

STATISTICAL ANALYSIS PLAN

Protocol No: MEIN/14/FEB-PWV/001 (FORWARD)

Version Number: 2.0

Date of Issue: 2018-03-16

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Sponsor:	Menarini International Operations Luxembourg S.A.
Title of Protocol:	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)
Protocol Version/Date:	1.4, 2016-03-30
CRF Version:	22-09-2016
Supersedes SAP Version:	1.0, 2018-02-05

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Document authorization

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Consistency check with the Protocol (one option to be selected)

- ☐ This is to confirm that as part of the SAP finalization consistency check with the current protocol / protocol amendment was performed by the trial statistician, and no changes to the protocol (statistical section) are required
- ☐ Changes to the analysis principles were required, and the responsible team has confirmed commitment to update the study protocol
- ☒ Changes to the analysis principles were required (as outlined in revision history section of this SAP), however it was not feasible to update the study protocol, since trial already ended at the time of deviation identification.

Heike Hucke
Trial Statistician
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Change control

Date	Author	Reason	Version
2018-03-14	Heike Huckle	Explaining why the parameters PON1 and PON2 as specified in the protocol cannot be analyzed as planned (ref. section 3.2). References to these parameters had already been omitted in version 1.0	V2.0
2018-02-05	Heike Huckle	NA; Initial version	V 1.0

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LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
CKD-EPI	Chronic Kidney Disease Epidemiology collaboration
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CV risk score	CadioVascular risk score
DD	Drug Dictionary (WHO Coding Thesaurus)
DMP	Data Management Plan
DVP	Data Validation Plan
ECG	Electrocardiogram
EOT	End of Trial
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
hsCRP	High-sensitivity CRP
IMP	Investigational Medicinal Product
IRB	Independent Review Board
LOCF	Last Observation Carried Forward
MDA	Malondialdehyde
MPO	Myeloperoxidase
MedDRA	Medical Dictionary for Regulatory Activities
n.a.	Not applicable
NTproBNP	N-terminal Propeptid BNP

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Abbreviation	Description
Ox-LDL	Oxidized Low-Density Lipoprotein cholesterol
PON1	Paraoxonase 1
PON2	Paraoxonase 2
PP	Per-Protocol
PWA	Pulse Wave Analysis
PWV	Pulse Wave Velocity
PT	Preferred Term
QC	Quality Control
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software package
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
sICAM	Soluble Intercellular Cellular Adhesion Molecule
sUA	Serum Urate Concentration
sVCAM	Soluble Vascular Cell Adhesion Molecule-1
TEAE	Treatment Emergent Adverse Event
TLFs	Tables, Listings, Figures
TMF	Trial Master File
TNF- α	Tumour Necrosis Factor Alpha
TS	Trial Statistician
TSH	Thyroid Stimulating Hormone
ULT	Urate Lowering Therapy
vWF	Von Willebrand Factor
WHO	World Health Organization

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1 STUDY MATERIAL

The following material was considered for this SAP:

Document	Version, Date
Protocol, incl. last amendment	1.4: 2016-03-30
CRF	22-09-2016
DMP	2.0, 2018-01-23
DVP	2.0, 2018-01-23

2 STUDY INFORMATION

2.1 Primary objective

The primary objective is the comparison of the effects of febuxostat and allopurinol on Pulse Wave Velocity (PWV) after 36 weeks of treatment.

2.2 Secondary objective

- 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), 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

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- 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 centers only)
- Safety and tolerability

2.3 Study design

This study is designed as a randomized, active-controlled, open label, evaluator blind, parallel group, multi-center, multi-national, Phase IV trial. Patients will be randomized 1:1 to receive febuxostat or allopurinol.

There will be approx. 35 sites in the following countries: Germany, the Netherlands, Italy, Poland, Serbia, Romania.

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).

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, changes in urine albumin excretion as evaluated by first morning albumin/creatinine ratio will be also measured by a central laboratory.

