26 February 2015
EMA/CHMP/176388/2015 – corr.2
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Adenuric

International non-proprietary name: febuxostat

Procedure No. EMEA/H/C/000777/II/0037

Marketing authorisation holder (MAH): Menarini International Operations Luxembourg S.A.

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC	Area Under Curve
BDRM	Blind Data Review Meeting
b.i.d.	bis in die (twice daily)
BP	Blood Pressure
BR	Breath Rate
BUN	Blood Urea Nitrogen
CA	Competent Authority
CDSU	Central Drug Safety Unit
CI	Confidence interval
CHF	Congestive Heart Failure
CLcr	Creatinine Clearance
cp	capsule
CRF	Case Report Form
CRO	Contract Research Organization
CTLS	Clinical Tumor Lysis Syndrome
DSM	Drug Safety Manager
DSUR	Development Safety Update Report
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
HM	Haematologic malignancy
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-treat

IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LLT	Lowest Level Term
LOCF	Last observation carry forward
LTLS	Laboratory Tumor Lysis Syndrome
NSADR	Non-serious Adverse Drug Reaction
N	Non-serious Adverse Event
PK	Pharmacokinetics
PP	Per-protocol
PR	Pulse rate
PS	Performance Status
PT	Preferred Term
QA	Quality Assurance
q.d.	quaque die (every day)
RBC	Red Blood Cell
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Commitee
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
ß-HCG	Human Chorionic Gonadotropine
sUA	serum Uric Acid
SUSAR	Suspected Unexpected Serious Adverse Reaction
BT	Body Temperature
TESS	Treatment Emergent Sign and Symptoms
TLS	Tumor Lysis Syndrome
TMF	Trial Master File
UA	Uric Acid
ULN	Upper Limit of Normal
WBC	White Blood Cell
XO	Xanthine Oxidase

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Menarini International Operations Luxembourg S.A. submitted to the European Medicines Agency on 7 August 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product: **For presentations: See Annex A**	**International non-proprietary name**
Adenuric	febuxostat

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

The Marketing authorisation holder applied for new indication for prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS). Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC. The Package Leaflet was proposed to be updated in accordance.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0117/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0117/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Additional data protection / marketing exclusivity

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 23 June 2011. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Andrea Laslop Co-Rapporteur: N/A

PRAC Rapporteur: Jan Neuhauser

Timetable	Actual dates
Submission date	7 August 2014
Start of procedure:	22 August 2014
Rapporteur's preliminary assessment report circulated on:	17 October 2014
PRAC Rapporteur's preliminary assessment report circulated on:	20 October 2014
PRAC Rapporteur's updated assessment report circulated on:	29 October 2014
PRAC RMP advice and assessment overview adopted by PRAC:	6 November 2014
Rapporteur's revised assessment report circulated on:	14 November 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 November 2014
MAH's responses submitted to the CHMP on:	19 December 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	27 January 2015
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	27 January 2015
PRAC Rapporteur's updated assessment report on the MAH's responses circulated on:	4 February 2015
PRAC RMP advice and assessment overview adopted by PRAC:	12 February 2015
Rapporteur's revised assessment report on the MAH's responses circulated on:	20 February 2015
CHMP opinion:	26 February 2015
The CHMP adopted a report on the significant clinical benefit for Adenuric in comparison with existing therapies on:	26 February 2015

2. Scientific discussion

2.1. Introduction

Adenuric (febuxostat) is a potent, non-purine selective inhibitor of xanthine oxidase that inhibits the formation of uric acid from xanthine. The active ingredient in febuxostat immediate-release tablets for oral administration is 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid.

Febuxostat is currently approved 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)". In the EU the product was approved on 21st April 2008.

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

Tumor Lysis Syndrome (TLS) is the most common disease-related emergency encountered by physicians caring for patients with haematologic cancers. It represents a critical and possibly fatal complication resulting from the rapid lysis of large numbers of tumour cells, observed most often after initial treatment with chemotherapy.

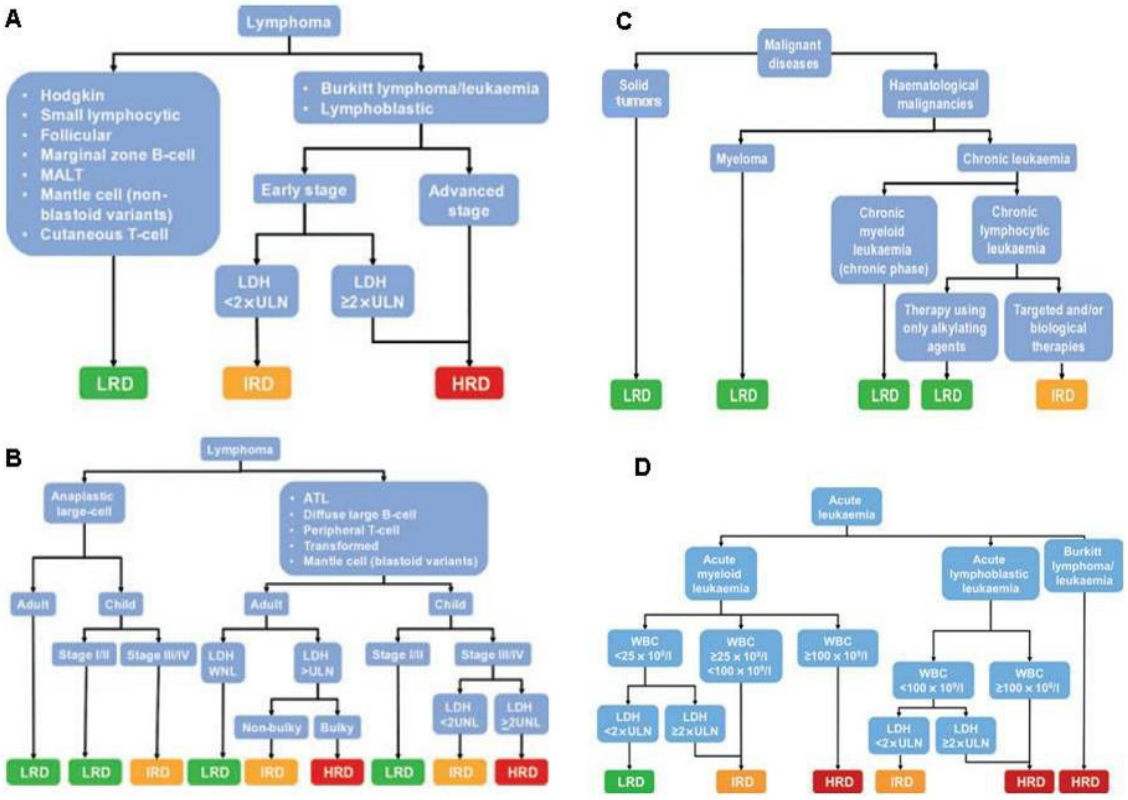
The current classification system distinguishes between Laboratory TLS (LTLS) and Clinical TLS (CTLS). LTLS is considered to be present if at least 2 laboratory parameters (among serum values of uric acid, potassium, phosphate or calcium) are more than or less than normal (see Table 1) at presentation or if they change by at least 25% from baseline:

Table 1. Criteria for LTLS definition

ANALYTE	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	25% increase
Calcium	≤ 1.75 mmol/L	25% decrease

CTLS is present when LTLS is accompanied by at least one of the following significant clinical complications: increased creatinine level, seizures, cardiac dysrhythmia or death. 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. The following algorithm (see figure 1) stratifies malignancies in low risk disease (LRD), intermediate risk disease (IRD) and high risk disease (HRD) on the basis of the different risk of developing TLS (<1%, 1-5% and >5%) respectively:

Figure 1. TLS risk algorithm



Note: ATL: Adult T-cell lymphoma; LDH: lactate dehydrogenase; WNL: Within Normal Limits; ULN: Upper Limit of Normal; WBC: White Blood Cells; LRD: Low Risk Disease; IRD: Intermediate Risk Disease; HRD: High Risk Disease. For chronic lymphoid leukaemia (CLL), IRD is defined not only when treatment targeted and/or biological therapies are used instead of only alkylating a gents, b ut a lso i n t he p resence o f a n e levated W BC (≥ 5 0 x 1 09/L)

Though the occurrence of TLS depends not only on serum uric acid (sUA) level but also on potassium, phosphorus and calcium values, sUA plays a key role in the developing of TLS. In fact, urate induces acute kidney injury not only by intra-renal crystallization but also by crystal independent mechanism, such as renal vasoconstriction, impaired auto regulation, decreased renal blood flow oxidation and inflammation. According to Coiffier et al, the risk of developing TLS or more simply the risk of developing acute renal impairment is significantly increased in patients with higher levels of sUA versus those with lower levels. In addition, the risk of developing TLS was increased by a factor of 1.75 for every mg/dL increase in serum UA, ($p<0.0001$) while the risk for renal events was increased by a factor of 2.21 ($p=0.0012$) for every mg/dL increase in sUA. This observation underlines the importance of preventing/containing the UA increases during chemotherapy in this patient population. Based on published data, LTLS incidence ranges from 12% up to 42%, whereas the range for CTLS rate of occurrence is tighter, being from 3% to 6%. Though no precise estimation of TLS incidence could be provided, epidemiological data highlight that TLS occurs both in adult and paediatric patients at a similar rate, as reported in a large analysis where both patient populations were included. The potential severity of TLS complications requires measures for TLS prevention and, in case it occurs, for its treatment. Risk oriented prophylaxis and appropriate interventions are the key to preventing or managing TLS and are almost identical in adult and paediatric populations. Strategies to prevent and treat hyperuricaemia associated with TLS encompass both general measures (clinical monitoring and adequate hydratation) and pharmacological measures. In accordance with the current recommendations for the evaluation of risk and prophylaxis of TLS as per expert panel

consensus (Cairo M et al, 2010) general measures are always recommended regardless of TLS risk grade, whereas pharmacological prophylaxis with allopurinol is recommended in patients with IRD and with rasburicase in patients with HRD (see Table 2).

Table 2. Recommendations for TLS prophylaxis by TLS risk grade

Low risk disease (LRD)	Intermediate risk disease (IRD)	High risk disease (HRD)
Prophylaxis recommendations		
Monitoring Hydration ±Allopurinol	Monitoring Hydration Allopurinol	Monitoring Hydration Rasburicase‡

‡Contraindicated in patients with a history consistent with glucose-6 phosphate dehydrogenase. In these patients, rasburicase should be substituted with allopurinol.

Based on the above mentioned guidelines and recommendations, in patients at low risk the "watch and wait" approach is recommended 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 (Cairo M et al, 2010; Coiffier et al., 2008).
This variation application proposed to extend the febuxostat's indication to: "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 already approved in adults for the management of hyperuricaemia in conditions where urate/uric acid deposition has already occurred (including history, or presence of, tophus and/or gouty arthritis) at doses of 80mg and 120mg once daily. The dose proposed for registration in the new indication is 120 mg once daily (QD).

2.2. Non-clinical aspects

2.2.1. Introduction

The MAH submitted a non-clinical study "Preliminary Juvenile Toxicity Study in the CD Rat by a Four-Week Repeated Oral (Gavage) Administration (Dose Range-Finding Study)", number "KIV0001".

The PDCO discussed the completed studies and considered that these are compliant with the latest Agency's Decision (P/0117/2014) of 6 May 2014.

The PDCO finalised on 18 July 2014 this partially completed compliance procedure and confirmed the compliance of all those studies contained in the agreed paediatric investigation plan that were to be completed until this date.

2.2.2. Ecotoxicity / environmental risk assessment

The environmental risk assessment (ERA) submitted for the initially approved indication demonstrated that febuxostat is considered unlikely to represent a risk for the environment following the prescribed usage.

As regards the use of febuxostat in the new therapeutic indication, it is worth noting that TLS occurs in a very limited number of patients (well below the number of patients with gout) and the use of febuxostat in TLS is foreseen only as a short-term treatment, not being TLS a chronic disease. Additionally, the proposed posology is limited to a maximum of 120 mg once daily.

As a whole, the new indication for the treatment of TLS is expected to increase the environmental burden of febuxostat to only less than 10%, therefore the potential increase of environmental exposure to the drug substance is deemed not significant and it is unlikely that Febuxostat could represent a risk for the environment.

2.2.3. Discussion on non-clinical aspects

Study "KIV0001" was conducted in accordance with the requirements of current Good Laboratory Practice Standards.

The primary objective of this preliminary dose range finding study was to assess the potential toxicity of febuxostat, a xanthine oxidase inhibitor, when administered orally to juvenile Sprague-Dawley rats for 4 weeks from Day 21 of age. The second objective was to aid in the selection of doses for a definitive study in juvenile rats which will assess toxicity and evaluate effects on growth and development.

Febuxostat was administered once daily by oral gavage at doses of 0 (vehicle), 3, 12, and 48 mg/kg/day. Six (6) rats per sex were assigned to a group at each dose level. All doses were administered at 5 ml/kg in a vehicle consisting of 0.5% (w/v) methylcellulose (MC) solution. A further 24 male and 24 female rats were assigned to each febuxostat group; these animals were treated with the same dosing procedure for one day or daily for four weeks and were used for toxicokinetic evaluation.

Criteria for evaluation of potential toxicity included toxicokinetics, clinical condition, detailed physical examinations, body weight, food consumption, haematology (peripheral blood), blood chemistry, cholinesterase analysis, urinalysis, organ weight (kidneys and thyroids including parathyroids), macropathology and histopathology (kidneys). Scheduled necropsy was conducted after 4 weeks of dosing (6 rats/sex/group).

The dose levels used in this study (0, 3, 12 and 48 mg/kg/day) were selected with reference to the results of the previous studies in adult animals.
In order to compare the toxicity profile of adult and juvenile animals based on the results of the previous studies in adult animals, the high dose level for this dose-range finding study in juvenile animals was set at 48 mg/kg/day, and middle and low dose levels set at 12 and 3 mg/kg/day, respectively, in a common ratio of four (4).

