements of the participating countries.
All clinical work conducted under this protocol is subject to GCP rules. This includes audit/inspections by the Sponsor, and/or by national/international Health Authority representatives at any time. All Investigators must agree to the inspection of the study site, facilities, and of study related records by the Health Authority representatives and/or by the Sponsor, and/or its delegates, which must be performed in accordance with national laws concerning personal data protection.

14.1 Ethics Committees

Before starting the study in a study site, study protocol and relevant documentation (Patient information leaflet, the informed consent Form and the Investigator's Brochure) must be submitted to and approved by the Institutional Review Board/Ethics Committees (IRB/EC) and the Competent Authorities (CAs) of the participating countries.
In addition, all local national legal requirements for the conduct of a clinical study have to be followed prior to the start of the study. Any amendment to the protocol, before implementation, will be submitted to the ECs for approval, after prior discussion between the Sponsor and the Co-ordinating Investigator.
The CAs and IRB/ECs of the participating countries will be informed about any changes in the study protocol, the end of the study, or the premature study termination as appropriate and within the requested time period.

14.2 Informed consent

Prior to the subject's enrolment into the study and before performing any study-related procedures, the Investigator - or its authorised delegate - shall obtain the subject's written, dated and signed informed consent to participate into the study and to the confidential disclosure, processing and transferring necessary documentation of the subject's health and personal data to CRO, Sponsor and its Affiliates, the competent Health Authorities and any other institutions (even if located outside the European Economic Area), as legally required and in accordance with the applicable privacy laws.

Institution and Investigator undertake to duly inform patients about personal data processing and the relevant applicable privacy rights before their participation into the study.

Prior to be submitted to the patient, *the Patient Information and Informed Consent form (PIC)* must be approved in the corresponding local language and in accordance with local laws and regulations by the IRB/EC.
In the patient information leaflet, patients will be given information and fully comprehensive explanation in easily understandable terms of the study procedures, regarding the benefits, restrictions, discomforts, and risks in taking part in the study, the properties of the Investigational Medicinal Product

(IMP), the method of assignment to treatments, and any medically accepted and readily available treatment other than the IMP.
Patients will also be informed about the measures taken to ensure their confidentiality according to the pertinent legislation. The Investigator should provide the patient with an emergency telephone number.
After being duly informed and interviewed by the Investigator, the patient freely has to date and sign a PIC before being enrolled into the study and before undergoing any study procedure. The Investigator must store the original of the signed PIC in the Investigator's File, and the patient will be provided with a copy of it.
If a protocol amendment would affect the terms of the PIC, it will be revised to reflect the protocol change and submitted to IRB/EC for approval.
The Investigator will ensure that this new consent form is signed by all patients subsequently entered in the study and those currently in the study, if affected by the amendment.

14.3 Patient's Insurance

For patients participating in the study, Sponsor has stipulated an insurance policy in accordance with local regulatory requirements.
Details on the insurance company, the insurance number and conditions will be made available to patients in the PIC and/or provided as a separate document, in accordance with national requirements.
A copy of the insurance certificate will be provided to each Investigator and will be filed in the Investigator's File at the sites and in the study's Trial Master File (TMF).

The Investigator must notify to Sponsor immediately upon notice of any claims or lawsuits.

15. CONFIDENTIALITY AND DATA PROTECTION LAWS COMPLIANCE

By signing the study protocol, the Institution and the Investigator (including their appointed staff) acknowledge that the performance of the study will imply processing of personal data. Personal data processing is regulated by the Sponsor national legislation as well as local laws (i.e. the country where the study is conducted): such provisions will apply mandatorily. The Sponsor specifies that strict compliance with the applicable data protection laws by any parties and relevant employees who take part in the study is an essential condition for the appointment of and the collaboration with research institutions, investigators, CROs, etc.

The parties shall acknowledge that according to the applicable privacy laws, Sponsor and Institution/s will act as independent data controllers while CRO and Investigator/s will act as data processors. Before the beginning of the Study, the Institution will appoint in writing its Principal Investigator as data processor.
Given the sensitive nature of data processed in the frame of the Study, the parties undertake to adopt adequate safety measures (physical, logical, organisational, technical, I.T. etc) to warrant that data will always be processed safely and in compliance with privacy laws