Eligible patients will be randomized to treatment with allopurinol 100 mg or febuxostat 80 mg (1:1 ratio). Up-titration of allopurinol or febuxostat to the maximum dose permitted in the study may be performed between Week 2 and Week 10, see flow chart below for details.

A follow-up safety assessment will be performed by a phone call 2 weeks after study termination.

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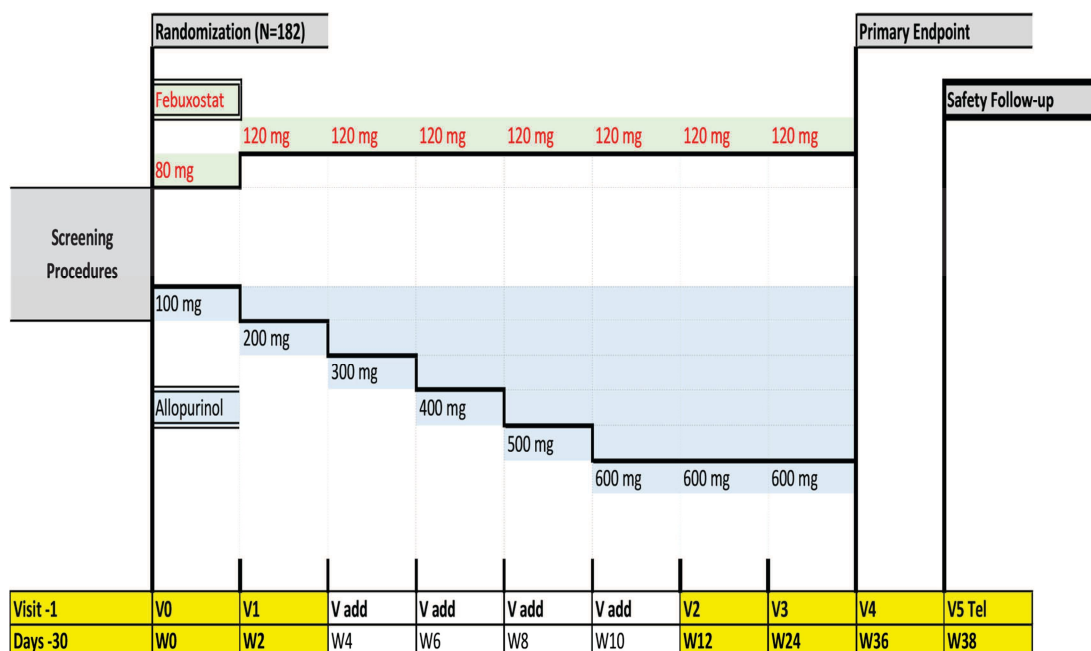
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Trial flow chart



Notes:

	Day -30 to Week -1	Day 0	Week 2 ± 4 days	Week 12 ± 4 days	Week 24 ± 4 days	Week 36 ± 4 days	Week 38 + 3 days after
	Visit -1	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5 Phone call
	Screening	Randomization	On Treatment Visit	On Treatment Visit	On Treatment Visit	End of Study visit	Safety Follow up
Inclusion/exclusion crit.	X						
Informed consent	X						
Randomization		X					
Medical history	X						
Concomitant medications	X	X	X	X	X	X	
Physical examination	X			X	X	X	
Vital signs (BP, HR body temperature)	X	X		X	X	X	
Height, Body Weight, demography	X						
12-Lead ECG	X						
Pulse Wave Analysis (PWA): PWV, arterial stiffness, central blood pressure, augmentation index		X		X	X	X	
BNP, NTproBNP		X		X	X	X	