This preliminary study in juvenile rats identified the kidney as the potential target organ of toxicity.
Effects in the kidney of rats administered 48 mg/kg/day were marked. This dose exceeds the maximum tolerated dose, and is considered too high for the definitive juvenile toxicity study in rats which will assess potential toxic effects and effects on growth and development of juvenile rats in detail.
Febuxostat-related histopathologic changes were detected in the kidney of one male administered 3 mg/kg/day, therefore, a lower dose should be considered for subsequent studies; however, 3 mg/kg/day administered to females did not elicit adverse effects. Thus, within the limitations of this preliminary study, the no-observed-adverse-effect level (NOAEL) was less than 3 mg/kg/day for males and was 3 mg/kg/day for females. However, the suggested dose levels in the above outlined conclusion of the MAH seem applicable for further evaluations.

2.2.4. Conclusion on the non-clinical aspects

The results of the preliminary study in juvenile rats suggest that dose levels for a definitive juvenile toxicity study be 1, 3, 10 and 30 mg/kg/day. For the scope of this specific variation application this study is not relevant. However, the suggested dose levels seem applicable for further evaluations.

Considering the above data, febuxostat is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study	**Study Identifier**	**Objective(s) of the Study**	**Study Design & Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration1**	**Number of Subjects (#male/ #female)**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status; Type of Report**
Efficacy & Safety	FLO-01	Primary objective To compare the efficacy of Febuxostat with Allopurinol, in terms of serum uric acid (sUA) level control and preservation of renal function after seven days of treatment (Day 8) starting from 2 days prior to chemotherapy (Day 1). Secondary objectives ☐ To compare	Randomized, Double Blind, Multicentre, Phase III Pivotal Study Versus Allopurinol	Febuxostat: 120 mg daily Allopurinol: 200mg, 300mg or 600mg daily	346 (214/132)	Patients undergoing chemotherapy for hematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS)	7-9 days	Complete; Full

		the efficacy of Febuxostat with Allopurinol, in terms of: - maintenance of sUA levels ≤7.5 mg/dL; - occurrence of laboratory TLS (LTLS) according to Cairo-Bishop criteria; - occurrence of clinical TLS (CTLS) according to Cairo-Bishop criteria. ☐ To compare the safety of Febuxostat with Allopurinol.						

2.4. Clinical efficacy

2.4.1. Main study

Study Title: FLO-01 Febuxostat for Tumorlysis Syndrome Prevention in Hematologic Malignancies: A Randomized, Double Blind, Phase III Study versus Allopurinol (Florence study).

Methods

The study was a randomized, double blind, multicentre, phase III, pivotal study with Febuxostat (120 mg daily), versus Allopurinol (200 mg, 300 mg or 600 mg daily, upon investigator choice) in patients undergoing chemotherapy for hematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS). Treatment was given for 7-9 days (starting 2 days prior chemotherapy) and a final follow-up visit was performed two weeks after randomization. 79 active study centres in 11 European countries (Croatia, Czech Republic, Germany, Hungary, Italy, Poland, Romania, Russia, Serbia, Spain and Ukraine) and in Brazil were involved.

Study participants

Inclusion criteria

Patients meeting ALL the following criteria were eligible for entry into the study:

1. Male or female patients
   a. aged ≥18 years, and
   b. scheduled for first cytotoxic chemotherapy cycle, regardless of the line of treatment, because of hematologic malignancies, and
   c. at intermediate or high risk of TLS and
   d. with sUA levels < 10 mg/dL at randomization (Visit 1), and
   e. candidate to Allopurinol treatment or have no access to Rasburicase

2. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3.

3. Female of childbearing potential might be enrolled providing a negative pregnancy test at screening and using a highly effective method of birth control resulting in a low failure rate (i.e. less than 1% per year).

4. Able to give written informed consent before any study related procedure.

5. Able to attend all the visits scheduled in the study.

6. Life expectancy > 1 months.

Exclusion criteria

Patients were not eligible to participate in the study if they met ANY of the following exclusion criteria:

1. Patients known to be hypersensitive to Febuxostat or Allopurinol or to any of the components of the formulations.

2. Patients with hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactase malabsorption.

3. Patients with ischemic heart disease or congestive heart failure (CHF). ("Uncontrolled" ischemic heart disease was introduced with protocol amendment 1)

4. Pregnant or breast feeding women.

5. Patients with sUA levels $\geqslant$10 mg/dL at randomization (Visit 1).

6. Patients receiving Febuxostat, Allopurinol or any other urate lowering therapy (e.g. Rasburicase, probenecid) within 30 days prior to randomization.

7. Patients receiving mercaptopurine and azathioprine within 14 days prior to randomization.

8. High risk patients NOT candidate to Allopurinol treatment.

9. Patients with severe renal insufficiency.

10. Patients with severe hepatic insufficiency.

11. Patients with diagnosis of LTLS or CTLS at randomization (Visit 1).

12. Patients with any serious concomitant illness which, in the opinion of the Investigator, is incompatible with the protocol.

13. Patients receiving any other investigational agent within 30 days prior to randomization (Visit 1).

Treatments

Test product: Febuxostat and Placebo oral capsules.

- Standard dose: Febuxostat 120 mg/day; one cp q.d.
- High dose: Febuxostat 120 mg/day; one cp q.d. + 1 cp q.d. filled in with placebo.
- Low Dose: Febuxostat 120 mg/day; one cp q.d.

Reference Product: Allopurinol oral capsules.

- Standard dose: Allopurinol 300 mg/day

- High dose: Allopurinol 600 mg/day
- Low Dose: Allopurinol 200 mg/day

Objectives

Primary Objective

- To compare the efficacy of Febuxostat with Allopurinol, in terms of serum uric acid (sUA) level control and preservation of renal function after seven days of treatment (Day 8) starting from 2 days prior to chemotherapy (Day 1).

Secondary Objective

- to compare the efficacy of Febuxostat with Allopurinol in terms of maintenance of sUA levels 7.5 mg/dL and in terms of occurrence of laboratory TLS (LTLS) and clinical TLS (CTLS) according to Cairo-Bishop criteria.
- to compare the safety of Febuxostat with Allopurinol.

Outcomes/endpoints

Primary Efficacy Endpoint

The primary efficacy analysis was based on the following co-primary endpoints:

• Area under the curve of sUA from baseline (Day 1) to the evaluation visit (Day 8) (AUC sUA 1-8).

• Change in serum creatinine level from baseline (Day 1) to the Evaluation Visit (Day 8).

Secondary Efficacy Endpoints

• Assessment of the treatment responder rate.

- Treatment response is defined as the maintenance of sUA $\leq$7.5 mg/dL from the start of chemotherapy (Day 3) to the Evaluation Visit (Day 8).
- Treatment failure is defined as the presence of two or more consecutive values of sUA missing or > 7.5 mg/dL.

• Assessment of LTLS, from start of chemotherapy (Day 3) to the Evaluation Visit (Day 8) based on local laboratory results.

According to the Cairo-Bishop criteria, LTLS was defined by the presence of 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.

• Assessment of CTLS, from start of chemotherapy (Day 3) to the Evaluation Visit (Day 8).

According to the Cairo-Bishop criteria, CTLS was defined by the presence of LTLS in addition to 1 or more of the following significant clinical complications:

- renal insufficiency,
- cardiac arrhythmias,
- sudden death
- seizures.

The grade of CTLS was defined by the maximal grade of the clinical manifestation.

Sample size

The expected benefit of the Febuxostat group in respect to the Allopurinol group during the treatment period was assumed as:

- at least an absolute reduction of 100 mg x h/dL for the AUCsUA1-8 which correspond to a 15% decrease of Allopurinol in case it confirms the published data of AUCsUA1-8 = 646 mg x h/dL, with a common SD = 285 mg x h/dL;

- no change in mean Serum Creatinine level from baseline to the end of treatment for the Febuxostat group while Allopurinol has an increase of 13% in the mean Serum Creatinine (corresponding to 0.2 mg/dL considering a baseline mean Serum Creatinine = 1.5 mg/dL with a SD = 0.6 mg/dL).

According to the MAH, 340 patients (170 patients per arm) would be sufficient to achieve approximately 80% power. Assuming aroud 10% screening failure rate, approximately 380 patients would need to be screened.

Randomisation

After re-checking the eligibility criteria on Visit 1 (Day 1), eligible patients were randomized to one of the 2 possible treatment arms (Febuxostat or Allopurinol) as per treatment code, delivered through IVRS/IWRS, in accordance with the randomization list. Randomization was stratified according to TLS risk (intermediate or high) and baseline sUA level (<7.5 mg/dL and >7.5 mg/dL); this information was entered by the Investigator during the IVRS/IWRS randomization procedure.

Blinding (masking)

The treatment allocation was double-blinded. As the size and the shape of the Allopurinol 100 mg and Febuxostat 120 mg tablets differ as well as the posology scheme of Allopurinol high dosage (taken twice a day), double blind conditions were secured by encapsulation of the treatment tablets. Tablets of Febuxostat and Allopurinol were over-encapsulated. Likewise, corresponding placebo capsules were produced. Differences in weight were compensated by adequate filling material. The Investigator was to unblind the treatment allocation in the course of the clinical trial only if it was relevant to the safety of the patient, reporting the reason.

Statistical methods

Analysis Populations:

Four populations were defined for this study:
- the Safety Population
- the ITT Population
- and the PP Population

Safety Population: included all randomized patients who received at least one dose of study drug (N=346).

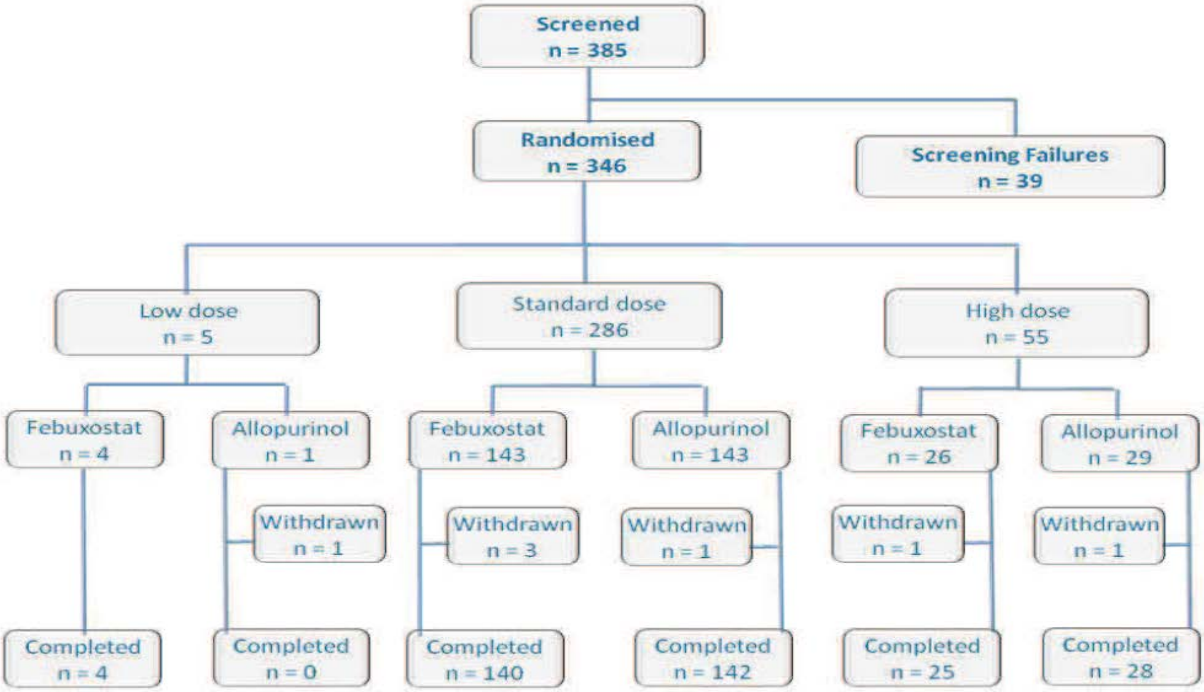
Intention-to-Treat (ITT) population: included all randomized patients (N=346). The primary efficacy analysis was run on the ITT population which included 346 patients, 173 allocated to Febuxostat and 173 to Allopurinol.

Per Protocol (PP) population: included all patients of the ITT population excluding patients who experienced major protocol violation(s) (N=309). The PP population was used to perform confirmatory analysis on the primary efficacy evaluation.

A total of 346 patients (214 males and 132 females) were randomized and all of them received the study treatment, thus constituting both the ITT and the safety and populations.
All statistical tests were generally two-sided with a significance level of a=0.05, unless otherwise specified.
The primary efficacy analysis includes stratification variables as covariates;

The 2 co-primary endpoints were analysed through analysis of covariance (ANCOVA) in order to test the difference in treatment efficacy quantified by AUC sUA1-8 and change (%) in serum creatinine level between treatment arms.

Participant flow



Recruitment

The study was initiated (first subject enrolled) on October the 1st 2012 and was completed on October the 11th 2013.

Conduct of the study

The original protocol was dated February 29th, 2012. There were three amendments, only one of which was substantial and concerned changes to improve patient comfort, a clarification regarding ischemic heart disease and congestive heart failure in the exclusion criteria section and an update of the SmPC.

Baseline data

This study included 346 (214 males and 132 females) adult (20-87 years, mean age 58.4 years) patients with haematological malignancies (chronic lymphocytic leukaemia (CLL), lymphoma and acute leukaemia (AL)).

Regarding ethnicity, 331 (95.6%) patients were Caucasian, 1 (0.3%) was Black and 14 (4.1%) were of other ethnicity.

