MENARINI RICERCHE

FLORET

FEBUXOSTAT FOR TUMOR LYSIS SYNDROME PREVENTION
IN HEMATOLOGICAL MALIGNANCIES OF PAEDIATRIC PATIENTS AND ADULTS

# CLINICAL TRIAL PROTOCOL

**FINAL VERSION 1.0, 12 APR 2016**

## OPEN LABEL, MULTI-CENTRE, PARALLEL GROUP STUDY TO COMPARE THE PHARMACOKINETICS (PK), PHARMACODYNAMICS (PD) AND SAFETY OF FEBUXOSTAT BETWEEN PEDIATRIC PATIENTS (≥6<18 YEARS OF AGE) AND ADULTS

| | |
|---|---|
| **Study code** | **FLO-02** |
| **Study Nick Name/ Acronym** | **FLORET** |
| **EudraCT-Number** | **2016-001445-61** |
| **Investigational Medicinal Product** | **febuxostat** |
| **Development phase of study** | **Phase I/II** |

**SPONSOR**

Menarini Ricerche S.p.A.
Clinical Research
Via Sette Santi, 1
50131 Florence - Italy
Phone: +39 05556809990
[redacted]

**CO-ORDINATING INVESTIGATOR**

[redacted]

**CRO**

[redacted]

**STATEMENT OF CONFIDENTIALITY**

The information in this document contains trade secrets and proprietary commercial information of Menarini Group that is privileged or confidential and may not be disclosed unless such disclosure is required by law. In any case, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed without written authorisation by Menarini Group.

# 1. SIGNATURES

The signatories have read the clinical trial protocol titled ***"Open label, multi-centre, parallel group study to compare the pharmacokinetics (PK), pharmacodynamics (PD) and safety of febuxostat between pediatric patients (≥6<18 years of age) and adults" - Final Version 1.0, 12 Apr 2016***> - carefully and agree to adhere to its provisions. Changes to the protocol have to be stated by the Sponsor in amendments to the clinical trial protocol which, if they are substantial, have to be authorized by the Competent Authorities and Ethics Committees before translating them into action.

| **Sponsor's Representative** | **Signature** | **Date** |
|---|---|---|
| [redacted] | | |

| **Co-ordinating Investigator** | **Signature** | **Date** |
|---|---|---|
| [redacted] | | |

# PRINCIPAL INVESTIGATOR'S STATEMENT

a) Clinical Statement

My signature below documents my agreement with the contents of this clinical trial protocol titled *"**Open label, multi-centre, parallel group study to compare the pharmacokinetics (PK), pharmacodynamics (PD) and safety of febuxostat between pediatric patients (≥6<18 years of age) and adults" - Final Version 1.0 dated 12 Apr 2016 -*** with regard to the execution of the study and the required documentation/data collection. I agree to comply with this clinical trial protocol in its entirety and with the ICH guidelines for Good Clinical Practice (GCP).

b) Anti-Corruption Statement

I agree to - I will and I will cause any of my collaborators to - perform any activity in accordance with the principles of any international anti-corruption legislations, such as OECD Convention on Combating Bribery of Foreign Public Officials in International Business Transactions, UK Bribery Act and US Foreign Corrupt Practices Act, including Italian Legislative Decree 231/2001. In particular, along the performance of the study, I will not - and I will cause any of my collaborators not to - directly or indirectly offer, pay, give, or promise to pay or give or receive any payment or gift of any money or thing of value to or from any government officer to influence any acts or decisions or to induce such officer to use its influence to effect or influence the decision of the relevant government body or any other decision maker. I accept to promptly inform the Sponsor in writing in case of violations of or deviations from any of the above prescriptions in the conduct of the study and I acknowledge and accept Sponsor's rights to conduct audits in order to verify compliance with the above during or in connection with the performance of the study. I agree and accept that a violation of any of the above prescriptions may result in the termination of the research activities of the site I work in and/or the entire study.

| **Principal Investigator** | **Signature** | **Date** |
|---|---|---|
| ..... (printed name) | ..... | ..... |

## 2. PROTOCOL SYNOPSIS

| | |
|---|---|
| **Study Title** | Open label, multi-centre, parallel group study to compare the pharmacokinetics (PK), pharmacodynamics (PD) and safety of febuxostat between pediatric patients (≥6<18 years of age) and adults. |
| **Sponsor Code** | FLO-02 |
| **Nick name/Acronym** | FLORET |
| **Phase** | Phase I/II |
| **Indication** | Tumor Lysis Syndrome (TLS) |
| **No. of sites** | Approximately 40 sites. |
| **Investigational Medicinal Product** | Febuxostat film-coated tablets. |
| **Treatment regimen** | Eligible patients will receive oral administration of the following dose of febuxostat per age group:<br>- Children (from 6 to less than 12 years of age)[1]<br>Cohort 1: 40 mg once daily;<br>Cohort 2: 60 mg once daily.<br>- Adolescents (from 12 to less than 18 years of age)[1]<br>Cohort 3: 80 mg once daily;<br>Cohort 4: 120 mg once daily.<br>- Adults (equal or major than 18 years of age)<br>120 mg once daily.<br>The two dose levels for children and adolescents groups will be administered sequentially (Cohort 2 after Cohort 1, and Cohort 4 after Cohort 3), whereas Cohort 1, Cohort 3 and adults treatments will start simultaneously at the study beginning.<br>The minimum treatment duration will be of 7 days. However, treatment may be prolonged up to 9 days according to chemotherapy duration, as per Investigator's judgment. |

| | |
|---|---|
| **Design** | Open label, multi-centre, parallel group study. |
| **Primary objectives** | The primary objectives of this study are:<br>▪ To assess the pharmacokinetics (PK) of febuxostat in pediatric patients (≥6<18 years of age) and in adults suffering from hematological malignancies at intermediate to high risk of TLS.<br>▪ To compare the febuxostat exposure in pediatric patients (≥6<18 years of age) with the one achieved in adults administered with a dose of 120 mg/QD. |
| **Secondary objectives** | ▪ To compare the pharmacodynamics (PD) of febuxostat between pediatric patients (≥6<18 years of age) and adults.<br>▪ To evaluate and compare the PK/PD relationship of febuxostat in pediatric patients (≥6<18 years of age) and adults.<br>▪ To evaluate the safety of febuxostat between pediatric patients (≥6<18 years of age) and adults.<br>▪ To evaluate the occurrence of Laboratory TLS (LTLS) and Clinical TLS (CTLS) according to Cairo and Bishop Criteria (see Appendix I: Definition of LTLS and CTLS).<br>▪ To assess the age-appropriate formulation acceptability in children. |
| **Study duration** | Individual study period: approximately 3 weeks.<br>Screening should occur up to 1 week (+2 days of accepted timeframe window) prior to the Start of Treatment (Day 1). Febuxostat treatment will start 2 days before chemotherapy and continue for 7-9 days (Day 7 to Day 9). A follow-up visit will occur at Day 14 (±2 days of accepted timeframe window). |
| **Inclusion criteria** | *Patients meeting ALL the following criteria will be eligible to enter the study:*<br>[redacted] male and female children of 6 to less than 12 years of age, adolescents of 12 to less than 18 years of age, and adults:<br>a. scheduled for first cytotoxic chemotherapy cycle, regardless of the line of treatment, because of |

hematologic malignancies, and

b. at intermediate or high risk for TLS, and

c. with serum uric acid (sUA) levels < 10 mg/dL at Visit 1 (Day 1), and

d. with no access to rasburicase;

[redacted]

| | |
|---|---|
| **Exclusion criteria** | *Patients will not be eligible to participate in the study if they meet ANY of the following exclusion criteria:*<br>1. patients known to be hypersensitive to febuxostat or to any components of the formulation;<br>[redacted]<br>6. patients with severe renal insufficiency;<br>7. patients with severe hepatic insufficiency;<br>8. patients with diagnosis of Laboratory TLS (LTLS) or Clinical TLS (CTLS) at Visit 1 (Day 1).<br>[redacted] |
| **Study procedures and PK/PD, Clinical and Safety assessments** (see also Flow Chart) | Written informed consent shall be provided by adult patients or by parents (one or both, according to local regulations) or the legal guardian for children and adolescents prior to start any study procedures.<br><br>**Screening Visit (Day -9 to Day 1):**<br>▪ assessment of inclusion/exclusion criteria;<br>▪ demographic data collection;<br>▪ medical and medication history;<br>▪ physical examination and vital signs (i.e. blood pressure |

| | |
|---|---|
| | [BP], heart rate [HR], breathing rate [BR], body temperature [T]);<br>▪ performance status (PS) evaluation;<br>▪ 12 lead ECG;<br>▪ blood sampling and urine collection for safety laboratory tests, including pregnancy test (if applicable);<br>▪ record of adverse events.<br><br>***NOTE-1***: Study procedures under Screening Visit may occur also on more than one day.<br>***NOTE-2:*** Results of safety laboratory tests (biochemistry, hematology, coagulation, urinalysis and pregnancy test, when appropriate) and ECG, which have been performed in the context of the standard patient's management, can be recorded in the e-CRF under Screening Visit procedures, provided that they have been done within 24 hours prior to the Screening Visit.<br>***NOTE-3***: Re-screening is allowed but requires sponsor/medical monitor's approval. A patient may maximally be re-screened once.<br><br>**Visit 1, Start of Treatment (Day 1: two days prior to chemotherapy):**<br><br><u>*Prior to study drug administration:*</u><br>▪ record of adverse events and change in concomitant medications.<br>▪ re-check of inclusion/exclusion criteria and confirmation of patient's eligibility;<br>▪ physical examination and vital signs;<br>▪ PS evaluation;<br>▪ blood sampling and urine collection for safety laboratory tests (***NOTE***: safety laboratory tests performed within 24 hours prior to Day 1 are accepted and do not need to be repeated on Visit 1);<br>▪ blood sampling for centralized laboratory test (sUA); |

| | |
|---|---|
| | ▪ assessment of LTLS/CTLS;<br>▪ allocation of investigational medicinal product (IMP) treatment box as per IxRS assignment.<br><br>*Study drug administration:*<br>▪ administration of febuxostat.<br><br>*After study drug administration:*<br>▪ assessment of the age-appropriate formulation acceptability only for children.<br>***NOTE***: Screening Visit and Visit 1 (Day 1) may occur on the same day. Common assessments will be performed only once.<br><br>**Visit 2 (Day 2):**<br>▪ record of adverse events and change in concomitant medications;<br>▪ vital signs;<br>▪ PS evaluation;<br>▪ pre-dose PK blood sampling;<br>▪ blood sampling for safety laboratory tests, including centralized laboratory test (sUA);<br>▪ study drug administration;<br>▪ assessment of the age-appropriate formulation acceptability (only for children).<br><br>**Visit 3 (Day 3):**<br>▪ record of adverse events and change in concomitant medications;<br>▪ vital signs;<br>▪ PS evaluation;<br>▪ 12 lead ECG;<br>▪ pre-dose PK blood sampling;<br>▪ blood sampling for safety laboratory tests, including centralized laboratory test (sUA);<br>▪ study drug administration;<br>▪ assessment of the age-appropriate formulation |

| | |
|---|---|
| | acceptability (only for children);<br>▪ assessment of LTLS/CTLS;<br>▪ starting of chemotherapy regimen.<br><br>**Visit 4-7 (Day 4-7):**<br>On each day from Day 4 to Day 7, the following assessments will be performed:<br>▪ record of adverse events and change in concomitant medications;<br>▪ vital signs;<br>▪ PS evaluation;<br>▪ pre-dose PK blood sampling;<br>▪ blood sampling for safety laboratory tests, including centralized laboratory test (sUA);<br>▪ study drug administration;<br>▪ assessment of the age-appropriate formulation acceptability (only for children);<br>▪ 4 additional post-dose PK blood samplings ONLY at Visit 7 (Day 7) at the assigned sampling time intervals: 0.5-2 hours, 2-4 hours, 4-6 hours and 6-8 hours;<br>▪ urine collection for safety laboratory tests ONLY at Visit 4 (Day 4);<br>▪ assessment of LTLS/CTLS.<br><br>**Visit 8, Evaluation Visit (Day 8):**<br>On Day 8, at treatment Evaluation Visit, the following assessments will be performed:<br>▪ record of adverse events and change in concomitant medications;<br>▪ physical examination and vital signs;<br>▪ PS evaluation;<br>▪ 12 lead ECG;<br>▪ PK blood sampling (pre-dose PK sampling for patients scheduled to prolong hypouricemic treatment);<br>▪ blood sampling for safety laboratory tests, including |

| | |
|---|---|
| | centralized laboratory test (sUA);<br>▪ urine collection for safety laboratory tests;<br>▪ assessment of LTLS/CTLS.<br>***ONLY for patients scheduled to prolong hypouricemic treatment:***<br>▪ study drug administration;<br>▪ assessment of the age-appropriate formulation acceptability (only for children).<br><br>**Visit 9 (Day 9):**<br>***To be performed ONLY for patients scheduled to prolong hypouricemic treatment:***<br>▪ record of adverse events and change in concomitant medications;<br>▪ vital signs;<br>▪ PS evaluation;<br>▪ study drug administration;<br>▪ assessment of the age-appropriate formulation acceptability (only for children);<br>▪ blood sampling for safety laboratory tests.<br><br>**Visit 10, Follow-up/End of Study Visit (Day 14±2):**<br>A final safety Follow-up/End of Study Visit will be performed at Day 14 (±2):<br>▪ record of adverse events and change in concomitant medications;<br>▪ physical examination and vital signs;<br>▪ PS evaluation;<br>▪ 12 lead ECG;<br>▪ blood sampling and urine collection for safety laboratory tests.<br><br>***NOTE***:<br>**Blood safety laboratory tests** will be performed at the Local |

| | |
|---|---|
| | Laboratory and will include: albumin, alkaline phosphatase, amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN)/urea, serum creatinine, serum uric acid (sUA), sodium, chloride, potassium, phosphorus, calcium, total bilirubin, direct bilirubin, gamma-glutamyl transpeptidase (GGT), glucose, lactate dehydrogenase (LDH), total proteins, prothrombin time/prothrombin activity, international normalized ratio (INR), platelets, red blood cells (RBC), hemoglobin, hematocrit and white blood cells (WBC) with differential count (absolute and %), and beta human chorionic gonadotropin (β-HCG) if applicable.<br><br>**Urinalysis** will be performed at the Local Laboratory and will include: pH, density, proteins, glucose, ketones, nitrite, RBC, WBC, epithelial cells, casts, bacteria, yeasts and crystals.<br><br>**Blood samples for centralized laboratory test (sUA) and for PK tests** will be collected and analyzed in a Central Laboratory. |
| **Primary endpoints** | Pharmacokinetic endpoints derived from the study will include:<br>▪ Primary PK parameters: CL/F, Vd/F and Ka.<br>▪ Derived PK parameters: AUC and $C_{max.}$ |
| **Secondary endpoints** | ▪ Pharmacodynamic endpoint:<br>– Area under the curve of sUA from baseline (Visit 1, Day 1) to the Evaluation Visit (Visit 8, Day 8) (AUC sUA $_{1\text{-}8}$) based on central laboratory results.<br><br>▪ PK/PD endpoint:<br>– The PK/PD relationship will be evaluated based on sUA levels and febuxostat exposure.<br><br>▪ Clinical endpoints:<br>– Incidence of Laboratory TLS (LTLS) from Start of Chemotherapy (Visit 3, Day 3) to the Evaluation Visit |

| | |
|---|---|
| | (Visit 8, Day 8), based on local laboratory results.<br>– Incidence and grading of Clinical TLS (CTLS) from Start of Chemotherapy (Visit 3, Day 3) to the Evaluation Visit (Visit 8, Day 8) based on local laboratory results.<br><br>▪ Safety endpoints:<br>– Incidence, severity (both through Mild/Moderate/Severe scale and NCI-CTCAE grade), seriousness and treatment causality of Treatment-Emergent Signs and Symptoms (TESS).<br>***NOTE***: An AE is considered as 'Treatment-Emergent Signs and Symptoms (TESS)' if it occurs for the first time or if it worsens in terms of seriousness or severity after the first study drug intake (Visit 1, Day 1).<br>– Frequency of clinically significant abnormalities in physical examination, safety laboratory tests, vital signs and 12 Lead ECG.<br>– Change in PS according to Karnofsky/Lansky scales.<br><br>▪ Assessment of the age-appropriate formulation acceptability (only for children). |
| **Sample size** | A sample size of approximately 24 patients will be included in the Pharmacokinetic population for each age and dose group (pediatric cohorts 1-4 and adults).<br>[redacted]<br>Assuming a 10% screening failure rate, around 135 patients should be screened in order to enroll approximately a total |

| | |
|---|---|
| | number of 120 patients. |
| **Analysis populations** | ▪ **Safety population**: all patients who received at least one dose of study drug.<br>▪ **Pharmacokinetic (PK) population**: all patients who received at least one dose of study drug and have a reliable drug plasma concentration measurement relevant for the pharmacokinetic parameter of interest.<br>▪ **Intention to Treat (ITT) population**: all patients allocated to a treatment box.<br>▪ **Per Protocol (PP) population**: all patients of the ITT population excluding those who experienced major protocol violation(s).<br>▪ **Per Protocol PK (PP-PK) population:** all patients from PK population who do not have any major protocol violation(s) relevant for PK analyses. |
| **Statistical analyses** | **Primary analyses:**<br>All pharmacokinetic results (e.g., PK variables and plasma concentrations) will be summarized by dose and age group using appropriate graphs and descriptive statistics [i.e., number of patients (n), mean, standard deviation (SD), geometric mean, 95% confidence intervals, coefficient of variation (CV%), median, minimum, and maximum].<br>Relevant PK parameters (e.g., AUC, $C_{max}$) in children and adolescents will be descriptively compared to those in adults to demonstrate sufficient similarity of febuxostat pharmacokinetics.<br>The pharmacokinetic analyses will be conducted on the PK population and for exploratory reasons on the PP-PK population.<br><br>**Secondary analyses**:<br>▪ Pharmacodynamics: treatment efficacy will be assessed by AUC sUA analyzed by Central Laboratory from Day 1 |

to Day 8 (AUC $sUA_{1-8}$). Comparisons will be made between febuxostat doses among the age groups and carried out on ITT and PK population.

- PK/PD: observed exposure-response data will be descriptively and graphically summarized by age and dose group. [redacted]

  The aim of this analysis is to support the assumption of a comparable PK/PD relationship between pediatric patients (≥6<18 years of age) and adults and to evaluate if potential deviations in PK are clinically relevant. This analysis will be conducted on PK population.

- Clinical: incidence of LTLS and CTLS will be summarized through descriptive statistics by febuxostat dose and age group and their statistical comparison will be performed using a Chi Square test. Clinical endpoint analyses will be run on ITT population and for exploratory reasons on PP-population.

- Safety:

  – adverse events will be coded using the MedDRA dictionary. The incidence, severity, seriousness and causality of each TESS will be summarized by system organ class, preferred term by febuxostat dose and age group;

  – reasons for early termination will be summarized by febuxostat dose and age group;

  – laboratory findings and changes in PS will be reported by febuxostat dose and age group.

  All safety analyses will be run on the safety population.

- Assessment of the age-appropriate formulation

| | |
|---|---|
| | acceptability will be evaluated through a patient diary and summarized by means of descriptive statistics by febuxostat dose in children. The analysis will be conducted on the safety population. |

## 2.1 SCHEMATIC STUDY DESIGN

| STUDY VISITS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Treatment Period | | | | | | | | | |
| **Screening** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9** | **V10** |
| ***Day -9–1*** | ***Day 1*** | ***Day 2*** | ***Day 3*** | ***Day 4*** | ***Day 5*** | ***Day 6*** | ***Day 7*** | ***Day 8*** | ***Day 9*** | ***Day 14±2*** |

**Start of Treatment** — **Start of Chemotherapy** — **Evaluation** — **End of Study**

| FEBUXOSTAT TREATMENT REGIMEN | | | |
|---|---|---|---|
| **ADULTS** | **≈24 patients: febuxostat 120 mg/QD** | | |
| **CHILDREN** | **first ≈24 patients (40 mg/QD)** | → | **futher ≈24 patients (60 mg/QD)** |
| **ADOLESCENTS** | **first ≈24 patients (80 mg/QD)** | → | **futher ≈24 patients (120 mg/QD)** |

***NOTE***: ≈24 adults will receive oral administration of febuxostat 120 mg once daily. The two dose levels per age group in children and adolescents will be administered sequentially: the first ≈24 children and the first ≈24 adolescents will receive the doses of 40 mg and 80 mg once daily, respectively. Afterwards, the higher febuxostat doses will be administered to the following ≈24 children and ≈24 adolescents: 60 mg once daily for children and 120 mg once daily for adolescents.

## 2.2 STUDY FLOW-CHART

| PROCEDURE | STUDY VISITS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Prior to any study procedures | Screening Visit Day -9 to Day 1 | Treatment Period | | | | | | | Evaluation Visit 8 Day 8 | Visit 9[g] Day 9 | End of Study Visit 10 Day 14±2 |
| | | | Visit 1 Day 1 | Visit 2 Day 2 | Visit 3 Day 3 | Visit 4 Day 4 | Visit 5 Day 5 | Visit 6 Day 6 | Visit 7 Day 7 | | | |
| Informed consent | X | | | | | | | | | | | |
| Inclusion/exclusion criteria | | X | X | | | | | | | | | |
| Demographics | | X | | | | | | | | | | |
| Medical history | | X | | | | | | | | | | |
| Prior and concomitant medication | | X | X | X | X | X | X | X | X | X | X | X |
| Physical examination | | X | X | | | | | | | X | | X |
| PS evaluation[a] | | X | X | X | X | X | X | X | X | X | X | X |
| Vital signs | | X | X | X | X | X | X | X | X | X | X | X |
| 12-Lead ECG | | X | | | X | | | | | X | | X |
| Safety Lab Tests[b] | | X | X | X | X | X | X | X | X | X | X | X |
| Centralized Lab Test[c] | | | X | X | X | X | X | X | X | X | | |
| PK blood sampling[d] | | | | X | X | X | X | X | X[e] | X | | |
| Pregnancy Test[b] | | X | | | | | | | | | | |
| Urinalysis[b] | | X | X | | | X | | | | X | | X |
| LTLS/CTLS | | | X | | X | X | X | X | X | X | | |
| Study drug allocation through IxRS | | | X | | | | | | | | | |
| Study drug administration[f] | | | X | X | X | X | X | X | X | X[g] | X | |
| Assessment of the age-appropriate formulation acceptability | | | X | X | X | X | X | X | X | X[g] | X | |
| Adverse events | | X | X | X | X | X | X | X | X | X | X | X |
| Start of Chemotherapy[h] | | | | | X | | | | | | | |

a= Performance status evaluation according to Karnofsky performance status (KPS) scale for patients aged 16 years and older and Lansky Play performance status (LPS) scale for patients aged less than 16 years, as per Guideline CIBMTR 2009.
b= Safety lab tests, Urinalysis and Pregnancy test (if applicable) will be performed locally to guarantee the management of the patient.
c= Blood sampling for centralized lab test (sUA) is collected in conjunction with safety lab tests, whenever possible .
d= One daily pre-dose sampling at all visits from Day 2 to Day 8.
e= Four additional post-dose PK samples to collect on Day 7 at the following time intervals: 0.5-2 hours, 2-4 hours, 4-6 hours and 6-8 hours.
f= The two dose levels per age group will be sequentially administered in children and adolescents. The first 24 children will receive the lower dose of 40 mg once daily, and the first 24 adolescents the dose of 80 mg once daily. Higher doses will be subsequently administered: 60 mg once daily to children and 120 mg once daily to adolescents.
g= To be performed ONLY for patients scheduled to prolong hypouricemic treatment.
h = Chemotherapy shall be started on Day 3 (Visit 3) and will continue as per Investigator's judgment.

# 3. INVESTIGATOR(S) AND STUDY ADMINISTRATIVE STRUCTURE

| | |
|---|---|
| **Co-ordinating Investigator** | [redacted] |

| | |
|---|---|
| **Sponsor** | **Menarini Ricerche S.p.A.**<br>**Clinical Research**<br>**Via Sette Santi, 1**<br>**50131 Florence, Italy** |
| Corporate Director of Clinical Research / Sponsor's Representative | [redacted] |
| Head of Corporate Therapeutic Areas Oncology, Immunology & Antinfective | [redacted] |
| Clinical Research Physician | [redacted] |
| Study Manager | [redacted] |
| Head of Corporate Biostatistic and Data Management | [redacted] |
| Biostatistician | [redacted] |
| Data Manager | [redacted] |
| Senior Corporate Pharmacokineticist | [redacted] |

| | |
|---|---|
| **Sponsor's Pharmaceutical Manufacturer of the IMP** | **A. Menarini Research & Business Service GmbH**<br>**Pharmaceutical Development Department**<br>**Glienicker Weg 125**<br>**12489 Berlin, Germany** |
| Head of the Department of Pharmaceutical Development | [redacted] |
| Packaging, Labelling, and Distribution of the IMP | [redacted] |

| | |
|---|---|
| **Sponsor's Pharmacovigilance Unit** | **Laboratorios Menarini S.A. -Menarini Group**<br>**Clinical Research**<br>**C/ Alfons XII, 587**<br>**08918, Badalona, Spain** |
| Drug Safety Manager | [redacted] |

| | |
|---|---|
| **Quality Assurance** | [redacted] |
| Head of Quality Assurance & GXP compliance | [redacted] |

| | |
|---|---|
| **CRO** | [redacted] |

| | |
|---|---|
| **Central Laboratory Pharmacokinetic** | **Menarini Ricerche,**<br>**Clinical Laboratory**<br>**Via Tito Speri, 10**<br>**00071 Pomezia, Roma (Italy)** |
| Central Lab Project Manager | [redacted] |
| **Central Laboratory** | **R.T.C. Research Toxicology Centre S.p.A.**<br>**Clinical Laboratory**<br>**Via Tito Speri, 12/14**<br>**00071 Pomezia, Rome, Italy** |

| | |
|---|---|
| Scientific Responsible of the Service/Study | [redacted] |
| Central Lab and Logistics | [redacted] |

| | |
|---|---|
| **IxRS** | [redacted] |

# 4. TABLE OF CONTENTS

## 4.1 GLOSSARY

| | |
|---|---|
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ALCL | Anaplastic Large Cell Lymphoma |
| ALL | Acute Lymphoblastic Leukemia |
| ALT | Alanine Aminotransferase |
| AML | Acute Myelogenous Leukemia |
| APEX | Allopurinol-Placebo-controlled Efficacy study of febuXostat |
| AST | Aspartate Aminotransferase |
| ATL | Adult T-cell Lymphoma |
| AUC | Area Under Curve |
| BL | Burkitt Lymphoma/Leukaemia |
| BP | Blood Pressure |
| BR | Breath Rate |
| BUN | Blood Urea Nitrogen |
| CA | Competent Authority |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CI | Confidence Interval |
| CL | Clearance |
| CLcr | Creatinine Clearance |
| CL/F | Apparent clearance |
| CLL | Chronic Lymphocytic Leukemia |
| $C_{max}$ | Maximum plasma Concentration |
| CML | Chronic Myeloid Leukemia |
| CONFIRMS | CONfirmation of Febuxostat In Reducing and Maintaining Serum urate |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTLS | Clinical Tumor Lysis Syndrome |
| CV | Coefficient of Variation |
| CYP | CytochromeP450 |
| [redacted] | [redacted] |
| DLBCL | Diffuse Large B-Cell Lymphoma |
| DSM | Drug Safety Manager |
| DSUR | Development Safety Update Report |
| EC | European Commission |
| ECG | Electrocardiogram |
| eCRF | electronic Case Report Form |
| EMA | European Medicines Agency |
| ER | Exposure Response |
| EU | European Union |
| EXCEL | fEbuXostat Comparative Extension Long-term study |
| FACT | Febuxostat versus Allopurinol Controlled Trial |
| FEB | FEBuxostat |
| FL | Follucular Lymphoma |
| FOCE | First-Order Conditional Estimation |
| FOCUS | Febuxostat Open-label Clinical trial of Urate-lowering efficacy and Safety |
| GCP | Good Clinical Practice |
| GGT | Gamma-Glutamyl Transpeptidase |
| GLP | Good Laboratory Practice |
| ß-HCG | Beta-Human Chorionic Gonadotropine |
| HL | Hodgkin Lymphoma |
| HR | Heart Rate |

| | |
|---|---|
| HRD | High Risk Disease |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| ID | Identification number |
| IMP | Investigational Medicinal Product |
| INR | International Normalized Ratio |
| IRB/IEC | Institutional Review Board/Independent Ethics Committees |
| IRD | Intermediate Risk Disease |
| ITT | Intent-to-treat |
| IxRS | Interactive Voice / Web Response System |
| Ka | Absorption rate constant |
| KPS | Karnofsky Performance Status |
| LC-MS/MS | Liquid Chromatography-tandem Mass Spectrometry |
| LDH | Lactate DeHydrogenase |
| LL | Lymphoblastic Lymphoma |
| LOCF | Last Observation Carried Forward |
| LPS | Lansky Play Performance Status |
| LRD | Low Risk Disease |
| LTLS | Laboratory Tumor Lysis Syndrome |
| MALT | Mucosa-Associated Lymphoma Tissue |
| MCL | Mantel Cell Lymphoma |
| NCI | National Cancer Institute |
| NHL | Non-Hodgkin Lymphoma |
| NSADR | Non-serious Adverse Drug Reaction |
| NSAE | Non-serious Adverse Event |
| OBJF | OBJective Function |
| PCTFE | PolyChloroTriFluoroEthylene |
| PD | Pharmacodynamic |
| PIP | Pediatric Investigational Plan |
| PK | Pharmacokinetics |
| PP | Per-protocol |
| PS | Performance Status |
| PT | Preferred Term |
| PTCL | Peripheral T-Cell Lymphoma |
| PVC | PolyVinyl Chloride |
| QA | Quality Assurance |
| QD | Quaque Die (once day) |
| RBC | Red Blood Cell |
| RTC | Research Toxicology Center |
| SADR | Serious Adverse Drug Reaction |
| SAE | Serious Adverse Event |
| [redacted] | [redacted] |
| sC | serum Creatinine |
| SD | Standard Deviation |
| SIV | Site Initiation Visit |
| SmPC | Summary of Product Characteristics |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SST | Serum-Separating Tube |
| sUA | serum Uric Acid |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| T | Body temperature |
| TESS | Treatment Emergent Sign and Symptoms |

| | |
|---|---|
| TLS | Tumor Lysis Syndrome |
| TMF | Trial Master File |
| $T_{max}$ | Time to $C_{max}$ |
| UA | Uric Acid |
| UGT | Uridine Diphosphate Glucuronosyltransferase |
| ULN | Upper Limit of Normal |
| US | United States |
| Vd/F | Apparent volume of distribution |
| VPC | Visual Predictive Check |
| WBC | White Blood Cell |
| WHO | World Health Organisation |
| WNL | Within Normal Limit |
| XDH | Xanthine Dehydrogenase |
| XO | Xanthine Oxidase |

# 5. ETHICAL AND LEGAL ASPECTS

## 5.1 GENERAL 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 Harmonization -Good Clinical Practice (ICH-GCP) Guidelines, EU-Directive 2001/20 of April 4, 2001, and national requirements of the participating country(ies).