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	Day -30 to Week -1	Day 0	Week 2 ± 4 days	Week 12 ± 4 days	Week 24 ± 4 days	Week 36 ± 4 days	Week 38 + 3 days after
	Visit -1	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5 Phone call
	Screening	Randomization	On Treat- ment Visit	On Treat- ment Visit	On Treat- ment Visit	End of Study visit	Safety Follow up
Serum Uric Acid	X		X	X	X	X	
Oxidative stress parameters: MDA, MPO, Ox-LDL, PON1 and PON 2		X		X	X	X	
Markers of inflammation: hsCRP, TNF-α, plasma fi- brinogen		X		X	X	X	
Markers of endothelial activa- tion/adhesion: sVCAM, sICAM, vWF, e-selectine (selected sites)		X		X	X	X	
Fasting lipid levels	X			X	X	X	
eGFR		X		X	X	X	
Urine Albumin excretion measured as Albumin to cre- atinine ratio		X		X	X	X	
Tender and swollen joint count		X		X	X	X	
Cigarette smoking, alcohol consumption	X	X	X	X	X	X	X
Urine pregnancy test		X				X	
Safety Laboratory Tests	X			X	X	X	
IMP dispense		X	X	X	X		
IMP accountability			X	X	X	X	
Adverse events	X	X	X	X	X	X	X

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.

2.4 Planned sample size

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, in total 182.

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3 GENERAL INFORMATION

3.1 Background details

The data will be transferred to SAS from the Clinical Data Management System Viedoc. If applicable external data will also be transferred to SAS for presentation of these data in the statistical analyses.

The SAP will be finalized before database lock and unblinding.

3.2 Deviations from the trial protocol with regard to statistical analyses

Due to a misinterpretation by project team the secondary endpoint parameters 'Paraoxonase 1 (PON1)' and 'Paraoxonase 2 (PON2)' were not measured [for enzymatic activity](#), but [genetic tests were performed](#) instead. Since these genetic tests were not planned by the protocol they have not been included in the database nor mentioned in sec 2.2 and 5.7.2. Therefore, no analysis can be performed for PON1 and PON2 as planned in the protocol.

3.3 Individual protocol deviations

Any deviation from protocol will be discussed case by case before database lock or unblinding whether the deviation has to be regarded as minor or as major (and therefore lead to exclusion from particular analysis populations).

The assessment of individual protocol deviations will be made in a Data Review Meeting. A complete listing of protocol deviations and the judgment for assessment of subject disposition will be signed before database lock. All deviations along with the disposition of each subject will be recorded in a separate database member that will become part of the study database. A description of all major protocol violations will be included in the table part of the CSR.

Criteria for major protocol violations will at least include:

- Any substantial violation of in- or exclusion criteria.
- Use of prohibited concomitant medication that may interfere with the assessment of efficacy.
- Receipt of wrong dose of study medication. Randomization errors.
- Trial subjects that developed study withdrawal criteria but were not withdrawn, receipt of wrong dose, use of concomitant medications not allowed
- Non-compliance regarding intake of study drug, i.e. less than 60% or more than 120% of required study drug intake since last visit (see also section 5.3)

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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.

4 ANALYSIS POPULATIONS

The disposition of subjects will be displayed according to the following analysis populations:

- Safety (SAF) population,
- Full Analysis Set (FAS),
- Per-Protocol (PP) population.

4.1 Safety population

All patients randomized to any of the two treatment groups and having taken at least one dose of IMP.

4.2 Full analysis set population

The full analysis population (FAS) includes all randomized patients who have taken at least one dose of IMP. and performed at least one primary efficacy assessment (PWV) after randomization.

4.3 Per-protocol population

The per-protocol (PP) populations are a subset of the FAS population.

Two separate per-protocol populations will be considered:

Per-protocol population 1 (PP1) includes all patients randomized to either of the two treatment groups and having completed the study without any major protocol violation as per blinded data review meeting. Patients must have completed all the planned study visits and have been evaluated for the primary endpoint of the study at the final visit.

Per-protocol population 2 (PP2) includes all patients randomized to either of the two treatment groups and having completed the study without major protocol violations which might have an impact on the evaluation of the primary objective of the study.