2 Baseline and general characteristics

Table 2.1 [Baseline and general characteristics]: Demographics characteristics (ITT population)_

		Febuxostat (N=173)	Allopurinol (N=173)	Overall (N=346)
Age (years)	N	173	173	346
	Mean	58.51	58.26	58.39
	Median	61.00	60.00	60.00
	StdDev	14.259	13.264	13.751
	Min	20.00	20.00	20.00
	Max	87.00	85.00	87.00
BMI (kg/m^2)	N	173	171	344
	Mean	25.77	27.61	26.68
	Median	25.00	27.40	26.25
	StdDev	4.726	5.311	5.101
	Min	14.90	16.40	14.90
	Max	46.10	52.70	52.70
Height (cm)	N	173	171	344
	Mean	168.76	169.67	169.21
	Median	170.00	170.00	170.00
	StdDev	9.643	9.862	9.749
	Min	145.00	140.00	140.00
	Max	192.00	195.00	195.00
Weight (kg)	N	173	173	346
	Mean	73.48	79.35	76.42
	Median	71.40	80.00	76.00
	StdDev	14.923	16.220	15.837
	Min	42.10	44.00	42.10
	Max	124.00	140.00	140.00
Ethnicity	Overall	173/(50.00%)	173/(50.00%)	346/(100.00%)
	Black	1/(0.58%)	0/(0.00%)	1/(0.29%)
	Caucasian	167/(96.53%)	164/(94.80%)	331/(95.66%)
	Other	5/(2.89%)	9/(5.20%)	14/(4.05%)
Pregnancy	Overall	173/(50.00%)	173/(50.00%)	346/(100.00%)
	Negative	17/(9.83%)	14/(8.09%)	31/(8.96%)
	Not applicable	108/(62.43%)	106/(61.27%)	214/(61.85%)

		Febuxostat (N=173)	Allopurinol (N=173)	Overall (N=346)
	Not childbearing potential	48/(27.75%)	52/(30.06%)	100/(28.90%)
	Positive	0/(0.00%)	1/(0.58%)	1/(0.29%)
Sex	Overall	173/(50.00%)	173/(50.00%)	346/(100.00%)
	Female	65/(37.57%)	67/(38.73%)	132/(38.15%)
	Male	108/(62.43%)	106/(61.27%)	214/(61.85%)

Note2: Pregnancy category 'Not applicable' refers to male patients

The large majority of patients were Caucasian (over 95%), with a mean age of 58.4 years, ranging from 20 to 87 years. There was a higher proportion (around 62%) of male subjects and some other minor imbalances (e.g. slightly higher percentage of patients affected by acute leukaemia and lymphoma in the Febuxostat arm, higher percentage of patients affected by chronic lymphoid leukaemia in the Allopurinol group, differences in medical history and concomitant medication prior to first drug intake etc.) which all in all did not have any noteworthy impact on the outcome of the study with its (co-)primary endpoint sUA-decrease and unaffected kidney function (latter measured by serum creatinine levels).

Numbers analysed

Number of Subjects planned and analysed:

- Planned: ~ 340 patients
- Randomized: 346 patients (Febuxostat: 173 patients; Allopurinol: 173 patients)
- Safety Population: 346 patients (Febuxostat: 173 patients; Allopurinol: 173 patients)

- Intent-to-Treat (ITT) population: 346 patients (Febuxostat: 173 patients; Allopurinol: 173 patients)
- Per Protocol (PP) population: 309 patients (Febuxostat: 151 patients; Allopurinol: 158 patients)

A total of 385 patients were screened, of which 346 were randomised. A total of 39 screened patients were excluded before randomisation because of screening failures.

The main reasons for excluding these patients are summarized in Table 3.

Table 3: Reasons for screening failures (N=39)

Reason SF	N (%)
NON-COMPLIANT WITH EXCLUSION CRITERIA	8(20.5%)
NON-COMPLIANT WITH INCLUSION CRITERIA	22(56.4%)
OTHER	9(23.1%)

Source data: Table 1.1, Appendix 16.1.9..2.

Table 10-4: Patients who discontinued the study after randomization (discontinuations)

Treatment	Reason	Analysis Population	Attended *End-of-study* visit
Febuxostat	Death	ITT	No
Febuxostat	Death	ITT	No
Allopurinol	Withdrawal by patient	ITT	No
Febuxostat	Death	ITT	No
Allopurinol	Withdrawal by patient	ITT	No
Allopurinol	Protocol Violation	ITT	No
Febuxostat	Patient refused to come to scheduled Visit 10	ITT	No

Outcomes and estimation

o Primary Efficacy Analysis

The 2 co-primary endpoints were analysed through analysis of covariance (ANCOVA) in order to test the difference in treatment efficacy quantified by AUC sUA1-8 and change (%) in serum creatinine level from baseline (Day 1) to the Evaluation Visit (Day 8) between treatment arms. The two ANCOVA models included the treatment as a major covariate, adjusted for the two stratification factors (i.e.: TLS risk and sUA levels).

One patient allocated to Febuxostat and one patient allocated to Allopurinol treatment group were excluded from "sUA AUC1-8"- analysis due to missing data at baseline. Thus, sUA AUC1-8 was calculated on 172 patients in each treatment group.

Mean (SD) sUA at baseline (Day 1) showed no significant differences between Febuxostat and Allopurinol arms (5.6 ± 1.82 and 5.8 ± 1.77 mg/dL respectively, p=0.3008). Mean (SD) sUA at Evaluation Visit (Day 8) was significantly lower in Febuxostat compared to Allopurinol arm (2.7 ±1.76 and 3.9 ± 1.51 mg/dL respectively, p <.0001).

Area under the curve of sUA (AUC sUA 1-8)

Mean (SD) sUA AUC1-8 was significantly lower in Febuxostat in comparison with Allopurinol arm (514.0 ± 225.71 vs 708.0 ± 234.42 mg x h/dL respectively with p <.0001).

The time course of mean sUA from baseline to the Evaluation Visit (Day 8) is shown in Figure 2.

Figure 2: Time course of mean sUA from baseline to the Evaluation Visit (Day 8)- ITT poulation.

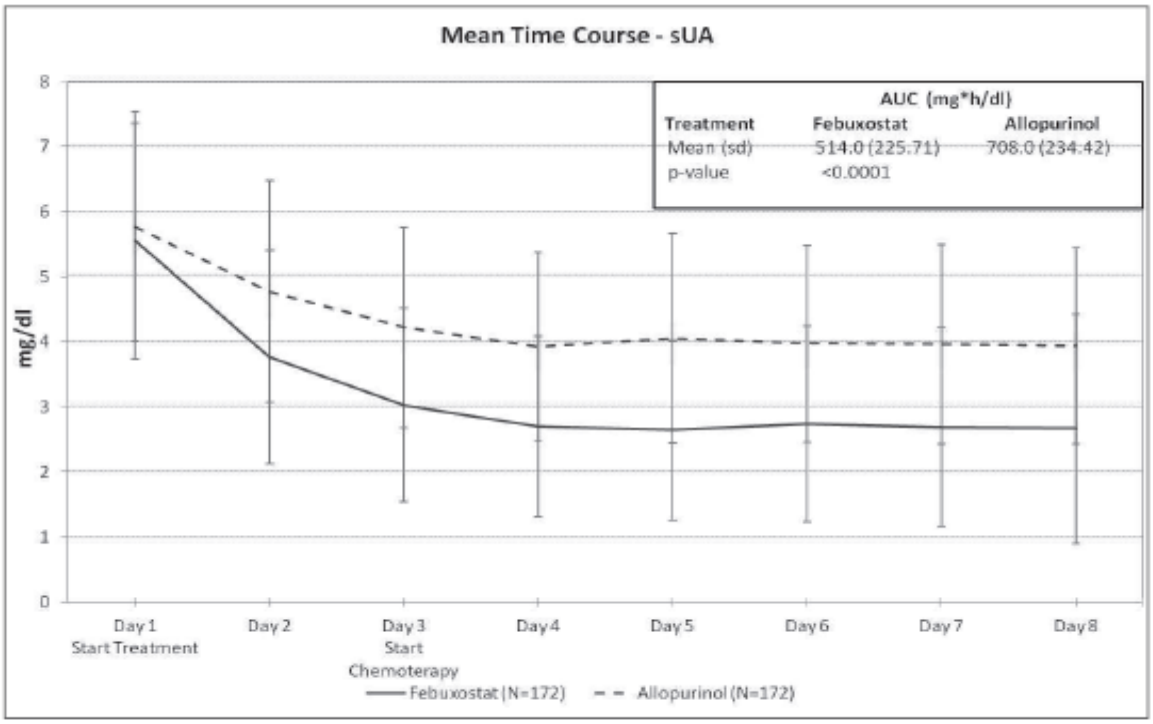


Figure 11-1: Time course of mean sUA from baseline to the Evaluation Visit (Day 8)-ITT population

Note: Mean sUA AUC_{1-8} is provided in the square (with p-value obtained through ANCOVA model).
Source data: Figure 1, Appendix 16.1.9.2

From Day 2 to the Evaluation Visit (Day 8) mean sUA level was significantly lower in Febuxostat in comparison with Allopurinol arm at each time point (details also in Table 14.2.3 of the study report).

The mean difference between the two treatment arms was of 1 mg/dL or above at each of the above mentioned time points.

Change (%) in Serum creatinine levels from baseline (Day 1) to the Evaluation Visit (Day 8)

Two patients allocated to Allopurinol treatment group were excluded from this analysis due to missing data at baseline. Thus, change (%) in serum creatinine level was calculated on 173 and 171 patients in Febuxostat and Allopurinol treatment group respectively.

Febuxostat was to be considered active in controlling renal function if no positive change in the mean serum creatinine level (final vs. baseline) had occurred or if any positive change in the mean serum creatinine level (final vs. baseline) had been significantly lower than that in the allopurinol arm (Figure 3).

Figure 3: Time course of serum creatinine level and of mean absolute change in serum creatinine level.

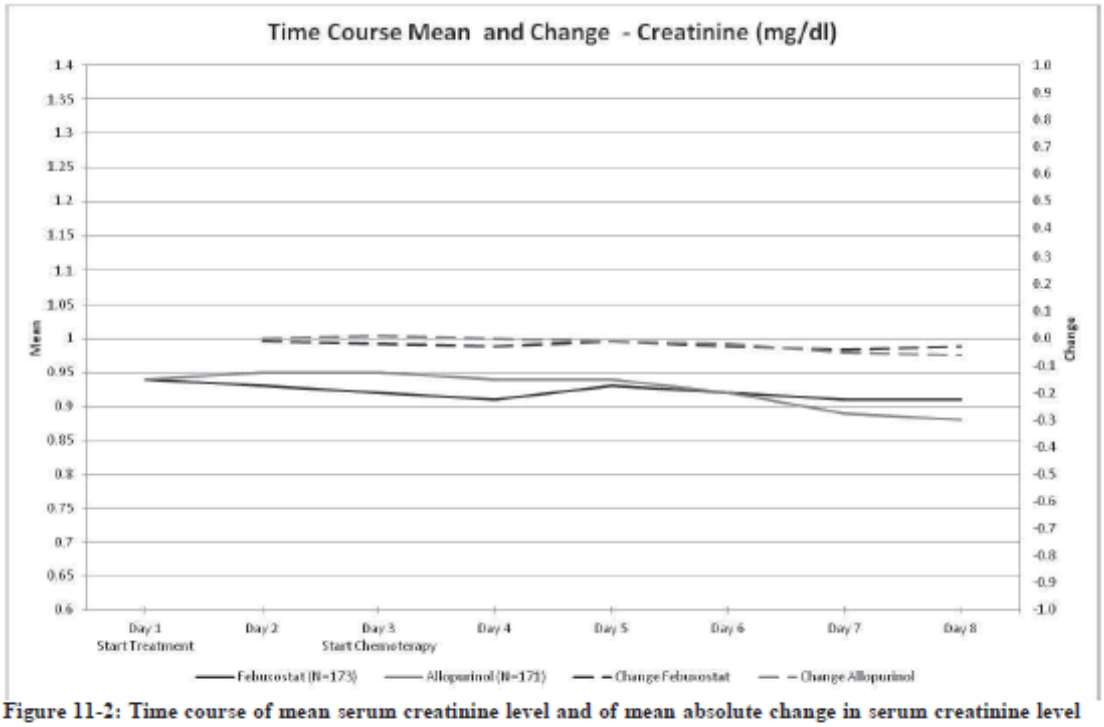


Figure 11-2: Time course of mean serum creatinine level and of mean absolute change in serum creatinine level (both mg/dL) - ITT population
Source data: Figure 2, Appendix 16.1.9.2

Mean (SD) serum creatinine level at baseline (Day 1) showed no significant differences between treatment groups (0.94 ± 0.347 and 0.94 ± 0.266 mg/dL in Febuxostat and Allopurinol arm respectively, p=0.5689) as well as at the Evaluation Visit (Day 8) (0.91 ± 0.359 and 0.88 ± 0.273 mg/dL in Febuxostat and Allopurinol arm respectively, p=0.8881).

Mean (SD) change (%) in serum creatinine level from baseline (Day 1) to the Evaluation Visit (Day 8) showed no significant differences between Febuxostat and Allopurinol treatment group (-0.83 ±26.977 and -4.92 ± 16.695 % respectively, with p=0.0903 obtained through ANCOVA model).

No significant difference between treatment groups was found in terms of change (%) of serum creatinine level at any time point.

The time course of both mean serum creatinine level and of mean change in serum creatinine level was also analysed to provide a quantitative scenario of the change in renal function during the treatment period. As shown in Figure 3, neither mean serum creatinine level nor mean change in serum creatinine level showed any significant difference between treatment groups at any time point.

Sensitivity analyses confirmed the results of primary efficacy analysis when it was performed without imputation of missing data (ITT population) and when it was performed on the per protocol (PP) population. Moreover, results of primary analysis with the additional covariate “country” in the ANCOVA model confirmed the results obtained in the main primary efficacy analysis showing no significant impact for country effect (p=0.4107), whereas it showed a highly significant treatment effect in favour of febuxostat (p<.0001).

Sensitivity analysis

As sensitivity analysis for the primary efficacy evaluation the following approaches were used:

• The primary analysis without any substitution for missing values (ITT population)

• The primary analysis applied to the PP population

• The primary analysis with 'Country' as additional covariate in the ANCOVA model (ITT population)

o Secondary efficacy analysis

The secondary efficacy analysis involved the sUA response rate and the assessment for LTLS and CTLS. All secondary efficacy analyses were performed only in the ITT population and not repeated in the PP population due to the low number of cases.

sUA response rate

No significant difference was detected between treatment groups in terms of sUA response rate (p=0.1993). Treatment failure rate was low (2.9%) in the overall ITT population, and even lower in the Febuxostat treatment group in comparison to the Allopurinol treatment group (1.7 vs 4.0% respectively). Descriptive statistics are provided in Table 4.