Furthermore, the study will be conducted in agreement with Sponsor's or Contract Research Organisation's (CRO's) Standard Operating Procedures' (SOP) requirements as agreed. The agreed SOPs are listed in the project management plan and monitoring plan of the study.

All clinical work conducted under this protocol is subject to GCP rules. This includes audits/inspections by the Sponsor and/or its delegate (e.g. CRO), and/or by national/international Health Authority representatives at any time. All Investigators must agree to the audits/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.

## 5.2 INDEPENDENT ETHICS COMMITTEE AND LEGAL REQUIREMENTS

Before starting the study in a study site, study protocol and relevant documentation must be submitted to and approved by the Institutional Review Board/Independent Ethics Committees (IRB/IEC) 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. The CAs and IRB/IECs 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.

## 5.3 PATIENT INFORMATION AND DECLARATION OF CONSENT

Before any study-related procedures may be performed, informed consent must be obtained from the patient (adult) or by patient's parents (one or both, according to local regulation) or legal guardian (child and adolescent), by means of a signed declaration.

The Informed Consent Form (ICF) must be approved in the corresponding local language and in accordance with local laws and regulations by the IRB/IEC prior to be submitted to the patient and/or parents/legal guardian.

In the information leaflet, patients and/or parents/legal guardian will be given information and fully

comprehensive explanation in easily understandable terms of the study procedures, regarding the benefits, restrictions, discomforts, and risks for themselves or for their minor 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 and/or parents/legal guardian will also be informed about the measures taken to ensure their or their minor confidentiality according to the pertinent legislation.

After being duly informed and interviewed by the Investigator, the patient or parents/legal guardian freely has to date and sign an ICF before their or their minor enrolment into the study and before undergoing any study procedure. The Investigator must store the original of the signed ICF in the Investigator's File, and the patient or parents/legal guardian will be provided with a copy of it. The process of obtaining the ICF has to be documented in the source documents.

If a protocol amendment would affect the terms of the ICF, it will be revised to reflect the protocol change and submitted to IRB/IEC for approval. The Investigator will ensure that this new consent form is signed by all patients or by the parents/legal guardian of all minors subsequently entered in the study and those currently in the study, before the changes take effect on their participation in the trial.

## 5.4 PATIENT INSURANCE

For patients participating in the study, Menarini Ricerche S.p.A. 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 ICF 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).

## 5.5 DOCUMENTATION OF STUDY-RELATED DATA AND RECORD RETENTION

It is the responsibility of the Investigator to document all study-related data for each patient in a case report form (CRF). For this study, an electronic CRF (eCRF) will be used. The Investigator has to guarantee the accuracy of the documented data and has to comment any missing or spurious data.

In addition to the eCRF the Investigator will maintain adequate records that fully document the participation of the patient in the clinical study including the study assessments (patient source data documentation). Details on the source data documentation are provided in section 10.3. As required by ICH-GCP guidelines, the Investigator will keep patients' records and essential documents until at least two years after the last approval of a marketing application in an ICH region; until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed since the

formal discontinuation of clinical development of the IMP.

Patients' data (e.g.: eCRFs, laboratory data) have to be archived for the same period of time. These documents should be retained for a longer period however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

No study documents should be destroyed without prior written agreement between Sponsor and Investigator. Should the Investigator wish moving the study record to another location, he/she must notify the Sponsor in writing.

## 5.6 CONFIDENTIALITY

By signing the study protocol, the Investigator affirms that any information provided by the Sponsor will be maintained in confidence, and that such information will be divulged to IRB/IECs or CAs only under an appropriate understanding of confidentiality with such a committee or institution.

In order to maintain the patient's confidentiality, all data collected by the Investigator will be recorded pseudonymously in the eCRF. Patient's data will be identified by a unique patient number. The Investigator agrees that within national regulatory restrictions and ethical considerations, representatives of the Sponsor, any regulatory agency, and IRB/IEC may consult study source documents in order to verify data in the eCRF. Patient medical records pertinent to the study will be reviewed by the study monitor to assure adequate source documentation, accuracy, and completeness of eCRFs. The review will be conducted in accordance with relevant SOPs and with strict adherence to professional standards of confidentiality, GCP, and the relevant data protection legislation.

## 5.7 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/IECs and the CAs in the participating countries have to approve these amendments before implementation.

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

## 5.8 STUDY COMMENCEMENT

The study can commence in an individual study site only after all prerequisites are fulfilled according to ICH/GCP guidelines, any local regulatory requirements, and the Sponsor/CRO's SOPs.

## 5.9 PATIENT'S SAFETY

If any event(s) related to the conduct of the study or the development of the IMP affects the safety of the study participants, the Sponsor and the Investigator will take appropriate urgent safety measures to protect the patients against any immediate hazard. The CAs and IRB/IECs will be informed forthwith about these new events and the measures taken.

## 5.10 DATA PROPERTY/PUBLICATION POLICY

All data generated in the study (e.g. eCRFs, the structured data files in the clinical database system, the results of the statistical evaluation, and medical interpretation as well as the final clinical study report) are the property of Menarini Ricerche S.p.A.

It is intended that study design and main results will be published on www.clinicaltrials.gov. In addition, the results of the study may be published as scientific literature. Results may also be used in submissions to CAs and IRB/IECs. The conditions mentioned below are intended only to protect confidential commercial information (patents, etc.), and not to restrict publication.

All information concerning febuxostat (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the Investigator by Menarini Ricerche S.p.A. and not previously published) is considered confidential by Menarini Ricerche S.p.A. and will remain the sole property of Menarini Ricerche S.p.A. The Investigator agrees not to use it for other purposes without written consent from Menarini Ricerche S.p.A.

Menarini Ricerche S.p.A. will use the information obtained in this clinical study in connection with the development of febuxostat and therefore may disclose it to other Investigators or concerned CAs in the European Union or abroad. In order to allow for the use of information derived from this clinical study, the Investigator has an obligation to provide Menarini Ricerche S.p.A. with complete test results and all data recorded during this study.

Prior to submitting the results of this study for publication or presentation, the Investigator will allow Menarini Ricerche S.p.A. at least 60 days time to review and comment upon the publication manuscript. Menarini Ricerche S.p.A. will provide any manuscript of the results of this study at least 60 days before publishing to the authors for a complete review. In accordance with generally recognized principles of scientific collaboration, co-authorship with any Menarini Ricerche S.p.A. personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

It is agreed, that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the Investigator until Menarini Ricerche S.p.A. has reviewed/commented and agreed to any publication.

## 5.11 DATA PROTECTION

### 5.11.1 General Principles on Personal Data Compliance

The site, the Principal Investigator, the Central Laboratory, the CRO as well as their appointed staff and service providers acknowledge that:

(a) the performance of the study will imply processing of sensitive personal data;

(b) personal data processing is regulated by the applicable local laws (i.e. the laws of the country where the study is conducted) as well as by the Sponsor's national legislation. In particular, it is hereby acknowledged that being the Sponsor a company incorporated under Italian law, it has to mandatorily comply with Italian legal provisions on data protection: therefore they shall cooperate with the Sponsor to allow the fulfilment of such obligations. For the avoidance of doubt, it is hereby clarified that only the Sponsor and its service providers are bound by Italian legal provisions on data protection;

(c) strict compliance with the applicable data protection laws and instructions by any parties and their employees who take part to the study, is deemed by the Sponsor as an essential condition for the appointment of the collaboration with the research site, the Principal Investigator, the CRO, etc.

### 5.11.2 Data Controllers and Data Processors

The parties acknowledge that according to the applicable privacy laws, Sponsor and sites will act as independent data controllers while CRO, the Centralised Laboratory and the Principal Investigator will act as data processors respectively of the Sponsor and of their respective site. Before the beginning of the study, the sites will appoint in writing their respective Principal Investigator as data processors (and by signing this protocol, the latter undertakes to ensure that he/she is appointed as Data Processor by their respective sites before the start of the study).

### 5.11.3 Duties of the Parties involved in the performance of the study

Collection and use of patients' personal data (i.e. subjects' data), including their biological samples, will be carried out in full respect of the information notices duties, privacy rights, fundamental freedoms and dignity of data subjects. All the parties involved in this study undertake to adopt adequate measures to warrant that data will always be processed securely and in compliance with privacy laws.

The site, the Principal Investigator, the Sponsor, the CRO and the Centralised Laboratory as well as their appointed staff and service providers, each in its respective field of competence and within the limits of their specific role in the study, shall implement the following safety measures (physical, logical, organizational, technical, electronic, I.T. etc) to ensure adequate protection of the personal data of the patients involved in the study. In particular,

**(i) DATA SAFETY**. The site and/or the Principal Investigator shall adopt all the necessary measures to prevent or minimize the risks of theft, partial or total loss, accidental disclosure or illegal/unauthorized access to patient's data or Sponsor's proprietary confidential information; to this extent, before the beginning of the study, the sites and/or the Principal Investigator shall ensure that the actual measures they have implemented are fit-for-purpose and law-compliant, and in particular:

- in order to minimise the risk of unauthorized access and theft, the hardware on which patients' personal data are stored shall be placed in a restricted-access area, accessible only to those individuals who need to retrieve the patients' personal data included in the database for professional purposes; the same safeguards shall be put in place for non-electronic databases;
- any electronic database containing the patients' personal data is password-protected, by a strong password and it must be often updated (e.g.: it is at least 8 character long and updated at least every three months) and that adequate cryptographic protection measures are in place (these include, for example, file system or database cryptography, or any other equivalent IT measure which renders data unintelligible to those who are not authorised to access them);
- security measures are implemented also on the files or databases which contain the "key" to match the patients' personal data (i.e. name, surname, etc.) with their respective "Patient IDs" (as defined at point (iv) below).

The site shall, upon request from the Sponsor and/or the CRO, provide detailed written information about the measures listed above.

The CRO shall ensure that the selected sites for the study have implemented the above listed measures.

**(ii) TRANSMISSION OF DATA**. All the parties that transfer data through internet and/or to the centralised database(s) used to process study's data or to generate statistical analyses shall implement secure protocols based on cryptographic standards which make data unintelligible to unauthorized individuals.

**(iii) SECURITY OF THE CENTRALISED DATA BASE**. The centralised database held by the Sponsor shall have the following safeguards in place:

- appropriate authentication methods, which differentiate between different users according to their respective roles so as to ensure that access to a specific set of subjects' data is permitted exclusively to those for whom access to such data is essential in the context of their work for the study;
- appropriate measures to ensure that the authentication credentials are periodically updated (i.e. password change);

**(iv) PSEUDO ANONYMISATION**. All personal data that may allow identification of the patients involved in the study shall be adequately dissociated from the other data pertaining to the study ("pseudo-anonymisation" process). The Principal Investigator shall adequately dissociate the identification data of patients from the data pertaining to the study by linking results to a an alphanumerical code ("Patient ID") so as to ensure that only anonymous data are transmitted to the Sponsor, the Centralised Laboratory and/or the CRO.

Site/Principal Investigator shall securely store a separate list (e.g. identification log) with the identification code, together with all signed informed consents, in accordance with the security measures as defined above. The Principal Investigator and/or the site will maintain these documents for the longest period of time allowed by the applicable laws and this protocol, and in any case until further communication from the Sponsor.

Biological samples and any other examination (e.g. X-ray, ECG) shall bear Patient ID, and in no case will they bear other information that may lead to the direct or indirect identification of the patient.

**(v) TRAINING**. The parties shall ensure that any personnel involved in the study have received proper training on data protection issues.

All actions related to the implementation of the afore mentioned measures shall be provided by the Sponsor and/or the CRO to the competent authorities (including data protection authorities) and Ethics Committees if and when requested. If such authorities or the Sponsor consider the implementation of the afore mentioned measures insufficient to guarantee an adequate level of protection of the patients' personal data, the parties undertake to adopt all the necessary activities to overcome such remarks to assure the full compliance with the data protection laws.

### 5.11.4 Information notice on personal data protection and pseudo-anonymisation

Prior to patients' enrolment in the study, the Principal Investigator and/or the site (including their personnel) shall provide each patient with adequate, law-compliant "information notices and consent forms to process personal data" as included in the ICF (or, as the case may be, through a separate, specific form) provided by the Sponsor or delegated CRO and shall collect his/her written

consent to the processing of personal data according to the actual performance conditions in which the study is carried out.

The ICF (or the separate form) shall inform patients/parent of minors/legal guardian that consent to the processing of personal data is required to take part in the study, that if they withdraw from the study they may ask that their personal data be deleted and their samples destroyed and will specify that in this last case the results of tests that have already been performed will not be deleted and will remain in the database. The ICF (or the separate form) shall also specify that data may be transferred abroad including countries whose laws do not ensure the same level of personal data protection as that of the patient.

# 6. BACKGROUND INFORMATION

## 6.1 DISEASE AND STUDY RATIONALE

The Tumor Lysis Syndrome (TLS) is the most common disease-related emergency encountered by physicians caring for children or adults with hematologic cancers. TLS represents a critical and possibly fatal complication resulting from the rapid lyses of large numbers of tumor cells, observed most often after initial treatment with chemotherapy [2, 3]. It is estimated that from 5% to 30% of patients affected by hematological malignancies have renal insufficiency during initial chemotherapy.

In this condition, the rapid release of intracellular metabolites can alter the normal homeostatic and electrolyte balances, potentially leading to hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia. The precipitation/crystallization of uric acid or calcium phosphate in renal tubules may then lead to impaired renal function/failure which in turn may further exacerbate the degree of electrolytes imbalances.

According to Coiffier *et al.* [3], the risk of developing TLS, or more simply the risk of developing acute renal impairment, is significantly increased in patients with higher levels of uric acid *versus* those with lower levels. For every mg/dL increase in sUA, the risk of TLS raises by a factor 1.75 ($p$<0.0001), while the risk of renal events by a factor 2.21 ($p$=0.0012). This observation underlines the importance of preventing/containing the uric acid increase during chemotherapy.

The potential severity of complications resulting from TLS requires measures for prevention and prompt treatment. Recognition of risk factors, close monitoring of *at risk patients* and appropriate pharmacological interventions are the keys for preventing/managing TLS.

An international TLS consensus panel of pediatric and adult oncologists, experts in TLS pathophysiology, prophylaxis and management, has recently developed a final model of low, intermediate and high risk TLS classification and associated TLS prophylaxis recommendations [4]. Indeed, between adult and pediatric populations no major differences exist in terms of:

1) Clinical manifestations: clinical symptoms both in adults and children may include nausea, vomiting, lethargy, edema, fluid overload, congestive heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope and possibly sudden death. Clinical manifestations commonly present within 12-72 hours after cytotoxic therapy administration [5].

2) Diagnosis: Laboratory TLS (LTLS) is diagnosed if levels of 2 or more serum values of uric acid, potassium, phosphate or calcium are more or less than normal at presentation, or if they change by at least 25% from baseline (see Appendix I: Definition of LTLS and CTLS). The only significant

difference between adults and children is the threshold of phosphate, which is higher in children in an age-dependent way [5-7].

The diagnosis of Clinical TLS (CTLS) is based on the same criteria both in children and adults and requires the presence of one or more between increased creatinine level ≥ 1.5 ULN, cardiac arrhythmia/sudden death or seizure in addition to the diagnosis of LTLS. Again, the diagnostic pathway is the same between adults and children, with a clarification about the creatinine ULN. Finally, the same grading system for TLS can be applied both in adults and children (see Appendix III: TLS Risk Assessment), using the respective creatinine ULN.

3) Treatment: according to international guidelines and recommendations, the best management of TLS is prevention. In particular, in patients at low risk, the "watch and wait" approach with close monitoring is considered appropriate; whereas, in patients at intermediate risk, allopurinol is recommended in addition to hydration; finally, in patients at high risk, rasburicase should be used along with hydration [3, 4].

Allopurinol is considered an effective and tolerated treatment for TLS; however, there may be some limitations with its use, i.e. the need to reduce dose in patients with renal impairment, which is a frequent condition in this patient population, the potential for drug interactions, the rare occurrence of serious side effects including hypersensitivity reactions, and the inability to reach/maintain the sUA target levels in some patients.

Rasburicase is a recombinant form of urate-oxidase that catalyzes the oxidation of uric acid into allantoin, an inactive and soluble metabolite. Rasburicase is more potent than allopurinol, but it retains some disadvantages, such as the intravenous administration, possible severe hypersensitivity reactions, and the formation of neutralizing antibodies. These issues, together with the high cost of the treatment, strongly limit the use of rasburicase in clinical practice.

On April 8$^{th}$ 2015 febuxostat 120 mg strength, an orally administered, non-purine, selective xanthine oxidase/xanthine dehydrogenase inhibitor, has been approved for the prevention and treatment of hyperuricemia in adult patients undergoing chemotherapy for hematologic malignancies at intermediate to high risk of TLS [8]. The approval was based on the results of the randomized, double blind, phase III pivotal study FLORENCE, which is moreover the largest randomized trial performed in the TLS setting so far (see section 6.2.2).

Febuxostat addresses an important unmet medical need and adds to the armamentarium of available treatments for the prevention and management of hyperuricemia in adult patients undergoing chemotherapy for hematologic malignancies.

The medical need of TLS management in the pediatric population can be considered even higher than

in adults. In fact, age is an independent risk factor for TLS development [9] and Acute Lymphoblastic Leukemia (ALL), the most common pediatric hematologic malignancy, has a particularly high proliferation rate and high sensitiveness to chemotherapy, thus predisposing children to a possible massive TLS with even fatal outcomes. Treatment possibilities for the management of TLS in pediatric patients miss an age-appropriate oral formulation of allopurinol. Therefore, children can receive a fully correct (weight-adjusted) TLS prophylaxis only with an intravenous treatment with rasburicase. Hence, considering the high cost and the limited access to rasburicase in some of the EU 28 countries, an age-appropriate febuxostat formulation certainly deserves clinical evaluation and may represent a valid alternative to the present therapy.

TLS usually develops in patients with aggressive Non-Hodgkin Lymphoma (NHL), Acute Lymphoblastic Leukemia (ALL), or Acute Myelogenous Leukemia (AML) [10]. In the pediatric population, TLS is more frequent in B-cell ALL or in Burkitt's lymphoma with high tumor burden [11-13]. An overall TLS incidence of 4.4% was reported in two multicentre studies of 1791 children and adolescents with NHL [11] and, of these, TLS occurred in 8.4% of patients with Burkitt's lymphoma or B-cell ALL.

As children and adolescents do not show any major differences in TLS diagnosis, management or treatment in respect of the adult population, the FLORENCE study results in adults strongly suggest that febuxostat could be of significant benefit also in children and adolescents. Starting from the assumption that the clinical condition of hyperuricemia in patients with hematological malignancies undergoing chemotherapy is similar between adults and children, it is reasonable to assume that the exposure-response (ER) relationship between the two populations could be similar. In this context, the present study aims at showing that the febuxostat exposure levels achieved in children and adolescents with the selected doses are similar to those achieved in adults receiving 120 mg febuxostat once daily. The proposed Pharmacodynamic (PD) assessment, namely AUC sUA Days 1-8, corresponds to the primary efficacy parameter which was evaluated in the phase III pivotal study FLORENCE in adults [8]. The Pharmacokinetic (PK) and PK/PD modeling and simulation analyses will apply to the PK and PD observed data in order to investigate the relationship between PK/PD and age as main covariate. Therefore, the efficacy and safety data collected in the pivotal phase III study FLORENCE in adults will be bridged to the pediatric population by solely PK, as well as by PK/PD analyses, showing a full matching of febuxostat drug exposure and exposure/response between the adult and pediatric populations.

## 6.2 INVESTIGATIONAL MEDICINAL PRODUCT: FEBUXOSTAT

Febuxostat is an orally administered, non-purine, selective xanthine oxidase (XO)/xanthine dehydrogenase (XDH) inhibitor. XO inhibitors reduce sUA levels by impeding the transformation of

hypoxanthine to xanthine and of xanthine to uric acid; both conversions are catalyzed by XO and XDH enzymes; the active sites of these enzymes are structurally equivalent and XDH readily converts to XO in mammals. In the European Union (EU), febuxostat (trade name ADENURIC®) received marketing approval in April 2009 at doses of 80 mg or 120 mg once daily (QD) for the treatment of chronic hyperuricemia of conditions where urate deposition has already occurred (including a history or presence of tophus and/or gouty arthritis). In the United States (US), febuxostat (trade name ULORIC® 40 mg and 80 mg /QD) received FDA approval in February 2009 for the chronic management of hyperuricemia in patients with gout, while in Japan it was approved for the treatment of hyperuricemia with or without gout (FEBURIC® 10 mg to 60 mg/QD).

Finally, on April 8th 2015 [8], the European Commission (EC) has granted the variation of previous marketing authorization for febuxostat 120 mg strength, adding the following indication: prevention and treatment of hyperuricemia in adult patients undergoing chemotherapy for hematologic malignancies at intermediate to high risk of TLS (ADENURIC® SmPc, Appendix II: EU SmPCs for adenuric® ).

### 6.2.1 Non-clinical data

Following single- or multiple-dose administration of febuxostat, dose-proportional increases in the maximum plasma concentration ($C_{max}$) and in the area under the plasma concentration-time curve (AUC) is observed over the 10-240 mg dose range. The time to $C_{max}$ ($t_{max}$) is approximately 1 hour. Circulating febuxostat is substantially bound to albumin (approximately 99%), with an apparent volume of distribution at steady state of approximately 0.7 L/kg [14]. There is no appreciable accumulation when febuxostat is administered every 24 hours. The apparent mean terminal elimination half-life of febuxostat typically ranges from 5 to 8 hours. Febuxostat is metabolized mainly by conjugation via uridine diphosphate-glucuronosyltransferase (UGT) enzymes or to a smaller extent by oxidative metabolism via cytochrome P450 (CYP) enzymes to form active metabolites.

In preclinical studies, febuxostat was more potent than allopurinol in inhibiting XO and decreasing sUA levels. *In vitro*, the drug concentrations resulting in 50% inhibition of the activity of XO/XDH derived from bovine milk, mouse liver or rat liver were 1.4, 1.8 and 2.2 nmol/L for febuxostat compared with 1700, 380 and 100 nmol/L for allopurinol [15]. *In vivo*, in chimpanzees (similar to humans in terms of purine metabolite levels and urate excretion), sUA levels were reduced after 24, 48 and 72 hours with febuxostat by 56%, 70% and 74%, and with allopurinol by 28%, 42% and 45%, each 5 mg/kg/day orally for 3 days [16].

A specific toxicology program has been run to fulfill the requirements of the febuxostat pediatric development [17]. Effects in non-clinical studies were generally observed at exposures in excess of the maximum human exposure. In both adult and juvenile rats, dose-limiting toxicities were associated

with obstructive nephropathies due to the precipitation of xanthine in urine. These findings are considered a consequence of species-specific purine metabolism and urine composition, and are deemed of no relevance for the clinical development. As already reported for allopurinol, the nephrotoxic effects of XO inhibitors is species-related, being observed in rodents and dogs, but not in humans [18]. In fact, the rate of purine biosynthesis is slower in humans and the volume of urine is larger compared to rodents [19]. For this reason, xanthine concentration in human urine does not reach the same high levels reported in animal toxicology studies following febuxostat treatment. Therefore, the formation of xanthine crystals is not expected at the febuxostat dose levels recommended for adult humans and neither for children and adolescents from 6 to 17 years of age.

Further details on non-clinical pharmacology, pharmacokinetics (PK) also in special populations, and adult toxicology can be found in the EU Summary of Product Characteristics (SmPC)/Investigator Brochure (IB).

### 6.2.2 Clinical experience

The pharmacodynamic effects of oral febuxostat have been examined in healthy subjects, where it dose-dependently reduced the mean sUA levels from baseline by 25-70%, and the 24-hour urinary uric acid excretion by 46-66% relative to placebo after 8 days of treatment. Both effects seemed to reach plateau at dosages >120 mg/day [20]. The effects of food intake, anti-acid consumption, age and sex on the pharmacokinetics of oral, once-daily febuxostat were not considered to be clinically significant in studies in healthy volunteers [21, 22].

The anti-hyperuricemic efficacy of oral, once-daily febuxostat has been evaluated in adult patients with gout and hyperuricemia in several randomized, multicentre trials. One double-blind, placebo-controlled dose-response study [23] and three trials with allopurinol as comparator: FACT (Febuxostat *versus* Allopurinol Controlled Trial), a phase III, 52-week, double-blind study (n= 760) [24]; APEX (Allopurinol-Placebo-controlled Efficacy study of febuXostat), a phase III, 28-week, double-blind, placebo-controlled study (n= 1067) [25]; EXCEL (fEbuXostat Comparative Extension Long-term study), a long-term, non blind extension study in patients completing FACT and APEX (n= 735) [26]; and CONFIRMS (CONfirmation of Febuxostat In Reducing and Maintaining Serum urate), a phase III, randomized, double-blind, allopurinol-controlled study (n= 2269) [27]. The dose-response and FACT trials excluded patients with a serum creatinine level >1.5 mg/dL, while APEX included patients with moderate renal impairment (serum creatinine level of 1.6-2.0 mg/dL). In addition, the long-term efficacy and tolerability of febuxostat were assessed in the FOCUS (Febuxostat Open-label of Urate-lowering efficacy and Safety) study (n= 116), a long-term, non comparative extension of the dose-response trial [28].

In the dose-response study [23], febuxostat was significantly more effective than placebo at reducing

sUA levels. After 4 weeks of treatment, a greater proportion of patients receiving febuxostat 40, 80 or 120 mg/day *versus* placebo had sUA levels <6.0 mg/dL (56%, 76%, 94% *versus* 0%; all $p< 0.001$). Furthermore, febuxostat had significantly greater urate-lowering efficacy than allopurinol in both the FACT [24] and the APEX [25] trials. Indeed, in these phase III pivotal studies, the non-inferiority and superiority of both the febuxostat 80 mg (51%) and 120 mg (63%) treatment groups compared with the allopurinol 300/100 mg (22%) group were demonstrated with respect to the primary efficacy endpoint (proportion of subjects with last 3 serum urate levels <6.0 mg/dL). The response rate in the febuxostat 120 mg group was statistically significant greater compared to that in the febuxostat 80 mg group. The urate-lowering effect (all treatment groups) was observed by week 2 of therapy and was maintained throughout the course of treatment [24, 26]. Dosage adjustment of febuxostat was not required in patients with mild or moderate renal impairment, and there was no statistically significant effects of mild or moderate hepatic impairment on the pharmacokinetics of multiple-dose febuxostat 80 mg daily and its oxidative metabolites [29].

Febuxostat was generally well tolerated in patients with gout and hyperuricemia and most treatment-related adverse events were of mild to moderate severity. In a pooled analysis of the FACT and APEX phase III trials on 1043 patients, the most commonly reported adverse events were liver function test abnormalities (3.5%), diarrhea (2.7%), headache (1.8%), nausea (1.7%), and rash (1.5%). Diarrhea, nausea and vomiting were more frequent in patients treated concomitantly with colchicines.

The safety and efficacy of febuxostat over allopurinol in patients with hematologic malignancies at intermediate to high risk for TLS was investigated in the multicenter, double blind, randomized, parallel-group, comparative phase III pivotal study FLORENCE [30]. Overall, 346 patients were randomized to receive febuxostat or allopurinol for 7-9 days, starting 2 days prior to induction chemotherapy. Study treatment was blinded, while daily dose (low/standard/high containing allopurinol 200/300/600 mg or fixed febuxostat 120 mg) depended on Investigator's choice. The co-primary endpoints, sUA area under curve (AUC $sUA_{1-8}$) and serum creatinine change, were assessed from baseline to Day 8 through analysis of covariance with two-sided overall significance level of 5%. Secondary endpoints included treatment responder rate, laboratory and clinical TLS incidence, and safety. Results of the FLORENCE study [30] provided clear evidence of the superiority of febuxostat over allopurinol in terms of reduction of the exposure to sUA ($p < 0.0001$), a well established surrogate endpoint for TLS and renal impairment, in patients undergoing chemotherapy for hematologic malignancies at intermediate to high risk of TLS. Noteworthy, febuxostat achieved a significant higher sUA reduction compared to allopurinol since the first 24 hours of treatment. Moreover, results of the FLORENCE trial [30] provided evidence that febuxostat is active in preserving renal function in the target population. No safety concerns raised from febuxostat in comparison to allopurinol treatment. These results showed that febuxostat is a more effective treatment alternative to allopurinol in reducing

the risk of TLS and renal events in patients with hematologic malignancies at intermediate to high risk of TLS, also providing the advantage of a fixed once daily dose without the need for dose adjustments in case of renal impairment.