Investigator and Institution (including their personnel) shall comply with the applicable privacy laws and Sponsor instructions on the protection of personal data. Such an obligation will include by way of example: (i) the duty to provide the subjects involved in the Study with adequate, law-compliant notice such as the "information notice and consent form to process personal data"; (ii) the duty to collect the consent of the subjects involved in the Study prior to their participation; (iii) the duty to respect privacy rights of any data subjects as established by applicable privacy laws; (iv) the duty to adopt all physical, logical, organizational, technical and I.T. security measures in accordance with applicable privacy laws.
By signing the study protocol, the Investigator (and his/her appointed staff) affirms that any information and all the study documents provided by the Sponsor will be maintained in confidence.
None of this material may be disclosed to any party not directly involved in the study without written permission from Sponsor.
Investigator must assure the patient's anonymity will be maintained. The Investigator will keep a separate log of the patient's study numbers, names, addresses and telephone numbers. The Investigator will maintain this for the longest period of time allowed from own institution and in any case, till further communication from Sponsor. The Investigator will supply the Sponsor with all the data/results from the study. All information concerning the study and the drug is confidential and the property of the Sponsor.
The Sponsor will prepare the final report, including the statistical and clinical evaluations. The Investigator's agreement and signature will be obtained and a copy will be provided to the Investigator. Only the Principal Investigator will sign the final report. Sponsor reserves the right to publish and present data and results of the present study at scientific meetings, or to submit these clinical trial data to national and international Regulatory Authorities. The Investigator may not use the results of this study for publication or presentation without authorization from Sponsor.

16. RECORDS RETENTION

The Investigator should keep all study-related documents, as specified in ICH/GCP Section 8 “Essential Documents for the Conduct of a Clinical Trial” and all study documents as specified by the applicable regulatory requirement(s), in the Investigator's Trial Centre File.

The Investigator will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility.

The Sponsor must be notified in writing of the name and address of the new custodian.

If it becomes necessary for the Sponsor and/or a Regulatory Authority to review any documentation related to this study, the Investigator must permit access to such documentation.

Any difficulty in storing original documents should be discussed with the Sponsor personnel prior to initiation of the study".

17. PROTOCOL MODIFICATIONS

The protocol must be read thoroughly by everybody whom the information therein concerns and the instructions must be exactly followed.

Changes in the study protocol will require a protocol amendment. Such amendments will be agreed upon and approved in writing by all signatories of the protocol. If amendments are substantial, i.e. are likely to have an impact on the safety of the patients, or to change the interpretation of the scientific documents in support of the conduct of the study, or if they are otherwise significant, the IRB/ECs and the CAs in the participating countries have to approve these amendments before implementation.

Changes which have no significant impact on medical or scientific validity of the study will be agreed upon and approved in writing by all signatories of the protocol and the IRB/EC will be notified of this protocol amendment.

Any substantial amendments of the protocol will be integrated in an updated study protocol. The Principal Investigator must ensure full compliance with the updated study protocol.

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SIGNATURE PAGE- Approval Page

APPROVAL PAGE

(to be kept in original in the Sponsor Trial Master File, in the CRO's Trial Master File and in the Trial Center File of the coordinating centre. Copy of signed pages should be filled in the Trial Center File of each involved centre.)

Study Title: : 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 (Acronym: the FORWARD Trial)

Code: MEIN/14/FEB-PWV/001

EUDRA-CT number: 2014-005567-33

The signers confirm that they have read and approved the protocol

Study Medical Expert: ELENA ANDREASSI MARINELLI

Signature & Date: 01/04/2016

Co-ordinating Investigator(s): CLAUDIO BORGHI

Signature & Date: 1/4/2016

Statistician: MARTIN OVČAROV

Signature & Date: 05/04/2016

Investigator's approval Page

INVESTIGATOR'S APPROVAL PAGE

(to be kept in original in the Trial Center File and in the CRO's Trial Center File)

I understand that all information concerning the product Febuxostat (Adenuric®) supplied by Menarini International Operations Luxembourg S.A .in connection with this study protocol are confidential information. This information includes: Protocol, Investigator's Brochure, Case report Form, and any other confidential documents supplied in the context of this study.

I understand that any change in this study protocol must be approved in writing by the sponsor , the Co-ordinating Investigator and the Ethics Committee before implementation, except where necessary to eliminate apparent immediate hazard to patients.

I confirm that I will conduct the study according to this protocol (except when mutually agreed to in writing with the sponsor), in accordance with the Good Clinical Practice (GCP), the Declaration of Helsinki and laws and regulations in the Country where the study is to be conducted.

I confirm that I will record and report all adverse events occurring during the study, according to this protocol.

I confirm that I am informed of need to record retention and that no data can be destroyed without the written consent of the sponsor.

Principal Investigator: _____

Signature & Date: _____

APPENDICES

Appendix 1: Declaration of Helsinki

Appendix 2: the Joint Task Force of the European Society of Cardiology and other European Societies on cardiovascular disease prevention in clinical practice

Appendix 3: SmPC Febuxostat: (ADENURIC®).

Appendix 4: SmPC Allopurinol (Allopurinol TEVA) .

Appendix 5: "Preliminary criteria for the classification of the acute arthritis of primary gout - ACR 1977"

Appendix 6a: Hepatic Adverse Event additional information form

Appendix 6b: Cutaneous Adverse Event additional information form