Table 4: Descriptive statistics for sUA Response Rate – ITT population

sUA Response Rate	Febuxostat (n=173)	Allopurinol (n=173)	Overall (n=346)
Success	170/(98.3%)	166/(96.0%)	336/(97.1%)
Failure	3/(1.7%)	7/(4.0%)	10/(2.9%)
Overall	173/(100.0%)	173/(100.0%)	346/(100.0%)

Note: The Overall percentage is based on the patients in the single treatment group population (reported in the header of columns)
Source data: Table 3.2.1, Appendix 16.1.9.2

Note: "treatment failure sUA" was defined as the presence of two or more consecutive values of sUA missing or >7.5 mg/dL.

LTLS assessment

No significant difference was detected between treatment groups in terms of LTLS incidence (p=0.8488). LTLS incidence was 8.1% and 9.2% in Febuxostat and Allopurinol treatment group_respectively. Descriptive statistics are provided in Table 5.

Table 5: Descriptive statistics for LTLS assessment – ITT population

LTLS	Febuxostat (n=173)	Allopurinol (n=173)	Overall (n=346)
Yes	14/(8.1%)	16/(9.2%)	30/(8.7%)
No	159/(91.9%)	157/(90.8%)	316/(91.3%)
Overall	173/(100.0%)	173/(100.0%)	346/(100.0%)

Note: The Overall percentage is based on the patients in the single treatment group population (reported in the header of columns)
Source data: Table 3.2.3, Appendix 16.1.9.2

CTLS assessment

No significant difference was detected between treatment groups in terms of CTLS incidence (p=1.0000). CTLS incidence was 1.7% and 1.2% in Febuxostat and Allopurinol treatment group respectively. Descriptive statistics are provided in Table 6.

Table 6: Descriptive statistics for CTLS assessment – ITT population

CTLS	Febuxostat (n=173)	Allopurinol (n=173)	Overall (n=346)
Yes	3/(1.7%)	2/(1.2%)	5/(1.4%)
No	170/(98.3%)	171/(98.8%)	341/(98.6%)
Overall	173/(100.0%)	173/(100.0%)	346/(100.0%)

Note: The Overall percentage is based on the patients in the single treatment group population (reported in the header of columns)
Source data: Table 3.2.5, Appendix 16.1.9.2

o Exploratory analyses

The following exploratory analyses were performed:

- Primary efficacy variables generated with local laboratory data on ITT population (Table 7).

Table 7: Descriptive statistics for sUA AUC_{1-8} and change (%) of Creatinine from baseline (Day 1) to Evaluation visit (Day 8) generated with local laboratory data- ITT population

sUA AUC_{1-8} (mgxh/dL)	Febuxostat (N=151)	Allopurinol (N=158)	Overall (N=309)	p-value
N	172	173	345	< .0001
Mean (±SD)	524.22 (±234.162)	707.54 (±228.040)	616.15 (±248.361)	
Creatinine Change (%)	Febuxostat (N=151)	Allopurinol (N=158)	Overall (N=309)	p-value
N	173	173	346	0.1258
Mean (±SD)	-1.92 (±26.633)	-5.69 (±17.438)	-3.81 (±22.557)	

Note: p-value obtained through ANCOVA model

- Primary efficacy variables by subgroups on ITT population (Table 8 and Table 9).

Table 8: sUA AUC_{1-8} (mean±SD) by treatment and subgroups

Sub group	Category		AUC_{1-8} mg x h/dL		p-value
			Febuxostat	Allopurinol	
sUA level	≤ 7.5 mg/dL	n	153	153	< .0001
		Mean + SD	472.3 ± 190.47	672.7 ± 217.02	
	> 7.5 mg/dL	n	19	19	0.0313
		Mean + SD	850.5 ± 208.13	992.0 ± 169.05	
TLS Risk	Intermediate	n	142	143	< .0001
		Mean + SD	506.2 ± 224.78	709.9 ± 223.45	
	High	n	30	29	0.0053
		Mean + SD	551.0 ± 230.28	698.2 ± 286.83	
Creatinine level	≤ ULN	n	165	162	< .0001
		Mean + SD	498.2 ± 213.75	697.3 ± 232.88	
	> ULN	n	7	9	0.7974
		Mean + SD	887.5 ± 182.96	859.3 ± 197.67	
PS score	≤ 2	n	168	167	< .0001
		Mean + SD	515.9 ± 227.36	708.0 ± 236.54	
	= 3	n	4	5	0.0804
		Mean + SD	437.1 ± 135.00	704.7 ± 165.34	
Disease Type	AL	n	34	25	< .0001

		Mean + SD	491.2 ± 248.55	649.7 ± 260.51	
	CLL+LYM	n	138	147	< .0001
		Mean + SD	519.7 ± 220.34	717.9 ± 229.19	

Note: p-value refers to ANCOVA model with stratification factors (TLS risk and sUA level) and treatment as covariates
Note: AL= Acute Leukaemia; CLL= Chronic Lymphoid Leukaemia; LYM= Lymphoma

Table 9: Change (%) in serum creatinine level from Day1 to Day8 (mean±SD) by treatment and subgroups

Sub group	Category		Change (%) in Serum Creatinine level from Day1 to Day8		p-value
			Febuxostat	Allopurinol	
sUA level	≤ 7.5 mg/dL	n	154	152	0.1245
		Mean + SD	-0.35 ± 24.538	-4.03 ± 16.973	
	> 7.5 mg/dL	n	19	19	0.4833
		Mean + SD	-4.74 ± 42.637	-12.11 ± 12.431	
TLS Risk	Intermediate	n	142	143	0.2136
		Mean + SD	-0.46 ± 24.334	-3.41 ± 16.681	
	High	n	31	28	0.1427
		Mean + SD	-2.52 ± 37.225	-12.64 ± 14.751	
Creatinine level	≤ ULN	n	166	162	0.0524
		Mean + SD	0.45 ± 26.469	-4.34 ± 16.458	
	> ULN	n	7	9	0.0515
		Mean + SD	-31.19 ± 21.774	-15.40 ± 18.481	
PS score	≤ 2	n	169	166	0.0822
		Mean + SD	-0.66 ± 26.891	-4.91 ± 16.694	
	= 3	n	4	5	0.9585
		Mean + SD	-8.12 ± 34.015	-5.43 ± 18.716	
Disease Type	AL	n	34	25	0.3243
		Mean + SD	-8.05 ± 22.264	-11.04 ± 12.211	
	CLL+LYM	n	139	146	0.0832
		Mean + SD	0.94 ± 27.794	-3.88 ± 17.162	

Note: p-value refers to ANCOVA model with stratification factors (TLS risk and sUA level) and treatment as covariates
Note: AL= Acute Leukaemia; CLL= Chronic Lymphoid Leukaemia; LYM= Lymphoma

Exploratory analyses performed in subpopulations of patients with different baseline characteristics (baseline hyperuricaemia sUA level ≤7.5 mg/dL vs. >7.5 mg/dL, creatinine level ≤ ULN vs. > ULN, type of haematological malignancy - AL vs. CLL+Lymphoma, ECOG PS score ≤2 vs. = 3 and TLS risk grade Intermediate vs. High) showed that the efficacy profile of febuxostat is maintained in terms of reduction of sUA (well established surrogate endpoint for TLS) and preserving renal function, in patients undergoing chemotherapy for haematological malignancies at intermediate to high risk of TLS.

Summary of main study(ies)

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as

the benefit risk assessment (see later sections).

Table: Summary of Efficacy for trial FLO-01

Title: FEBUXOSTAT FOR TUMOR LYSIS SYNDROME PREVENTION IN HEMATOLOGIC MALIGNANCIES: A RANDOMIZED, DOUBLE BLIND, PHASE III STUDY VERSUS ALLOPURINOL			
Study identifier	EudraCT 2012-000776-42		
Design	A pivotal randomized, phase III, multicentre, double blind trial in 346 male and female adult (20-87 years) patients to compare the efficacy of Febuxostat with Allopurinol, in terms of serum uric acid (sUA) level control and preservation of renal function in patients with haematological malignancies at intermediate or high risk of TLS.		
	Minimum treatment duration: Duration of main phase: Average patient duration of Participation: Overall study duration (i.e. from the first patient in to the last follow up visit of the last patient):		7 days (starting from 2 days prior to the start of chemotherapy); treatment could be prolonged up to 9 days according to chemotherapy duration (as per Investigator's judgment). approximately 3 weeks. approximately 13 months October 1st 2012 – October 11th 2013
Hypothesis	Superiority of Febuxostat versus Allopurinol in the prevention and treatment of hyperuricemia in patients with haematological malignancies at intermediate to high risk of developing TLS.		
Treatment groups	Febuxostat 120 mg Placebo oral capsules.		p.o. , 7-9 days, n=173 randomised
	Allopurinol 300mg, 600mg or 200mg/day.		p.o., 7-9 days, n=173 randomised
Endpoints and definitions	Co-Primary endpoint:		AUC sUA1-8 and change (%) in serum creatinine level from baseline (Day 1) to the Evaluation Visit (Day 8) between treatment arms.
	Secondary endpoint		sUA response rate and the assessment for LTLS and CTLS.
	Exploratory analyses:		Conducted in subpopulations of patients with different baseline characteristics (baseline hyperuricaemia sUA level, creatinine level, type of haematological malignancy.
Database lock	Date of the report: 28/07/2014		

Results and analysis				
Analysis description	**Primary analysis**			
Analysis population and time point description	Intention-to-Treat (ITT) population: All randomized patients (N=346). sUA from baseline (Day 1) to the Evaluation Visit (Day 8) (AUC sUA1-8) and change in serum creatinine level from baseline (Day 1) to the Evaluation Visit (Day 8).			
Descriptive statistics and estimate variability	Treatment group	Febuxostat	Allopurinol	
	Number of subjects	173	173	
	Descriptive statistics for sUA AUC1-8 (mg x h/dL) - ITT population	514.04 (±225.712)	707.96 (±234.422)	

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

This was a pivotal phase III, randomized, double-blind, multicentre study to demonstrate the efficacy of febuxostat 120 mg QD in the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS). Febuxostat was to be compared with Allopurinol in terms of sUA level reduction and preserving renal function in the intended target population.

The study design was considered acceptable by CHMP and in accordance with the EMA scientific advice (EMEA/H/SA/2153/1/2011/II). Based on guidelines and recommendations of the international TLS consensus expert panel, allopurinol represents the current standard treatment for patients at intermediate risk for TLS, in addition to hydration. In patients at high risk, rasburicase is the recommended option (Cairo M et al, 2010; Coiffier et al., 2008).

The choice of the febuxostat dosage equal to 120 mg daily was based on the observation that this dose (which matches the higher dose approved in gout) was safely administered in clinical trials in more than 1000 subjects (healthy volunteers and gout patients) for a mean duration of treatment of approximately 400 days displaying a safety profile similar to the 80 mg dose but with a higher efficacy in terms of sUA reduction. In this respect, it should be noticed that following the administration of multiple febuxostat 80 or 120 mg QD oral doses to healthy subjects, the mean serum urate values were reduced from baseline by an average of 55% and 66% respectively with steady state urate concentrations achieved within the first week of dosing. In addition, no dose adjustment was required for mild to moderate renal impairment. Therefore, the most effective dose of febuxostat in gout was deemed to be the best choice in the TLS setting with the aim to prevent the acute and extensive increase in sUA following chemotherapy. This choice was also endorsed by the CHMP.

In clinical practice Allopurinol 300 mg is the most commonly used dose in patients at intermediate risk of TLS. As Rasburicase is not widely used, high risk patients also receive allopurinol, in a higher dose, mainly equal to 600 mg per day. Allopurinol, however, requires a dose adjustment (reduction to 200 mg/day) in patients with renal impairment. Therefore, the Allopurinol arm with 'flexible dosage' (300 mg/day-600 mg/day, reduced to 200 mg/day in case of renal insufficiency) was selected by the Investigator according

to the locally approved SmPC and local clinical practice. In this study, patients at high risk of TLS were included if they were considered eligible for allopurinol treatment or had no access to treatment with rasburicase.

Only the Allopurinol dose was altered, whilst the Febuxostat dose (120 mg) always remained the same. In order to simulate a higher dose in the (blinded) Febuxostat-group, placebo capsules were utilised as a second dose as in the regimen of Allopurinol 600 mg. The dose was reduced in case of moderate renal insufficiency, defined as an estimated CrCl (Creatinine-Clearance) between 30 and 59 ml/min both inclusive, calculated with the Cockroft-Gault method.

Treatment in both groups (febuxostat and allopurinol) was started 2 days prior to chemotherapy due to the known slow onset of allopurinol, requiring up to at least 2 days to decrease uric acid. The regular scheduled treatment duration was 7 to 9 days, selected by the investigator on the basis of the chemotherapy regimen administered to each individual patient. The short treatment period is acceptable considering the acuteness of the indication (TLS) sought for, where a rapid decrease in sUA is essential.

The inclusion and exclusion criteria are acceptable. As stated under the inclusion criteria, patients included in the study were at intermediate or high risk of TLS (284 (82.1%) patients were at intermediate risk whereas 62 (17.9%) were at high risk). Overall, baseline sUA level was 7.5 mg/dL in 303 (87.6%) patients and > 7.5 mg/dL in 43 (12.4%) patients. The TLS risk (intermediate vs high) and baseline sUA level (7.5 mg/dL vs >7.5 mg/dL) were balanced among treatment groups due to the randomization procedure. Patients at high risk were only accepted, if they were still eligible to Allopurinol treatment or had no access to treatment with Rasburicase and would have been otherwise treated with Allopurinol. Nevertheless, this approach has the benefit of not only including intermediate but also high risk patients in the study.

No meaningful differences were found between the 2 treatment groups (febuxostat vs. allopurinol) with respect to demographic characteristics and the ethnicities are representative of the European target population.