Globally the post-marketing exposure to febuxostat during the reporting period from 21 April 2014 to 20 April 2015 was 1.781.064 patient-years. A total of 1.435 ADRs from spontaneous and post-marketing solicited sources were reported. The review of interval and cumulative data revealed no new safety concerns, no changes in characteristics of ADRs or increase in reporting frequency, no significant new information on drug interactions, experiences during pregnancy or lactation, experiences in special patient groups, effects of long term treatment, or prescription errors. Overall, no information that could alter the consolidated clinical benefit of febuxostat in the approved indications was collected [31].

## 6.3 RISK-BENEFIT ASSESSMENT

Febuxostat is approved in the European Union for the treatment of gout at dosages of 80 mg and 120 mg once a day, while the 120 mg strength has recently received marketing approval by the EC [8] for the prevention and treatment of hyperuricemia in adult patients undergoing chemotherapy for hematologic malignancies at intermediate to high risk of TLS. Therefore, the adult population participating to the present trial can benefit from an early access to an effective and safe treatment, whereas the pediatric population will be exposed to potential risk, which can be considered low taking into account the following evidences:

1) TLS is a life-threatening condition that may occur rapidly in children. Children hematologic malignancies are typically highly proliferative and highly chemosensitive. Thus, while chemotherapy may be strongly effective for them, it may also determine massive TLS with fatal outcomes. It is therefore essential to protect children with the best available and more suitable therapeutic strategy. It is worth noting that at the moment an oral age-appropriate formulation of allopurinol is not available in Europe. The present study is part of the febuxostat Pediatric Investigational Plan agreed with the Pediatric Committee of the EMA [32] and endorsed by the EMA [17].

2) A specific toxicology program has been run to fulfill the requirements of the febuxostat pediatric development [17]. In both adult and juvenile rats, dose-limiting toxicities were associated with obstructive nephropathies due to the precipitation of xanthine in urine. These findings are considered a consequence of species-specific purine metabolism and urine composition, and are deemed of no relevance for febuxostat clinical development. Indeed, the formation of xanthine crystals is not expected at the febuxostat dose levels recommended for adult humans and neither for children and adolescents from 6 to 17 years of age.

3) Febuxostat efficacy in the prevention/treatment of hyperuricemia in adult patients undergoing

chemotherapy for hematologic malignancies at intermediate to high risk of TLS was extensively proven by the FLORENCE study [30] and febuxostat 120 mg strength was recently approved for the prevention and treatment of hyperuricemia in this patient population (ADENURIC® SmPC Appendix II: EU SmPCs for adenuric® ).

4) Febuxostat safety profile in adults has been broadly explored in the gout and TLS experience. In the clinical development for the gout indication, more than 4000 subjects received at least one febuxostat dose; more than 2500 subjects were exposed to febuxostat 80 mg, and more than 1000 to febuxostat 120 mg; and the mean duration of dosing in the 80 mg and 120 mg groups was approximately 350 and 400 days, respectively. Febuxostat was safe and generally well tolerated at doses of 80 mg, 120 mg and 240 mg (two times the maximum clinical dose). Adverse drug reactions (ADRs) were mostly mild or moderate in severity. The worldwide post-marketing experience confirmed the safety of febuxostat in the gout and adult TLS setting [31]. In the phase III FLORENCE study [30] comparing febuxostat to allopurinol for the prevention of hyperuricemia in adult patients with hematologic malignancies at intermediate to high risk for TLS, 173 patients were exposed to febuxostat 120 mg for a mean time of approximately 7 days. No safety concerns raised from febuxostat treatment. Adverse drug reactions (ADRs) occurred with the same incidence of allopurinol (6.4%) and, noteworthy, all febuxostat ADRs were mild or moderate in severity. Neither serious ADRs, nor study drug-related deaths occurred.

5) The pediatric febuxostat doses were selected based on predicted exposures ($C_{max}$ and AUC) which were considered to be safe (i.e., exposure not greater than that observed in adults receiving 240 mg dose in previous clinical studies), and efficacious (i.e., febuxostat exposure following a 120 mg dose to adults was effective in controlling sUA levels throughout the chemotherapy treatment period).

6) In order to reduce any risk or discomfort associated with blood sampling in children and adolescents, a population PK design allowing to minimize the number of blood samples has been adopted.

Finally, the potential risk for the pediatric population associated with the participation to this study is estimated low, also considering the sequential administration of the two different treatment doses per age group, while the expected benefit is predicted to be quite relevant. In fact, no major differences in the TLS diagnosis and management are present between adults and children, thus the superior reduction of sUA levels obtained by febuxostat in comparison to allopurinol in adults is highly expected to be confirmed in the pediatric population. The present PK/PD study has been designed to explore the PK/PD profile of febuxostat in the pediatric population in comparison to adults, and to possibly define the best dose, in terms of safety and efficacy, to be administered to children and adolescents, while avoiding/minimizing inappropriate exposure to non efficacious/non safe treatment, as per guideline CHMP/EWP/147013/2004 [33].

# 7. STUDY OBJECTIVES

## 7.1 PRIMARY OBJECTIVE

The primary objectives of this trial are:

- To assess the pharmacokinetics (PK) of febuxostat in pediatric patients (≥6<18 years of age) and in adults suffering from hematological malignancies at intermediate to high risk of TLS.
- To compare the febuxostat exposure in pediatric patients (≥6<18 years of age) with the one achieved in adults administered with a dose of 120 mg/QD.

## 7.2 SECONDARY OBJECTIVES

The secondary objectives of this trial are:

- To compare the pharmacodynamics (PD) of febuxostat between pediatric patients (≥6<18 years of age) and adults.
- To evaluate and compare the PK/PD relationship of febuxostat in pediatric patients (≥6<18 years of age) and adults.
- To evaluate the safety of febuxostat between pediatric patients (≥6<18 years of age) and adults.
- To evaluate the occurrence of Laboratory TLS (LTLS) and Clinical TLS (CTLS) according to Cairo and Bishop Criteria (see Appendix I: Definition of LTLS and CTLS).
- To assess the age-appropriate formulation acceptability in children.

# 8. INVESTIGATIONAL PLAN

## 8.1 OVERALL STUDY DESIGN AND PLAN DESCRIPTION

This trial is designed as an open label, multi-centre, parallel group study to be conducted in approximately 40 sites. A total of 120 patients are expected to be treated in this trial distributed in 3 age-cohorts: 48 children (aged 6 to less than 12 years), 48 adolescents (aged 12 to less than 18 years) [1] and 24 adults, suffering from hematological malignancies at intermediate to high risk of TLS, with no access to rasburicase, and scheduled to receive the first cycle of cytotoxic chemotherapy regardless of line of treatment. The evaluation of TLS risk will be based on the classification model issued by Cairo and co-workers and published in the British Journal of Haematology [4], as reported in Appendix III: TLS Risk Assessment.

Potential hematologic patients at intermediate to high risk of TLS will be assessed for eligibility at the Screening Visit, which should be held up to 1 week (+2 days of accepted timeframe window) prior to the Start of Treatment (Day -9 to Day 1). The Start of Treatment (Visit 1, Day 1) will be scheduled 2 days prior to the planned start of first chemotherapy cycle; Screening Visit and Visit 1 (Day 1) may coincide.

After confirmation that all inclusion and none of the exclusion criteria are met, eligible patients will receive oral administration of the following dose of febuxostat per age group:

- Children

Cohort 1: 40 mg once daily;

Cohort 2: 60 mg once daily.

- Adolescents

Cohort 3: 80 mg once daily;

Cohort 4: 120 mg once daily.

- Adults

120 mg once daily.

The two dose levels per children and adolescent groups will be sequentially administered to cohort. The first ≈24 children will receive the lower dose of 40 mg once daily and the first ≈24 adolescents the dose of 80 mg once daily. Afterwards, the higher doses will be administered: 60 mg once daily to children, and 120 mg once daily to adolescents. Cohort 1, Cohort 3 and adults treatments will start simultaneously. The control group of adult patients has been chosen to allow the comparison of PK/PD parameters between the pediatric (≥6<18 years) and the adult populations.

The final total number of patients/patients distributed in each age/dose cohort might slightly deviate

from the planned number since patients who satisfactory passed the screening have the right to be treated.

Treatment will start two days prior to the planned beginning of chemotherapy and will continue for 7 to 9 consecutive days, on the basis of chemotherapy duration that will be decided by the Investigator. A Follow Up/End of Study Visit (Visit 10, Day 14±2 days) will be performed for each patient at Day 14 (±2 days of accepted timeframe).

Overall, the study will include 10 to 11 pre-planned visits, depending on the selected hypouricemic treatment duration:

Screening Visit (Day -9 to Day 1)

***NOTE***: re-screening will be allowed but requires sponsor/medical monitor's approval. A patient may maximally re-screened once.

Visit 1 (Day 1): Start of Treatment

Visit 2 (Day 2) to Visit 7 (Day 7): Treatment Period

Visit 8 (Day 8): Evaluation Visit

Visit 9 (Day 9): Optional, in case of prolonged treatment

Visit 10 (Day 14±2): Follow-Up/End of Study Visit

Regardless of the selected hypouricemic treatment duration, the treatment period for the assessment of the primary endpoints will start at Visit 1 (Day 1), corresponding to the patient's baseline, and will terminate after seven days of hypouricemic treatment, which is expected to be five days following chemotherapy initiation.

The average duration of each patient participation in this trial will be of approximately 3 weeks.

## 8.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

The present phase I/II trial has been designed taking into account the relevant published literature, available scientific guidelines and recommendations, standard clinical practice and the results of the phase III FLORENCE study [30] in adults. The study has been designed in order to avoid/minimize inappropriate exposure to non efficacious/non safe febuxostat doses in the pediatric population, as per guideline CHMP/EWP/147013/2004 [33].

The study outline was part of the febuxostat Pediatric Investigational Plan (PIP) agreed with the Pediatric Committee of the European Medicines Agency [32] and endorsed by the EMA [17].

The primary objective of this phase I/II study is to assess the pharmacokinetics (PK) of febuxostat in

pediatric patients (≥6<18 years of age) in order to ascertain that the systemic exposure attained with the selected doses is comparable to that achieved in adults administered with a dose of 120 mg/QD. The secondary objectives are to compare the pharmacokinetic/pharmacodynamics (PK/PD) and safety of febuxostat between pediatric patients (≥6 and <18 years) and adults. The required sample size encompasses approximately 24 patients per treatment dose in children and adolescents groups, and ≈24 patients in the adults group. The choice of the 120 mg once daily febuxostat dosage for adults resembles that already successfully and safely used in the phase III FLORENCE study [30], whereas two different febuxostat dosages, both expected to result in an exposure to febuxostat not exceeding that seen with 240 mg once daily in adults, will be tested in each pediatric subset of patients in order to allow a PK study of febuxostat in the target population.

The pharmacokinetic of febuxostat has been extensively investigated both in adult healthy subjects and in patients with hyperuricemia and gout. In general, febuxostat PK parameters estimated by population PK analyses in patients are consistent with those obtained from healthy subjects, indicating that healthy subjects are representative for PK assessment in the patient population with gout. Pharmacokinetic analyses in special populations demonstrated that dosage adjustment is not required in patients with mild or moderate renal impairment [29]. The investigation on the influence of covariates such as age, weight and gender on febuxostat PK, PD and safety were considered not clinically meaningful, suggesting no need of dose adjustment based on these parameters in adult patients [22]. These data were taken into account to optimize the sample size of the present study, as per guideline CHMP/EWP/147013/2004 [33]. According to the PK profile of febuxostat, the pharmacokinetics in adolescent patients is expected to be similar to the one in adults, whilst minor differences in the pharmacokinetics of children aged 6 to 11 years are expected.

To resemble the FLORENCE study outline [30] and the future clinical practice, patients with hematological malignancies who are scheduled to be treated with cytotoxic chemotherapy, regardless of the line of treatment, and at intermediate to high risk of TLS, will be screened. Eligible patients will receive treatment for 7 to 9 consecutive days, starting from 2 days prior to chemotherapy. Children and adolescents will be administered one out of the two dose levels of febuxostat, 40 or 60 mg for children, and 80 or 120 mg for adolescents. As for an extreme cautious approach, the two dose levels in children and adolescents will be sequentially administered (Cohort 2 after Cohort 1 and Cohort 4 after Cohort 3). The first ≈24 children will receive the lower dose of 40 mg once daily, and the first ≈24 adolescents the dose of 80 mg once daily. Afterwards, the higher doses will be administered: 60 mg once daily to children and 120 mg once daily to adolescents. Adults will receive 120 mg once daily in accordance to the treatment schedule previously adopted in the FLORENCE study [30]. No restriction will be applied to the enrolment of patients with different types of hematological malignancies, nor to the chemotherapy regimen with the exception of those including investigational products. The inclusion of

patients with hematological malignancies at intermediate to high risk of developing TLS is deemed appropriate considering the results of the FLORENCE study [30] and that patients at high TLS risk will be included only providing that they either have no access or have contraindications to rasburicase, and would be otherwise treated with allopurinol.

## 8.3 SELECTION OF STUDY POPULATION

After providing informed consent, the eligibility of patients to enter this study will be assessed based on inclusion and exclusion criteria that will be checked at Screening Visit (Day -9 to Day 1) and some of them at Visit 1 (Day 1). Patients will be included only if they meet all inclusion criteria (see section 8.3.1) and any of the exclusion criteria (see section 8.3.2).

### 8.3.1 Inclusion criteria

[redacted]

male and female children of 6 to less than 12 years of age, adolescents of 12 to less than 18 years of age and adults from 18 years:

a. scheduled for first cytotoxic chemotherapy cycle, regardless of the line of treatment, because of hematologic malignancies, and
b. at intermediate or high risk of TLS [4], and
c. with serum uric acid (sUA) levels < 10 mg/dL at Visit 1 (Day 1), and
d. with no access to rasburicase;

[redacted]

[redacted]

[redacted]

### 8.3.2 Exclusion criteria

[redacted]

1. patients known to be hypersensitive to febuxostat or to any of the components of the formulation;

[redacted]

6. patients with severe renal insufficiency;
7. patients with severe hepatic insufficiency;
8. patients with diagnosis of Laboratory TLS (LTLS) or Clinical TLS (CTLS) at Visit 1 (Day 1).

[redacted]

### 8.3.3 Withdrawal of patients from therapy or assessment

Participation in the study is strictly voluntary and patients have the right to withdraw from the study at any time for any reasons without giving explanation. This will not affect their rights for future medical care. Patients may also be withdrawn at the Investigator's discretion or at specific Sponsor's request at any time.

Patients should not receive further study medication and will be withdrawn from the study (study termination) in case of medical emergency or necessity including but not limited to:

- adverse events with a possible, probable or certain drug-causality as per Investigator's judgment of severity grade ≥3 CTCAE version 4.03;
- appearance of skin rash or of any signs which may indicate allergic/hypersensitivity reactions (***NOTE***: in case of severe allergic/hypersensitivity reactions, febuxostat must not be re-started in patients at any time; for guidance please refer to the EU SmPC, Appendix III: TLS Risk

Assessment);

- severe hepatic insufficiency;
- severe renal insufficiency;
- investigator's judgment if treatment discontinuation is considered in the interest of the patient's safety.
- protocol violation (e.g. prohibited medication, poor compliance with study procedures/treatment);
- patient's request.

In the event that the patient is withdrawn from the study for whatever reason, the Investigator must be informed immediately and the date, reasons (if known), and circumstances for premature discontinuation will be documented in the source patient's record and in the corresponding section of the eCRF.

Any patient who is discontinued from the treatment for one of the above reported reasons should undergo the procedures required for Visit 8-Evaluation (see section 8.6.1.6) immediately after the discontinuation. The safety Follow Up/End of Study (Visit 10, Day 14±2 days) should be performed as well, according to protocol schedule (see section 8.6.1). If study participation is terminated due to an AE or for any safety reasons, the patient has to be followed-up (with additional examinations, if necessary) according to the medical judgment of the Investigator, until the abnormal condition is resolved or the Investigator deems further observations or examinations as no longer medically indicated.

If a patient prematurely terminates the study, data already collected will be used and analysed for the purpose of the study. In regard to biological samples already collected, the patient will be asked if samples already obtained but not yet analysed shall be destroyed or analysed.

## 8.4 IDENTITY OF THE INVESTIGATIONAL PRODUCT

### 8.4.1 Description of Investigational Medicinal Product

| | |
|---|---|
| INN (if applicable) | |
| Chemical Name (if applicable) | [redacted] |
| Doses: | 40 mg/day, 60 mg/day, 80 mg/day, 120 mg/day. |
| Dosage form | 20 mg oral film coated tablet,<br>80 mg oral film coated tablet, |

| | |
|---|---|
| | 120 mg oral film coated tablet. |

### 8.4.2 Packaging, labeling, and storage

The packaging and labeling of IMP will be performed under the responsibility of the Department of Pharmaceutical Development, A. Menarini Research & Business Service GmbH, Glienicker Weg 125, 12489 Berlin, Germany.

The febuxostat film coated tablets (20 mg) are packed in blisters consisting of a laminated aluminium foil (OPA 25 µm / Al 45 µm / PVC 60 µm) sealed with rigid aluminium foil (20 µm hard aluminium foil with heat seal lacquer), synonym: Al-Al blisters.

The febuxostat film coated tablets (80 mg and 120 mg) are packed in blisters consisting of a PCTFE (polychlorotrifluoroethylene) / PVC based film lamination (ACLAR RX-160 15 µm / PVC 250 µm) sealed with a 20 µm lacquered push through aluminium foil.

The IMP will be provided in treatment boxes (blister cards) to be dispensed starting from Visit 1 (Day 1). The blisters (primary packaging) will be permanently fixed in blister cards (secondary packaging).

For the 40 mg dose cohort, the blister cards will contain 28 febuxostat film coated tablets (20 mg) (2 tablets of 20 mg daily intake, medication for 14 days incl. surplus).

For the 60 mg dose cohort, the blister cards will contain 42 febuxostat film coated tablets (20 mg) (3 tablets of 20 mg daily intake, medication for 14 days incl. surplus).

For the 80 mg dose cohort, the blister cards will contain 14 febuxostat film coated tablets (80 mg) (1 tablet of 80 mg daily intake, medication for 14 days incl. surplus).

For the 120 mg dose cohort and adult treatment group, the blister cards will contain 14 febuxostat film coated tablets (120 mg) (1 tablet of 120 mg daily intake, medication for 14 days incl. surplus).

Labeling: the IMP will be labeled in compliance with the current valid international and corresponding national requirements. The treatment box (blister card) labels will have a peel-off section which has to be attached to the corresponding section in the drug accountability log upon dispensing of the IMP. The peel-off part reports the treatment box number to identify the treatment as assigned through IxRS. The fixed section of the label will report the contents of the treatment box and the instructions how to administer and store the IMP.

Storage: at the study site, the IMP has to be stored at controlled room temperature. The following storage recommendations are in place: “Do not store below 15°C and above 25 °C” and “Store in the original package”. The IMP must be kept in a secure area, out of reach of children and inaccessible to unauthorized individuals.

### 8.4.3 Drug accountability

Upon receipt of all IMP, study site personnel will open the shipment package, verify the contents as stated on the enclosed shipping form, and confirm the receipt through IxRS.

The IxRS will be used to record the IMP delivery to the study site, the inventory at the site, the use by each patient, including dates, quantities, batch/serial numbers, expiry dates, and the unique code numbers assigned to the IMP (treatment box number) and patients (patient number).

The Investigator will be responsible for documenting the dispensing of the IMP to the patient by entering the treatment box number in the source document and in the eCRF when the treatment is administered to in- as well as out-patient regimen. Furthermore, the number of tablets dispensed and any used/unused IMP will be recorded by the Investigator in the study specific drug accountability form.

### 8.4.4 Destruction of surplus medication

At the end of the study, all remaining IMP will be reconciled under the responsibility of the Investigator at the site. The IMP will be subsequently returned to the Department of Pharmaceutical Development, A. Menarini Research & Business Service GmbH or appointed depots.

## 8.5 TREATMENTS

### 8.5.1 Treatment Allocation

The study will be performed according to an open design; no blinding technique will be adopted.

Eligible patients will receive study treatment at Visit 1 (Day 1) after completing the relevant "prior to drug administration" procedures and re-checking of the eligibility criteria.

The IMP box assignment will be performed by means of the IxRS system (see section 10.1.2) without any randomized allocation. The first ≈24 children will be allocated to the 40 mg dose, the following ≈24 children to the 60 mg dose. The first ≈24 adolescents will be allocated to the 80 mg dose, the following ≈24 adolescents to the 120 mg dose. The ≈24 adults will be allocated to the 120 mg dose.

For children, the 20 mg febuxostat tablets will be used, whereas for adolescents and adults the market product ADENURIC® 80 mg and 120 mg will be employed as represented below:

**Table 1. Febuxostat: Treatment dose and form**

| Patient Population | Treatment dose | Treatment form |
|---|---|---|
| Children | febuxostat 40 mg | 2 tablets 20 mg |
| | febuxostat 60 mg | 3 tablets 20 mg |
| Adolescents | ADENURIC® 80 mg | 1 tablet 80 mg |

| | | |
|---|---|---|
| | ADENURIC® 120 mg | 1 tablet 120 mg |
| Adults | ADENURIC® 120 mg | 1 tablet 120 mg |

### 8.5.2 Treatment administration - frequency and duration of application

Eligible patients will receive oral administration of the following dose of febuxostat per age group:

- Children

Cohort 1: 40 mg once daily;

Cohort 2: 60 mg once daily.

- Adolescents

Cohort 3: 80 mg once daily;

Cohort 4: 120 mg once daily.

- Adults

120 mg once daily.

Minimum treatment duration will be of 7 days starting from Visit 1 (Day 1), which shall occur 2 days prior to the planned start of first chemotherapy cycle. The Investigator will be given the possibility to prolong the treatment duration up to 9 days on the basis of the chemotherapy regimen administered to the patient.

### 8.5.3 Treatment compliance

The study treatment will be dispensed at each study visit starting from Visit 1 (Day 1) to Visit 7 (Day 7) at the site by the Investigator. The Investigator will be given the possibility to prolong treatment duration up to 9 days on the basis of the chemotherapy regimen chosen.

The Investigator will be responsible for documenting the dispensation of the IMP to the patient by entering the treatment box number in the source document and in the eCRF when the treatment is administered to in- as well as out-patients. Furthermore, the number of tablets dispensed and any used/unused IMP will be recorded by the Investigator in the study specific drug accountability form, including dates, quantities, batch/serial numbers, expiry dates, and the unique code numbers assigned to the IMP (treatment number) and patients (patient number).

### 8.5.4 Dosage modification

No dose adjustment is allowed.

### 8.5.5 Concomitant Medication

Patients are not allowed to receive:

- any other investigational agent
- any other hypouricemic agent, such as allopurinol, rasburicase or probenecid;
- mercaptopurine/azathioprine.

In case of concomitant use of theophylline in patients receiving febuxostat 120 mg strength, a careful monitoring is recommended during the treatment period. In particular, theophylline blood levels have to be controlled.

Concomitant and prior (i.e. within 30 day before Visit 1, Day 1) medications shall be carefully checked because the use of the above reported medications may represent an exclusion criterion to make the patient eligible to participate in the study and to receive the study treatment. Furthermore, the regular and occasional use of any concomitant medication has to be recorded starting from Screening Visit until the final Follow Up/End of Study Visit (Visit 10, Day 14±2 days).

Patients have to receive adequate hydration: increased hydration ranging from 2 to 3 $L/m^2$ per day is recommended according to TLS management guidelines.

Concomitant and prior (i.e. within 30 day before Visit 1, Day 1) medications will be recorded in eCRF.

## 8.6 STUDY PROCEDURES AND ASSESSMENTS

### 8.6.1 Study Schedule

A maximum of 11 study visits are scheduled including Screening, as depicted in the study flow chart (see section 2.1) and summarized below.

Starting from Start of Treatment (Visit 1, Day 1) to the Evaluation Visit (Visit 8, Day 8), site visits must be performed daily; an additional visit can be scheduled on Day 9 (Visit 9) for patients requiring 9 days of treatment, upon Investigator's decision to prolong the treatment duration. Visits may occur as in-hospital or as ambulatory visits, according to the local clinical practice.

The Follow up/End of Study Visit is scheduled at Day 14 (± 2 days).

The treatment period can last from 7 to 9 days, evaluated by the Investigator on the base of the chemotherapy regimen administered to the patient. All assessments that are relevant to the study endpoints will be collected during the treatment period (Day 1-Day 7) and at the Evaluation Visit (Visit 8, Day 8). Each patient will complete the study at the time of the Follow up/End of Study Visit (Visit 10, Day 14 ± 2 days).

A summary of the study assessments at each visit is specified below.

Written informed consent shall be provided by adult patients or by parents (one or both, according to local regulations) or by legal guardian for children and adolescents, PRIOR to start any study procedures.

#### 8.6.1.1 Screening Visit (Day -9 to Day 1)

Potentially eligible patients with hematological malignancies scheduled for first cytotoxic chemotherapy cycle will undergo the following procedures:

- assessment of inclusion/exclusion criteria;
- demographic data collection;
- medical history;
- prior and concomitant medication;
- physical examination and vital signs (i.e. blood pressure [BP], heart rate [HR], breathing rate [BR], body temperature [T]);
- Karnofsky performance status (KPS) / Lansky Play performance status (LPS) evaluation;
- 12 Lead ECG;
- blood sampling and urine collection for safety laboratory tests, including pregnancy test (if applicable);
- record of adverse events.

***NOTE-1***: Study procedures under Screening Visit may occur also on more than one day.

***NOTE-2:*** Results of safety laboratory tests (biochemistry, haematology, coagulation, urinalysis and pregnancy test, when appropriate) and ECG which have been performed in the context of the standard patient's management can be recorded in the e-CRF under Screening Visit procedures, provided that they have been done within 24 hours prior to the Screening Visit (Visit 1, Day 1).

***NOTE-3:*** Re-screening is allowed but requires sponsor/medical monitor's approval. A patient may maximally be re-screened once.

#### 8.6.1.2 Visit 1, Start of Treatment (Day 1)

Start of Treatment Visit will be performed 2 days prior to the scheduled chemotherapy. During the Start of Treatment Visit, the following procedures will be performed:

<u>Prior to the drug administration:</u>

- record of adverse events and change in concomitant medication;
- re-check of inclusion/exclusion criteria and patient's eligibility confirmation;
- physical examination and vital signs;
- KPS/LPS evaluation;
- blood sampling and urine collection for safety laboratory tests (***NOTE:*** safety laboratory tests performed within 24 hours do not need to be repeated at Visit 1, Day 1);
- blood sampling for centralized laboratory test (sUA); whenever possible blood sampling for centralized laboratory test (sUA) will be collected in conjunction with safety laboratory tests to reduce the patient's discomfort of additional venopunctures;
- assessment of LTLS/CTLS;
- allocation of investigational medicinal product (IMP) treatment box as per IxRS assignment.

Study drug administration:

- administration of febuxostat as per age group.

After study drug administration:

- assessment of the age-appropriate formulation acceptability (only for children).

***NOTE***: Screening Visit and Visit 1 (Day 1) may occur on the same day. Common assessments will be performed only once.

#### 8.6.1.3 Visit 2 (Day 2)

- record of adverse events and change in concomitant medications;
- vital signs;
- KPS/LPS evaluation;
- pre-dose PK blood sampling;
- blood sampling for safety laboratory test, including centralized laboratory test (sUA);
- study drug administration;
- assessment of the age-appropriate formulation acceptability (only for children).

#### 8.6.1.4 Visit 3 (Day 3)

- record of adverse events and change in concomitant medications;
- vital signs;
- KPS/LPS evaluation;
- 12 Lead ECG;
- pre-dose PK blood sampling;
- blood sampling for safety laboratory test, including centralized laboratory test (sUA);
- study drug administration;
- assessment of the age-appropriate formulation acceptability (only for children);
- assessment of LTLS/CTLS;
- starting of chemotherapy regimen.

#### 8.6.1.5 Visits 4-7 (Days 4-7)

On each day from Day 4 to Day 7, the following assessments will be performed:

- record of adverse events and change in concomitant medications;
- vital signs;
- KPS/LPS evaluation;
- pre-dose PK blood sampling;
- blood sampling for safety laboratory test, including centralized laboratory test (sUA);
- study drug administration;
- assessment of the age-appropriate formulation acceptability (only for children);
- 4 additional post-dose PK blood sampling ONLY at Day 7 (Visit 7) at the assigned sampling time intervals: 0.5-2 hours, 2-4 hours, 4-6 hours and 6-8 hours;
- urine collection for safety laboratory tests ONLY at Day 4 (Visit 4);
- assessment of LTLS/CTLS.

#### 8.6.1.6 Visit 8 (Day 8)

On Day 8, an Evaluation Visit will be performed, including the following assessments:

- record of adverse events and change in concomitant medications;
- physical evaluation and vital signs;
- KPS/LPS evaluation;
- 12 Lead ECG;
- PK blood sampling (it is a pre-dose PK sampling for patients scheduled to prolong hypouricemic treatment);
- blood sampling for safety laboratory test including centralized laboratory test (sUA);
- urine collection for safety laboratory tests;
- assessment of LTLS/CTLS.

***ONLY for patients scheduled to prolong hypouricemic treatment:***

- study drug administration;
- assessment of the age-appropriate formulation acceptability (only for children).

#### 8.6.1.7 Visit 9 (Day 9)

***To be performed ONLY for patients scheduled to prolong hypouricemic treatment:***

- record of adverse events and change in concomitant medications;
- vital signs;
- KPS/LPS evaluation;
- study drug administration;
- assessment of the age-appropriate formulation acceptability (only for children);
- blood sampling for safety laboratory tests.