4.4 Subgroup analyses

No subgroup analyses are planned.

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5 STATISTICAL ANALYSES

All statistical analyses will be performed using SAS® for Windows (Version 9.3 or later). Descriptive statistics will always be given by treatment group. For baseline and basic variables, they will also be given for the entire population. Unless otherwise noted below all analyses will be based on the FAS population.

If not stated otherwise the following standard descriptive statistics will be presented:

Descriptive statistics for continuous data

Number of subjects (N), arithmetic mean, standard deviation (SD), minimum, lower quartile, median, upper quartile and maximum will be presented. Usually mean and quartiles will have 1 decimal more, SD 2 decimals more than the original values (as given with min, max); N has no decimals. These descriptive statistics will be determined for measured values and for differences to baseline.

Descriptive statistics for categorical data

Absolute frequencies (N) and relative frequencies (%) will be presented with 0 or 1 decimal, respectively. For changes from baseline, shift tables may be generated.

Inferential statistics

If not stated otherwise all statistical tests will be performed two-sided and at a type I error probability of $\alpha=0.05$. 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."

All confidence intervals (CI) will be derived two-sided and at a confidence probability of $1-\alpha = 0.95$.

Listings

All patient data will be listed by patient sorted by treatment group. Identification variables will be center number, patient number and treatment. Any derived data listed will also be stored permanently and will be calculated as outlined in section 8.1 of this SAP.

5.1 Conventions

5.1.1 Baseline definition

Baseline is defined as the last value on or prior to randomization and before first IMP administration.

5.1.2 Missing data

The primary end point will be analyzed by two approaches, without any kind of imputation and with imputation of missing data. For the primary end point missing data will be imput-

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ed using the Last Observation Carried Forward (LOCF) approach. For the purpose of evaluating the robustness two further approaches will be performed:

- imputations based on the means of available data within a treatment group at a given time point will be conducted if feasible.
- no imputation at all will be done

For the secondary end points, missing values will also be imputed by use of the LOCF approach.

5.1.3 Pooling of centers

All tables will be presented in total over all participating countries and centers. The distribution of number of patients per country will be present in the disposition section of the report.

5.2 Demographic and other background data

5.2.1 Basic description

The disposition of subjects (cf. Section 4) will be tabulated by treatment and for the entire population. Details on protocol deviations will be listed.

Discontinued patients will be described by frequency distributions including the reasons and in individual listings.

Demographic data (gender, age (categorical and continuous), weight, height, body mass index (BMI), race, ethnic group) will be summarized in tables and presented for the SAF, FAS and PP2 population stratified by treatment group. Other baseline or background data, e.g. disease-specific information, will comprise descriptive tables for the SAF and PP2 population for the following variables:

- Smoking status at screening and randomization
- Alcohol consumption at screening and randomization
- Vital Signs (Systolic and diastolic blood pressure, pulse and body temperature) at screening and randomization
- ECG evaluation (normal/abnormal)
- Physical examination (normal/abnormal)
- Gout History and CV Risk Score

The following background data will only be listed:

- Medical history

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- Prior and concomitant procedures and surgeries (except those noted under Cancer treatment history)
- Childbearing potential and urine pregnancy test

5.3 IMP exposure, compliance

Treatment compliance will be monitored from Visit -1 to Visit 4 (end of study treatment).

The amount of study medication taken by the subject will be derived by counting the number of tablets dispensed and returned in the blister which will be recorded in the eCRF.

The patient compliance for the study treatment period is calculated as described in section 8.1.

A patient who has taken at least 60% and no more than 120% of the required study drug intake since the last visit will be considered compliant.

All IMP treatment details will be listed.

5.4 Medical history, physical examination

Data on medical history and physical examination will be listed. Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Codes will be reviewed by a Medical Expert and approved by the sponsor before data base lock.