Evaluation of the co-primary endpoint was based on two pairs of hypotheses to assess superiority. According to the Statistical Analysis Plan (SAP), both null-hypotheses would need to be rejected to achieve the primary efficacy endpoint in this trial. In particular, the second pair of hypotheses for change in serum creatinine does not seem to be an adequate reflection of the second important objective ‘preservation of renal function after seven days of treatment’, as this objective would not necessarily require a comparison to the active arm, but could be explored based on change to baseline information in the Febuxostat arm. Hypotheses are however put down assuming that renal function would deteriorate under Allopurinol (increase of 13% in the mean serum creatinine), and would stay constant over time under Febuxostat. In the primary efficacy analysis performed on the intention to treat population, mean change in serum creatinine levels from baseline (Day 1) to the Evaluation Visit (Day 8) was negative in both febuxostat and allopurinol groups. Consistently, the time course of mean change (%) in serum creatinine did not show any significant difference between treatment groups at any time point. This was due to the fact that renal function stayed equally stable over time on average in both treatment arms, and hence the superiority of febuxostat over allopurinol (as postulated in the correspondingly planned statistical superiority test, SAP) could not be demonstrated. The underlying planning assumption of decreased renal function over time for allopurinol was not confirmed by empirical clinical data in the trial. From the data presented by the MAH, it appears that the desired demonstration of preservation of renal function after seven days of treatment under febuxostat could have found a better translation to statistical testing objectives, either via a more general non-inferiority assessment or via intra-febuxostat-arm change to baseline evaluation. The MAH acknowledged that the co-primary endpoint was formally not met. Any justification of why/how this issue can be overcome in the interpretation of the trial outcome per se illustrates that the original trial’s objectives have not been

optimally translated to statistically testable endpoints and hypotheses. Hence, from a methodological point of view the described deficiency persists. However, although this co-primary endpoint failed to show superiority, the CHMP is of the opinion that the demonstration of superiority versus allopurinol in terms of improved control of sUA levels that is seen as a clinically well-established surrogate endpoint for TLS and renal impairment overrules this deficiency from an clinical perspective.

Efficacy data and additional analyses

AUC_{sUA1-8} was significantly lower with febuxostat than in the allopurinol treatment group (514.0 ± 225.71 vs 708.0 ± 234.42). The difference was statistically highly significant ($p < .0001$).

Morever, the time course of mean sUA showed that from Day 2 to the Evaluation Visit (Day 8) the mean sUA level was significantly lower in the febuxostat group compared to the allopurinol group at each time point and the mean difference between the two treatment arms was 1 mg/dL or above at each of the time point.

A significant sUA reduction began on Day 2 already, i.e. only 24 hours after the onset of febuxostat treatment and was maintained over the measurement period (day 2-8). The fact that significant sUA reduction with febuxostat begins on Day 2 already (i.e. only 24 hours after beginning treatment) is likely to be of clinical relevance for those patients in whom chemotherapy administration cannot be delayed. In contrast, allopurinol with its slow onset of action requires up to at least 2 days for a decrease in uric acid, which could allow urate nephropathy to develop.

Sensitivity analyses confirmed the result of primary efficacy analysis when it was performed without imputation of missing data (ITT population) and when performed on the per protocol (PP) population. Moreover, results of primary analysis with the additional covariate “Country” in the ANCOVA model confirmed the results obtained in the main primary efficacy analysis, showing no significant impact for a “country effect” ($p=0.4107$), whereas it showed a highly significant treatment effect in favour of febuxostat ($p<.0001$).

Finally, primary efficacy analysis was confirmed also in different subpopulations (i.e. baseline hyperuricaemia sUA level ≤7.5 mg/dL vs. >7.5 mg/dL, creatinine level ≤ULN vs. >ULN, type of haematological malignancy - AL vs. CLL+Lymphoma, ECOG PS score ≤2 vs.= 3 and TLS risk grade Intermediate vs. High). The primary efficacy analysis performed on the ITT population did not show any significant difference in mean change (%) in serum creatinine level from baseline (Day 1) to the Evaluation Visit (Day 8) between Febuxostat and Allopurinol treatment groups (-0.83 ± 26.98 vs -4.92 ± 16.70 respectively, $p=0.0903$). The time course analysis of change (%) in serum creatinine level did not show any significant difference between treatment arms at any time point. Moreover, the time course analysis of both mean serum creatinine level and of absolute change in serum creatinine from baseline to Day 8 showed that the change in serum creatinine was negligible in both treatment groups without any significant difference at any time point.

All sensitivity analyses confirmed the lack of significant differences between treatment groups in terms of mean change (%) in serum creatinine level from baseline (Day 1) to the Evaluation Visit (Day 8).

No significant difference was found in terms of LTLS or CTLS incidence between febuxostat and allopurinol ($p=0.8488$ and $p=1.000$, respectively).

During the procedure, the MAH was asked to justify the proposed indication i.e. both “prevention” and “treatment” of hyperuricaemia. The MAH clarified that Tumor Lysis Syndrome (TLS) represents a critical and possibly fatal complication resulting from the rapid lysis of large numbers of tumour cells, observed most often after initial treatment with chemotherapy. The resulting metabolic derangements, including hyperuricaemia, hyperkalemia, hyperphosphatemia and hypocalcemia may lead to serious clinical complications, such as renal dysfunction, cardiac failure, seizures or death. The risk of developing TLS is significantly increased in patients with higher levels of UA versus those with lower levels. The

management of hyperuricaemia for prevention and treatment of TLS in adults and children is the same, unless a failure in achieving or maintaining sUA level control occurs. This is confirmed by the current guidelines (Cairo and Bishop, 2004; Coiffier et al., 2008,), with the only exception of patients who develop acute hyperuricaemia despite prophylactic treatment with allopurinol, for whom rasburicase is indicated. Consistently, the indication approved for rasburicase is "Treatment and prophylaxis of acute hyperuricaemia, in order to prevent acute renal failure, in adults, children and adolescents (aged 0 to 17 years) with haematological malignancy with a high tumour burden and at risk of a rapid tumour lysis or shrinkage at initiation of chemotherapy".

The Phase III pivotal study showed that febuxostat was superior over allopurinol in terms of reduction of sUA, in patients undergoing chemotherapy for haematological malignancies at intermediate to high risk of TLS. In the subgroup of patients with hyperuricaemia at baseline, febuxostat showed statistically significant lower sUA levels over time than allopurinol, demonstrating superiority of febuxostat over allopurinol in the treatment of hyperuricaemic patients at risk of TLS. The CHMP concluded that the demonstration of superiority versus allopurinol in terms of improved control of sUA levels that is seen as a clinically well-established surrogate endpoint for TLS and risk factor for renal impairment sufficiently demonstrates efficacy in the new therapeutic indication.

Currently there are only two options available for treating hyperuricaemia occurring with chemotherapy in patients with haematologic malignancies (TLS), namely allopurinol (in patients at intermediate to high risk) and rasburicase (in high risk patients). During the procedure the MAH was also asked to justify whether febuxostat would be sufficient in those cases where otherwise rasburicase is considered, i.e. patients at high risk of TLS requiring intensive chemotherapy. The MAH clarified that according to the current recommendations for the evaluation of risk and prophylaxis of TLS in adults and children with malignant diseases (Cairo et al., 2010), only the TLS risk grade should drive the choice of the treatment for prophylaxis, regardless of the intensity of the chemotherapy regimen. Patients with intermediate TLS risk grade should receive allopurinol whereas patients at high TLS risk grade should receive rasburicase unless clinically contraindicated or unavailable Consistently, the FLORENCE trial included patients who were candidate for allopurinol because defined as intermediate TLS risk grade or patients who were at high TLS risk but with no access to rasburicase. The exploratory analyses performed in subpopulations of patients with different baseline characteristics (including TLS risk grade Intermediate vs. High) showed that the efficacy profile of febuxostat is maintained in terms of reduction of sUA (well established surrogate endpoint for TLS) and preserving renal function, in patients undergoing chemotherapy for haematological malignancies at intermediate to high risk of TLS.

The CHMP therefore agreed that the indication should read as follows:"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)".

2.4.3. Conclusions on the clinical efficacy

The Phase III pivotal study showed that febuxostat was superior over allopurinol in terms of reduction of sUA (a well-established surrogate endpoint for TLS and renal impairment) in patients undergoing chemotherapy for haematological malignancies (HM) at intermediate to high risk of TLS. Moreover, the results of this trial provide evidence that febuxostat is effective in preserving renal function.

The efficacy profile of febuxostat is maintained regardless of baseline hyperuricaemia (sUA level >7.5 mg/dL), creatinine level, type of HM, ECOG PS score and TLS risk grade as confirmed by the exploratory analyses performed in subpopulations of patients with different baseline characteristics. A significantly higher sUA reduction compared to allopurinol is achieved after only 24 hours, which is a relevant factor in the prevention of urate-nephropathy, especially in patients in whom chemotherapy cannot be delayed.

On the whole, efficacy analyses provided clear evidence for a benefit of febuxostat over allopurinol in terms of control of sUA level throughout the whole treatment period while preserving renal function. Furthermore, the risk of TLS and renal events is known to increase for every mg/dl increase of sUA and febuxostat provided a mean sUA reduction of at least 1 mg/dL compared to allopurinol in the course of the trial. Thus, febuxostat is expected to provide a better control of sUA levels (and thereby lower the risk of TLS-consequences, e.g. renal damage) in patients with with intermediate and high risk TLS undergoing chemotherapy, as compared to allopurinol.

2.5. Clinical safety

Introduction

A completed clinical development program has fully evaluated the safety and efficacy of Febuxostat 80 and 120 mg tablets for the chronic management of hyperuricemia in patients with gout. In addition, postmarketing safety information for Febuxostat is available.

Safety data for the newly proposed indication (Prevention and treatment of hyperuricemia in adult patients undergoing chemotherapy for hematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS)) were available from one randomized, double blind, multicentre, phase III, pivotal study with Febuxostat (120 mg daily), versus Allopurinol (200 mg, 300 mg or 600 mg daily, upon investigator choice) in patients undergoing chemotherapy for hematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS).

Patient exposure

173 subjects have been exposed to at least one dose of febuxostat 120 mg and 173 subjects received at least one dose of Allopurinol (200/300/600 mg) in the clinical development programme for the new proposed indication.

Mean exposure to study treatment was 7.6 ± 0.92 days for the overall safety population, with no differences observed between the treatment groups (7.5 ± 0.85 days in the Febuxostat group and 7.6± 0.99 days in the Allopurinol group).

Details on exposure are provided in Table 10 below:

Table 10: Exposure to study treatments – Safety Population

	Febuxostat (N=173)	Allopurinol (N=173)	Overall (N=346)
N	173	173	346
Mean (±SD)	7.54 (±0.853)	7.59 (±0.988)	7.56 (±0.922)
Median	7.00	7.00	7.00
Min.; Max.	6.00 ; 9.00	2.00 ; 9.00	2.00 ; 9.00

Note: value reported in days of exposure
Source: Table 6.1.2, Appendix 16.1.9.2

Demographic and baseline characteristics are summarized in Table 12 and Table 11 respectively.

As described in Table 11, the number (%) of patients in Allopurinol arm treated at low/standard/high dose was 1(0.5%), 143 (82.7%) and 29 (16.8%) respectively.

Table 11: Baseline characteristics - ITT population

		Febuxostat (N=173)	Allopurinol (N=173)	Overall (N=346)
HM	Overall	173/(50.0%)	173/(50.0%)	346/(100.0%)
	AL	34/(19.7%)	25/(14.5%)	59/(17.1%)
	CLL	80/(46.2%)	94/(54.3%)	174/(50.3%)
	Lymphoma	59/(34.1%)	54/(31.2%)	113/(32.6%)
TLS risk	Overall	173/(50.0%)	173/(50.0%)	346/(100.0%)
	High	30/(17.3%)	32/(18.5%)	62/(17.9%)
	Intermediate	143/(82.7%)	141/(81.5%)	284/(82.1%)
sUA level	Overall	173/(50.0%)	173/(50.0%)	346/(100.0%)
	≤ 7.5 mg/dL	151/(87.3%)	152/(87. 9%)	303/(87.6%)
	> 7.5 mg/dL	22/(12.7%)	21/(12.1%)	43/(12.4%)
Dose	Overall	173/(50.0%)	173/(50.0%)	346/(100.0%)
	High	26/(15.0%)	29/(16.8%)	55/(15.9%)
	Low	4/(2.3%)	1/(0.5%)	5/(1.4%)
	Standard	143/(82.7 %)	143/(82.7%)	286/(82.7%)
LDH (U/L)	N	172	170	342
	Mean (±SD)	622.32 (± 865.263)	500.59 (± 503.411)	561.81 (± 710.457)
	Median (Min.; Max.)	410.50 (91.62 ; 8727.00)	331.50 (118.56 ; 3428.00)	379.50 (91.62 ; 8727.00)
Creatinine (mg/dL)	N	173	173	346
	Mean (±SD)	0.96 (± 0.285)	0.98 (± 0.255)	0.97 (± 0.270)
	Median (Min.; Max.)	0.94 (0.31 ; 2.19)	0.97 (0.34; 1.97)	0.96 (0.31 ; 2.19)

Note: Percentages calculated from the number of subjects belong to ITT population in the respective treatment group. Rows and columns overall percentages calculated on the overall ITT population
Note: Assessments performed at Visit 1 were considered as Baseline. Only in case Screening Visit and Visit 1 occurred within 24 hours and according to the study protocol the assessments were performed only at Screening Visit, Screening Visit assessments were considered as Baseline

Mean exposure to study treatment was 7.6 ± 0.92 days for the overall safety population, with no differences observed between the treatment groups, which is in relation to the proposed indication

The majority of subjects included in the study were male (61.85%), Caucasian (95.66%) and the mean age was 58.4 years.