#### 8.6.1.8 Visit 10, Follow-up/End of Study (Day 14 ± 2)

A final safety Follow-up/End of Study Visit will be performed at Day 14 (± 2):

- record of adverse events and change in concomitant medications;
- physical examination and vital signs;
- KPS/LPS evaluation;
- 12 Lead ECG;

- blood sampling and urine collection for safety laboratory tests.

## 8.6.2 Assessment of Pharmacokinetics/Pharmacodynamics

### 8.6.2.1 Pharmacokinetic parameters

Pharmacokinetic parameters will be calculated from the plasma concentration data using a limited sampling model with nonlinear mixed-effects modeling methods.

A list of parameters that can be estimated according to the PK structural model are defined in Table 2 below. Additional PK parameters may be estimated [redacted]

Methods for PK parameters estimation are described in section 9.3.2.

**Table 2. Pharmacokinetic parameters**

| | |
|---|---|
| $C_{max}$ | Maximum plasma concentration |
| $T_{max}$ | Time to $C_{max}$ |
| Vd/F | Apparent volume of distribution |
| CL/F | Apparent clearance |
| Ka | Absorption rate constant |
| $AUC_{(0-t)}$ | The area under the plasma concentration versus time curve from time 0 to time of the last quantifiable concentration |
| $AUC_{(0-\tau)}$ | The area under the plasma concentration versus time curve over the dosing interval, where tau is the length the dosing interval (24 hours) |
| $AUC_{(0-\infty)}$ | The area under the plasma concentration versus time curve from time zero to infinity |

### 8.6.2.2 Sampling and handling of blood samples for drug assays

#### 8.6.2.2.1 Drug assay

In order to assess febuxostat pharmacokinetics following repeated dose administration in children, adolescent and adult patients, blood samples will be collected on Visits 2, 3, 4, 5, 6, 7 and 8 (i.e., after the first treatment administration and on each following visit until the Evaluation Visit). These blood samples will be drawn at trough together with the safety laboratory blood samples. Four additional blood samples are required for each patient on Visit 7 (Day 7) at the selected sampling intervals: 0.5-2 hours, 2-4 hours, 4-6 hours and 6-8 hours post study drug intake.

[redacted]

#### 8.6.2.2.2 Analytical methods

The concentrations of febuxostat in plasma will be quantified using a [redacted]-[redacted] bioanalytical method by Menarini Ricerche S.p.A. (Italy). The method will be fully validated according to established Good Laboratory Practice (GLP) guidelines and international regulatory recommendations.

### 8.6.2.3 Centralized Laboratory Evaluation for Pharmacodynamic Parameter

At each Visit starting from Visit 1 (Day 1) until Evaluation Visit (Visit 8, Day 8), a centralized laboratory test (sUA) will be used for pharmacodynamic parameter sUA. Whenever possible, sampling will be collected in conjunction with safety laboratory tests to reduce the patient's discomfort of additional venopunctures. All samples for centralized laboratory test will be processed at the site and the serum shipped to be centrally analyzed at the Central Laboratory.

[redacted]

[redacted]

### 8.6.3 Assessment of Safety

#### 8.6.3.1 Medical History

General medical history and ongoing hematological malignancy medical history will be collected at the Screening Visit in order to obtain all information necessary to confirm the inclusion of the patient in the study.

General medical history will include all the diseases (excluding the ongoing hematological malignancy) and conditions, either chronic or not, which are needed to assess inclusion/exclusion criteria and those which are relevant according to the Investigator.

The ongoing hematological malignancy medical history will include the type of tumor (i.e. lymphoma, leukemia), the date of diagnosis and the presence or absence of renal dysfunction and/or involvement.

#### 8.6.3.2 Physical Examinations and Vital signs

A complete physical examination will be performed at Screening, Start of Treatment, Evaluation and Follow up/End of Study Visits. It includes a general appearance observation and a complete exam of the following body areas: HEENT/Neck, Lymph Nodes, Thyroid, Abdomen, Skin, Cardiovascular, Respiratory, Gastrointestinal, Neurological, Musculoskeletal/Extremities.

Vital signs will be recorded throughout the study at each visit. The following parameters will be measured:

- Heart rate (HR, beats/min);
- Blood pressure (BP, systolic and diastolic, mmHg);
- Breathing rate (BR, breaths/min);
- Body Temperature (T, °C).

#### 8.6.3.3 Safety Laboratory Evaluation

Patient's safety will be monitored daily at each Visit through laboratory tests. Safety laboratory assessments shall include all parameters for the evaluation of LTLS/CTLS, according to Cairo and Bishop Criteria (see Appendix I: Definition of LTLS and CTLS).

Safety tests will be locally performed in order to ensure prompt patient's management.

The laboratory print-outs should be identified with the patient number. All print-outs should be dated and signed by the Investigator and filed in the patient's record. The current valid version of the respective normal ranges as well as any update needs to be notified to the Sponsor. Any out of range value shall be clinically assessed by the Investigator. Safety laboratory results as well as clinical assessments for out of range values will be recorded in eCRF.

The volume of blood to be drawn for each assay will amount to a maximum of 4 ml.

Urinalysis will be performed at Screening, Visit 1, Visit 4, Visit 8 and repeated at Visit 10. Urinalysis test results shall be clinically assessed by the Investigator and the only assessments have to be recorded in eCRF.

Tests are shown in Table 3.

**Table 3: Serum, Blood and Urine Sample Analyte Listing**

| SERUM CHEMISTRY | HEMATOLOGY | URINALYSIS |
|---|---|---|
| Creatinine | Haemoglobin | pH |
| sUA | Haematocrit | Density |
| Potassium | RBC count | |
| Phosphorus | Platelet count | |
| Calcium | WBC count and (absolute and %): | Nitrite |
| BUN / Urea | neutrophil | Protein |
| Albumin | lymphocyte | Glucose |
| Alkaline phosphatase | eosinophil | Ketones |
| Amylase | | |
| Glucose | basophil | RBC |
| Total protein | monocytes | WBC |
| Total bilirubin and Direct bilirubin | | Epithelial cells |
| ALT and AST | | Casts |
| LDH | | Bacteria |
| GGT | | Yeast |
| INR | | Crystals |
| prothrombin time/prothrombin activity | | |
| Sodium | | |
| Chloride | | |
| Beta-HCG (ONLY at Screening if applicable) | | |
| **ESTIMATED PARAMETERS** | | |
| CLcr calculation according to Cockcroft and Gault formula | | |

In order to guarantee the proper management of the patient, any additional sampling or examination is allowed anytime, upon Investigator judgment.

#### 8.6.3.4 12 Lead ECG

12 Lead ECG will be performed locally, using standard equipment available at site, at the following Visits: Screening Visit, Visit 3, Visit 8 and Visit 10.

Standard 12 Lead ECG will be performed at rest in supine position. All ECG print-outs should be identified with patient number, year of birth, and gender, as well as with the date and time of recording. All print-outs should be assessed, dated and signed by the Investigator and stored in the patient's record.

#### 8.6.3.5 Performance Status evaluation

Performance Status (PS) evaluation will be carried out throughout the study at each visit. The Karnofsky PS scale will be used for patients aged 16 years and older; the Lansky Play PS scale will be used for patients aged less than 16 years [34-38]. (see Appendix IV: Karnofsky and Lansky Play performance status scales).

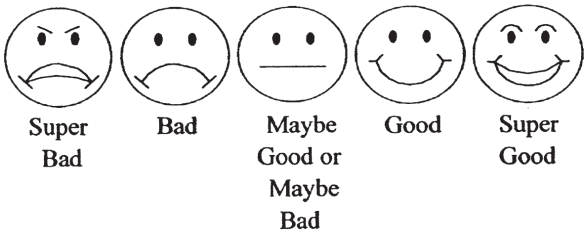
### 8.6.4 LTLS and CTLS Assessment

Investigators will assess the occurrence of LTLS and CTLS based on local laboratory tests, at Visit 1 (Day 1) and then on each study visit starting from Visit 3 (Day 3) until Evaluation Visit (Visit 8, Day 8). The baseline assessment (Visit 1, Day 1) will be performed prior to the Start of Treatment in order to confirm the patient's eligibility.

Investigators will follow the Cairo and Bishop criteria reported in Appendix I: Definition of LTLS and CTLS for their evaluation; they will document the occurrence of LTLS and CLTS in patient's medical record and report it in the relevant section of the eCRF.

### 8.6.5 Assessment of the age-appropriate formulation acceptability

As per EMA guideline of August 1st 2013[39], the acceptability of febuxostat tablets in children will be assessed through a 5-point hedonic scale anchored with the word super bad and super good [40] immediately after drug intake as reported below:




## 8.7 ADVERSE EVENT DEFINITIONS, MONITORING/ RECORDING AND MANAGEMENT

### 8.7.1 Definitions

#### 8.7.1.1 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 unfavorable 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.

#### 8.7.1.2 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. **Unassessable**: 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.

#### 8.7.1.3 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. Unassessable

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

5. Unlikely
6. Not related

#### 8.7.1.4 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 fulfill the conditions for the definition of Serious AE/ADR.

***NOTE***: Hospitalization for chemotherapy administration shall not qualify as adverse event.

#### 8.7.1.5 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 a significant abnormality.

In addition, the Investigator will adopt the NCI-CTCAE v 4.03 (Common Terminology Criteria Adverse Event) for grading each AE (please refer to Appendix V: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Published: May 28, 2009 (v 4.03: June 14, 2010). U.S.Department of Health and Human Services – National Institute of Health – National Cancer Institute for details).

#### 8.7.1.6 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 (the SmPC of ADENURIC® 120 mg and the safety section from the Febuxostat IB, last version available).

#### 8.7.1.7 Serious Unexpected Adverse Drug Reaction (SUSAR)

Any serious adverse event judged by the Investigator or the Sponsor as drug-related (see section 8.7.1.3), and considered as unexpected qualifies as a serious unexpected ADR (SUSAR).

SUSARs are subject to expedited reporting, as specified in section 8.7.3.2, as having a "Reasonable Possibility" of relationship with the IMP.

### 8.7.2 Monitoring and Recording of Adverse Events

At each visit the Investigator will assess any occurred subjective or objective AE, starting from the informed consent signature to the End of Study Visit (Visit 10, **Day 14**, ±2days).

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 on the respective eCRF-AE recording pages 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 the eCRF.

In addition, if after the end of the study the Investigator becomes aware of any AEs or follow-up in AEs already recorded, this information can be recorded in the eCRF until it is available.

### 8.7.3 Management of Serious Adverse Events (SAEs)

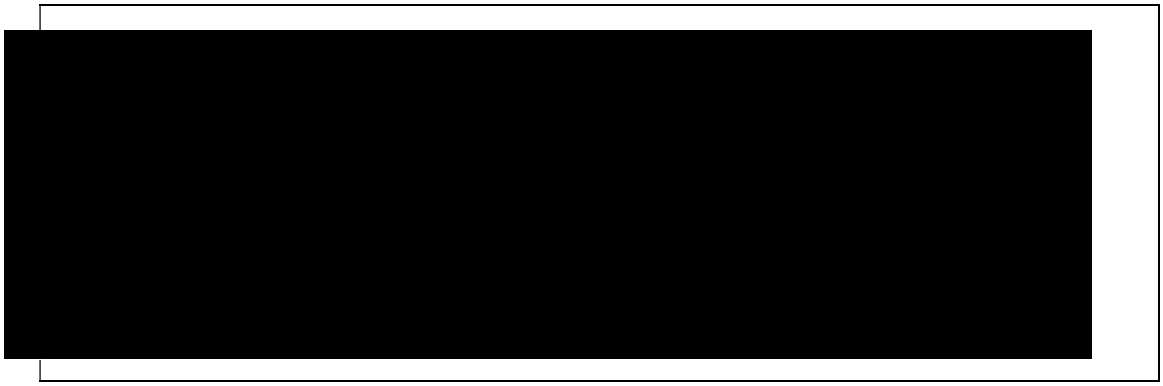
#### 8.7.3.1 Reporting Duties of the Investigator

The Investigator must record all the available information concerning any SAE (whether or not deemed related to the investigational drug) in the corresponding section of the e-CRF, eCRF-AE pages, **no later than 24 hours** after the first knowledge of the occurrence of the event.

Once the information is saved, a notification e-mail will be automatically generated and sent to the Sponsor's DSM, so that the SAE can be retrieved.

The Investigator will be provided with the paper CRF-AE pages to be used only in case of breakdown of the e-CRF System. In such case, the Investigator will be responsible for sending the paper CRF-AE pages form **no later than 24 hours** after the first knowledge and inserting the data in eCRF as soon as the system works again.

Whenever the paper CRF-AE pages are used, they must be submitted by fax or e-mail to the Sponsor's DSM:



For the initial SAE the Investigator should enter at least the following data:

- AE medical term.
- Seriousness criteria.
- Causality assessment.
- Study Code and Patient Identification (patient number) [when the paper CRF-AE pages are used].
- Reporter's name and telephone number for clarification [when the paper CRF-AE pages are used].

If not already reported, the full description of the event and outcome must follow within 1 working day.

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 that will be provided to the Investigator.

The mentioned FU forms duly filled will be sent by the Investigators to the Sponsor's DSM by fax or e-mail, while for the possible photographic documentation the Investigator will contact the Sponsor's DSM for receiving adequate instruction for sending.

The Sponsor's confirmation of reception of the AE report must be kept in the patient's records.

Any questions arise during the processing and medical review of the SAE will be managed by means of electronic queries (i.e. queries in the e-CRF). In case of breakdown of the e-CRF System, queries will be sent by fax or e-mail.

Any information provided by the Investigator as a query reply or as a follow-up AE report will be processed in the same way as the initial AE report within the required timeframe.

When relevant, also the eCRF pages concerning medical history, concomitant medication, and laboratory tests will be retrieved by the Sponsor's DSM.

Any further significant information and supporting documentation that become 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 Sponsor's DSM 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.

#### 8.7.3.2 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 Sponsor's DSM or CRO receives the notification of the SUSAR:

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

The Sponsor shall ensure that all relevant new information will be also expeditedly 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.

### 8.7.4 Management of Non-Serious Adverse Events (NSAEs) and/or laboratory abnormalities

The Investigator must record all the available information concerning any NSAE (whether or not deemed related to the investigational drug) in the corresponding section of the e-CRF, eCRF-AE pages, **within 5 calendar days** after the first knowledge of the occurrence of the event.

Once the information is saved, a notification e-mail will be automatically generated and sent to the Sponsor's DSM, so the NSAE can be retrieved

When relevant, also the CRF pages concerning medical history, concomitant medication, and laboratory test will be retrieved by the Sponsor's DSM.

Any further significant 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 Sponsor's DSM.

In addition, during the clinical trial, abnormalities in laboratory analyses (newly occurring after ICF signature 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. However, all abnormalities in laboratory values should be collected and reviewed by Sponsor on a bi-monthly basis.

### 8.7.5 Management of Pregnancy Exposure Cases

The Investigator is expected to record in the provided "Pregnancy Exposure Report Form" any case of pregnancy exposure occurring in a female patient or in a patient's partner enrolled on the study while participating in the study, occurring during the treatment and follow-up periods. The mentioned form will be sent by fax or email to the Sponsor's DSM within 5 days after the being made aware of the pregnancy.

The "Pregnancy Exposure Report Form" are distributed to the sites to be used for this purpose.

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 eCRF as a SAE and managed as above described.

### 8.7.6 Annual Safety Reporting

Once a year throughout the clinical trial, the Sponsor will assure the submission to the concerned national CAs and IRB/IECs of a safety report (Development Safety Update Report, DSUR), taking into account all new safety information received during the reporting period.

### 8.7.7 Breaking of the Randomization Code

The study will be performed according to an open, non-randomized design. Breaking of the Randomization Code procedure is not applicable to this trial.

### 8.7.8 Serious and Non-serious Adverse Events Follow-up

After the End of Study Visit, the Investigator is not requested to actively follow-up the patient unless ongoing SAEs or non-serious AEs of special interest are present. However, if after the end of the trial, the Investigator becomes aware of any reportable SAEs, they should be duly reported to the Sponsor. These SAEs should be recorded in the eCRF until it is available. If the eCRF is not available, the paper SAE report form will be used as a backup.

Patients who discontinued the treatment for safety reason will be followed until the event disappears, the patient's condition stabilizes,, or until recovery from all toxic effects and longer in case of expected delayed toxicity.

## 8.8 PHARMACOKINETIC/PHARMACODYNAMIC AND SAFETY ENDPOINTS

### 8.8.1 Primary Endpoints

Pharmacokinetic endpoints will include:

- Primary PK parameters: CL/F, Vd/F and Ka.
- Derived PK parameters: AUC, $T_{max}$ and $C_{max.}$

### 8.8.2 Secondary Endpoints

- Pharmacodynamic:
  - Area under the curve of sUA from baseline (Visit 1, Day 1) to the Evaluation Visit (Visit 8, Day 8) (AUC sUA $_{1-8}$) based on central laboratory results.
- PK/PD:
  - The PK/PD relationship will be evaluated based on sUA levels and febuxostat exposure.
- Clinical:

- Incidence of Laboratory TLS (LTLS), from Start of Chemotherapy (Visit 3, Day 3) to the Evaluation Visit (Visit 8, Day 8), based on local laboratory results;
- Incidence and grading of Clinical TLS (CTLS), from Start of Chemotherapy (Visit 3, Day 3) to the Evaluation Visit (Visit 8, Day 8), based on local laboratory results;

- Safety:
  - Incidence, severity (both through Mild/Moderate/Severe scale and NCI-CTCAE grade), seriousness and treatment causality of Treatment Emergent Signs and Symptoms (TESS);

***NOTE***: An AE is considered as 'Treatment-Emergent Signs and Symptoms (TESS)' if it occurs for the first time or if it worsens in terms of seriousness or severity after the first study drug intake (Visit 1, Day 1).

  - Frequency of clinically significant abnormalities in physical examination, safety laboratory tests, vital signs and 12-Lead-ECG;
  - Change in PS according to Karnofsky/Lansky scale.
- Assessment of the age-appropriate formulation acceptability in children.

# 9. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 9.1 DETERMINATION OF SAMPLE SIZE

A sample size of approximately 24 patients should be included in the Pharmacokinetic population for each age and dose group (cohort 1-4, adults). A total of 120 patients was estimated to be sufficient to [redacted] Assuming a 10% screening failure rate, approximately 135 patients should be screened in order to obtain the planned total number of 120 patients exposed to treatment.

## 9.2 ANALYSIS POPULATIONS

- **Safety population**: all patients who received at least one dose of study drug.
- **Pharmacokinetic (PK) population**: all patients who received at least one dose of study drug and have a reliable drug plasma concentration measurement relevant for the pharmacokinetic parameter of interest.
- **Intention to Treat (ITT) population:** all patients allocated to a treatment box.
- **Per Protocol (PP) population: all patients of the ITT population** excluding those who experienced major protocol violation(s).
- **Per Protocol PK (PP-PK) population:** all patients from PK population who do not have any major protocol violation(s) relevant for PK analyses.

## 9.3 STATISTICAL ANALYSIS

### 9.3.1 Descriptive statistics

All study variables will be presented by dose and age group, by using the appropriate descriptive statistics according to the variable nature, unless otherwise specified:

- Continuous variables: number of non-missing observations, mean, standard deviation, standard error of the mean, minimum, median, maximum.
- Categorical variables: number of non-missing observations and column percentages (N, %).

### 9.3.2 Population Pharmacokinetic (Pop-PK) analysis

The plasma concentration data will be analyzed in children, adolescent and adults by nonlinear mixed-effects modeling methods. These methods give both estimates of the population pharmacokinetic parameters and their measures of variability, along with estimates of each patient's parameters.

[redacted]

[redacted]

### 9.3.3 Primary analysis

All pharmacokinetic results (e.g., PK parameters and plasma concentrations) will be summarized by dose and age group using appropriate graphs and descriptive statistics (i.e., number of patients (n), mean, standard deviation (SD), geometric mean, 95% confidence intervals, coefficient of variation (CV%), median, minimum, and maximum).

Relevant PK parameters (e.g., AUC, $C_{max}$) in children and adolescents will be descriptively compared to those in adults to demonstrate sufficient similarity of febuxostat pharmacokinetics.

The primary analyses will be conducted on the PK population and for exploratory reasons on the PP-PK population.

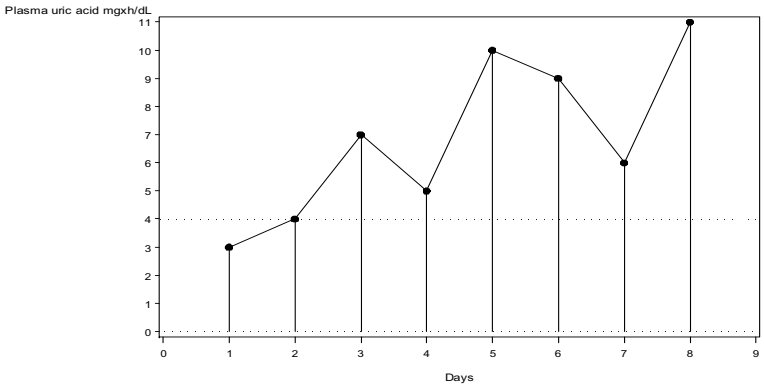
### 9.3.4 Secondary analysis

- ***Pharmacodynamic endpoint***:

Area under plasma uric acid concentration curves (AUC $sUA_{1-8}$) from baseline (Visit 1, Day 1) to the Evaluation Visit (Visit 8, Day 8) will be computed for dose and age group using a trapezoidal rule which approximates the integral or the area under a curve.

A graphic example is provided in order to show which is the area considered to calculate AUC.

Figure 1




The trapezoidal rule is a numerical method to be used to approximate the integral or the area under a curve. Trapezoidal rule first involves dividing the area into a number of strips of equal width, with low limit identified with a and upper limit with b. Then, approximating the area of each strip by the area of the trapezium formed and summing these approximations, the final numerical result will be the area under the curve.

The trapezoidal rule will be presented by mean of a definite integral:

$$\int_a^b f(x)dx$$

Last observation carried forward method (LOCF) will be applied for patients who discontinued the study prematurely and a linear interpolation method will be used to impute the missing data between visits.

The pharmacodinamic analysis will be run on PK population and for exploratory reasons on ITT population.

- ***PK/PD endpoint:***

Observed exposure-response data will be descriptively and graphically summarized by age and dose group. [redacted]

The aim of this analysis is to support the assumption of a comparable PK/PD relationship between pediatric patients (≥6<18 years of age) and adults and to evaluate if potential deviations in PK are clinically relevant.

This analysis will be conducted on the PK population.

[redacted]

- ***Clinical endpoints: Incidence of LTLS and CTLS***
  - The assessment for LTLS from Start of Chemotherapy (Visit 3, Day 3) to the Evaluation Visit (Visit 8, Day 8) will be defined as:

    1: PRESENCE — 2 or more laboratory abnormalities including: a 25% increase or levels above normal for serum uric acid, potassium, and phosphate or a 25% decrease or levels below normal for calcium.

    0: ABSENCE — less than 2 laboratory abnormalities including: a 25% increase or levels above normal for serum uric acid, potassium, and phosphate or a 25% decrease or levels below normal for calcium.
  - The assessment for CTLS from Start of Chemotherapy (Visit 3, Day 3) to the Evaluation Visit (Visit 8, Day 8) is defined as:

    1: PRESENCE — presence of LTLS in addition to 1 or more of the following significant clinical complications: renal insufficiency, cardiac arrhythmias, sudden death and seizures.

    0: ABSENCE — absence of LTLS or absence of any significant clinical complications: renal insufficiency, cardiac arrhythmias, sudden death and seizures.

    Chi Square test will be used to compare statistically the rate incidence of LTLS and CTLS by dose and age group.

The efficacy analyses will be run on the ITT population and for exploratory reasons on PP-population.

- ***Assessment of the age-appropriate formulation acceptability***

Assessment of the age-appropriate formulation acceptability will be evaluated through a 5-point

hedonic scale anchored with the word super bad and super good and summarized by means of descriptive statistics by febuxostat dose in children. The analysis will be conducted on the safety population.

### 9.3.5 Subgroup analysis

Subgroup analysis will be defined according to the nature of data.

### 9.3.6 Safety analysis

The safety analysis will be run on the safety population.

Safety analysis will consider AEs, laboratory parameter values, vital signs, physical examination, PS and 12-Lead ECG data.

Safety variables will include treatment emergent AEs/SAEs (TESS), namely any reported AE occurred or worsened after first study drug intake or clinically relevant change in safety laboratory parameters, physical examination, PS, 12-Lead ECG and vital signs.

TESS will be summarized by primary System Organ Class (SOC) and preferred term (PT). For each PT/SOC, the number of TESS, the number of patients with TESS, and the percentage of patients with TESS will be given. TESS will be listed by dose and age group and stratified by severity (both through mild, moderate, and severe scale and NCI-CTCAE grade), relationship to the IMP (related/ not related), and for those leading to study discontinuation.

Serious TESSs will be analyzed analogously as TESSs.

AEs/SAEs which are not considered TESS will be included in a separate listing.

Any AE/SAE with a relationship to the IMP other than “not related”, or “unlikely related” will be considered as treatment-related AEs/SAEs (i.e. ADRs/SADRs).

Laboratory parameters, vital signs, physical examination, PS and 12-Lead ECG will be summarized throughout appropriate descriptive statistics by dose and age group.

### 9.3.7 Data imputations

Overall, the missing value will not be imputed because an observed cases approach will be used.
For AUC sUA calculation the last observation carried forward method (LOCF) will be applied for patients who discontinued the study prematurely and a linear interpolation method will be used to impute the missing data between visits.

[redacted]

## 9.4 PROTOCOL VIOLATIONS AND DATA REVIEW MEETING

Categories of protocol violations will be defined before the lock of the study database and will be integrated in the Statistical Analysis Plan (SAP).

## 9.5 STATISTICAL ANALYSIS PLAN

The statistical analysis plan (SAP) will be finalized before the database lock of the study. The SAP will describe in detail study endpoints and the statistical analyses performed, including also additional analyses not planned in the protocol. In case of changes of the original primary endpoint or of the original primary analyses will occur during the study, a substantial protocol amendment will be generated.

Minor deviations (e.g. not involving changes in the primary endpoint and analysis) which might occur during the study will be detailed only in the SAP. All statistical analyses not pre-specified and run after database lock will be considered additional/exploratory analyses.

# 10. DATA QUALITY MANAGEMENT

## 10.1 DATA COLLECTION

Data collection activities will be carried out under the responsibility of the Sponsor. Patient data will be collected using the data capture systems described in the following sections. Patients will be identified by the patient study identification number (patient ID), assigned at the Screening Visit.

The patient ID will be a number composed of eight-digits CCCSSPPP:

- CCC is the international phone code of the country (with a leading zeros for countries that have a 1 or 2-digits phone code);
- SS is the site number in the country: it will start from 01 for each country and will be ascending;
- PPP is the patient number in the site; it will start from 001 for each site and will be ascending.

Data will be collected, processed, evaluated, reviewed and stored in anonymous form in accordance with applicable data protection regulations.

### 10.1.1 Case Report Forms

Clinical data collected during the study at sites will be recorded in an (e)CRF using Medidata RAVE which is a validated system. The Sponsor will be responsible to develop the eCRF based on this study protocol and to review and perform the user acceptance test of the eCRF in order to ensure protocol adherence.

The eCRF will be made available to the study personnel by means of the i-Medidata interface which is a validated system. The accounts will be individual and password-protected.

The Investigator or designee will be responsible for entering study data into the eCRF in accordance to the eCRF Completion Guidelines provided by the Sponsor. In order to improve the quality of data collection and cleaning, data shall be entered into the eCRF as closely as possible to the time when they become available and not later than within 5 working days. The eCRF data will not be considered as source data (the definition of the source data can be found in section 10.3).

Investigators will ensure the accuracy, completeness and consistency of data entered signing electronically the eCRF using the personal password.

An audit trail within the system will track all changes made to the data.

### 10.1.2 IxRS

The IxRS system [redacted], provided by [redacted] is a validated system used by the site personnel for the patient screening (including assignment of the patient ID), box assignment and

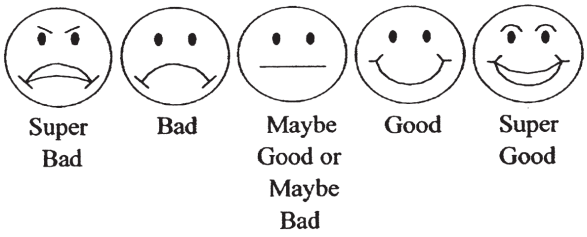
patient status change. Site staff will be provided with a personal user name and password to access to IxRS.

An IxRS user manual will be prepared by [redacted] and provided to site personnel by CRO.

Some data such as patient ID and visit dates collected through IxRS system could be automatically integrated in eCRF. The integration process will be detailed in a specific integration document.

### 10.1.3 Patient diary

As per EMA Guideline of August 1st 2013 [39], the acceptability of febuxostat tablets will be assessed in children through a 5-point hedonic scale anchored with the word super bad and super good [40]. Patients will complete a daily diary, they will mark, immediately after drug intake, the icon best representing their experience of the drug intake. Five levels of acceptability will be provided:




The assessment results will be entered in eCRF by the site personnel.

### 10.1.4 Central Laboratory/Examination data

The following Central Laboratories will be used during the study:

- Research Toxicology Center (RTC) - Pomezia, Rome (Italy) for plasma and serum samples logistic management and centralized laboratory test: sUA
- Menarini Ricerche S.p.A. - Pre-Clinical Research Department - Pomezia, Rome (Italy) for Pharmacokinetics analysis: febuxostat plasma concentrations

Central laboratories data will be managed according to internal laboratory SOPs and will be transferred to Menarini Clinical Research department for statistics and pharmacokinetics analyses.