5.5 Prior and concomitant medication

Any relevant medication ended within the screening period will be defined as 'Prior Medication' and will be summarized separately. Concomitant medications (medications started after the screening date) and Prior and Concomitant medications (medications started during the screening period but ended after this period or still ongoing will be summarized all together.

All details of prior and concomitant medications will be listed including, the route, dose, frequency, start and stop date and indication.

Medications will be coded using the WHO DD thesaurus in the version current at the time of database lock. Coding will be performed by the CRO and agreed upon with the sponsor before data base lock. (cf. DMP). For concomitant medications tables will show the frequencies of subjects by WHO DD preferred term. Prior medication will only be listed.

5.6 Concomitant non-pharmacological measures, pre-medication

Not applicable.

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5.7 Efficacy

The efficacy evaluation of the primary endpoint 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 based on the Per-Protocol 2 (PP2) population will be performed.

5.7.1 Primary endpoint

The primary efficacy endpoint is Pulse Wave Velocity (PWV) after 36 weeks of treatment with febuxostat or allopurinol.

At least two PWV measurements will be taken per visit. The evaluation of measurements will be performed by two independent laboratory teams. Values valid to be included in analysis will be selected by experienced medical experts. Details on processes related to the assessment and final selection of the PWV/PWA reports that will be used for the statistical analysis are described in the document named: “PWV/PWA reconciliation process” section 15.5 Appendix E of Data Management Plan. Mean values from all measurements considered to be valid will be calculated per visit and will result in one value per visit per parameter.

Analysis of covariance (ANCOVA) with the 36 weeks PWV value as dependent variable, treatment group as factor and age, baseline blood pressure, baseline PWV as covariates, will be used to compare the efficacy of the two treatment groups.

The assumptions of the underlying model such as normality of residuals and homogeneity of variance will be investigated using significance level of 0.1.

All covariates found not to be statistically significant at the 0.05 two-sided significance level, will be removed from the model and 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.

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

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

The LOCF method will be utilized for missing data imputations as described in section 5.1.2.

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5.7.2 Secondary endpoints

All secondary efficacy variables will be analyzed based on the FAS population.

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 for the parameters listed below. The LOCF method will be used for missing data imputations.

- 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),] after 12, 24 and 36 weeks of treatment
- Changes in lipid profile after 12, 24 and 36 weeks of treatment
- 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
- Pulse Wave Analysis (including modifications of PWV, arterial stiffness, central blood pressure and augmentation index) after 12, 24 and 36 weeks of treatment
- The primary parameter PWV over time (12 to 36 weeks) will be analyzed using a repeated measurement model
- 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 centers only)
- Tender and swollen joint count

Logistic regression will be used to analyze the parameters below for the difference between treatment groups at each time point where the dependent variable is defined as a binary outcome (e.g. 1 if urate concentration ≤ 6 mg/dl, 0 otherwise) and treatment group and baseline urate concentration will be included as independent variables.

- 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
- 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

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Proportional hazards model with treatment group as covariate will be used to investigate:

- Time to achieve sUA target levels for all patients with baseline sUA as additional covariate
- Time to achieve sUA target levels 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
- Time to achieve sUA target levels for all patients and stratified for sUA levels at baseline as follows: >8 and <9 mg/dl, >9 and <10 mg/dl, ≥ 10 mg/dl will additionally be presented

In case of deviation from proportional Hazard-assumption the log-rank-test will be used instead.

5.8 Pharmacokinetics / Pharmacodynamics

Not applicable.

5.9 Safety

All analyses will be performed for the SAF population.

5.9.1 Adverse events

Adverse events (AEs) will be coded by the CRO Safety Group according to the MedDRA thesaurus. Coding will be agreed upon with the Sponsor before database lock (cf. DMP).