Table 12: Demographic characteristics- ITT population

		Febuxostat (N=173)	Allopurinol (N=173)	Overall (N=346)
Age (years)	N	173	173	346
	Mean (±SD)	58.51 (±14.259)	58.26 (±13.264)	58.39 (±13.751)
	Median (Min.; Max.)	61.00 (20.00 ; 87.00)	60.00 (20.00 ; 85.00)	60.00 (20.00 ; 87.00)
BMI (kg/m^2)	N	173	171	344
	Mean (±SD)	25.77 (±4.726)	27.61 (±5.311)	26.68 (±5.101)
	Median (Min.; Max.)	25.00 (14.90 ; 46.10)	27.40 (16.40 ; 52.70)	26.25 (14.90 ; 52.70)
Height (cm)	N	173	171	344
	Mean (±SD)	168.76 (±9.643)	169.67 (±9.862)	169.21 (±9.749)
	Median (Min.; Max.)	170.00 (145.00 ; 192.00)	170.00 (140.00 ; 195.00)	170.00 (140.00 ; 195.00)
Weight (kg)	N	173	173	346
	Mean (±SD)	73.48 (±14.923)	79.35 (±16.220)	76.42 (±15.837)
	Median (Min.- Max.)	71.40 (42.10 ; 124.00)	80.00 (44.00 ; 140.00)	76.00 (42.10 ; 140.00)
Ethnicity	Overall	173/(50.00%)	173/(50.00%)	346/(100.00%)
	Black	1/(0.58%)	0/(0.00%)	1/(0.29%)
	Caucasian	167/(96.53%)	164/(94.80%)	331/(95.66%)
	Other	5/(2.89%)	9/(5.20%)	14/(4.05%)
Sex	Overall	173/(50.00%)	173/(50.00%)	346/(100.00%)
	Female	65/(37.57%)	67/(38.73%)	132/(38.15%)
	Male	108/(62.43%)	106/(61.27%)	214/(61.85%)

Note: For Sex and Ethnicity percentage calculated from the number of respective group.

Adverse events

The following sections refer to Treatment Emergent Signs or Symptoms (TESSs), which were defined as AEs/SAEs occurring for the first time or worsening in terms of seriousness, severity or relationship to the medicinal product after first drug intake.

In total, 229 (66.2%) patients experienced TESSs: n= 117 (67.6%) patients in the Febuxostat group and n=112 (64.7%) patients in the Allopurinol group. The overall number of TESS reported in each group was 635 in the Febuxostat group and 503 in the Allopurinol group.

Treatment Emergent Signs or Symptoms (TESSs):

In the pivotal Phase III study, the overall proportion of subjects with at least one TESS was similar between treatment groups, though a higher proportion of patients in Febuxostat group experienced moderate and severe TESSs (41.0% vs. 37.6% and 31.2% vs. 18.5% for moderate and severe TESSs in Febuxostat and Allopurinol group respectively). A total of 7.8% patients in the overall safety population experienced serious TESSs, with a higher proportion in Febuxostat treatment group (namely 12.1% vs. 3.5% in Febuxostat and Allopurinol group respectively).

A total of 45 TESSs satisfied the definition of serious, however none of them were judged by the investigator as treatment related in any treatment group.

A total of 3 TESSs leading to treatment withdrawal occurred in 1 (0.3%) patient, who was allocated to Febuxostat; the events were serious and, as above, were also judged to be not related to study treatment by the investigator.

An overview of TESSs (overall and treatment-related) reported during the study is provided in Table 13:

Table 13: Overview of TESSs, treatment-related TESSs and TESSs leading to treatment withdrawal – Safety Population

All TESSs				
		Febuxostat (N=173)	Allopurinol (N=173)	Overall (N=346)
Overall		117/(67.6%)|635	112/(64.7%)|503	229/(66.2%)|1138
Intensity	Mild	98/(56.6%)|339	97/(56.1%)|273	195/(56.4%)|612
	Moderate	71/(41.0%)|152	65/(37.6%)|155	136/(39.3%)|307
	Severe	54/(31.2%)|144	32/(18.5%)|75	86/(24.9%)|219
SAE	No	116/(67.1%)|598	112/(64.7%)|495	228/(65.9%)|1093
	Yes	21/(12.1%)|37	6/(3.5%)|8	27/(7.8%)|45
Treatment-related TESSs				
		Febuxostat (N=173)	Allopurinol (N=173)	Overall (N=346)
Overall		11/(6.4%)|13	11/(6.4%)|19	22/(6.4%)|32
Intensity	Mild	9/(5.2%)|10	6/(3.5%)|7	15/(4.3%)|17
	Moderate	2/(1.2%)|3	8/(4.6%)|9	10/(2.9%)|12
	Severe	0/(0.0%)|0	2/(1.2%)|3	2/(0.6%)|3
SAE	No	11/(6.4%)|13	11/(6.4%)|19	22/(6.4%)|32
	Yes	0/(0.0%)|0	0/(0.0%)|0	0/(0.0%)|0
TESSs leading to treatment withdrawal				
		Febuxostat (N=173)	Allopurinol (N=173)	Overall (N=346)
Overall		1/(0.6%)|3	0/(0.0%)|0	1/(0.3%)|3
SAE	No	0/(0.0%)|0	0/(0.0%)|0	0/(0.0%)|0
	Yes	1/(0.6%)|3	0/(0.0%)|0	1/(0.3%)|3
TESSs resulting in death				
		Febuxostat (N=173)	Allopurinol (N=173)	Overall (N=346)
Overall		6/(3.5%)|15	0/(0.0%)|0	6/(1.7%)|15
Relationship	No	6/(3.5%)|15	0/(0.0%)|0	6/(1.7%)|15
	Yes	0/(0.0%)|0	0/(0.0%)|0	0/(0.0%)|0

Note: Number of patients /(percentages calculated from the number of patients in the respective group)|Number of TESSs
Note: Treatment-related TESSs are those with relationship recorded as "certainly related", "probably related", "possibly related" or "unassessable/unclassifiable" on the AE page
Note: TESSs leading to treatment withdrawal are those occuring in early terminated patients with "drug permanently withdrawn" recorded as action taken on the AE page
Note: TESSs resulting in death are those with "death" recorded as event outcome on the AE page
Note: TESSs resulting in death include also those which started within the study period but resulted in death after the End of Study Visit
Source: Table 6.2.1.1, Table 6.2.1.2, Table 6.2.1.3 and Table 6.2.1.4, Appendix 16.1.9.2.

Table 14 provides an overview of common (reported in ≥5% patients in any treatment group) TESSs occurred in the Phase III pivotal trial.

Table 14: TESSs reported in ≥5% patients in any treatment group by MedDRA SOC, PT, and treatment – Safety Population

SOC	PT	Febuxostat (N=173)	Allopurinol (N=173)	Overall (N=346)
Blood and lymphatic system disorders	Overall	69/(39.9%)|164	61/(35.3%)|137	130/(37.6%)|301
	– Anaemia	39/(22.5%)|49	25/(14.5%)|31	64/(18.5%)|80
	– Febrile neutropenia	11/(6.4%)|13	7/(4.0%)|7	18/(5.2%)|20
	– Leukopenia	27/(15.6%)|28	27/(15.6%)|27	54/(15.6%)|55
	– Neutropenia	31/(17.9%)|33	41/(23.7%)|43	72/(20.8%)|76
	– Thrombocytopenia	25/(14.5%)|28	20/(11.6%)|21	45/(13.0%)|49
Cardiac disorders	Overall	11/(6.4%)|13	10/(5.8%)|12	21/(6.1%)|25
Gastrointestinal disorders	Overall	57/(32.9%)|101	50/(28.9%)|78	107/(30.9%)|179
	– Constipation	14/(8.1%)|16	11/(6.4%)|12	25/(7.2%)|28
	– Diarrhoea	16/(9.2%)|21	11/(6.4%)|13	27/(7.8%)|34
	– Nausea	22/(12.7%)|25	21/(12.1%)|23	43/(12.4%)|48
	– Vomiting	10/(5.8%)|11	12/(6.9%)|12	22/(6.4%)|23
General disorders and administration site conditions	Overall	40/(23.1%)|66	29/(16.8%)|47	69/(19.9%)|113
	– Mucosal inflammation	11/(6.4%)|11	3/(1.7%)|3	14/(4.0%)|14
	– Pyrexia	24/(13.9%)|26	18/(10.4%)|21	42/(12.1%)|47
Infections and infestations	Overall	24/(13.9%)|30	12/(6.9%)|14	36/(10.4%)|44
Investigations	Overall	36/(20.8%)|65	37/(21.4%)|59	73/(21.1%)|124
	– Platelet count decreased	10/(5.8%)|10	7/(4.0%)|7	17/(4.9%)|17
Metabolism and nutrition disorders	Overall	37/(21.4%)|64	33/(19.1%)|43	70/(20.2%)|107
	– Hyperglycaemia	6/(3.5%)|7	9/(5.2%)|10	15/(4.3%)|17
	– Hyperphosphataemia	9/(5.2%)|9	4/(2.3%)|4	13/(3.8%)|13
Musculoskeletal and connective tissue disorders	Overall	13/(7.5%)|16	10/(5.8%)|11	23/(6.6%)|27
Nervous system disorders	Overall	24/(13.9%)|29	13/(7.5%)|16	37/(10.7%)|45
	– Headache	15/(8.7%)|16	5/(2.9%)|5	20/(5.8%)|21
Psychiatric disorders	Overall	6/(3.5%)|7	13/(7.5%)|13	19/(5.5%)|20
Renal and urinary disorders	Overall	13/(7.5%)|13	6/(3.5%)|6	19/(5.5%)|19
Respiratory, thoracic and mediastinal disorders	Overall	12/(6.9%)|16	15/(8.7%)|16	27/(7.8%)|32
Skin and subcutaneous tissue disorders	Overall	12/(6.9%)|19	14/(8.1%)|16	26/(7.5%)|35
Vascular disorders	Overall	12/(6.9%)|14	12/(6.9%)|14	24/(6.9%)|28

Note: Number of patient (Percentage calculated from the number of subjects in the respective group)/ Number of TESSs
Source data: Table 6.2.2.1 Appendix 16.1.9.2

At a SOC level, the greatest proportion of patients experiencing TESSs was reported in blood and lymphatic system disorders (37.6% patients), gastrointestinal disorders (30.9% patients), investigations (21.1% patients), metabolism and nutrition disorders (20.2% patients) and general disorders and administration site conditions (19.9% patients).

At the Preferred term (PT) level, the most common TESSs included anaemia, febrile neutropenia, leukopenia, neutropenia, thrombocytopenia, constipation, diarrhoea, nausea, vomiting, mucosal inflammation, pyrexia, platelet count decreased, hyperglycaemia, hyperphosphataemia and headache. Among these events, some imbalance between treatment groups occurred; in particular, Febuxostat group retained a higher incidence of anaemia (22.5% vs. 14.5%), mucosal inflammation (6.4% vs. 1.7%), pyrexia (13.9% vs. 10.4%) and headache (8.7% vs. 2.9%), whereas Allopurinol treatment group retained a higher incidence of neutropenia (23.7% vs. 17.9%). No other notable difference between treatment groups was detected for the remaining above mentioned PTs.

Treatment-related TESSs:

TESSs which were judged by the investigator as treatment related were reported in a total n= 22 (6.4%) patients, without any difference between treatment groups being reported in n=11 (6.4%) patients in each treatment group. The majority of patients experiencing treatment-related TESSs had either mild or moderate treatment-related events, with a slightly higher proportion of patients experiencing moderate

treatment-related events in Allopurinol treatment group (1.2% vs 4.6% in Febuxostat and Allopurinol arm respectively).

Mild to moderate related TESSs occurring in ≥1% patients in any treatment group are shown in Table 15. The SOCs most frequently affected by mild and moderate treatment-related TESSs were investigations and gastrointestinal disorders, without imbalances between treatment groups. The most frequent mild and moderate treatment-related events were blood uric acid decreased and diarrhoea, both occurring in 3 (0.9%) patients in total.

Table 15: Mild and moderate treatment-related TESSs reported in ≥ 1% patients in any treatment group by MedDRA SOC, PT, and treatment - Safety Population

SOC	PT	Febuxostat (N=173)	Allopurinol (N=173)	Overall (N=346)
Gastrointestinal disorders	Overall	3/(1.7%)|4	3/(1.7%)|4	6/(1.7%)|8
	- Diarrhoea	2/(1.2%)|2	1/(0.6%)|1	3/(0.9%)|3
Investigations	Overall	3/(1.7%)|3	5/(2.9%)|6	8/(2.3%)|9
	- Blood uric acid decreased	3/(1.7%)|3	0/(0.0%)|0	3/(0.9%)|3
Skin and subcutaneous tissue disorders	Overall	1/(0.6%)|1	2/(1.2%)|2	3/(0.9%)|3
	- Pruritus	0/(0.0%)|0	2/(1.2%)|2	2/(0.6%)|2

Note: Number of patient (Percentage calculated from the number of subjects in the respective group)/ Number of TESSs
Note: Treatment-related TESSs are those with relationship recorded as 'certainly related', 'probably related', 'possibly related' or 'unassessable/unclassifiable' on the AE page

A total of 3 treatment-related TESSs judged as severe in intensity occurred in 2 (0.6%) patients, both allocated to Allopurinol treatment group (Table 16).