### 10.1.5 Data capture systems versions and validation documentation

Versions of the data capture systems can change during the study. The Sponsor will maintain a list of the data capture system versions used and the validation documentation of each version. The list and the validation documentation will be provided to the site at the site initiation visit (SIV) and will be updated at any data capture system version change.

## 10.2 CLINICAL DATA MANAGEMENT

Data Management will be carried out under the responsibility of the Sponsor. eCRF data will be electronically verified through the use of on-line and off-line checks. Discrepancies in the data will be resolved by means of electronic queries. Data will be locked by the data manager when all activities for the trial, including medical revision of the data, are complete and no more entries are expected.

Data from sources other than eCRF will be provided to the data manager on an agreed scheduled basis. The data manager has the responsibility to reconcile data captured in the eCRF, with external data sources. Discrepancies found in the reconciliation of the data, will be addressed by means of queries.

A clear overview of all clinical data management activities will be given in the data management plan.

## 10.3 SOURCE DATA

Source data are defined as all data in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial.

Original documents and data records include, but are not limited to hospital/patients' medical records, laboratory notes, ECG records, patients' identification forms, and pharmacy dispensing records. Study sites will also maintain a paper drug accountability forms for the IMP to document dispensed and returned IMP per patient.

Source data should be held available for perusal by the Sponsor representatives for the study or to other authorized persons such as auditors and inspectors of Regulatory Authorities.

Direct access to source data is defined as the permission to examine, analyze, verify and reproduce any records and reports that are important for evaluation of a clinical trial (see also 10.4.1). Any party allowed to 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 information.

Data should be consistent with the source documents and discrepancies, if any, should be explained in writing. All the original documentation pertinent to the study procedures must be available for review in each patient's record.

## 10.4 QUALITY CONTROL/QUALITY ASSURANCE

### 10.4.1 Study Monitoring

This trial will be monitored in accordance with the ICH Note for Guidance on Good Clinical Practice. Monitoring will be carried out under the responsibility of the CRO. The site monitor will perform visits to the trial sites along the study conduct. Facilities, study drug, storage area, eCRF, patient's source data, and all other study documentation will be inspected/reviewed by the site monitor for adherence to

the protocol and Good Clinical Practice. At each site visit, the monitor will review the eCRFs for completion and accuracy. Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and his/her staff. The Investigator agrees to allow access to all study related materials needed for the proper review of study conduct and to assist the monitor during the monitoring visits and during the data cleaning process. Monitoring procedures require that 100% of data are source data verified, particularly focusing on informed consents, adherence to inclusion/exclusion criteria, drug accountability, documentation of SAEs and the proper recording of efficacy and safety measurements. All monitoring activities will be described in detail in the study-specific monitoring plan.

### 10.4.2 Quality Assurance

Independent study audit(s) and/or inspection(s) may take place at any time during or after the trial. The independent audit/inspection can be carried by the Quality Assurance (QA) Department of the CRO, the independent QA Department of Research Toxicology Centre (RTC) S.p.A., or a Competent Authority. At all times, the confidentiality of subject related documents will be maintained.

# 11. PREMATURE TERMINATION OF THE WHOLE STUDY

The whole trial may be discontinued at the discretion of the Sponsor in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the investigational products due to:
  - Occurrence of significantly previously unknown AEs or unexpectedly high intensity or incidence of known AEs.
  - New evidence of unfavorable safety or efficacy findings (from clinical or non-clinical examinations, e.g. toxicology).
- The Sponsors decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Discontinuation of development of the IMP.

Competent Authorities and IRB/IECs will be informed about the discontinuation of the trial in accordance with applicable regulations.

# 12. END OF CLINICAL TRIAL AND ARCHIVING

The clinical trial will end with the collection and analysis of study data and the issue of the clinical study report. All essential documents will be archived by the Sponsor according to the relevant SOP.

## 12.1 ARCHIVING OF ELECTRONIC DOCUMENTATION/DATA

Duplicate electronic media such as CDs/DVDs (one for routine access and one for back-up) containing the patient data in PDF format (e.g. eCRFs) for each site will be prepared by the Sponsor or a delegate for archiving purposes. The electronic media, of a not re-printable type, will be appropriately labeled recording the files/data included. The files should contain at least the edata copy clearly reporting the system name, study code and the eCRF version used; also the electronic signature and the associated audit trails have to be included.

Patient data relevant for each site will be distributed to the Investigator, who has to confirm the receipt of the material, verify whether the provided electronic media represent a copy of data generated during the study and sign a dedicate form provided by the Sponsor, the signed form has to be collected and archived at the Sponsor.

Two copies of the same electronic media prepared for the sites or cumulative electronic media with the same content will be archived by the Sponsor. In addition the Sponsor is responsible to create 2 electronic media (one for routine access and one for back-up) containing an integrated SAS database with all study data (e.g. eCRF, IxRS, Central Laboratory), following appropriate refreshment procedures.

Investigators and Sponsor will be also responsible to refresh their electronic media approximately every 7 years to ensure long term archiving of files/data.

# 13. APPENDIX

## 13.1 APPENDIX I: DEFINITION OF LTLS AND CTLS

| **Diagnosis of LTLS:** LTLS is diagnosed if levels of 2 or more serum values of uric acid, potassium, phosphate or calcium are more than or less than normal at presentation or if they change by at least 25% from baseline. | | |
|---|---|---|
| **ELEMENT** | **VALUE** | **CHANGE FROM BASELINE** |
| Uric Acid | ≥ 476 µmol/L (or 8 mg/dL) | 25% increase |
| Potassium | ≥ 6.0 mmol/L | 25% increase |
| Phosphorus | ≥ 1.45 mmol/L (adults) or ≥ 2.1mmol/L (children) | 25% increase |
| Calcium | ≤ 1.75 mmol/L | 25% decrease |

For adolescents and adults, the values of phosphorus will be considered the same for the diagnosis of LTLS.

**Diagnosis of CTLS:** CTLS is present when LTLS is accompanied by at least one of the following significant clinical complication: increased creatinine level ≥ 1.5 ULN, cardiac arrhythmia/sudden death or seizure. Diagnostic pathway is quite the same between adults and children, with a clarification about the creatinine ULN (if not specified by the Local Laboratory, the value has to be age/gender adjusted according to the following: > 1 <12 years, both male and female, 61.6 µmol/L; ≥ 12 < 16 years, both male and female, 88 µmol/L; ≥ 16 years, female, 105.6 µmol/L; ≥ 16 years, male, 114.4 µmol/L).

| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|---|
| **LTLS** | - | + | + | + | + | + |
| **Creatinine** | ≤1.5 x ULN | 1.5 x ULN | >1.5-3.0 x ULN | >3.0-6.0 x ULN | >6.0 x ULN | death |
| **Arrhythmia** | none | Intervention not indicated | Non urgent medical intervention indicated | Symptomatic and incompletely controlled medically or controlled with device | Life-threatening | death |
| **Seizure** | none | - | 1 brief, generalized seizure; seizure(s) well controlled by anti convulsants or infrequent focal motor seizures not interfering with activities of daily living | Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizure despite medical intervention | Seizure of any kind which are prolonged, repetitive or difficult to control | death |

The CTLS grading classification (Cairo and Bishop, 2004)

## 13.2 APPENDIX II: EU SMPCS FOR ADENURIC®

### EU SMPCS FOR ADENURIC® 80 MG FILM-COATED TABLETS

#### 1. NAME OF THE MEDICINAL PRODUCT

ADENURIC 80 mg film-coated tablets

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg of febuxostat.

Excipient(s) with known effects:
Each tablet contains 76.50 mg of lactose (as monohydrate)

For the full list of excipients, see section 6.1.

#### 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pale yellow to yellow, film-coated, capsule shaped tablets, engraved with "80" on one side.

#### 4. CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

ADENURIC is indicated in adults.

##### 4.2 Posology and method of administration

Posology
The recommended oral dose of ADENURIC is 80 mg once daily without regard to food. If serum uric acid is > 6 mg/dL (357 µmol/L) after 2-4 weeks, ADENURIC 120 mg once daily may be considered.

ADENURIC works sufficiently quickly to allow retesting of the serum uric acid after 2 weeks. The therapeutic target is to decrease and maintain serum uric acid below 6 mg/dL (357 µmol/L).

Gout flare prophylaxis of at least 6 months is recommended (see section 4.4).

*Older people*
No dose adjustment is required in the elderly (see section 5.2).

*Renal* impairment
The efficacy and safety have not been fully evaluated in patients with severe renal impairment (creatinine clearance <30 mL/min, see section 5.2).
No dose adjustment is necessary in patients with mild or moderate renal impairment.

*Hepatic impairment*
The efficacy and safety of febuxostat has not been studied in patients with severe hepatic impairment (Child Pugh Class C).
The recommended dose in patients with mild hepatic impairment is 80 mg. Limited information is available in patients with moderate hepatic impairment.

*Paediatric population*
The safety and the efficacy of ADENURIC in children aged below the age of 18 years have not been established. No data are available.

Method of administration
Oral use
ADENURIC should be taken by mouth and can be taken with or without food.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see also section 4.8).

### 4.4 Special warnings and precautions for use

*Cardio-vascular disorders*
Treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended.
A numerical greater incidence of investigator-reported cardiovascular APTC events (defined endpoints from the Anti-Platelet Trialists' Collaboration (APTC) including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) was observed in the febuxostat total group compared to the allopurinol group in the APEX and FACT studies (1.3 vs. 0.3 events per 100 Patient Years (PYs)), but not in the CONFIRMS study (see section 5.1 for detailed characteristics of the studies). The incidence of investigator-reported cardiovascular APTC events in the combined Phase 3 studies (APEX, FACT and CONFIRMS studies) was 0.7 vs. 0.6 events per 100 PYs. In the long-term extension studies the incidences of investigator-reported APTC events were 1.2 and 0.6 events per 100 PYs for febuxostat and allopurinol, respectively. No statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure.

*Medicinal product allergy / hypersensitivity*
Rare reports of serious allergic/hypersensitivity reactions, including life-threatening Stevens-Johnson Syndrome, Toxic epidermal necrolysis and acute anaphylactic reaction/shock, have been collected in the post-marketing experience. In most cases, these reactions occurred during the first month of therapy with febuxostat. Some, but not all of these patients reported renal impairment and/or previous hypersensitivity to allopurinol. Severe hypersensitivity reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) were associated with fever, haematological, renal or hepatic involvement in some cases.
Patients should be advised of the signs and symptoms and monitored closely for symptoms of allergic/hypersensitivity reactions (see section 4.8). Febuxostat treatment should be immediately stopped if serious allergic/hypersensitivity reactions, including Stevens-Johnson Syndrome, occur since early withdrawal is associated with a better prognosis. If patient has developed allergic/hypersensitivity reactions including Stevens-Johnson Syndrome and acute anaphylactic reaction/shock, febuxostat must not be re-started in this patient at any time.

*Acute gouty attacks (gout flare)*
Febuxostat treatment should not be started until an acute attack of gout has completely subsided. Gout flares may occur during initiation of treatment due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits (see section 4.8 and 5.1). At treatment initiation with febuxostat flare prophylaxis for at least 6 months with an NSAID or colchicine is recommended (see section 4.2).
If a gout flare occurs during febuxostat treatment, it should not be discontinued. The gout flare should be managed concurrently as appropriate for the individual patient. Continuous treatment with febuxostat decreases frequency and intensity of gout flares.

*Xanthine deposition*
In patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. As there has been no experience with febuxostat, its use in these populations is not recommended.

*Mercaptopurine/azathioprine*
Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine. Where the combination cannot be avoided patients should be closely monitored. A reduction of dosage of mercaptopurine or azathioprine is recommended in order to avoid possible haematological effects (see section 4.5).

*Organ transplant recipients*
As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended (see section 5.1).

*Theophylline*
Co-administration of febuxostat 80 mg and theophylline 400mg single dose in healthy subjects showed absence of any pharmacokinetic interaction (see section 4.5). Febuxostat 80 mg can be used in patients concomitantly treated with theophylline without risk of increasing theophylline plasma levels. No data is available for febuxostat 120 mg.

*Liver disorders*
During the combined phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0%). Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgment (see section 5.1).

*Thyroid disorders*
Increased TSH values (>5.5 µIU/mL) were observed in patients on long-term treatment with febuxostat (5.5%) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function (see section 5.1).

*Lactose*
Febuxostat tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**4.5 Interaction with other medicinal products and other forms of interaction**

*Mercaptopurine/azathioprine*
On the basis of the mechanism of action of febuxostat on XO inhibition concomitant use is not recommended. Inhibition of XO by febuxostat may cause increased plasma concentrations of these drugs leading to toxicity (see section 4.4). Drug interaction studies of febuxostat with drugs that are metabolized by XO have not been performed.

Drug interaction studies of febuxostat with cytotoxic chemotherapy have not been conducted. No data is available regarding the safety of febuxostat during cytotoxic therapy.

*Rosiglitazone/CYP2C8 substrates*
Febuxostat was shown to be a weak inhibitor of CYP2C8 in vitro. In a study in healthy subjects, coadministration of 120 mg febuxostat QD with a single 4 mg oral dose of rosiglitazone had no effect on the pharmacokinetics of rosiglitazone and its metabolite N-desmethyl rosiglitazone, indicating that febuxostat is not a CYP2C8 enzyme inhibitor in vivo. Thus, co-administration of febuxostat with rosiglitazone or other CYP2C8 substrates is not expected to require any dose adjustment for those compounds.

*Theophylline*
An interaction study in healthy subjects has been performed with febuxostat to evaluate whether the inhibition of XO may cause an increase in the theophylline circulating levels as reported with other XO inhibitors. The results of the study showed that the co-administration of febuxostat 80 mg QD with theophylline 400 mg single dose has no effect on the pharmacokinetics or safety of theophylline. Therefore no special caution is advised when febuxostat 80 mg and theophylline are given concomitantly. No data is available for febuxostat 120 mg.

*Naproxen and other inhibitors of glucuronidation*
Febuxostat metabolism depends on Uridine Glucuronosyl Transferase (UGT) enzymes. Medicinal products that inhibit glucuronidation, such as NSAIDs and probenecid, could in theory affect the elimination of febuxostat. In healthy subjects concomitant use of febuxostat and naproxen 250 mg twice daily was associated with an increase in febuxostat exposure ($C_{max}$, 28%, AUC 41% and $t_{1/2}$ 26%). In clinical studies the use of naproxen or other NSAIDs/Cox-2 inhibitors was not related to any clinically significant increase in adverse events.

Febuxostat can be co-administered with naproxen with no dose adjustment of febuxostat or naproxen being necessary.

*Inducers of glucuronidation*
Potent inducers of UGT enzymes might possibly lead to increased metabolism and decreased efficacy of febuxostat. Monitoring of serum uric acid is therefore recommended 1-2 weeks after start of treatment with a potent inducer of glucuronidation. Conversely, cessation of treatment of an inducer might lead to increased plasma levels of febuxostat.

*Colchicine/indometacin/hydrochlorothiazide/warfarin*
Febuxostat can be co-administered with colchicine or indomethacin with no dose adjustment of febuxostat or the co-administered active substance being necessary.

No dose adjustment is necessary for febuxostat when administered with hydrochlorothiazide.

No dose adjustment is necessary for warfarin when administered with febuxostat. Administration of febuxostat (80 mg or 120 mg once daily) with warfarin had no effect on the pharmacokinetics of warfarin in healthy subjects. INR and Factor VII activity were also not affected by the co-administration of febuxostat.

*Desipramine/CYP2D6 substrates*
Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro*. In a study in healthy subjects, 120 mg ADENURIC QD resulted in a mean 22% increase in AUC of desipramine, a CYP2D6 substrate indicating a potential weak inhibitory effect of febuxostat on the CYP2D6 enzyme *in vivo*. Thus, co-administration of febuxostat with other CYP2D6 substrates is not expected to require any dose adjustment for those compounds.

*Antacids*
Concomitant ingestion of an antacid containing magnesium hydroxide and aluminium hydroxide has been shown to delay absorption of febuxostat (approximately 1 hour) and to cause a 32% decrease in $C_{max}$, but no significant change in AUC was observed. Therefore, febuxostat may be taken without regard to antacid use.

### 4.6 Fertility, pregnancy and lactation

*Pregnancy*
Data on a very limited number of exposed pregnancies have not indicated any adverse effects of febuxostat on pregnancy or on the health of the foetus/new born child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development or parturition (see section 5.3). The potential risk for human is unknown. Febuxostat should not be used during pregnancy.

*Breastfeeding*
It is unknown whether febuxostat is excreted in human breast milk. Animal studies have shown excretion of this active substance in breast milk and an impaired development of suckling pups. A risk to a suckling infant cannot be excluded. Febuxostat should not be used while breastfeeding.

*Fertility*
In animals, reproduction studies up to 48 mg/kg/day showed no dose-dependent adverse effects on fertility (see section 5.3). The effect of ADENURIC on human fertility is unknown.

**4.7 Effects on ability to drive and use machines**

Somnolence, dizziness, paraesthesia and blurred vision have been reported with the use of Febuxostat. Patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that ADENURIC does not adversely affect performance.

**4.8 Undesirable effects**

*Summary of the safety profile*
The most commonly reported adverse reactions in clinical trials (4,072 subjects treated at least with a dose from 10 mg to 300 mg) and post-marketing experience are gout flares, liver function abnormalities, diarrhoea, nausea, headache, rash and oedema. These adverse reactions were mostly mild or moderate in severity. Rare serious hypersensitivity reactions to febuxostat, some of which were associated to systemic symptoms, have occurred in the post-marketing experience.

*Tabulated list of adverse reactions*
Common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000) adverse reactions occurring in patients treated with febuxostat are listed below.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

*Table 1: Adverse reactions in combined phase 3, long-term extension studies and post-marketing experience*

| | |
|---|---|
| Blood and lymphatic system disorders | Rare<br>Pancytopenia, thrombocytopenia |
| Immune system disorders | Rare<br>Anaphylactic reaction*, drug hypersensitivity* |
| Endocrine disorders | Uncommon<br>Blood thyroid stimulating hormone increased |
| Eye disorders | Rare<br>Blurred vision |
| Metabolism and nutrition disorders | Common***<br>Gout flares<br>Uncommon<br>Diabetes mellitus, hyperlipidemia, decrease appetite, weight increase<br>Rare<br>Weight decrease, increase appetite, anorexia |
| Psychiatric disorders | Uncommon<br>Libido decreased, insomnia<br>Rare<br>Nervousness |
| Nervous system disorders | Common<br>Headache<br>Uncommon<br>Dizziness, paraesthesia, hemiparesis, somnolence, altered taste, hypoaesthesia, hyposmia |

| | |
|---|---|
| Ear and labyrinth disorders | Rare<br>Tinnitus |
| Cardiac disorders | Uncommon<br>Atrial fibrillation, palpitations, ECG abnormal |
| Vascular disorders | Uncommon<br>Hypertension, flushing, hot flush |
| Respiratory system disorders | Uncommon<br>Dyspnoea, bronchitis, upper respiratory tract infection, cough |
| Gastrointestinal disorders | Common<br>Diarrhoea**, nausea<br>Uncommon:<br>Abdominal pain, abdominal distension, gastro-oesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort<br>Rare<br>Pancreatitis, mouth ulceration |
| Hepato-biliary disorders | Common<br>Liver function abnormalities**<br>Uncommon<br>Cholelithiasis<br>Rare<br>Hepatitis, jaundice*, liver injury* |
| Skin and subcutaneous tissue disorders | Common<br>Rash (including various types of rash reported with lower frequencies, see below)<br>Uncommon<br>Dermatitis, urticaria, pruritus, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash papular<br>Rare<br>Toxic epidermal necrolysis*, Stevens-Johnson Syndrome*, angioedema*, drug reaction with eosinophilia and systemic symptoms*, generalized rash (serious)*, erythema, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash pruritic*, rash erythematous, rash morbilliform, alopecia, hyperhidrosis |
| Musculoskeletal and connective tissue disorders | Uncommon<br>Arthralgia, arthritis, myalgia, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis<br>Rare<br>Rhabdomyolysis*, joint stiffness, musculoskeletal stiffness |
| Renal and urinary disorders | Uncommon<br>Renal failure, nephrolithiasis, haematuria, pollakiuria, proteinuria<br>Rare<br>Tubulointerstitial nephritis*, micturition urgency |
| Reproductive system and breast disorder | Uncommon<br>Erectile dysfunction |
| General disorders and administration site conditions | Common<br>Oedema<br>Uncommon<br>Fatigue, chest pain, chest discomfort<br>Rare<br>Thirst |
| Investigations | Uncommon<br>Blood amylase increase, platelet count decrease, WBC decrease, lymphocyte count decrease, blood creatine increase, blood creatinine increase, haemoglobin decrease, blood urea increase, blood triglycerides increase, blood cholesterol increase, haematocritic decrease, blood lactate dehydrogenase increased, |

| | |
|---|---|
| | blood potassium increase<br>Rare<br>Blood glucose increase, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase |

* Adverse reactions coming from post-marketing experience
** Treatment-emergent non-infective diarrhoea and abnormal liver function tests in the combined Phase 3 studies are more frequent in patients concomitantly treated with colchicine.
*** See section 5.1 for incidences of gout flares in the individual Phase 3 randomized controlled studies.

*Description of selected adverse reactions*
Rare serious hypersensitivity reactions to febuxostat, including Stevens-Johnson Syndrome, Toxic epidermal necrolysis and anaphylactic reaction/shock, have occurred in the post-marketing experience. Stevens-Johnson Syndrome and Toxic epidermal necrolysis are characterised by progressive skin rashes associated with blisters or mucosal lesions and eye irritation. Hypersensitivity reactions to febuxostat can be associated to the following symptoms: skin reactions characterised by infiltrated maculopapular eruption, generalised or exfoliative rashes, but also skin lesions, facial oedema, fever, haematologic abnormalities such as thrombocytopenia and eosinophilia, and single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis) (see section 4.4).

Gout flares were commonly observed soon after the start of treatment and during the first months. Thereafter, the frequency of gout flare decreases in a time-dependent manner. Gout flare prophylaxis is recommended (see section 4.2 and 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

Patients with an overdose should be managed by symptomatic and supportive care.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antigout preparation, preparations inhibiting uric acid production, ATC code: M04AA03

Mechanism of action

Uric acid is the end product of purine metabolism in humans and is generated in the cascade of hypoxanthine → xanthine → uric acid. Both steps in the above transformations are catalyzed by xanthine oxidase (XO). Febuxostat is a 2-arylthiazole derivative that achieves its therapeutic effect of decreasing serum uric acid by selectively inhibiting XO. Febuxostat is a potent, non-purine selective inhibitor of XO (NP-SIXO) with an *in vitro* inhibition Ki value less than one nanomolar. Febuxostat has been shown to potently inhibit both the oxidized and reduced forms of XO. At therapeutic concentrations febuxostat does not inhibit other enzymes involved in purine or pyrimidine metabolism, namely, guanine deaminase, hypoxanthine guanine phosphoribosyltransferase, orotate phosphoribosyltransferase, orotidine monophosphate decarboxylase or purine nucleoside phosphorylase.

Clinical efficacy and safety

The efficacy of ADENURIC was demonstrated in three Phase 3 pivotal studies (the two pivotal APEX and FACT studies, and the additional CONFIRMS study described below) that were conducted in 4101 patients with hyperuricaemia and gout. In each phase 3 pivotal study, ADENURIC demonstrated superior ability to lower and maintain serum uric acid levels compared to allopurinol. The primary efficacy endpoint in the APEX and FACT studies was the proportion of patients whose last 3 monthly serum uric acid levels were < 6.0 mg/dL (357 µmol/L). In the additional phase 3 CONFIRMS study, for which results became available after the marketing authorisation for ADENURIC was first issued, the primary efficacy endpoint was the proportion of patients whose serum urate level was < 6.0 mg/dL at the final visit. No patients with organ transplant have been included in these studies (see section 4.2).

*APEX Study*: The Allopurinol and Placebo-Controlled Efficacy Study of Febuxostat (APEX) was a Phase 3, randomized, double-blind, multicenter, 28-week study. One thousand and seventy-two (1072) patients were randomized: placebo (n=134), ADENURIC 80 mg QD (n=267), ADENURIC 120 mg QD (n=269), ADENURIC 240 mg QD (n=134) or allopurinol (300 mg QD [n=258] for patients with a baseline serum creatinine ≤1.5 mg/dL or 100 mg QD [n=10] for patients with a baseline serum creatinine >1.5 mg/dL and ≤2.0 mg/dL). Two hundred and forty mg febuxostat (2 times the recommended highest dose) was used as a safety evaluation dose.

The APEX study showed statistically significant superiority of both the ADENURIC 80 mg QD and the ADENURIC 120 mg QD treatment arms *versus* the conventionally used doses of allopurinol 300 mg (n = 258) /100 mg (n = 10) treatment arm in reducing the sUA below 6 mg/dL (357 µmol/L) (see Table 2 and Figure 1).

*FACT Study*: The Febuxostat Allopurinol Controlled Trial (FACT) Study was a Phase 3, randomized, double-blind, multicenter, 52-week study. Seven hundred sixty (760) patients were randomized: ADENURIC 80 mg QD (n=256), ADENURIC 120 mg QD (n=251), or allopurinol 300 mg QD (n=253).

The FACT study showed the statistically significant superiority of both ADENURIC 80 mg and ADENURIC 120 mg QD treatment arms *versus* the conventionally used dose of allopurinol 300 mg treatment arm in reducing and maintaining sUA below 6 mg/dL (357 µmol/L).

Table 2 summarises the primary efficacy endpoint results:

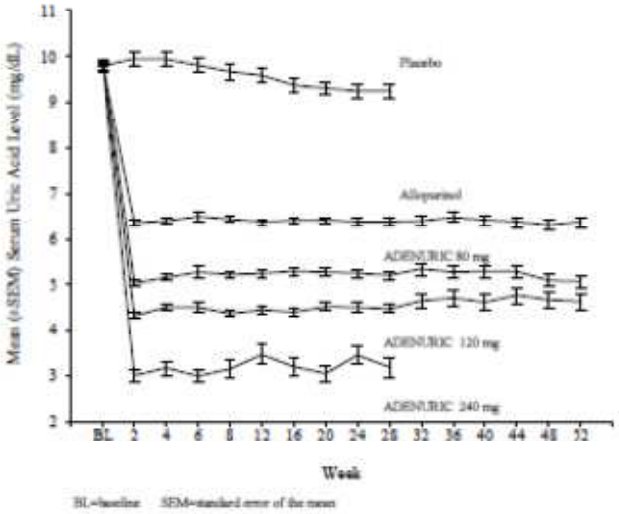
**Table 2**
**Proportion of Patients with Serum Uric Acid Levels <6.0 mg/dL (357 µmol/L)**
**Last Three Monthly Visits**

| Study | ADENURIC 80 mg QD | ADENURIC 120 mg QD | Allopurinol 300 / 100 mg QD[1] |
|---|---|---|---|
| APEX (28 weeks) | 48%* (n=262) | 65%*,# (n=269) | 22% (n=268) |
| FACT (52 weeks) | 53%* (n=255) | 62%* (n=250) | 21% (n=251) |
| Combined Results | 51%* (n=517) | 63%*,# (n=519) | 22% (n=519) |

[1] results from subjects receiving either 100 mg QD (n=10: patients with serum creatinine >1.5 and ≤2.0 mg/dL) or 300 mg QD (n=509) were pooled for analyses.
* $p < 0.001$ vs allopurinol, # $p < 0.001$ vs 80 mg

The ability of ADENURIC to lower serum uric acid levels was prompt and persistent. Reduction in serum uric acid level to <6.0 mg/dL (357 µmol/L) was noted by the Week 2 visit and was maintained throughout treatment. The mean serum uric acid levels over time for each treatment group from the two pivotal Phase 3 studies are shown in Figure 1.

**Figure 1 Mean Serum Uric Acid Levels in Combined Pivotal Phase 3 Studies**




Note: 509 patients received allopurinol 300 mg QD; 10 patients with serum creatinine >1.5 and < 2.0 mg/dL were dosed with 100 mg QD. (10 patients out of 268 in APEX study).
240 mg febuxostat was used to evaluate the safety of febuxostat at twice the recommended highest dose.

CONFIRMS Study: The CONFIRMS study was a Phase 3, randomized, controlled, 26-week study to evaluate the safety and efficacy of febuxostat 40 mg and 80 mg, in comparison with allopurinol 300 mg or 200 mg, in patients with gout and hyperuricaemia. Two thousand and two hundred-sixty nine (2269) patients were randomized: ADENURIC 40 mg QD (n=757), ADENURIC 80 mg QD (n=756), or allopurinol 300/200 mg QD (n=756). At least 65% of the patients had mild-moderate renal impairment (with creatinine clearance of 30-89 mL/min). Prophylaxis against gout flares was obligatory over the 26-week period.
The proportion of patients with serum urate levels of < 6.0 mg/dL (357 µmol/L) at the final visit, was 45% for 40 mg febuxostat, 67% for febuxostat 80 mg and 42% for allopurinol 300/200 mg, respectively.

*Primary endpoint in the sub-group of patients with renal impairment*
The APEX Study evaluated efficacy in 40 patients with renal impairment (i.e., baseline serum creatinine > 1.5 mg/dL and ≤2.0 mg/dL). For renally impaired subjects who were randomized to allopurinol, the dose was capped at 100 mg QD. ADENURIC achieved the primary efficacy endpoint in 44% (80 mg QD), 45% (120 mg QD), and 60% (240 mg QD) of patients compared to 0% in the allopurinol 100 mg QD and placebo groups.

There were no clinically significant differences in the percent decrease in serum uric acid concentration in healthy subjects irrespective of their renal function (58% in the normal renal function group and 55% in the severe renal dysfunction group).