Treatment-emergent adverse events (TEAE) will be analyzed, i.e. all new and worsening pre-existing adverse events occurring after first IMP administration up until end of trial. It is assumed that for each increase in intensity of an AE a new entry of the AE will be done by the investigator; hence such cases will be analyzed like different phases of the same AE.

A descriptive analysis will be performed. Global incidences along with the number of events and number of patients with events per primary system organ classes (SOC) and preferred terms (PT) will be calculated for

- All TEAE irrespective of the causality assessment
Related TEAEs (Certainly, Probably, Possibly Related and Unassessable)
- TEAEs by worst severity
- Serious TEAEs
- TEAEs without serious

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This analysis comprises the following set of tables split by treatment group:

- Global incidence
- Incidences by primary system organ classes (SOC) and incidences of PT within primary SOC sorted according to the Internationally Agreed Order

Multiple counts within a PT or SOC (repeated or different included terms or changes in descriptors) will be counted only once for the calculation of incidences.

A listing of "special cases" containing subject identification, age, sex, AE descriptors, start and end of treatment will be prepared for the following types of TAEs:

- Serious adverse events (SAE)
- Adverse events which led to death
- Adverse events which led to discontinuation

All adverse events recorded since signing of the ICF will be listed in the data part of the report. Only TEAEs will be summarized in the tables.

5.9.2 Vital signs

Vital signs parameters (systolic/diastolic blood pressure, pulse, body weight, axillary body temperature) will be assessed at screening, visit 0, 2, 3 and at end of the trial.

Descriptive analyses of values and their changes from baseline will be performed.

5.9.3 Safety laboratory variables

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.

Frequency tables for the semi-quantitative urinalysis results will be presented by visit.

Frequency tables or listings for values classified as clinically significant by the investigator will be provided per time point if applicable.

5.10 Other variables

Not applicable.

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5.11 Interim analyses

Not applicable.

6 QUALITY CONTROL

The responsible Project Manager will review the SAP before it is provided to the Sponsor for review. The SAP will be signed off only when approval from the Sponsor's representative is received.

Log files of all SAS® programs needed for analysis will be checked for errors, warnings and suspicious notes by the statistical programmer. All findings will be either eliminated or commented upon. The final version of each program will be stored along with its log file in the electronic archive.

All programs will be validated by the author.

The agreement of the program outputs with the SAP, their consistency and plausibility will be checked by the TS. Moreover, the TS will review the outputs regarding completeness, readability and comprehensibility.

7 REFERENCES

No specific references were used.

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8 APPENDICES

8.1 Formulas for derived variables

Variable	Description
Durations between two dates	Later date minus earlier date plus 1, expressed in days. (Remark: Duration will be 1, if both dates are the same.)
Subject compliance (%)	Number of tablets actually taken x 100 / expected number of tablets which should have been taken.
Number of tablets actually taken	Difference between the number of tablets handed out to the patient and the number of unused tablets returned or declared lost by the patient
Expected number of tablets per visit	Number of days of date of visit x – date of visit x-1
Total expected number of tablets taken	(Sum of number of all days of date visit x – date visit x-1) + 1
Compliant per visit	Compliance \geq 60% and no more than 120% of the required study drug intake since the last visit

8.2 List of Tables, Listings, Figures

A complete lists of tables, listings figures (TLFs) will be given in a separate document which can be updated without updating the SAP. The list will serve as a reference for both the Sponsor, the trial statistician and the statistical programmer and includes the totality of statistical output to be produced. Therefore, this list will be approved by both parties before commencing the statistical programming.

All output will be headed with an appropriate heading specifying the study ID and abbreviated study title.

All output will be dated and have page numbers in the form 'Page [x / y]' where x denotes the current page within an output and y the total number of pages of that output.

All statistical output will identify the underlying analysis populations and indicate the number of patients / events in this population (N) and the number of patient/events actually contributing to the particular output (n). All statistical output will be presented per treatment group and in total (if applicable).

All patient listings will contain additionally to the patient identification the analysis population and the treatment group.