Table 16: Severe treatment-related TESSs by MedDRA SOC, PT, and treatment - Safety Population

System Organ Class	Preferred Term	Febuxostat (N=173)	Allopurinol (N=173)	Overall (N=346)
Gastrointestinal disorders	Overall	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
	- Nausea	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
Hepatobiliary disorders	Overall	0/(0.0%)|0	1/(0.6%)|2	1/(0.3%)|2
	- Cholestasis	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
	- Hepatotoxicity	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1

Note: Number of patient (Percentage calculated from the number of subjects in the respective group)/ Number of TESSs
Note: Treatment-related TESSs are those with relationship recorded as 'certainly related', 'probably related', 'possibly related' or 'unassessable/unclassifiable' on the AE page

Table 17: Treatment-related TESSs by MedDRA SOC, PT, and treatment -Safety Population

SOC	PT	Febuxostat (N=173)	Allopurinol (N=173)	Overall (N=346)
Blood and lymphatic system disorders	Overall	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
	Thrombocytopenia	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
Cardiac disorders	Overall	2/(1.2%)|2	0/(0.0%)|0	2/(0.6%)|2
	Bundle branch block left	1/(0.6%)|1	0/(0.0%)|0	1/(0.3%)|1
	Sinus tachycardia	1/(0.6%)|1	0/(0.0%)|0	1/(0.3%)|1
Gastrointestinal disorders	Overall	3/(1.7%)|4	3/(1.7%)|5	6/(1.7%)|9
	Abdominal pain upper	1/(0.6%)|1	1/(0.6%)|1	2/(0.6%)|2
	Diarrhoea	2/(1.2%)|2	1/(0.6%)|1	3/(0.9%)|3
	Nausea	1/(0.6%)|1	1/(0.6%)|2	2/(0.6%)|3
	Vomiting	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
General disorders and administration site conditions	Overall	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
	Oedema peripheral	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
Hepatobiliary disorders	Overall	0/(0.0%)|0	1/(0.6%)|2	1/(0.3%)|2
	Cholestasis	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
	Hepatotoxicity	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
Investigations	Overall	3/(1.7%)|3	5/(2.9%)|6	8/(2.3%)|9
	Alanine aminotransferase increased	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
	Aspartate aminotransferase increased	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
	Blood urea increased	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
	Blood uric acid decreased	3/(1.7%)|3	0/(0.0%)|0	3/(0.9%)|3
	Gamma-glutamyltransferase increased	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
	QRS axis abnormal	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
	pH urine increased	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
Metabolism and nutrition disorders	Overall	1/(0.6%)|1	1/(0.6%)|1	2/(0.6%)|2
	Decreased appetite	1/(0.6%)|1	0/(0.0%)|0	1/(0.3%)|1
	Diabetes mellitus	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
Musculoskeletal and connective tissue disorders	Overall	1/(0.6%)|1	0/(0.0%)|0	1/(0.3%)|1
	Muscular weakness	1/(0.6%)|1	0/(0.0%)|0	1/(0.3%)|1
Psychiatric disorders	Overall	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
	Insomnia	0/(0.0%)|0	1/(0.6%)|1	1/(0.3%)|1
Skin and subcutaneous tissue disorders	Overall	1/(0.6%)|1	2/(1.2%)|2	3/(0.9%)|3
	Hyperhidrosis	1/(0.6%)|1	0/(0.0%)|0	1/(0.3%)|1
	Pruritus	0/(0.0%)|0	2/(1.2%)|2	2/(0.6%)|2
Vascular disorders	Overall	1/(0.6%)|1	0/(0.0%)|0	1/(0.3%)|1
SOC	PT	Febuxostat (N=173)	Allopurinol (N=173)	Overall (N=346)
	Haemorrhage	1/(0.6%)|1	0/(0.0%)|0	1/(0.3%)|1

Note: Number of patient (Percentage calculated from the number of subjects in the respective group)/ Number of TESSs
Note: Treatment-related TESSs are those with relationship recorded as 'certainly related', 'probably related', 'possibly related' or "unassessable/unclassifiable' on the AE page
Source data: Table 6.2.3, Appendix 16.1.9.2

Serious adverse event / deaths / other significant events

Serious adverse event:

A total of 45 serious TESSs occurred in 27 (7.8%) patients, with a higher proportion in Febuxostat treatment group (12.1% vs 3.5% in Febuxostat and Allopurinol arm respectively), however none of them were judged by the investigator as treatment related in any treatment group.

The SOCs most frequently affected by serious TESSs (including fatal events) were infections and infestations with 13 events occurring in 10 (2.9%) patients in total, blood and lymphatic system disorders with 10 events occurring in 6 (1.7%) patients in total and *investigations* with 4 events occurring in 4 (1.2%) patients in total. Apart from a higher number of serious TESSs belonging to the SOC infections and infestations and a slightly higher percentage of patients experiencing such events in Febuxostat treatment group, namely 11 events in 8 (4.6%) patients and 2 events in 2 (1.2%) patients in Febuxostat and Allopurinol arm respectively, no remarkable difference between treatment groups occurred at the SOC level.

The most frequently serious TESSs by PT were *pneumonia* occurring in 7 (2.0%) patients in total and febrile neutropenia, occurring in 4 (1.2%) patients in total. Both type of events occurred in a slightly higher number and percentage of patients in Febuxostat treatment group, namely 5 (2.9%) and 2 (1.2%) patients in Febuxostat and Allopurinol treatment group respectively for pneumonia and 3 (1.7%) and 1 (0.6%) patients in Febuxostat and Allopurinol treatment group respectively for febrile neutropenia.

A summary of the serious TESSs reported in ≥1% patients overall by SOC and PT is provided in Table 18.

Table 18: Serious TESSs reported in ≥1% patients overall by MedDRA SOC, PT, and treatment Safety Population

Table 12-4: Serious TESSs reported in ≥ 1% patients overall by MedDRA SOC, PT, and treatment - Safety Population

SOC	PT	Febuxostat (N=173)	Allopurinol (N=173)	Overall (N=346)
Blood and lymphatic system disorders	Overall	4/(2.3%)|7	2/(1.2%)|3	6/(1.7%)|10
	Febrile neutropenia	3/(1.7%)|3	1/(0.6%)|1	4/(1.2%)|4
Infections and infestations	Overall	8/(4.6%)|11	2/(1.2%)|2	10/(2.9%)|13
	Pneumonia	5/(2.9%)|5	2/(1.2%)|2	7/(2.0%)|7
Investigations	Overall	3/(1.7%)|3	1/(0.6%)|1	4/(1.2%)|4

Note: Number of patient (Percentage calculated from the number of subjects in the respective group)/ Number of TESSs
Source data: Table 6.3.1, Appendix 16.1.9.2

A total of 3 TESSs leading to treatment withdrawal occurred in 1 (0.3%) patient, who was allocated to Febuxostat; the events were serious and, as above, were judged by the investigator as not related to study treatment.

Other serious adverse events:

Other serious events not resulting in death are displayed in Table 19. Twenty-two serious TESSs not resulting in death occurred in 17 patients in the Febuxostat treatment group, whereas 8 serious TESSs not resulting in death occurred in 6 patients in Allopurinol treatment group. Overall, the types of events were expected in the light of the study population, with the exception of cerebral ischaemia which occurred to patient 390702, allocated to Febuxostat treatment group, and was assessed as unlikely related to study treatment, by both the Investigator and the Sponsor. No serious TESSs with outcome other than fatal led to treatment withdrawal.

Table 19: Patients with serious TESSs not resulting in death – Safety Population

Treatment group	PT	Outcome	Seriousness
Allopurinol	Pneumonia	resolved	Requires or prolongs hospitalization
Febuxostat	Tumour lysis syndrome	resolved	Requires or prolongs hospitalization
Febuxostat	Sepsis	resolved	Life-threatening
Febuxostat	Pneumonia	not resolved	Other: CHEST DISCOMFORT TO INSPIRE
Febuxostat	Febrile neutropenia	not resolved	Life-threatening
Febuxostat	Hypovolaemia	resolved	Requires or prolongs hospitalization
Febuxostat	Bronchitis	not resolved	Requires or prolongs hospitalization
Febuxostat	Atrial fibrillation	resolved	Requires or prolongs hospitalization
Allopurinol	Hypokalaemia	resolved	Persistent or significant disability or incapacity
Allopurinol	Pneumonia	resolved	Other: LEFT SIDE PNEUMONIE
Allopurinol	Hypotension	resolved	Requires or prolongs hospitalization
Allopurinol	Febrile neutropenia	resolved	Requires or prolongs hospitalization
	Platelet count decreased	resolved with sequelae	Requires or prolongs hospitalization
Febuxostat	Headache	resolved	Requires or prolongs hospitalization
Febuxostat	Febrile neutropenia	resolved	Requires or prolongs hospitalization
	Leukopenia	resolved	Requires or prolongs hospitalization
	Anaemia	resolved	Requires or prolongs hospitalization
	Platelet count decreased	resolved	Requires or prolongs hospitalization
Febuxostat	Headache	resolved	Requires or prolongs hospitalization
Febuxostat	Blood bilirubin increased	not resolved	Requires or prolongs hospitalization
	Leukopenia	resolved	Other: GRADE 4 , RELATED TO CHEMOTHERAPY
	Neutropenia	resolved	Other: RELATED TO CHEMOTHERAPY
Febuxostat	White blood cell count decreased	resolved	Requires or prolongs hospitalization
Febuxostat	Pleural effusion	resolved	Requires or prolongs hospitalization
Febuxostat	Cerebral ischaemia	not resolved	Persistent or significant disability or incapacity
Febuxostat	Pneumonia	resolved	Other: DYSPNOE AND HYPOXEMIA WHICH NEEDED OXYGENE
Febuxostat	Abdominal pain	resolved	Requires or prolongs hospitalization
Allopurinol	Neutropenia	resolved	Requires or prolongs hospitalization
	Thrombocytopenia	resolved	Requires or prolongs hospitalization
Febuxostat	Pyrexia	unknown	Requires or prolongs hospitalization

2 and Listing 7, Appendix 16.2.7

Deaths:

A total of 15 TESSs with fatal outcome (including also those which started within the study period but resulted in death after the End of Study Visit) occurred in 6 (1.7%) patients, all allocated to Febuxostat treatment group. None of them was judged by the investigator as related to study treatment. Only 3 out of these 6 patients experienced TESSs with a fatal outcome during the study period, i.e. before their End of Study Visit (one patient experienced fatal pneumonia, sepsis and septic shock, one patient experienced fatal myocardial ischaemia and acute cardiac failure, one patient experienced fatal haematuria, sepsis and shock). The 3 fatal events reported by the third patient led also to treatment withdrawal (see Table 21).

On the other hand, 3 patients experienced TESSs during the study period which had a fatal outcome after the respective End of Study Visit (by PT: one patient experienced fatal bronchitis, one patient experienced fatal atrial fibrillation, pneumonia and renal failure, one patient experienced fatal febrile neutropenia, pneumonia and respiratory failure). It should be noted that the second patient received commercial Allopurinol 300 mg twice daily while on study (with "AE renal failure" as indication) up to 2 days prior patient's death. This was reported as a protocol deviation.

Finally, two further patients (one allocated to Febuxostat and another to Allopurinol treatment group) experienced not treatment-related TESSs with fatal outcome that were notified to the Sponsor although their onset date occurred after the End of Study Visit.

List of deaths occurred in the study are summarized in Table 20:

Table 20: Patients with TESSs with fatal outcome – Safety Population

Treatment group	Fatal TESSs by PT
Febuxostat	Pneumonia Sepsis Septic shock
Febuxostat	Myocardial ischaemia Cardiac failure acute
Febuxostat	Haematuria Sepsis Shock
Febuxostat	Bronchitis
Febuxostat	Atrial fibrillation Pneumonia Renal failure
Febuxostat	Febrile neutropenia Pneumonia Respiratory failure

Table 21: Patients with TESSs leading to treatment withdrawal – Safety Population

Treatment group	PT	Outcome	Action taken
Febuxostat	Haematuria	Death	Drug withdrawn permanently
	Sepsis	Death	Drug withdrawn permanently
	Shock	Death	Drug withdrawn permanently

Other significant adverse events:

Six TESSs leading to dose reduction occurred in 4 patients in Febuxostat treatment group, whereas no TESSs leading to dose reduction occurred in Allopurinol treatment group (note: only Allopurinol dose reduction was actually allowed). These events are displayed in Table 22.

Three of these events were considered related to study drug and were by PT blood uric acid decreased. These events occurred in 3 consecutive patients enrolled at the same study site. The other events leading to dose reduction were tumour lysis syndrome, renal failure and hyperphosphataemia, all occurring in one patient which was considered by the MAH as a Special Case with lack of drug effect.

Table 22: Patients with TESSs leading to dose reduction – Safety Population

Treatment group	PT	Outcome	Related
Febuxostat	Tumour lysis syndrome	resolved	No
	Renal failure	resolving	No
	Hyperphosphataemia	resolved	No
Febuxostat	Blood uric acid decreased	resolved	Yes
Febuxostat	Blood uric acid decreased	resolved	Yes
Febuxostat	Blood uric acid decreased	resolved	Yes

Laboratory findings

Serum biochemistry:

In the phase III pivotal trial, the following parameters had meaningful changes:

- LDH: a trend for decrease in mean LDH value occurred in both treatment groups with no notable difference between them. Such decrease was expected as a result of the efficacy of the chemotherapy regimens over the haematological diseases
- sUA: a trend for decrease in mean sUA value occurred in both treatment groups and was more pronounced in Febuxostat group. Such decrease occurred up to Visit 8 and Visit 9 (for patients who prolonged the treatment) consistently with the administration period of study drug. Besides,

it was expected as a result of the efficacy of both Febuxostat and Allopurinol in lowering sUA and was more pronounced in Febuxostat group consistently with the efficacy results.

No consistent trends for change over time were seen for any of the remaining serum biochemistry parameters during the study in any treatment group. A higher mean LDH value, consistent with its higher mean baseline, was detected in Febuxostat group at each visit with the exception of Visit 9. A lower mean sUA value was detected in Febuxostat compared to Allopurinol group at each visit since Visit 2 up to the end of treatment period, consistently with the efficacy results. No notable difference in other serum chemistry results was seen between the treatment groups.

Less than 5% of patients with baseline normal or abnormal (not clinically significant) value experienced a shift to a clinically significant abnormal postbaseline result for any serum biochemistry parameters at any selected time point (namely at Visit 3, i.e. start of chemotherapy, at Visit 8, i.e. Evaluation Visit and at Visit 10, i.e. End of Study Visit) in any treatment group, with no remarkable differences between treatment groups.

Haematology:

In the phase III pivotal trial, the following parameters had meaningful changes:

•Haemoglobin (Hb): a slight trend for decrease in mean Hb value occurred in both treatment groups with no notable difference between them

•Haematocrit (Htc): a slight trend for decrease in mean Htc value occurred in both treatment groups with no notable difference between them

•Absolute lymphocyte count: a trend for decrease in mean absolute lymphocyte count occurred in both treatment groups and was slightly more pronounced in Febuxostat group

•Absolute monocyte count: a trend for decrease in mean absolute monocyte count occurred in both treatment groups with no notable difference between them

•Absolute neutrophil count: a trend for decrease in mean absolute neutrophil count occurred in both treatment groups with no notable difference between them. Its clinical relevance was remarked by a relevant increase in the percentage of patients with absolute neutrophil count assessed as abnormal clinically significant at the End of Study Visit, which occurred in the overall safety population (from 4.6% at baseline to 20.9% at the End of Study Visit) and in both treatment groups with no notable difference between them (namely 5.8% to 20.1% and 3.5% to 21.8% at baseline and End of Study Visit in Febuxostat and Allopurinol group respectively).