An analysis in patients with gout and renal impairment was prospectively defined in the CONFIRMS study, and showed that febuxostat was significantly more efficacious in lowering serum urate levels to < 6 mg/dL compared to allopurinol 300 mg/200 mg in patients who had gout with mild to moderate renal impairment (65% of patients studied).

*Primary endpoint in the sub group of patients with sUA ≥ 10 mg/dL*
Approximately 40% of patients (combined APEX and FACT) had a baseline sUA of ≥ 10 mg/dL. In this subgroup ADENURIC achieved the primary efficacy endpoint (sUA < 6.0 mg/dL at the last 3 visits) in 41% (80 mg QD), 48% (120 mg QD), and 66% (240 mg QD) of patients compared to 9% in the allopurinol 300 mg/100 mg QD and 0 % in the placebo groups.

In the CONFIRMS study, the proportion of patients achieving the primary efficacy endpoint (sUA < 6.0 mg/dL at the final visit) for patients with a baseline serum urate level of ≥ 10 mg/dL treated with febuxostat 40 mg QD was 27% (66/249), with febuxostat 80 mg QD 49% (125/254) and with allopurinol 300 mg/200 mg QD 31% (72/230), respectively.

*Clinical Outcomes: proportion of patients requiring treatment for a gout flare*
APEX study: During the 8-week prophylaxis period, a greater proportion of subjects in the febuxostat 120 mg (36%) treatment group required treatment for gout flare compared to febuxostat 80 mg (28%), allopurinol 300 mg (23%) and placebo (20%). Flares increased following the prophylaxis period and gradually decreased over time. Between 46% and 55% of subjects received treatment for gout flares from Week 8 and Week 28. Gout flares during the last 4 weeks of the study (Weeks 24-28) were observed in 15% (febuxostat 80, 120 mg), 14% (allopurinol 300 mg) and 20% (placebo) of subjects.

FACT study: During the 8-week prophylaxis period, a greater proportion of subjects in the febuxostat 120 mg (36%) treatment group required treatment for a gout flare compared to both the febuxostat 80 mg (22%) and allopurinol 300 mg (21%) treatment groups. After the 8-week prophylaxis period, the incidences of flares increased and gradually decreased over time (64% and 70% of subjects received treatment for gout flares from Week 8-52). Gout flares during the last 4 weeks of the study (Weeks 49-52) were observed in 6-8% (febuxostat 80 mg, 120 mg) and 11% (allopurinol 300 mg) of subjects.

The proportion of subjects requiring treatment for a gout flare (APEX and FACT Study) was numerically lower in the groups that achieved an average post-baseline serum urate level <6.0 mg/dL, <5.0 mg/dL, or <4.0 mg/dL compared to the group that achieved an average post-baseline serum urate level ≥6.0 mg/dL during the last 32 weeks of the treatment period (Week 20-Week 24 to Week 49 - 52 intervals).

During the CONFIRMS study, the percentages of patients who required treatment for gout flares (Day 1 through Month 6) were 31% and 25% for the febuxostat 80 mg and allopurinol groups, respectively. No difference in the proportion of patients requiring treatment for gout flares was observed between the febuxostat 80 mg and 40 mg groups.

*Long-term, open label extension Studies*
EXCEL Study (C02-021): The Excel study was a three years Phase 3, open label, multicenter, randomised, allopurinol-controlled, safety extension study for patients who had completed the pivotal Phase 3 studies (APEX or FACT). A total of 1,086 patients were enrolled: ADENURIC 80 mg QD (n=649), Adenuric 120 mg QD (n=292) and allopurinol 300/100 mg QD (n=145). About 69 % of patients required no treatment change to achieve a final stable treatment. Patients who had 3 consecutive sUA levels >6.0 mg/dL were withdrawn.
Serum urate levels were maintained over time (i.e. 91% and 93% of patients on initial treatment with febuxostat 80 mg and 120 mg, respectively, had sUA <6 mg/dL at Month 36).

Three years data showed a decrease in the incidence of gout flares with less than 4% of patients requiring treatment for a flare (i.e. more than 96% of patients did not require treatment for a flare) at Month 16-24 and at Month 30-36.

46% and 38%, of patients on final stable treatment of febuxostat 80 or 120 mg QD, respectively, had complete resolution of the primary palpable tophus from baseline to the Final Visit.

FOCUS Study (TMX-01-005) was a 5 years Phase 2, open-label, multicenter, safety extension study for patients who had completed the febuxostat 4 weeks of double blind dosing in study TMX-00-004.

116 patients were enrolled and received initially febuxostat 80 mg QD. 62% of patients required no dose adjustment to maintain sUA <6 mg/dL and 38% of patients required a dose adjustment to achieve a final stable dose.

The proportion of patients with serum urate levels of <6.0 mg/dL (357 µmol/L) at the final visit was greater than 80% (81-100%) at each febuxostat dose.

During the phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0%). These rates were similar to the rates reported on allopurinol (4.2%) (see section 4.4). Increased TSH values (>5.5 µIU/mL) were observed in patients on long-term treatment with febuxostat (5.5%) and patients with allopurinol (5.8%) in the long term open label extension studies (see section 4.4).

**5.2 Pharmacokinetic properties**

In healthy subjects, maximum plasma concentrations ($C_{max}$) and area under the plasma concentration time curve (AUC) of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. For doses between 120 mg and 300 mg, a greater than dose proportional increase in AUC is observed for febuxostat. There is no appreciable accumulation when doses of 10 mg to 240 mg are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours.

Population pharmacokinetic/pharmacodynamic analyses were conducted in 211 patients with hyperuricaemia and gout, treated with ADENURIC 40-240 mg QD. In general, febuxostat pharmacokinetic parameters estimated by these analyses are consistent with those obtained from healthy subjects, indicating that healthy subjects are representative for pharmacokinetic/pharmacodynamic assessment in the patient population with gout.

*Absorption*
Febuxostat is rapidly ($t_{max}$ of 1.0-1.5 h) and well absorbed (at least 84%). After single or multiple oral 80 and 120 mg once daily doses, $C_{max}$ is approximately 2.8-3.2 µg/mL, and 5.0-5.3 µg/mL, respectively. Absolute bioavailability of the febuxostat tablet formulation has not been studied.

Following multiple oral 80 mg once daily doses or a single 120 mg dose with a high fat meal, there was a 49% and 38% decrease in $C_{max}$ and a 18% and 16% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed where tested (80 mg multiple dose). Thus, ADENURIC may be taken without regard to food.

*Distribution*
The apparent steady state volume of distribution ($V_{ss}/F$) of febuxostat ranges from 29 to 75 L after oral doses of 10-300 mg. The plasma protein binding of febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 80 and 120 mg doses. Plasma protein binding of the active metabolites ranges from about 82% to 91%.

*Biotransformation*
Febuxostat is extensively metabolized by conjugation *via* uridine diphosphate glucuronosyltransferase (UDPGT) enzyme system and oxidation *via* the cytochrome P450 (CYP) system. Four pharmacologically active hydroxyl metabolites have been identified, of which three occur in plasma of humans. *In vitro* studies with human liver microsomes showed that those oxidative metabolites were formed primarily by CYP1A1, CYP1A2, CYP2C8 or CYP2C9 and febuxostat glucuronide was formed mainly by UGT 1A1, 1A8, and 1A9.

*Elimination*
Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of $^{14}C$-labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the active substance (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion,

approximately 45% of the dose was recovered in the faeces as the unchanged febuxostat (12%), the acyl glucuronide of the active substance (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).

*Renal impairment*
Following multiple doses of 80 mg of ADENURIC in patients with mild, moderate or severe renal impairment, the $C_{max}$ of febuxostat did not change, relative to subjects with normal renal function. The mean total AUC of febuxostat increased by approximately 1.8-fold from 7.5 µg·h/mL in the normal renal function group to 13.2 µg.h/mL in the severe renal dysfunction group. The $C_{max}$ and AUC of active metabolites increased up to 2- and 4-fold, respectively. However, no dose adjustment is necessary in patients with mild or moderate renal impairment.

*Hepatic impairment*
Following multiple doses of 80 mg of ADENURIC in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, the $C_{max}$ and AUC of febuxostat and its metabolites did not change significantly compared to subjects with normal hepatic function. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

*Age*
There were no significant changes observed in AUC of febuxostat or its metabolites following multiple oral doses of ADENURIC in elderly as compared to younger healthy subjects.

*Gender*
Following multiple oral doses of ADENURIC, the $C_{max}$ and AUC were 24% and 12% higher in females than in males, respectively. However, weight-corrected $C_{max}$ and AUC were similar between the genders. No dose adjustment is needed based on gender.

### 5.3 Preclinical safety data

Effects in non-clinical studies were generally observed at exposures in excess of the maximum human exposure.

*Carcinogenesis, mutagenesis, impairment of fertility*
In male rats, a statistically significant increase in urinary bladder tumours (transitional cell papilloma and carcinoma) was found only in association with xanthine calculi in the high dose group, at approximately 11 times human exposure. There was no significant increase in any other tumour type in either male or female mice or rats. These findings are considered a consequence of species specific purine metabolism and urine composition and of no relevance to clinical use.

A standard battery of test for genotoxicity did not reveal any biologically relevant genotoxic effects for febuxostat.

Febuxostat at oral doses up to 48 mg/kg/day was found to have no effect on fertility and reproductive performance of male and female rats.

There was no evidence of impaired fertility, teratogenic effects, or harm to the foetus due to febuxostat. There was high dose maternal toxicity accompanied by a reduction in weaning index and reduced development of offspring in rats at approximately 4.3 times human exposure. Teratology studies, performed in pregnant rats at approximately 4.3 times and pregnant rabbits at approximately 13 times human exposure did not reveal any teratogenic effects.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Tablet core*
Lactose monohydrate
Microcrystalline cellulose
Magnesium stearate
Hydroxypropylcellulose
Croscarmellose sodium
Silica, colloidal hydrated

*Tablet coating*
Opadry II, Yellow, 85F42129 containing:
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogols 3350
Talc
Iron oxide yellow (E172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Clear (Aclar/PVC/Aluminium) blister of 14 tablets.

ADENURIC 80 mg is available in pack sizes of 14, 28, 42, 56, 84 and 98 film-coated tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Menarini International Operations Luxembourg S.A.
1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/447/001
EU/1/08/447/002
EU/1/08/447/005

EU/1/08/447/006
EU/1/08/447/007
EU/1/08/447/008

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 April 2008
Date of latest renewal: 20 December 2012

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

**EU SMPCS FOR ADENURIC® 120 MG FILM-COATED TABLETS**

## 1. NAME OF THE MEDICINAL PRODUCT

ADENURIC 120 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 120 mg of febuxostat.

Excipient(s) with known effects:
Each tablet contains 114.75 mg of lactose (as monohydrate)

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablets).

Pale yellow to yellow, film-coated, capsule shaped tablets, engraved with "120" on one side

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ADENURIC is indicated for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

ADENURIC is indicated for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS).

ADENURIC is indicated in adults.

### 4.2 Posology and method of administration

Posology

*Gout*: The recommended oral dose of ADENURIC is 80 mg once daily without regard to food. If serum uric acid is > 6 mg/dL (357 µmol/L) after 2-4 weeks, ADENURIC 120 mg once daily may be considered.

ADENURIC works sufficiently quickly to allow retesting of the serum uric acid after 2 weeks. The therapeutic target is to decrease and maintain serum uric acid below 6 mg/dL (357µmol/L).

Gout flare prophylaxis of at least 6 months is recommended (see section 4.4).

*Tumor Lysis Syndrome*: The recommended oral dose of ADENURIC is 120 mg once daily without regard to food.
ADENURIC should be started two days before the beginning of cytotoxic therapy and continued for a minimum of 7 days; however treatment may be prolonged up to 9 days according to chemotherapy duration as per clinical judgment.

*Older people*
No dose adjustment is required in the elderly (see section 5.2).

*Renal impairment*
The efficacy and safety have not been fully evaluated in patients with severe renal impairment (creatinine clearance <30 mL/min, see section 5.2).
No dose adjustment is necessary in patients with mild or moderate renal impairment.

*Hepatic impairment*
The efficacy and safety of febuxostat has not been studied in patients with severe hepatic impairment (Child Pugh Class C).
Gout: The recommended dose in patients with mild hepatic impairment is 80 mg. Limited information is available in patients with moderate hepatic impairment.

Tumour Lysis Syndrome: in the pivotal Phase III trial (FLORENCE) only subjects with severe hepatic insufficiency were excluded from trial participation. No dose adjustment was required for enrolled patients on the basis of hepatic function.

*Paediatric population*
The safety and the efficacy of ADENURIC in children aged below the age of 18 years have not been established. No data are available.

*Method of administration*
Oral use
ADENURIC should be taken by mouth and can be taken with or without food.

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see also section 4.8).

**4.4 Special warnings and precautions for use**

*Cardio-vascular disorders*
*Treatment of chronic hyperuricaemia*
Treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended. A numerical greater incidence of investigator-reported cardiovascular APTC events (defined endpoints from the Anti-Platelet Trialists' Collaboration (APTC) including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) was observed in the febuxostat total group compared to the allopurinol group in the APEX and FACT studies (1.3 vs. 0.3 events per 100 Patient Years (PYs)), but not in the CONFIRMS study (see section 5.1 for detailed characteristics of the studies). The incidence of investigator-reported cardiovascular APTC events in the combined Phase 3 studies (APEX, FACT and CONFIRMS studies) was 0.7 vs. 0.6 events per 100 PYs. In the long-term extension studies the incidences of investigator-reported APTC events were 1.2 and 0.6 events per 100 PYs for febuxostat and allopurinol, respectively. No statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure.
*Prevention and treatment of hyperuricaemia in patients at risk of TLS*
Patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome treated with ADENURIC should be under cardiac monitoring as clinically appropriate.

*Medicinal product allergy / hypersensitivity*
Rare reports of serious allergic/hypersensitivity reactions, including life-threatening Stevens-Johnson Syndrome, Toxic epidermal necrolysis and acute anaphylactic reaction/shock, have been collected in the post-marketing experience. In most cases, these reactions occurred during the first month of therapy with febuxostat. Some, but not all of these patients reported renal impairment and/or previous hypersensitivity to allopurinol. Severe hypersensitivity reactions, including Drug Reaction with

Eosinophilia and Systemic Symptoms (DRESS) were associated with fever, haematological, renal or hepatic involvement in some cases.
Patients should be advised of the signs and symptoms and monitored closely for symptoms of allergic/hypersensitivity reactions (see section 4.8). Febuxostat treatment should be immediately stopped if serious allergic/hypersensitivity reactions, including Stevens-Johnson Syndrome, occur since early withdrawal is associated with a better prognosis. If patient has developed allergic/hypersensitivity reactions including Stevens-Johnson Syndrome and acute anaphylactic reaction/shock, febuxostat must not be re-started in this patient at any time.

*Acute gouty attacks (gout flare)*
Febuxostat treatment should not be started until an acute attack of gout has completely subsided. Gout flares may occur during initiation of treatment due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits (see sections 4.8 and 5.1). At treatment initiation with febuxostat flare prophylaxis for at least 6 months with an NSAID or colchicine is recommended (see section 4.2).
If a gout flare occurs during febuxostat treatment, it should not be discontinued. The gout flare should be managed concurrently as appropriate for the individual patient. Continuous treatment with febuxostat decreases frequency and intensity of gout flares.

*Xanthine deposition*
In patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. This has not been observed in the pivotal clinical study with ADENURIC in the Tumor Lysis Syndrome. As there has been no experience with febuxostat, its use in patients with Lesch-Nyhan Syndrome is not recommended.

*Mercaptopurine/azathioprine*
Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine. Where the combination cannot be avoided patients should be closely monitored. A reduction of dosage of mercaptopurine or azathioprine is recommended in order to avoid possible haematological effects (see section 4.5).

*Organ transplant recipients*
As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended (see section 5.1).

*Theophylline*
Co-administration of febuxostat 80 mg and theophylline 400mg single dose in healthy subjects showed absence of any pharmacokinetic interaction (see section 4.5). Febuxostat 80 mg can be used in patients concomitantly treated with theophylline without risk of increasing theophylline plasma levels. No data is available for febuxostat 120 mg.

*Liver disorders*
During the combined phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0%). Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgment (see section 5.1).

*Thyroid disorders*
Increased TSH values (>5.5 µIU/mL) were observed in patients on long-term treatment with febuxostat (5.5%) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function (see section 5.1).

*Lactose*
Febuxostat tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### 4.5 Interaction with other medicinal products and other forms of interaction

*Mercaptopurine/azathioprine*
On the basis of the mechanism of action of febuxostat on XO inhibition concomitant use is not recommended. Inhibition of XO by febuxostat may cause increased plasma concentrations of these drugs leading to toxicity (see section 4.4). Drug interaction studies of febuxostat with drugs that are metabolized by XO have not been performed.

Drug interaction studies of febuxostat with cytotoxic chemotherapy have not been conducted. In the Tumor Lysis Syndrome pivotal trial febuxostat 120 mg daily was administered to patients undergoing several chemotherapy regimens, including monoclonal antibodies. However, drug-drug and drug-disease interactions were not explored during this study. Therefore, possible interactions with any concomitantly administered cytotoxic drug cannot be ruled out.

*Rosiglitazone/CYP2C8 substrates*
Febuxostat was shown to be a weak inhibitor of CYP2C8 *in vitro*. In a study in healthy subjects, coadministration of 120 mg febuxostat QD with a single 4 mg oral dose of rosiglitazone had no effect on the pharmacokinetics of rosiglitazone and its metabolite N-desmethyl rosiglitazone, indicating that febuxostat is not a CYP2C8 enzyme inhibitor *in vivo*. Thus, co-administration of febuxostat with rosiglitazone or other CYP2C8 substrates is not expected to require any dose adjustment for those compounds.

*Theophylline*
An interaction study in healthy subjects has been performed with febuxostat to evaluate whether the inhibition of XO may cause an increase in the theophylline circulating levels as reported with other XO inhibitors. The results of the study showed that the co-administration of febuxostat 80 mg QD with theophylline 400 mg single dose has no effect on the pharmacokinetics or safety of theophylline. Therefore no special caution is advised when febuxostat 80 mg and theophylline are given concomitantly. No data is available for febuxostat 120 mg.

*Naproxen and other inhibitors of glucuronidation*
Febuxostat metabolism depends on Uridine Glucuronosyl Transferase (UGT) enzymes. Medicinal products that inhibit glucuronidation, such as NSAIDs and probenecid, could in theory affect the elimination of febuxostat. In healthy subjects concomitant use of febuxostat and naproxen 250mg twice daily was associated with an increase in febuxostat exposure ($C_{max}$ 28%, AUC 41% and $t_{1/2}$ 26%). In clinical studies the use of naproxen or other NSAIDs/Cox-2 inhibitors was not related to any clinically significant increase in adverse events.

Febuxostat can be co-administered with naproxen with no dose adjustment of febuxostat or naproxen being necessary.

*Inducers of glucuronidation*
Potent inducers of UGT enzymes might possibly lead to increased metabolism and decreased efficacy of febuxostat. Monitoring of serum uric acid is therefore recommended 1-2 weeks after start of treatment with a potent inducer of glucuronidation. Conversely, cessation of treatment of an inducer might lead to increased plasma levels of febuxostat.

*Colchicine/indometacin/hydrochlorothiazide/warfarin*
Febuxostat can be co-administered with colchicine or indomethacin with no dose adjustment of febuxostat or the co-administered active substance being necessary.

No dose adjustment is necessary for febuxostat when administered with hydrochlorothiazide.

No dose adjustment is necessary for warfarin when administered with febuxostat. Administration of febuxostat (80 mg or 120 mg once daily) with warfarin had no effect on the pharmacokinetics of

warfarin in healthy subjects. INR and Factor VII activity were also not affected by the co-administration of febuxostat.

*Desipramine/CYP2D6 substrates*
Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro*. In a study in healthy subjects, 120 mg ADENURIC QD resulted in a mean 22% increase in AUC of desipramine, a CYP2D6 substrate indicating a potential weak inhibitory effect of febuxostat on the CYP2D6 enzyme *in vivo*. Thus, co-administration of febuxostat with other CYP2D6 substrates is not expected to require any dose adjustment for those compounds.

*Antacids*
Concomitant ingestion of an antacid containing magnesium hydroxide and aluminium hydroxide has been shown to delay absorption of febuxostat (approximately 1 hour) and to cause a 32% decrease in $C_{max}$, but no significant change in AUC was observed. Therefore, febuxostat may be taken without regard to antacid use.

### 4.6 Fertility, pregnancy and lactation

*Pregnancy*
Data on a very limited number of exposed pregnancies have not indicated any adverse effects of febuxostat on pregnancy or on the health of the foetus/new born child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development or parturition (see section 5.3). The potential risk for human is unknown. Febuxostat should not be used during pregnancy.

*Breastfeeding*
It is unknown whether febuxostat is excreted in human breast milk. Animal studies have shown excretion of this active substance in breast milk and an impaired development of suckling pups. A risk to a suckling infant cannot be excluded. Febuxostat should not be used while breastfeeding.

*Fertility*
In animals, reproduction studies up to 48 mg/kg/day showed no dose-dependent adverse effects on fertility (see section 5.3). The effect of ADENURIC on human fertility is unknown.

### 4.7 Effects on ability to drive and use machines

Somnolence, dizziness, paraesthesia and blurred vision have been reported with the use of Febuxostat. Patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that ADENURIC does not adversely affect performance.

### 4.8 Undesirable effects

*Summary of the safety profile*
The most commonly reported adverse reactions in clinical trials (4,072 subjects treated at least with a dose from 10 mg to 300 mg) and post-marketing experience in gout patients are gout flares, liver function abnormalities, diarrhoea, nausea, headache, rash and oedema. These adverse reactions were mostly mild or moderate in severity. Rare serious hypersensitivity reactions to febuxostat, some of which were associated to systemic symptoms, have occurred in the post-marketing experience.

*Tabulated list of adverse reactions*
Common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000) adverse reactions occurring in patients treated with febuxostat are listed below.
The frequencies are based on studies and post-marketing experience in gout patients.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

*Table 1: Adverse reactions in combined phase 3, long-term extension studies and post-marketing experience in gout patients.*

| | |
|---|---|
| Blood and lymphatic system disorders | Rare<br>Pancytopenia, thrombocytopenia |
| Immune system disorders | Rare<br>Anaphylactic reaction*, drug hypersensitivity* |
| Endocrine disorders | Uncommon<br>Blood thyroid stimulating hormone increased |
| Eye disorders | Rare<br>Blurred vision |
| Metabolism and nutrition disorders | Common***<br>Gout flares<br>Uncommon<br>Diabetes mellitus, hyperlipidemia, decrease appetite, weight increase<br>Rare<br>Weight decrease, increase appetite, anorexia |
| Psychiatric disorders | Uncommon<br>Libido decreased, insomnia<br>Rare<br>Nervousness |
| Nervous system disorders | Common<br>Headache<br>Uncommon<br>Dizziness, paraesthesia, hemiparesis, somnolence, altered taste, hypoaesthesia, hyposmia |
| Ear and labyrinth disorders | Rare<br>Tinnitus |
| Cardiac disorders | Uncommon<br>Atrial fibrillation, palpitations, ECG abnormal, left bundle branch block (see section Tumor Lysis Syndrome), sinus tachycardia (see section Tumor Lysis Syndrome) |
| Vascular disorders | Uncommon<br>Hypertension, flushing, hot flush, haemorrhage (see section Tumor Lysis Syndrome) |
| Respiratory system disorders | Uncommon<br>Dyspnoea, bronchitis, upper respiratory tract infection, cough |
| Gastrointestinal disorders | Common<br>Diarrhoea**, nausea<br>Uncommon:<br>Abdominal pain, abdominal distension, gastro-oesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort<br>Rare<br>Pancreatitis, mouth ulceration |
| Hepato-biliary disorders | Common<br>Liver function abnormalities**<br>Uncommon<br>Cholelithiasis<br>Rare<br>Hepatitis, jaundice*, liver injury* |
| Skin and subcutaneous tissue disorders | Common<br>Rash (including various types of rash reported with lower frequencies, see below)<br>Uncommon<br>Dermatitis, urticaria, pruritus, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash papular |

| | |
|---|---|
| | Rare<br>Toxic epidermal necrolysis*, Stevens-Johnson Syndrome*, angioedema*, drug reaction with eosinophilia and systemic symptoms*, generalized rash (serious)*, erythema, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash pruritic*, rash erythematous, rash morbilliform, alopecia, hyperhidrosis |
| Musculoskeletal and connective tissue disorders | Uncommon<br>Arthralgia, arthritis, myalgia, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis<br>Rare<br>Rhabdomyolysis*, joint stiffness, musculoskeletal stiffness |
| Renal and urinary disorders | Uncommon<br>Renal failure, nephrolithiasis, haematuria, pollakiuria, proteinuria<br>Rare<br>Tubulointerstitial nephritis*, micturition urgency |
| Reproductive system and breast disorder | Uncommon<br>Erectile dysfunction |
| General disorders and administration site conditions | Common<br>Oedema<br>Uncommon<br>Fatigue, chest pain, chest discomfort<br>Rare<br>Thirst |
| Investigations | Uncommon<br>Blood amylase increase, platelet count decrease, WBC decrease, lymphocyte count decrease, blood creatine increase, blood creatinine increase, haemoglobin decrease, blood urea increase, blood triglycerides increase, blood cholesterol increase, haematocritic decrease, blood lactate dehydrogenase increased, blood potassium increase<br>Rare<br>Blood glucose increased, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase |

* Adverse reactions coming from post-marketing experience
** Treatment-emergent non-infective diarrhoea and abnormal liver function tests in the combined Phase 3 studies are more frequent in patients concomitantly treated with colchicine.
*** See section 5.1 for incidences of gout flares in the individual Phase 3 randomized controlled studies.

*Description of selected adverse reactions*
Rare serious hypersensitivity reactions to febuxostat, including Stevens-Johnson Syndrome, Toxic epidermal necrolysis and anaphylactic reaction/shock, have occurred in the post-marketing experience. Stevens-Johnson Syndrome and Toxic epidermal necrolysis are characterised by progressive skin rashes associated with blisters or mucosal lesions and eye irritation. Hypersensitivity reactions to febuxostat can be associated to the following symptoms: skin reactions characterised by infiltrated maculopapular eruption, generalised or exfoliative rashes, but also skin lesions, facial oedema, fever, haematologic abnormalities such as thrombocytopenia and eosinophilia, and single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis) (see section 4.4).

Gout flares were commonly observed soon after the start of treatment and during the first months. Thereafter, the frequency of gout flare decreases in a time-dependent manner. Gout flare prophylaxis is recommended (see section 4.2 and 4.4).

Tumor Lysis Syndrome
*Summary of the safety profile*
In the randomized, double-blind, Phase 3 pivotal FLORENCE (FLO-01) study comparing febuxostat with allopurinol (346 patients undergoing chemotherapy for haematologic malignancies and at intermediate-to-high risk of TLS), only 22 (6.4%) patients overall experienced adverse reactions, namely 11 (6.4%) patients in each treatment group. The majority of adverse reactions were either mild or moderate.
Overall, the FLORENCE trial did not highlight any particular safety concern in addition to the previous experience with ADENURIC in gout, with the exception of the following three adverse reactions (listed above in table 1).

Cardiac disorders:
Uncommon: Left bundle branch block, sinus tachycardia

Vascular disorders:
Uncommon: haemorrhage

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

Patients with an overdose should be managed by symptomatic and supportive care.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antigout preparation, preparations inhibiting uric acid production, ATC code: M04AA03

Mechanism of action

Uric acid is the end product of purine metabolism in humans and is generated in the cascade of hypoxanthine → xanthine → uric acid. Both steps in the above transformations are catalyzed by xanthine oxidase (XO). Febuxostat is a 2-arylthiazole derivative that achieves its therapeutic effect of decreasing serum uric acid by selectively inhibiting XO. Febuxostat is a potent, non-purine selective inhibitor of XO (NP-SIXO) with an *in vitro* inhibition Ki value less than one nanomolar. Febuxostat has been shown to potently inhibit both the oxidized and reduced forms of XO. At therapeutic concentrations febuxostat does not inhibit other enzymes involved in purine or pyrimidine metabolism, namely, guanine deaminase, hypoxanthine guanine phosphoribosyltransferase, orotate phosphoribosyltransferase, orotidine monophosphate decarboxylase or purine nucleoside phosphorylase.

Clinical efficacy and safety

*Gout*

The efficacy of ADENURIC was demonstrated in three Phase 3 pivotal studies (the two pivotal APEX and FACT studies, and the additional CONFIRMS study, described below) that were conducted in 4101 patients with hyperuricaemia and gout. In each phase 3 pivotal study, ADENURIC demonstrated superior ability to lower and maintain serum uric acid levels compared to allopurinol. The primary efficacy endpoint in the APEX and FACT studies was the proportion of patients whose last 3 monthly

serum uric acid levels were < 6.0 mg/dL (357 µmol/L). In the additional phase 3 CONFIRMS study, for which results became available after the marketing authorisation for ADENURIC was first issued, the primary efficacy endpoint was the proportion of patients whose serum urate level was < 6.0 mg/dL at the final visit. No patients with organ transplant have been included in these studies (see section 4.2).

*APEX Study*: The Allopurinol and Placebo-Controlled Efficacy Study of Febuxostat (APEX) was a Phase 3, randomized, double-blind, multicenter, 28-week study. One thousand and seventy-two (1072) patients were randomized: placebo (n=134), ADENURIC 80 mg QD (n=267), ADENURIC 120 mg QD (n=269), ADENURIC 240 mg QD (n=134) or allopurinol (300 mg QD [n=258] for patients with a baseline serum creatinine ≤1.5 mg/dL or 100 mg QD [n=10] for patients with a baseline serum creatinine >1.5 mg/dL and ≤2.0 mg/dL). Two hundred and forty mg febuxostat (2 times the recommended highest dose) was used as a safety evaluation dose.

The APEX study showed statistically significant superiority of both the ADENURIC 80 mg QD and the ADENURIC 120 mg QD treatment arms *versus* the conventionally used doses of allopurinol 300 mg (n = 258) /100 mg (n = 10) treatment arm in reducing the sUA below 6 mg/dL (357 µmol/L) (see Table 2 and Figure 1).

*FACT Study*: The Febuxostat Allopurinol Controlled Trial (FACT) Study was a Phase 3, randomized, double-blind, multicenter, 52-week study. Seven hundred sixty (760) patients were randomized: ADENURIC 80 mg QD (n=256), ADENURIC 120 mg QD (n=251), or allopurinol 300 mg QD (n=253).

The FACT study showed the statistically significant superiority of both ADENURIC 80 mg and ADENURIC 120 mg QD treatment arms *versus* the conventionally used dose of allopurinol 300 mg treatment arm in reducing and maintaining sUA below 6 mg/dL (357 µmol/L).

Table 2 summarises the primary efficacy endpoint results:

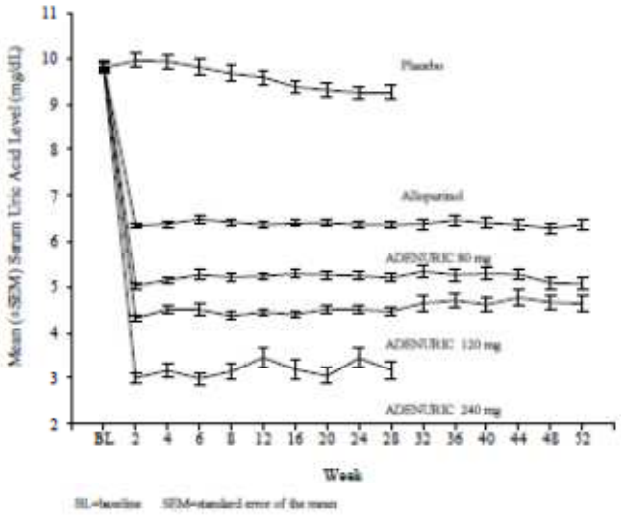
**Table 2**
**Proportion of Patients with Serum Uric Acid Levels <6.0 mg/dL (357 µmol/L)**
**Last Three Monthly Visits**

| Study | ADENURIC 80 mg QD | ADENURIC 120 mg QD | Allopurinol 300 / 100 mg QD[1] |
|---|---|---|---|
| APEX (28 weeks) | 48%[*] (n=262) | 65%[*,#] (n=269) | 22% (n=268) |
| FACT (52 weeks) | 53%[*] (n=255) | 62%[*] (n=250) | 21% (n=251) |
| Combined Results | 51%[*] (n=517) | 63%[*,#] (n=519) | 22% (n=519) |

[1] results from subjects receiving either 100 mg QD (n=10: patients with serum creatinine >1.5 and ≤2.0 mg/dL) or 300 mg QD (n=509) were pooled for analyses.
[*] $p < 0.001$ vs allopurinol, [#] $p < 0.001$ vs 80 mg

The ability of ADENURIC to lower serum uric acid levels was prompt and persistent. Reduction in serum uric acid level to <6.0 mg/dL (357 µmol/L) was noted by the Week 2 visit and was maintained throughout treatment. The mean serum uric acid levels over time for each treatment group from the two pivotal Phase 3 studies are shown in Figure 1.

**Figure 1 Mean Serum Uric Acid Levels in Combined Pivotal Phase 3 Studies**




Note: 509 patients received allopurinol 300 mg QD; 10 patients with serum creatinine >1.5 and < 2.0 mg/dL were dosed with 100 mg QD. (10 patients out of 268 in APEX study).
240 mg febuxostat was used to evaluate the safety of febuxostat at twice the recommended highest dose.

CONFIRMS Study: The CONFIRMS study was a Phase 3, randomized, controlled, 26-week study to evaluate the safety and efficacy of febuxostat 40 mg and 80 mg, in comparison with allopurinol 300 mg or 200 mg, in patients with gout and hyperuricaemia. Two thousand and two hundred-sixty nine (2269) patients were randomized: ADENURIC 40 mg QD (n=757), ADENURIC 80 mg QD (n=756), or allopurinol 300/200 mg QD (n=756). At least 65% of the patients had mild-moderate renal impairment (with creatinine clearance of 30-89 mL/min). Prophylaxis against gout flares was obligatory over the 26-week period.
The proportion of patients with serum urate levels of < 6.0 mg/dL (357 µmol/L) at the final visit, was 45% for 40 mg febuxostat, 67% for febuxostat 80 mg and 42% for allopurinol 300/200 mg, respectively.

*Primary endpoint in the sub-group of patients with renal impairment*
The APEX Study evaluated efficacy in 40 patients with renal impairment (i.e., baseline serum creatinine > 1.5 mg/dL and ≤2.0 mg/dL). For renally impaired subjects who were randomized to allopurinol, the dose was capped at 100 mg QD. ADENURIC achieved the primary efficacy endpoint in 44% (80 mg QD), 45% (120 mg QD), and 60% (240 mg QD) of patients compared to 0% in the allopurinol 100 mg QD and placebo groups.

There were no clinically significant differences in the percent decrease in serum uric acid concentration in healthy subjects irrespective of their renal function (58% in the normal renal function group and 55% in the severe renal dysfunction group).

An analysis in patients with gout and renal impairment was prospectively defined in the CONFIRMS study, and showed that febuxostat was significantly more efficacious in lowering serum urate levels to < 6 mg/dL compared to allopurinol 300 mg/200 mg in patients who had gout with mild to moderate renal impairment (65% of patients studied).

*Primary endpoint in the sub group of patients with sUA ≥ 10 mg/dL*
Approximately 40% of patients (combined APEX and FACT) had a baseline sUA of ≥ 10 mg/dL. In this subgroup ADENURIC achieved the primary efficacy endpoint (sUA < 6.0 mg/dL at the last 3

visits) in 41% (80 mg QD), 48% (120 mg QD), and 66% (240 mg QD) of patients compared to 9% in the allopurinol 300 mg/100 mg QD and 0 % in the placebo groups.

In the CONFIRMS study, the proportion of patients achieving the primary efficacy endpoint (sUA < 6.0 mg/dL at the final visit) for patients with a baseline serum urate level of ≥ 10 mg/dL treated with febuxostat 40 mg QD was 27% (66/249), with febuxostat 80 mg QD 49% (125/254) and with allopurinol 300 mg/200 mg QD 31% (72/230), respectively.

*Clinical Outcomes: proportion of patients requiring treatment for a gout flare*
Apex study: During the 8-week prophylaxis period, a greater proportion of subjects in the febuxostat 120 mg (36%) treatment group required treatment for gout flare compared to febuxostat 80 mg (28%), allopurinol 300 mg (23%) and placebo (20%). Flares increased following the prophylaxis period and gradually decreased over time. Between 46% and 55% of subjects received treatment for gout flares from Week 8 and Week 28. Gout flares during the last 4 weeks of the study (Weeks 24-28) were observed in 15% (febuxostat 80, 120 mg), 14% (allopurinol 300 mg) and 20% (placebo) of subjects.

Fact study: During the 8-week prophylaxis period, a greater proportion of subjects in the febuxostat 120 mg (36%) treatment group required treatment for a gout flare compared to both the febuxostat 80 mg (22%) and allopurinol 300 mg (21%) treatment groups. After the 8-week prophylaxis period, the incidences of flares increased and gradually decreased over time (64% and 70% of subjects received treatment for gout flares from Week 8-52). Gout flares during the last 4 weeks of the study (Weeks 49-52) were observed in 6-8% (febuxostat 80 mg, 120 mg) and 11% (allopurinol 300 mg) of subjects.

The proportion of subjects requiring treatment for a gout flare (APEX and FACT Study) was numerically lower in the groups that achieved an average post-baseline serum urate level <6.0 mg/dL, <5.0 mg/dL, or <4.0 mg/dL compared to the group that achieved an average post-baseline serum urate level ≥6.0 mg/dL during the last 32 weeks of the treatment period (Week 20-Week 24 to Week 49 - 52 intervals).

During the CONFIRMS study, the percentages of patients who required treatment for gout flares (Day 1 through Month 6) were 31% and 25% for the febuxostat 80 mg and allopurinol groups, respectively. No difference in the proportion of patients requiring treatment for gout flares was observed between the febuxostat 80 mg and 40 mg groups.

*Long-term, open label extension Studies*
EXCEL Study (C02-021): The Excel study was a three years Phase 3, open label, multicenter, randomised, allopurinol-controlled, safety extension study for patients who had completed the pivotal Phase 3 studies (APEX or FACT). A total of 1,086 patients were enrolled: ADENURIC 80 mg QD (n=649), Adenuric 120 mg QD (n=292) and allopurinol 300/100 mg QD (n=145). About 69 % of patients required no treatment change to achieve a final stable treatment. Patients who had 3 consecutive sUA levels >6.0 mg/dL were withdrawn.
Serum urate levels were maintained over time (i.e. 91% and 93% of patients on initial treatment with febuxostat 80 mg and 120 mg, respectively, had sUA <6 mg/dL at Month 36).

Three years data showed a decrease in the incidence of gout flares with less than 4% of patients requiring treatment for a flare (i.e. more than 96% of patients did not require treatment for a flare) at Month 16-24 and at Month 30-36.

46% and 38%, of patients on final stable treatment of febuxostat 80 or 120 mg QD, respectively, had complete resolution of the primary palpable tophus from baseline to the Final Visit.

FOCUS Study (TMX-01-005) was a 5 years Phase 2, open-label, multicenter, safety extension study for patients who had completed the febuxostat 4 weeks of double blind dosing in study TMX-00-004. 116 patients were enrolled and received initially febuxostat 80 mg QD. 62% of patients required no dose adjustment to maintain sUA <6 mg/dL and 38% of patients required a dose adjustment to achieve a final stable dose.

The proportion of patients with serum urate levels of <6.0 mg/dL (357 µmol/L) at the final visit was greater than 80% (81-100%) at each febuxostat dose.

During the phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0%). These rates were similar to the rates reported on allopurinol (4.2%) (see section 4.4). Increased TSH values (>5.5 µIU/mL) were observed in patients on long-term treatment with febuxostat (5.5%) and patients with allopurinol (5.8%) in the long term open label extension studies (see section 4.4).

*Tumor Lysis Syndrome*
The efficacy and safety of ADENURIC in the prevention and treatment of Tumor Lysis Syndrome was evaluated in the FLORENCE (FLO-01) study. ADENURIC showed a superior and faster urate lowering activity compared to allopurinol.
FLORENCE was a randomized (1:1), double blind, phase III, pivotal trial comparing ADENURIC 120 mg once daily with allopurinol 200 to 600 mg daily (mean allopurinol daily dose [± standard deviation]: 349.7 ± 112.90 mg) in terms of control of serum uric acid level. Eligible patients had to be candidates for allopurinol treatment or have no access to rasburicase. Primary endpoints were serum uric acid area under the curve (AUC $sUA_{1-8}$) and change in serum creatinine (sC) level both from baseline to Day 8.
Overall, 346 patients with haematological malignancies undergoing chemotherapy and at intermediate / high risk of Tumor Lysis Syndrome were included. Mean AUC $sUA_{1-8}$ (mgxh/dl) was significantly lower with ADENURIC (514.0 ± 225.71 vs 708.0 ± 234.42; least square means difference: -196.794 [95% confidence interval: -238.600 ; -154.988]; p < .0001). Furthermore, the mean serum uric acid level was significantly lower with ADENURIC since the first 24 hours of treatment and at any following time point. No significant difference in mean serum creatinine change (%) occurred between ADENURIC and allopurinol (-0.83 ± 26.98 vs -4.92 ± 16.70 respectively; least square means difference: 4.0970 [95% confidence interval: -0.6467 ; 8.8406]; p=0.0903). With regard to secondary endpoints, no significant difference was detected in terms of incidence of laboratory TLS (8.1% and 9.2% in ADENURIC and allopurinol arm, respectively; relative risk: 0.875 [95% confidence interval: 0.4408 ; 1.7369]; p=0.8488) nor of clinical TLS (1.7% and 1.2% in ADENURIC and allopurinol arm, respectively; relative risk: 0.994 [95% confidence interval: 0.9691 ; 1.0199]; p=1.0000). Incidence of overall treatment-emergent signs and symptoms and adverse drug reactions was 67.6% vs 64.7% and 6.4% vs 6.4% with ADENURIC and allopurinol respectively. In the FLORENCE study ADENURIC demonstrated a superior control of serum uric acid level compared to allopurinol in patients scheduled to receive the latter drug. No data comparing ADENURIC with rasburicase are currently available.
The efficacy and safety of febuxostat has not been established in patients with acute severe TLS, e.g. in patients who failed on other urate lowering therapies.

## 5.2 Pharmacokinetic properties

In healthy subjects, maximum plasma concentrations ($C_{max}$) and area under the plasma concentration time curve (AUC) of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. For doses between 120 mg and 300 mg, a greater than dose proportional increase in AUC is observed for febuxostat. There is no appreciable accumulation when doses of 10 mg to 240 mg are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours.

Population pharmacokinetic/pharmacodynamic analyses were conducted in 211 patients with hyperuricaemia and gout, treated with ADENURIC 40-240 mg QD. In general, febuxostat pharmacokinetic parameters estimated by these analyses are consistent with those obtained from healthy subjects, indicating that healthy subjects are representative for pharmacokinetic/pharmacodynamic assessment in the patient population with gout.

*Absorption*
Febuxostat is rapidly ($t_{max}$ of 1.0-1.5 h) and well absorbed (at least 84%). After single or multiple oral 80 and 120 mg once daily doses, $C_{max}$ is approximately 2.8-3.2 µg/mL, and 5.0-5.3 µg/mL, respectively. Absolute bioavailability of the febuxostat tablet formulation has not been studied.

Following multiple oral 80 mg once daily doses or a single 120 mg dose with a high fat meal, there was a 49% and 38% decrease in $C_{max}$ and a 18% and 16% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed where tested (80 mg multiple dose). Thus, ADENURIC may be taken without regard to food.

*Distribution*
The apparent steady state volume of distribution ($V_{ss}/F$) of febuxostat ranges from 29 to 75 L after oral doses of 10-300 mg. The plasma protein binding of febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 80 and 120 mg doses. Plasma protein binding of the active metabolites ranges from about 82% to 91%.

*Biotransformation*
Febuxostat is extensively metabolized by conjugation *via* uridine diphosphate glucuronosyltransferase (UDPGT) enzyme system and oxidation *via* the cytochrome P450 (CYP) system. Four pharmacologically active hydroxyl metabolites have been identified, of which three occur in plasma of humans. *In vitro* studies with human liver microsomes showed that those oxidative metabolites were formed primarily by CYP1A1, CYP1A2, CYP2C8 or CYP2C9 and febuxostat glucuronide was formed mainly by UGT 1A1, 1A8, and 1A9.

*Elimination*
Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of $^{14}C$-labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the active substance (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the faeces as the unchanged febuxostat (12%), the acyl glucuronide of the active substance (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).

*Renal impairment*
Following multiple doses of 80 mg of ADENURIC in patients with mild, moderate or severe renal impairment, the $C_{max}$ of febuxostat did not change, relative to subjects with normal renal function. The mean total AUC of febuxostat increased by approximately 1.8-fold from 7.5 µg.h/mL in the normal renal function group to 13.2 µg.h/mL in the severe renal dysfunction group. The $C_{max}$ and AUC of active metabolites increased up to 2- and 4-fold, respectively. However, no dose adjustment is necessary in patients with mild or moderate renal impairment.

*Hepatic impairment*
Following multiple doses of 80 mg of ADENURIC in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, the $C_{max}$ and AUC of febuxostat and its metabolites did not change significantly compared to subjects with normal hepatic function. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

*Age*
There were no significant changes observed in AUC of febuxostat or its metabolites following multiple oral doses of ADENURIC in elderly as compared to younger healthy subjects.

*Gender*
Following multiple oral doses of ADENURIC, the $C_{max}$ and AUC were 24% and 12% higher in females than in males, respectively. However, weight-corrected $C_{max}$ and AUC were similar between the genders. No dose adjustment is needed based on gender.

### 5.3 Preclinical safety data

Effects in non-clinical studies were generally observed at exposures in excess of the maximum human exposure.

*Carcinogenesis, mutagenesis, impairment of fertility*
In male rats, a statistically significant increase in urinary bladder tumours (transitional cell papilloma and carcinoma) was found only in association with xanthine calculi in the high dose group, at approximately 11 times human exposure. There was no significant increase in any other tumour type in either male or female mice or rats. These findings are considered a consequence of species specific purine metabolism and urine composition and of no relevance to clinical use.

A standard battery of test for genotoxicity did not reveal any biologically relevant genotoxic effects for febuxostat.

Febuxostat at oral doses up to 48 mg/kg/day was found to have no effect on fertility and reproductive performance of male and female rats.

There was no evidence of impaired fertility, teratogenic effects, or harm to the foetus due to febuxostat. There was high dose maternal toxicity accompanied by a reduction in weaning index and reduced development of offspring in rats at approximately 4.3 times human exposure. Teratology studies, performed in pregnant rats at approximately 4.3 times and pregnant rabbits at approximately 13 times human exposure did not reveal any teratogenic effects.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Tablet core*
Lactose monohydrate
Microcrystalline cellulose
Magnesium stearate
Hydroxypropylcellulose
Croscarmellose sodium
Silica, colloidal hydrated

*Tablet coating*
Opadry II, Yellow, 85F42129 containing:
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogols 3350
Talc
Iron oxide yellow (E172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Clear (Aclar/PVC/Aluminium) blister of 14 tablets.

ADENURIC 120 mg is available in pack sizes of 14, 28, 42, 56, 84 and 98 film-coated tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Menarini International Operations Luxembourg S.A.
1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/447/003
EU/1/08/447/004
EU/1/08/447/009
EU/1/08/447/010
EU/1/08/447/011
EU/1/08/447/012

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

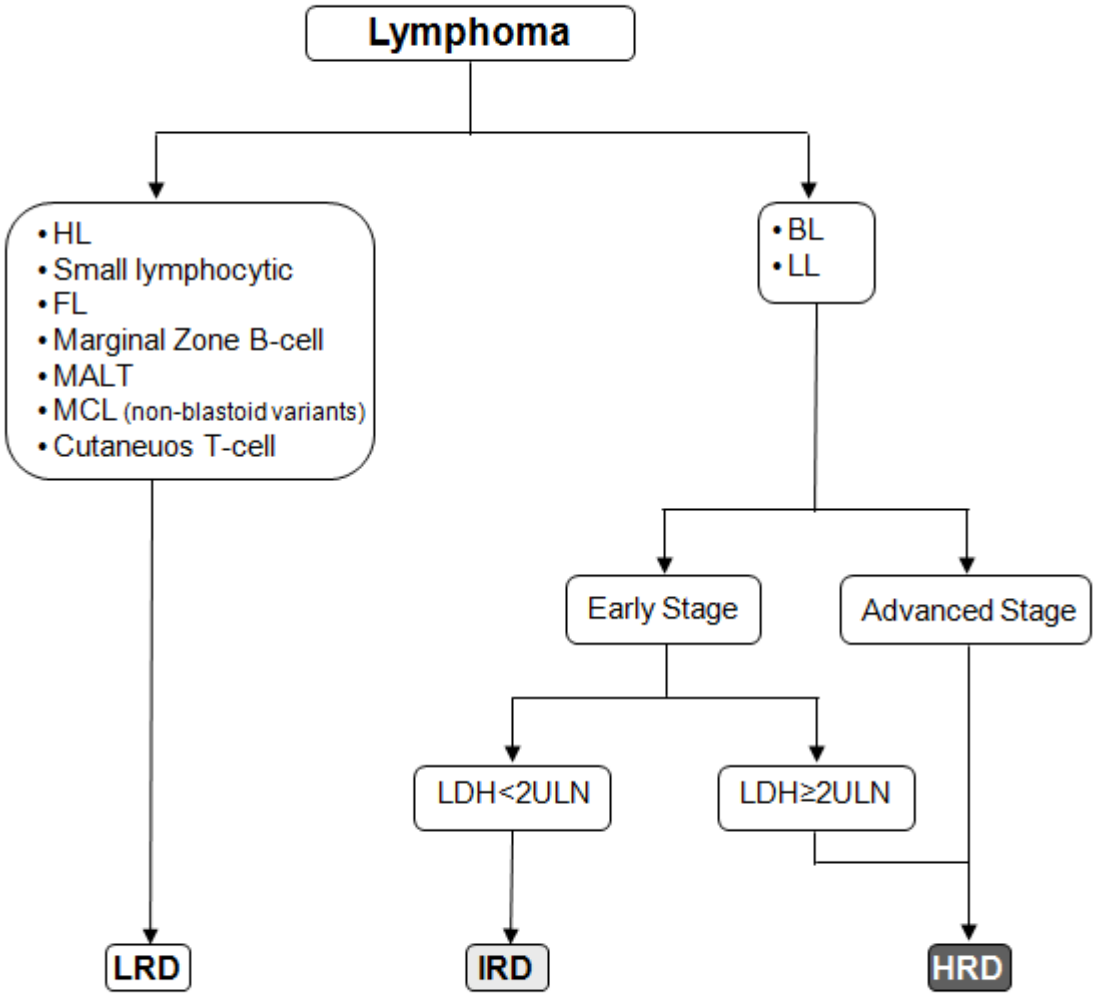
Date of first authorisation: 21 April 2008
Date of latest renewal: 20 December 2012

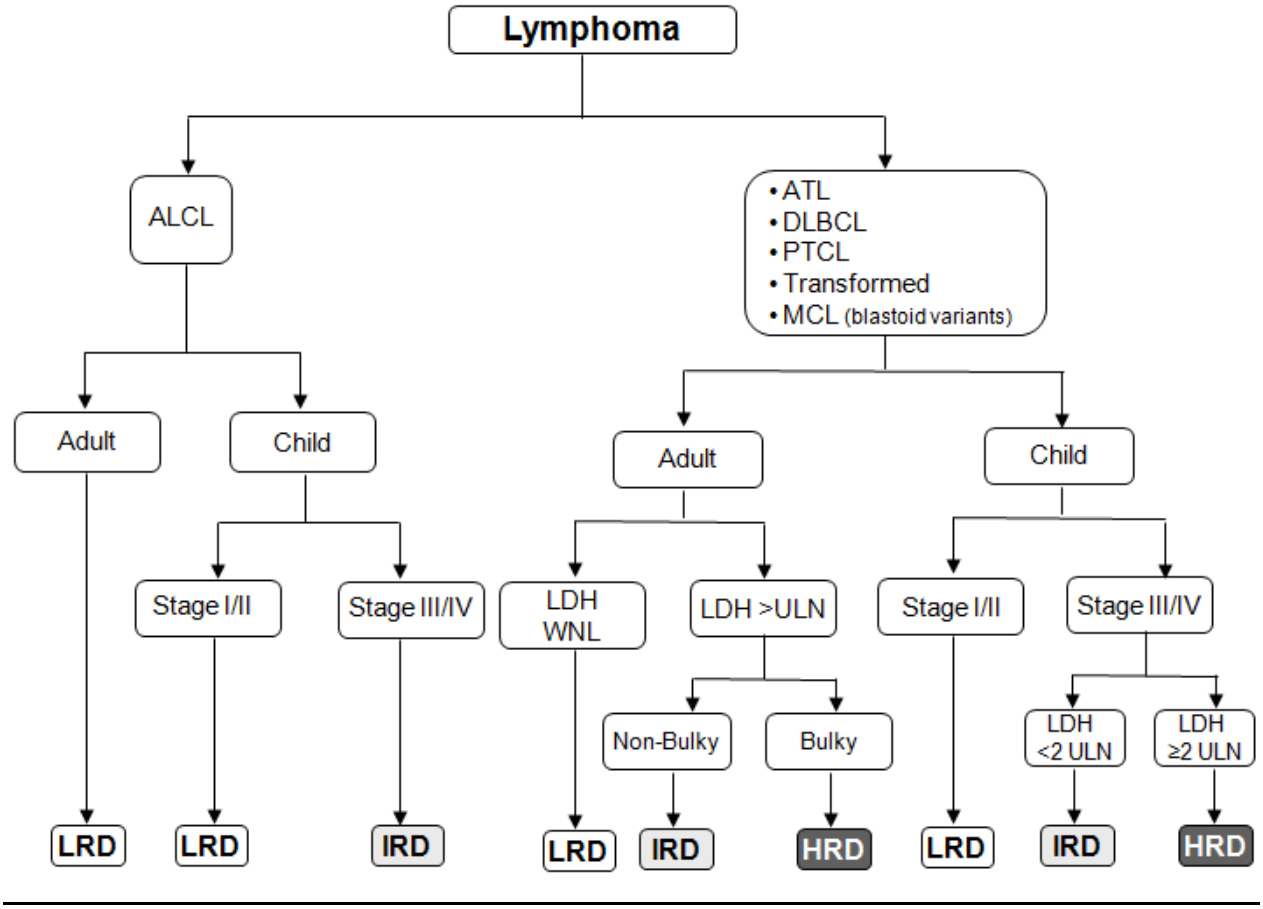
## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

## 13.3 APPENDIX III: TLS RISK ASSESSMENT

**PANEL A. MEDICAL DECISION TREE FOR LYMPHOMA**






**Important Note**

- Aggressive lymphoma according to 2008 WHO classification with Bulky disease (defined as one lymphnode/tumor > 10 cm in diameter) have to be considered IRD regardless of the LDH levels;
- Follicular large cell lymphoma (grade 3b) has to be considered as aggressive lymphoma according to 2008 WHO classification;
- Patients with LRD are intermediate-risk for TLS when renal dysfunction and/or renal involvement is present;
- Patients with IRD are high-risk for TLS when renal dysfunction and/or renal involvement is present OR when uric acid, phosphate and/or potassium levels are > ULN.

***Legend.*** *HL= Hodgkin lymphoma, FL= Follicular Lymphoma, MALT= Mucosa-Associated Lymphoid Tissue, MCL= Mantel Cell Lymphoma, BL= Burkitt Lymphoma/Leukaemia, LL= Lymphoblastic Lymphoma, ALCL= Anaplastic Large Cell Lymphoma, ATL= Adult T-cell Lymphoma, DLBCL= Diffuse Large B-Cell Lymphoma, PTCL= Peripheral T-cell Lymphoma, LDH= lactate dehydrogenase, ULN= Upper Limit of Normal, WNL= Within Normal Limit, LRD= Low Risk Disease, IRD= Intermediate Risk Disease, HRD= High Risk Disease.*

**PANEL B. MEDICAL DECISION TREE FOR LEUKEMIA**

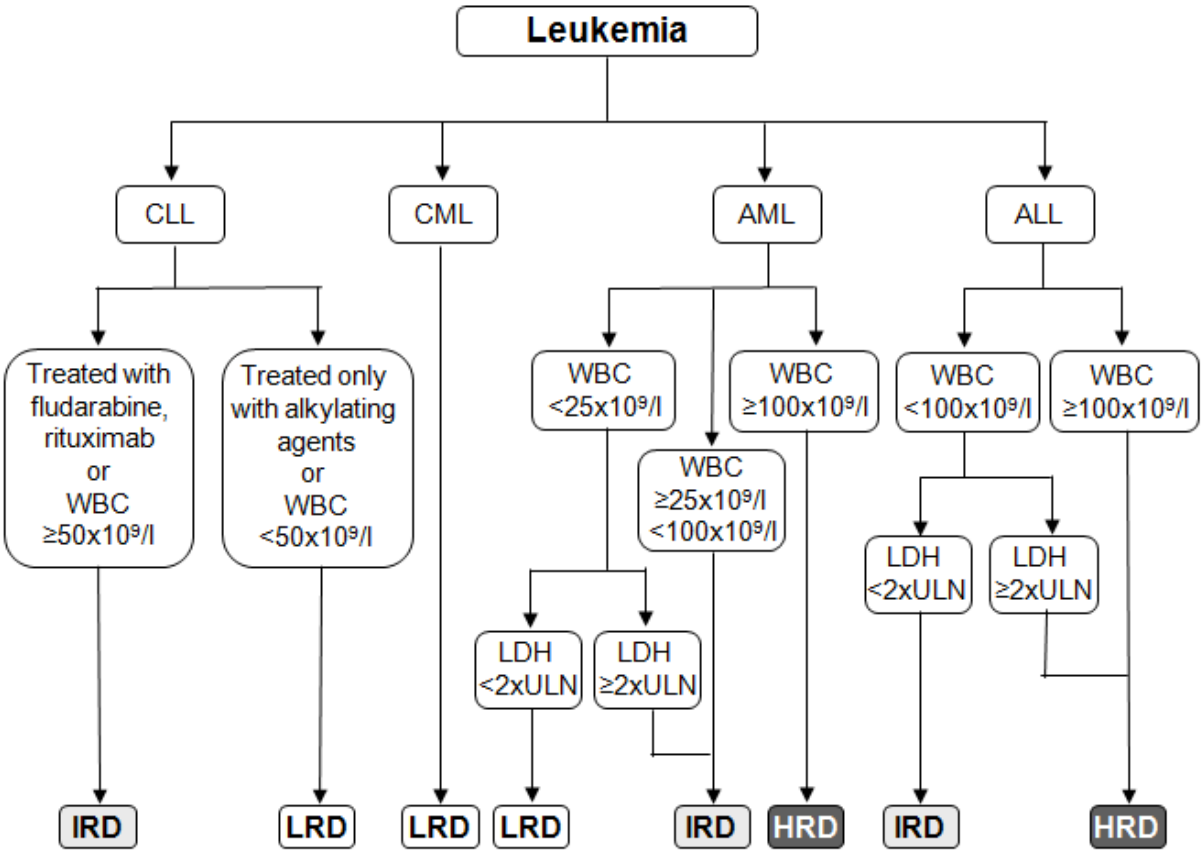



***Figure adapted from Cairo M, Coiffier B, Reiter A and Younes A on behalf of the TLS Expert Panel. British Journal of Haematology 2010 [4].***

**Important Note**

- Patients with LRD are intermediate-risk for TLS when renal dysfunction and/or renal involvement is present;
- Patients with IRD are high-risk for TLS when renal dysfunction and/or renal involvement is present OR when uric acid, phosphate and/or potassium levels are > ULN.

***Legend.*** *CLL= Chronic Lymphoid Leukaemia, CML= Chronic Myeloid Leukaemia, AML= Acute Myeloid Leukaemia, ALL= Acute Lymphoblastic Leukaemia, WBC= White Blood Count, LDH=Lactate Dehydrogenase, ULN= Upper Limit of Normal, LRD= Low Risk Disease, IRD= Intermediate Risk Disease, HRD= High Risk Disease.*

## 13.4 APPENDIX IV: KARNOFSKY AND LANSKY PLAY PERFORMANCE STATUS SCALES

The Karnofsky score runs from 100 to 10, where 100 is ”normal, no complaints, no evidence of disease” and 10 is “moribund, fatal process progressing rapidly”. For children aged from 6 to less than 16 years old the use of the Lansky Play performance scale is recommended as per guideline CIBMTR 2009 [34], where 100 is “fully active” and 10 is “completed disabled, not even passive play”.

| Karnofsky Scale (recipient age ≥ 16 years) | | Lansky Scale (recipient age <16 years) | |
|---|---|---|---|
| **Able to carry on normal activity; no special care is needed** | | **Able to carry on normal activity; no special care is needed** | |
| **100** | Normal, no complaints, no evidence of disease | **100** | Fully active |
| **90** | Able to carry on normal activity | **90** | Minor restriction in physically strenuous play |
| **80** | Normal activity with effort | **80** | Restricted in strenuous play, tires more easily, otherwise active |
| **Unable to work, able to live at home cares for most personal needs, a varying amount of assistance is needed** | | **Mild to moderate restriction** | |
| **70** | Cares for self, unable to carry on normal activity or to do active work | **70** | Both greater restrictions of, and less time spent in active play |
| **60** | Requires occasional assistance but is able to care for most needs | **60** | Ambulatory up to 50% of time, limited active play with assistance/supervision |
| **50** | Requires considerable assistance and frequent medical care | **50** | Considerable assistance required for any active play, fully able to engage in quiet play |
| **Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly** | | **Moderate to severe restriction** | |
| **40** | Disabled, requires special care and assistance | **40** | Able to initiate quite activities |
| **30** | Severely disabled, hospitalization indicated, although death not imminent | **30** | Needs considerable assistance for quiet activity |
| **20** | Very sick, hospitalization necessary | **20** | Limited to very passive activity initiated by others (e.g., TV) |
| **10** | Moribund, fatal process progressing rapidly | **10** | Completely disabled, not even passive play |

## 13.5 APPENDIX V: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) VERSION 4.0. PUBLISHED: MAY 28, 2009 (V 4.03: JUNE 14, 2010). U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES – NATIONAL INSTITUTE OF HEALTH – NATIONAL CANCER INSTITUTE

## 14. REFERENCES

1. U.S. Department of Health and Human Services, F.a.D.A., Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), *Guidance for Industry, E11 Clinical Investigation of Medicinal Products in the Pediatric Population.* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073143.pdf, December 2000.
2. Brown P, H.S., *"Acute Leukemia in children", excerpt from Conn's Current Therapy* 2009: p. 450-456.
3. Coiffier, B., et al., *Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review.* J Clin Oncol, 2008. **26**(16): p. 2767-78.
4. Cairo, M.S., et al., *Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus.* Br J Haematol, 2010. **149**(4): p. 578-86.
5. Cairo, M.S. and M. Bishop, *Tumour lysis syndrome: new therapeutic strategies and classification.* Br J Haematol, 2004. **127**(1): p. 3-11.
6. Cheng, M.H., et al., *Microchemical analysis for 13 constituents of plasma from healthy children.* Clin Chem, 1979. **25**(5): p. 692-8.
7. Gomez, P., et al., *Normal reference-intervals for 20 biochemical variables in healthy infants, children, and adolescents.* Clin Chem, 1984. **30**(3): p. 407-12.
8. EMA, *Commission Implementing Decision of 8.4.2015 amending the marketing authorisation granted by Decision C(2008)1648 for "Adenuric - febuxostat", a medicinal product for human use.* http://ec.europa.eu/health/documents/community-register/html/h447.htm, 2015.
9. Truong, T.H., et al., *Features at presentation predict children with acute lymphoblastic leukemia at low risk for tumor lysis syndrome.* Cancer, 2007. **110**(8): p. 1832-9.
10. Howard, S.C., D.P. Jones, and C.H. Pui, *The tumor lysis syndrome.* N Engl J Med, 2011. **364**(19): p. 1844-54.
11. Wossmann, W., et al., *Incidence of tumor lysis syndrome in children with advanced stage Burkitt's lymphoma/leukemia before and after introduction of prophylactic use of urate oxidase.* Ann Hematol, 2003. **82**(3): p. 160-5.
12. Annemans, L., et al., *Incidence, medical resource utilisation and costs of hyperuricemia and tumour lysis syndrome in patients with acute leukaemia and non-Hodgkin's lymphoma in four European countries.* Leuk Lymphoma, 2003. **44**(1): p. 77-83.
13. Montesinos, P., et al., *Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model.* Haematologica, 2008. **93**(1): p. 67-74.

14. Mayer, M.D., et al., *Pharmacokinetics and pharmacodynamics of febuxostat, a new non-purine selective inhibitor of xanthine oxidase in subjects with renal impairment.* Am J Ther, 2005. **12**(1): p. 22-34.
15. Osada, Y., et al., *Hypouricemic effect of the novel xanthine oxidase inhibitor, TEI-6720, in rodents.* Eur J Pharmacol, 1993. **241**(2-3): p. 183-8.
16. Komoriya, K., et al., *Hypouricemic effect of allopurinol and the novel xanthine oxidase inhibitor TEI-6720 in chimpanzees.* Eur J Pharmacol, 1993. **250**(3): p. 455-60.
17. EMA, *European Medicines Agency decision, P/0117/2014.* http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500167974.pdf, 2014.
18. Horiuchi, H., et al., *A comparative study on the hypouricemic activity and potency in renal xanthine calculus formation of two xanthine oxidase/xanthine dehydrogenase inhibitors: TEI-6720 and allopurinol in rats.* Res Commun Mol Pathol Pharmacol, 1999. **104**(3): p. 307-19.
19. Hitchings, G.H., *Effects of allopurinol in relation to purine biosynthesis.* Ann Rheum Dis, 1966. **25**(6 Suppl): p. 601-7.
20. Becker, M.A., et al., *Febuxostat (TMX-67), a novel, non-purine, selective inhibitor of xanthine oxidase, is safe and decreases serum urate in healthy volunteers.* Nucleosides Nucleotides Nucleic Acids, 2004. **23**(8-9): p. 1111-6.
21. Khosravan, R., et al., *Effect of food or antacid on pharmacokinetics and pharmacodynamics of febuxostat in healthy subjects.* Br J Clin Pharmacol, 2008. **65**(3): p. 355-63.
22. Khosravan, R., et al., *The effect of age and gender on pharmacokinetics, pharmacodynamics, and safety of febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase.* J Clin Pharmacol, 2008. **48**(9): p. 1014-24.
23. Becker, M.A., et al., *Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout.* Arthritis Rheum, 2005. **52**(3): p. 916-23.
24. Becker, M.A., et al., *Febuxostat compared with allopurinol in patients with hyperuricemia and gout.* N Engl J Med, 2005. **353**(23): p. 2450-61.
25. Schumacher, H.R., Jr., et al., *Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial.* Arthritis Rheum, 2008. **59**(11): p. 1540-8.
26. Becker, M.A., et al., *Clinical efficacy and safety of successful longterm urate lowering with febuxostat or allopurinol in subjects with gout.* J Rheumatol, 2009. **36**(6): p. 1273-82.

27. Becker, M.A., et al., *The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial.* Arthritis Res Ther, 2010. **12**(2): p. R63.
28. Schumacher, H.R., Jr., et al., *Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study.* Rheumatology (Oxford), 2009. **48**(2): p. 188-94.
29. Hair, P.I., P.L. McCormack, and G.M. Keating, *Febuxostat.* Drugs, 2008. **68**(13): p. 1865-74.

[redacted]

31. *PERIODIC SAFETY UPDATE REPORT for ACTIVE SUBSTANCE: febuxostat.* 2015. **13**.
32. S.A., M.I.O.L., *Febuxostat Pediatric Investigation Plan no: EMEA-001417-PIP01-12.* 2013.
33. (CHMP), C.f.M.P.f.H.u., *GUIDELINE ON THE ROLE OF PHARMACOKINETICS IN THE DEVELOPMENT OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION.* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003066.pdf, 2006.
34. CIBMTR, *Appendix L_Karnofsky/Lansky Play Performance Status.* National Marrow Donor Program and The medical College of Wisconsin, 2009. **A00428 revision 1**.
35. Lansky, S.B., et al., *The measurement of performance in childhood cancer patients.* Cancer, 1987. **60**(7): p. 1651-6.
36. Schag, C.C., R.L. Heinrich, and P.A. Ganz, *Karnofsky performance status revisited: reliability, validity, and guidelines.* J Clin Oncol, 1984. **2**(3): p. 187-93.
37. JH., K.D.B., *The Clinical Evaluation of Chemotherapeutic Agents in Cancer.* 1949. **MacLeod CM (Ed), Evaluation of Chemotherapeutic Agents**(Columbia Univ Press): p. 196.
38. EMA, *CPMP, Note for guidance on evaluation of anticancer medicinal products in man.* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003969.pdf, 2003.

39. EMA, *Guideline on pharmaceutical development of medicines for pediatric use.* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf, 2013.
40. Guinard, J.-X., *Sensory and consumer testing with children.* Trends in Food Science & Technology, 2001. **11**: p. 273–283.

[redacted]

MENARINI
RICERCHE

# OPEN LABEL, MULTI-CENTRE, PARALLEL GROUP STUDY TO COMPARE THE PHARMACOKINETICS (PK), PHARMACODYNAMICS (PD) AND SAFETY OF FEBUXOSTAT BETWEEN PEDIATRIC PATIENTS (≥6<18 YEARS OF AGE) AND ADULTS

| | |
|---|---|
| **Protocol Version(s)** | Final Version 1.0 dated 12 Apr 2016 |
| **Previous Amendment(s)** | Not applicable |
| **Study code** | FLO-02 |
| **Study Nick Name** | FLORET |
| **EudraCT-Number** | 2016-001445-61 |
| **Investigational Medicinal Product** | FEBUXOSTAT |

The contents of this **Non-Substantial Amendment No. 1 dated 02 Feb 2017** refers to changes made to the **Clinical Trial Protocol Final Version 1.0 dated 12 Apr 2016.**

Notification of this Non-Substantial Amendment No. 1 will be done through the Competent Authorities, Ethical Committees, and Investigators involved in the study as appropriate.

## 1. Reasons for the Amendment

The content of this Non-Substantial amendment refers to the modification on which blood specimen safety tests could be done (i.e. plasma or serum).

As the safety tests will be performed by each local laboratory to ensure prompt patient's management, blood analysis will be done according to each local standard practice based on each available validated analytical methods.

Such changes do not have any impact on the patient's safety evaluation as well as also in the evaluation of patient's protocol eligibility (i.e. inclusion criterion 1c: uric acid level <10 mg/dL at Visit 1). In particular, the uric acid analysis can be done in both specimen (plasma or serum) and the reference normal ranges are the same (Clinical Chemistry, Lawrence A. Laplan, Amadeo J. Pesce, Mosby, 1996 : p 501-502; Miles RR., et al. *Comparison of serum and heparinized plasma samples for measurement of chemistry* analytes., Clin Chem. 2004 Sep;50(9):1704-6.)

Moreover, Menarini Ricerche S.p.A. Clinical Research Organization and study team name/title have been updated as well as typos corrected.

## 2. Protocol changes in detail

*Report specific changes for relevant protocol section (including paragraph number and pages), additions should be highlighted as underlined, whereas deletions as ~~strike-out~~, reporting whenever possible the full affected changes. Alternatively, the tracked changes can be strictly limited to the affected lines.*

### ▪ Amendment to Protocol Cover:

Current version (page 1):

...

| SPONSOR | CO-ORDINATING INVESTIGATOR | CRO |
|---|---|---|
| Menarini Ricerche S.p.A.<br>Clinical ~~Researeh~~ Sciences<br>Via Sette Santi, 1<br>50131 Florence - Italy<br>Phone: +39 05556809990<br>[redacted] | [redacted] | [redacted] |

...

### ▪ Amendment to Protocol Section 2:

Current version (page 4/18):

**Section 2 Protocol Synopsis Inclusion Criteria (page 5-6), is amended as described below:**

*Patients meeting ALL the following criteria will be eligible to enter the study:*

1. male and female children of 6 to less than 12 years of age, adolescents of 12 to less than 18 years of age, and adults:
    a. scheduled for first cytotoxic chemotherapy cycle, regardless of the line of treatment, because of hematologic malignancies, and
    b. at intermediate or high risk for TLS, and
    c. with ~~serum~~ uric acid (sUA) levels < 10 mg/dL at Visit 1 (Day 1), and
    d. with no access to rasburicase;

***NOTE:***

Evaluation of uric acid could be done both in serum or plasma specimen based on local laboratory standard practices.

**Section 2 Protocol Synopsis Study procedures and PK/PD, Clinical and Safety assessments, (page 11-12), is amended as described below:**

***NOTE:***

**Blood safety laboratory tests** will be performed at the Local Laboratory and will include:
albumin, alkaline phosphatase, amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN)/urea, ~~serum~~ creatinine, ~~serum~~ uric acid (sUA), sodium, chloride, potassium, phosphorus, calcium, total bilirubin, direct bilirubin, gamma-glutamyl transpeptidase (GGT), glucose, lactate dehydrogenase (LDH), total proteins, prothrombin time/prothrombin activity, international normalized ratio (INR), platelets, red blood cells (RBC), hemoglobin, hematocrit and white blood cells (WBC) with differential count (absolute and %), and beta human chorionic gonadotropin (β-HCG) if applicable.

## ▪ Amendment to Protocol Section 3:

Current version (pages 19/21):

**Section 3 INVESTIGATOR(S) AND STUDY ADMINISTRATIVE STRUCTURE (page 19-21), is amended as described below:**

| | |
|---|---|
| **Sponsor** | **Menarini Ricerche S.p.A.**<br>**Clinical ~~Research~~ Sciences**<br>**Via Sette Santi, 1**<br>**50131 Florence, Italy** |
| Corporate Director of Clinical ~~Research~~ Sciences/Sponsor's Representative | [redacted] |
| ~~Head of Corporate Therapeutic Areas Oncology, Immunology & Antinfective~~ | [redacted] |

| | |
|---|---|
| Oncology & Immunology Corporate Director | [redacted] |
| Clinical Research Physician | [redacted] |
| Study Manager | [redacted] |
| Head of Corporate Biostatistic and Data Management | [redacted] |
| Biostatistician | [redacted] |
| Data Manager | [redacted] |
| ~~Senior Corporate Pharmacokineticist~~<br>Head of Corporate Clinical Pharmacology and Pharmacometrics | [redacted] |

## ▪ Amendment to Protocol Section 4:

Current version (pages 22/27):

**Section 4.1 GLOSSARY (page 25-27), is amended as described below:**

…

| | |
|---|---|
| CL | Clearance |
| ~~CLcr~~ | ~~Creatinine Clearance~~ |
| CL/F | Apparent clearance |

…..

| | |
|---|---|
| [redacted] | |
| ~~sC~~ | ~~serum Creatinine~~ |
| SD | Standard Deviation |

## ▪ Amendment to Protocol Section 6:

Current version (page 36/43):

**Section 6.1 Disease and Study Rationale, (pages 36-38), is amended as described below:**

…

According to Coiffier *et al.* [3], the risk of developing TLS, or more simply the risk of developing acute renal impairment, is significantly increased in patients with higher levels of uric acid *versus* those with lower levels. For every mg/dL increase in sUA, the risk of TLS raises by a factor 1.75 ($p$<0.0001), while the risk of renal events by a factor 2.21 ($p$=0.0012). This observation underlines the importance of preventing/containing the uric acid increase during chemotherapy.

...

2) Diagnosis: Laboratory TLS (LTLS) is diagnosed if levels of 2 or more ~~serum~~ values of uric acid, potassium, phosphate or calcium are more or less than normal at presentation, or if they change by at least 25% from baseline (see **Errore. L'origine riferimento non è stata trovata.**). The only significant difference between adults and children is the threshold of phosphate, which is higher in children in an age-dependent way [5-7].

## ▪ Amendment to Protocol Section 8:

Current version (page 45/72):

**Section 8.3.1 Inclusion Criteria (page 48-49), is amended as described below:**

[redacted]

[redacted] male and female children of 6 to less than 12 years of age, adolescents of 12 to less than 18 years of age and adults from 18 years:

a. scheduled for first cytotoxic chemotherapy cycle, regardless of the line of treatment, because of hematologic malignancies, and
b. at intermediate or high risk of TLS [4], and
c. with ~~serum~~ uric acid (sUA) levels < 10 mg/dL at Visit 1 (Day 1), and
d. with no access to rasburicase;

***NOTE:***

Evaluation of uric acid could be done both in serum or plasma specimen based on local laboratory standard practices.

**Section 8.6.3.3 Safety Laboratory Evaluation (page 62-63), is amended as described below:**

....

**Table 3: ~~Serum,~~ Blood and Urine Sample Analyte Listing**

| ~~SERUM~~ BIOCHEMISTRY | HEMATOLOGY | URINALYSIS |
|---|---|---|
| Creatinine<br>sUA<br>Potassium | Haemoglobin<br>Haematocrit<br>RBC count | pH<br>Density |

**Table 3: ~~Serum,~~ Blood and Urine Sample Analyte Listing**

| ~~SERUM~~ BIOCHEMISTRY | HEMATOLOGY | URINALYSIS |
|---|---|---|
| Phosphorus<br>Calcium<br><br>BUN / Urea<br>Albumin<br>Alkaline phosphatase<br>Amylase<br>Glucose<br>Total protein<br>Total bilirubin and Direct bilirubin<br>ALT and AST<br>LDH<br>GGT<br>INR<br>prothrombin time/prothrombin activity<br>Sodium<br>Chloride<br>Beta-HCG (ONLY at Screening if applicable) | Platelet count<br>WBC count and (absolute and %):<br>neutrophil<br>lymphocyte<br>eosinophil<br>basophil<br>monocytes | <br>Nitrite<br><br>Protein<br>Glucose<br>Ketones<br>RBC<br>WBC<br>Epithelial cells<br>Casts<br>Bacteria<br>Yeast<br>Crystals |
| ~~ESTIMATED PARAMETERS~~ | | |
| ~~CLcr calculation according to Cockcroft and Gault formula~~ | | |

## ▪ Amendment to Protocol Section 9:

Current version (page 73/79):

**Section 9.3.4 Clinical endpoints. Incidence of LTLS and CTLS (page 77), is amended as described below:**

- ***Clinical endpoints: Incidence of LTLS and CTLS***
  - The assessment for LTLS from Start of Chemotherapy (Visit 3, Day 3) to the Evaluation Visit (Visit 8, Day 8) will be defined as:

    1: PRESENCE — 2 or more laboratory abnormalities including: a 25% increase or levels above normal for ~~serum~~ uric acid, potassium, and phosphate or a 25% decrease or levels below normal for calcium.

    0: ABSENCE — less than 2 laboratory abnormalities including: a 25% increase or levels above normal for ~~serum~~ uric acid, potassium, and phosphate or a 25% decrease or levels below normal for calcium.

## ▪ Amendment to Protocol Section 13:

Current version (page 86/120):

**Section 13.1 Appendix I: Definition of LTLS and CTLS (page 86), is amended as described below:**

| **Diagnosis of LTLS:** LTLS is diagnosed if levels of 2 or more ~~serum~~ values of uric acid, potassium, phosphate or calcium are more than or less than normal at presentation or if they change by at least 25% from baseline. | | |
|---|---|---|
| **ELEMENT** | **VALUE** | **CHANGE FROM BASELINE** |
| Uric Acid | ≥ 476 µmol/L (or 8 mg/dL) | 25% increase |
| Potassium | ≥ 6.0 mmol/L | 25% increase |
| Phosphorus | ≥ 1.45 mmol/L (adults) or ≥ 2.1mmol/L (children) | 25% increase |
| Calcium | ≤ 1.75 mmol/L | 25% decrease |

For adolescents and adults, the values of phosphorus will be considered the same for the diagnosis of LTLS.

**SIGNATURES**

The signatories have read the clinical trial protocol amendment No. *1* dated *02 Feb 2017* to the clinical trial protocol titled ***"Open label, multi-centre, parallel group study to compare the pharmacokinetics (PK), pharmacodynamics (PD) and safety of febuxostat between pediatric patients (≥6<18 years of age) and adults"*** - Final Version *1.0*, dated *12 Apr 2016* - carefully and agree to adhere to its provisions.

**SPONSOR's Representative** **Signature** **Date**

[redacted]

**Co-ordinating Investigator**

[redacted]

## PRINCIPAL INVESTIGATOR'S STATEMENT

a) Clinical Statement

My signature below documents my agreement with the contents of this clinical trial protocol amendment No. ***1*** dated ***02 Feb 2017*** to the clinical trial protocol titled ***"Open label, multi-centre, parallel group study to compare the pharmacokinetics (PK), pharmacodynamics (PD) and safety of febuxostat between pediatric patients (≥6<18 years of age) and adults"*** - Final Version ***1.0,*** dated ***12 Apr 2016*** - with regard to the execution of the study and the required documentation/data collection. I agree to comply with this clinical trial protocol amendment in its entirety and with the ICH guidelines for Good Clinical Practice (GCP).

b) Anti-Corruption Statement

I agree to - I will and I will cause any of my collaborators to - perform any activity in accordance with the principles of any international anti-corruption legislations, such as OECD Convention on Combating Bribery of Foreign Public Officials in International Business Transactions, UK Bribery Act and US Foreign Corrupt Practices Act, including Italian Legislative Decree 231/2001. In particular, along the performance of the study, I will not - and I will cause any of my collaborators not to - directly or indirectly offer, pay, give, or promise to pay or give or receive any payment or gift of any money or thing of value to or from any government officer to influence any acts or decisions or to induce such officer to use its influence to effect or influence the decision of the relevant government body or any other decision maker. I accept to promptly inform the Sponsor in writing in case of violations of or deviations from any of the above prescriptions in the conduct of the study and I acknowledge and accept Sponsor's rights to conduct audits in order to verify compliance with the above during or in connection with the performance of the study. I agree and accept that a violation of any of the above prescriptions may result in the termination of the research activities of the site I work in and/or the entire study.

| **Principal Investigator** | **Signature** | **Date** |
|---|---|---|
| ..... | ..... | ..... |
| **(printed name)** | | |

MENARINI
RICERCHE

# OPEN LABEL, MULTI-CENTRE, PARALLEL GROUP STUDY TO COMPARE THE PHARMACOKINETICS (PK), PHARMACODYNAMICS (PD) AND SAFETY OF FEBUXOSTAT BETWEEN PEDIATRIC PATIENTS (≥6<18 YEARS OF AGE) AND ADULTS

| | |
|---|---|
| **Protocol Version(s)** | Final Version 1.0 dated 12 Apr 2016 |
| **Amendment** | Protocol Amendment No. 2, dated 03 Feb 2017 |
| **Previous Amendment(s)** | Protocol Amendment No. 1, dated 02 Feb 2017 |
| **Study code** | FLO-02 |
| **Study Nick Name** | FLORET |
| **EudraCT-Number** | 2016-001445-61 |
| **Investigational Medicinal Product** | FEBUXOSTAT |

The contents of this **Substantial Amendment No. 2 dated 03 Feb 2017** refers to changes made to the **Clinical Trial Protocol Final Version 1.0 dated 12 Apr 2016 and Amendment No. 1 dated 02 Feb 2017.**

Submission for approval of this Amendment No. 2 will be processed through the Competent Authority, Ethical Committees, and Investigators involved in the study in Hungary.

## 1. Reasons for the Amendment

Glomerular Filtration Rate (GFR) is usually accepted as the best overall index of kidney function. In clinical practice kidney function is evaluated by measuring the estimated Glomerular Filtration Rate (eGFR) or Creatinine Clearance.
According to the [1]international guidelines published in 2012 by KDIGO (Kidney Disease: Improving Global Outcomes) severe renal insufficiency (grade 4) corresponds to creatinine clearance <30 mL/min. For adult patients this classification is considered as the most appropriate and is the same category considered for the use of Febuxostat as reported in its SmPC.

For the pediatric population a more conservative approach is commonly applied, and it considers the corrected creatinine clearance with the cut off <60 mL/min/1.73 $m^2$ as the indicator of kidney damage.

As requested by the Hungarian National Institute of Pharmacy and Nutrition Agency, the exclusion of adult and paediatric patients with severe renal function will be based on the cut off of the clearance creatinine < 30 mL/min and < 60 mL/min/1.73 $m^2$, respectively. Therefore, the criteria relative to kidney function making the patients eligible to take part to the study as well as for treatment withdrawal because of severe renal failure will be accordingly specified along the protocol.

[1]Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1–150.; 2ADENURIC® SmPC, Appendix II:EU SmPCs for Adenuric®.

## 2. Protocol changes in detail

*Report specific changes for relevant protocol section (including paragraph number and pages), additions should be highlighted as underlined, whereas deletions as ~~strike-out~~, reporting whenever possible the full affected changes. Alternatively, the tracked changes can be strictly limited to the affected lines.*

### ▪ Amendment to Protocol Section 2 and Section 8:

Current version (page 4/18 and 45/72):

**Section 2 Protocol Synopsis Exclusion Criteria (page 7) and Section 8.3.2 Exclusion Criteria (page 49) is amended as described below:**

…

- patients with severe renal insufficiency~~:~~, as defined below calculated based on local clinical practice:

- adult patients with a clearance creatinine < 30 mL/min;
- pediatric patients with eGFR <60 mL/min/1.73 $m^2$.

…

**Section 8.3.3 Withdrawal of patients from therapy or assessment (page 49/50) is amended as described below:**

....

Patients should not receive further study medication and will be withdrawn from the study (study termination) in case of medical emergency or necessity including but not limited to:

- adverse events with a possible, probable or certain drug-causality as per Investigator's judgment of severity grade ≥3 CTCAE version 4.03;
- appearance of skin rash or of any signs which may indicate allergic/hypersensitivity reactions (***NOTE***: in case of severe allergic/hypersensitivity reactions, febuxostat must not be re-started in patients at any time; for guidance please refer to the EU SmPC, Appendix II:TLS Risk Assesment);
- severe hepatic insufficiency;
- severe renal insufficiency;
  ***NOTE***: renal insufficiency defined as below:
  - adult patients with a clearance creatinine < 30 mL/min;
  - pediatric patients with eGFR <60 mL/min/1.73 $m^2$.

.....

## SIGNATURES

The signatories have read the clinical trial protocol amendment No. *2* dated **03 Feb 2017** to the clinical trial protocol titled ***"Open label, multi-centre, parallel group study to compare the pharmacokinetics (PK), pharmacodynamics (PD) and safety of febuxostat between pediatric patients (≥6<18 years of age) and adults"*** - Final Version *1.0,* dated *12 Apr 2016* - carefully and agree to adhere to its provisions.

| **SPONSOR's Representative** | **Signature** | **Date** |
|---|---|---|
| [redacted] | | |

**Co-ordinating Investigator**

[redacted]

## PRINCIPAL INVESTIGATOR'S STATEMENT

a) Clinical Statement

My signature below documents my agreement with the contents of this clinical trial protocol amendment No. ***2*** dated 03 Feb 2017 to the clinical trial protocol titled ***"Open label, multi-centre, parallel group study to compare the pharmacokinetics (PK), pharmacodynamics (PD) and safety of febuxostat between pediatric patients (≥6<18 years of age) and adults"*** - Final Version ***1.0,*** dated ***12 Apr 2016*** - with regard to the execution of the study and the required documentation/data collection. I agree to comply with this clinical trial protocol amendment in its entirety and with the ICH guidelines for Good Clinical Practice (GCP).

b) Anti-Corruption Statement

I agree to - I will and I will cause any of my collaborators to - perform any activity in accordance with the principles of any international anti-corruption legislations, such as OECD Convention on Combating Bribery of Foreign Public Officials in International Business Transactions, UK Bribery Act and US Foreign Corrupt Practices Act, including Italian Legislative Decree 231/2001. In particular, along the performance of the study, I will not - and I will cause any of my collaborators not to - directly or indirectly offer, pay, give, or promise to pay or give or receive any payment or gift of any money or thing of value to or from any government officer to influence any acts or decisions or to induce such officer to use its influence to effect or influence the decision of the relevant government body or any other decision maker. I accept to promptly inform the Sponsor in writing in case of violations of or deviations from any of the above prescriptions in the conduct of the study and I acknowledge and accept Sponsor's rights to conduct audits in order to verify compliance with the above during or in connection with the performance of the study. I agree and accept that a violation of any of the above prescriptions may result in the termination of the research activities of the site I work in and/or the entire study.

| **Principal Investigator** | **Signature** | **Date** |
|---|---|---|
| ..... | ..... | ..... |
| **(printed name)** | | |