•Platelet count: a slight trend for decrease in mean platelet count occurred in both treatment groups and was slightly more pronounced in Febuxostat one

•White blood cells (WBC) count: a trend for decrease in mean WBC count occurred in both treatment groups and was slightly more pronounced in Febuxostat one

These trends for changes were expected in the light of the study population and the slight differences observed between treatment groups were likely due to their differences in terms of HM and of chemotherapy regimens. No clinically relevant trends for change over time were seen for any of the remaining haematology parameters during the study in either the Febuxostat or Allopurinol group. No notable difference in other haematology results was seen between the treatment groups.

Parameters for which ≥5% of patients with baseline normal or abnormal (not clinically significant) value experienced a shift to a clinically significant abnormal post-baseline result at any selected time point (namely at Visit 3, start of chemotherapy, at Visit 8, Evaluation Visit and at Visit 10, End of Study Visit) in any treatment group were as following:

•Absolute neutrophil count: 5.9% and 18.4% patients in total at Visit 8 and Visit 10 respectively, with no remarkable differences between treatment groups

•WBC count: 14.7% at Visit 10, with a slightly higher proportion in Allopurinol treatment group (15.6% and 19.6% in Febuxostat and Allopurinol arm respectively)

•Neutrophil (%): 11.8% patients in total at Visit 10, with no remarkable differences between treatment groups

•Platelet count: 8.8% patients in total at Visit 10, with no remarkable differences between treatment groups

•Hb: 4.1% patients in total at Visit 10, with a higher proportion in Febuxostat treatment group (6.9% and 2.6% in Febuxostat and Allopurinol arm respectively)

•Absolute lymphocyte count: 3.1% at Visit 10, with a slightly higher proportion in Febuxostat treatment group (5.4% and 1.4% in Febuxostat and Allopurinol arm respectively)

•Htc: 2.7% patients in total at Visit 10, with a higher proportion in Febuxostat treatment group (5.2% and 0.6% in Febuxostat and Allopurinol arm respectively)

These shifts occurred at time points consistent with the expected haematological toxicity of chemotherapy, and the differences observed between treatment groups were likely due to the heterogeneity of chemotherapy regimens administered to patients.

Individual clinically significant abnormalities

Adverse events relating to haematology abnormalities reported in ≥5% of patients overall were neutropenia (20.8% patients in total), anaemia (18.5% patients in total), leukopenia (15.6% patients in total) and thrombocytopenia (13.0% patients in total). No notable differences between treatment groups were seen for leukopenia and thrombocytopenia, whereas there was a higher incidence of anaemia in Febuxostat group (22.5% and 14.5% in Febuxostat and Allopurinol treatment group respectively) and a higher incidence of neutropenia in Allopurinol group (17.9% and 23.7% in Febuxostat and Allopurinol treatment group respectively).

Serious TESSs pertaining to haematology abnormalities were reported in small numbers of patients: leukopenia, neutropenia and platelet count decreased in 2 (0.6%) patients in total each, anaemia, thrombocytopenia and white blood cell count decreased in 1 (0.3%) patients in total each. No remarkable differences were seen between the treatment groups in the reporting of these serious TESSs.

Serious TESSs relating to serum biochemistry abnormalities were reported in small numbers of patients as well: blood bilirubin increase, hypokalaemia, tumour lysis syndrome and renal failure in 1 (0.3%) patient/each parameter. Hypokalaemia occurred in Allopurinol treatment group, whereas the others occurred in Febuxostat group.
Only one event of haematuria occurring in 1 (0.3%) patients in total (allocated to Febuxostat) was reported among serious TESSs pertaining to urinalysis abnormalities.

Urinalysis:

No clinically relevant trends for change over time were seen for any of parameter during the study in either Febuxostat or Allopurinol group. Less than 2% of patients with baseline normal or abnormal (not clinically significant) value experienced a shift to a clinically significant abnormal post-baseline result for urinalysis parameters at any selected time point (namely at Visit 3, start of chemotherapy, at Visit 8, Evaluation Visit and at Visit 10, End of Study Visit) in any treatment group, with no remarkable differences between treatment groups.

Vital Signs, Physical Findings and Other Observations Related to Safety:

No clinically significant treatment differences or changes from baseline were observed for any vital sign. At Visit 10 (End of Study) only a small percentage of patients for each baseline Performance Status (PS) score worsened in a higher PS score with no relevant unbalance between treatment groups. At Visit 10 (End of Study) only a small number of patients for each physical examination parameter worsened from either normal or abnormal not clinically significant to abnormal clinically significant findings. The parameter with the higher proportion of patients worsening from either normal or abnormal not clinically significant to abnormal clinically significant findings not linked with target HM was skin, with no relevant unbalance between treatment groups. At Visit 10 (End of Study) only 3 patients in each treatment group with either normal or abnormal not clinically significant baseline for 12-lead-ECG shifted to abnormal clinically significant findings.

Discontinuation due to adverse events

Seven (2.0%) patients, out of 346 randomised, discontinued the study after randomisation, thus resulting in a total of 339 patients completing the study. Three patients (allocated to Febuxostat) discontinued the study due to “Death”. Two patients (allocated to Allopurinol) discontinued the study due to “Withdrawal by patient”. One patient (allocated to Allopurinol) discontinued the study due to “Protocol Violation” and another patient (allocated to Febuxostat) discontinued the study due to “Patient refused to come to scheduled Visit 10”. None of these 7 discontinued patients attended the End-of-study visit (Table 23).

Table 23 - Patients who discontinued the study after randomization (discontinuations)

Treatment	Last Visit	Duration of treatment before discontinuation	Course of treatment	End of Treatment reason	Course of study	End of study reason
Febuxostat	11MAR2013	6	Premature End of Treatment	OTHER REASON	Premature Study termination	PATIENT DEAD
Febuxostat	02MAY2013	8	Regular end of Treatment	ADVERSE EVENT	Premature Study termination	DEATH
Allopurinol	15FEB2013	3	Premature End of Treatment	WITHDRAWAL BY PATIENT	Premature Study termination	Withdrawal by patient
Febuxostat	01APR2013	5	Premature End of Treatment	ADVERSE EVENT	Premature Study termination	DEATH
Allopurinol	29APR2013	5	Premature End of Treatment	WITHDRAWAL BY PATIENT	Premature Study termination	Withdrawal by patient
Allopurinol	11JUN2013	5	Premature End of Treatment	PROTOCOL VIOLATION	Premature Study termination	Protocol Violation
Febuxostat	11JUL2013	6	Regular end of Treatment	WITHDRAWAL BY PATIENT	Premature Study termination	PATIENT REFUSED TO COME TO SCHEDULED VISIT 10, VISIT WAS NOT DONE

Post marketing experience

The below table (Table 24) displays the worldwide post-marketing patient exposure by dose and by geographic area. Patient exposure, expressed in patient-year (PY) has been estimated by assuming that a patient takes 1 tablet a day for 365.25 days, whatever the dose.

Table 24. Estimated cumulative post-marketing patient exposure by dose and by geographic area at April 2014.

Strenght	North America	Europe	Asia and Middle East	Worldwide
10 mg	0	0	535,718	535,718
20 mg	0	0	757,191	757,191
40 mg	485,654	0	66,830	552,484
80 mg	158,800	663,831	54,608	877,239
120 mg	0	61,334	317	61,651
Total	644,454	725,165	1,414,664	2,784,283

Cumulatively, post-marketing exposure amounted to about 2.8 million PY, 725,165 of which in countries of the EEA. The EEA exposure at 120 mg amounted to 61,334 PY, corresponding to about 8% of the total EEA exposure. It is worth noting that this percentage is similar to the difference between the proportion of patients achieving targeted sUA levels <6 mg/dL at 80 (73%) and 120 mg (79%) at the final visit in Phase III studies for gout.

8,287 of spontaneously reported (non solicited) adverse drug reactions (ADRs) and 55 serious ADRs (SADRs) from post-marketing solicited sources have been collected worldwide in the post-marketing surveillance. These ADRs were described in 5,057 cases, 971 of which met the seriousness criteria for a total of 1,871 SADRs. Table 25 displays ADRs by System Organ Class (SOC) and seriousness.

Table 25. Cumulative post-marketing ADRs (spontaneous serious and non-serious and serious solicited) by SOC and Seriousness.

System Organ Class	Serious	Non-serious	Total spontaneous	Serious solicited
Infections and infestations	46	40	86	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	16	3	19	4
Blood and lymphatic system disorders	96	40	136	1
Immune system disorders	26	48	74	0
Endocrine disorders	2	7	9	0
Metabolism and nutrition disorders	76	666	742	7
Psychiatric disorders	30	126	156	0
Nervous system disorders	127	487	614	6
Eye disorders	27	67	94	0
Ear and labyrinth disorders	8	19	27	0
Cardiac disorders	162	70	232	5
Vascular disorders	42	61	103	4
Respiratory, thoracic and mediastinal disorders	74	98	172	1
Gastrointestinal disorders	115	810	925	2
Hepatobiliary disorders	83	69	152	2
Skin and subcutaneous tissue disorders	193	1200	1393	1
Musculoskeletal and connective tissue disorders	106	566	672	3
Renal and urinary disorders	197	240	437	6
Pregnancy, puerperium and perinatal conditions	0	0	0	0
Reproductive system and breast disorders	4	74	78	0
Congenital, familial and genetic disorders	0	0	0	0
General disorders and administration site conditions	183	707	890	3
Investigations	169	990	1159	2
Injury, poisoning and procedural complications	21	68	89	1
Surgical and medical procedures	12	10	22	3
Social circumstances	1	5	6	0
TOTAL	1816	6471	8287	55

The dose was known in 75% of collected cases: no difference was observed in the overall reporting rate by dose (2.37, 2.03 and 1.64 cases per 1000 PY at 40, 80 and 120 mg, respectively). For cases meeting the seriousness criteria the dose was known in 78% of cases; also for serious case no trend for a dose-relationship in the reporting rate was observed (0.36, 0.46 and 0.41 serious cases per 1000 PY at 40, 80 and 120 mg, respectively).

The SOC cumulating the greatest number of ADRs was “Skin and subcutaneous tissue disorders” (n = 1,393, 14% of which serious), where the most represented PT was “Rash” (listed, n = 426, 17 of which serious). The PT including the greatest number of SADRs was “Pruritus” (listed, n = 20), followed by “Rash”.

The second SOC in number of events was “Investigations” (n = 1,159, 15% of which serious), where the most represented PT was “Liver function test abnormal” (listed, n = 152, 14 of which serious) whereas the term cumulating the greatest number of SADRs was “Hepatic enzyme increased” (listed, n = 17). The second PT including the greatest number of SADRs was “Liver function test abnormal”.

The third SOC in number of events was “Gastrointestinal disorders” (n = 925, 12% of which serious), where the most represented PT was “Nausea” (listed, n = 225, 12 of which serious). The PT gathering the greatest number of SADRs was “Diarrhoea” (listed, n = 26), followed by “Nausea”.

The fourth SOC in number of events was “General disorders and administration site conditions” (n = 890, 21% of which serious), where the most represented PT was “Drug ineffective” (listed by definition, n = 141, 1 serious). The PT cumulating the greatest number of SADRs was “Drug interaction” (n = 27) where the most commonly reported interaction in serious cases was with azathioprine (listed). The second PT including the greatest number of SADRs was “Malaise” (n = 17); this term is unlisted, but it is very generic term and, accordingly was described in cases reporting an array of heterogeneous symptoms.

The fifth SOC in number of events was “Metabolism and nutrition disorders” (n = 742, 10% of which serious), where the most represented PT was “Gout”, referring to the LLT “Gout flares” (listed, n = 629, 31 serious), which was also the first PT in number of SADRs, whereas the second PT gathering the greatest number of serious events was “Dehydration” (n = 11, unlisted) which was described in most of cases concerning elderly patients often suffering from diarrhea or vomiting.

The sixth SOC in number of events was “Musculoskeletal and connective tissue disorders” (n = 672, 16% of which serious), where the most represented PT was “Arthralgia” (listed, n = 180, 26 of which serious). This PT, together “Rhabdomyolysis” (listed), was also the term cumulating the greatest number of serious events.

The seventh SOC in number of events was “Nervous system disorders” (n = 614, 21% of which serious), where the most represented PT was “Dizziness” (listed, n = 148, 14 of which serious). The PT cumulating the greatest number of SADRs was “Cerebrovascular accident” (n = 25, unlisted), followed by “Dizziness”. Concerning cerebrovascular accidents, these events more likely reflects cardiovascular co-morbidities of the target patient population, rather than being causally related to febuxostat. In fact, it is worth pointing out that hyperuricaemia itself is a risk factor for developing these kinds of events as widely described in the literature.

The eighth SOC in number of events was “Renal and urinary disorders” (n = 437, 45% of which serious), where the most represented PT was “Renal failure acute” (listed, n = 79, 78 of which serious), this PT, together “Renal failure” (listed n = 55 serious events), was the term cumulating the greatest number of SADRs. As for cerebrovascular accidents, renal events, and renal failure in particular, should be considered a very common consequence of hyperuricaemia (e.g., Fuldeore et al., 2011), rather than being associated to febuxostat treatment; hyperuricaemia itself is in the vast majority of cases a renal disease due to the impairment of uric acid excretion at the renal level. Actually there is evidence that febuxostat exerts some protection on the deterioration of the renal function in gout patients (Whelton et al., 2013). Furthermore, 3 studies (Filiopulos et al., 2013; Ivanov and Ivanova, 2013; Kanai et al., 2013) have confirmed the long-term efficacy and safety of febuxostat in patients with moderate to severe chronic kidney disease. Finally, although carried out in a limited number of patients, a recent study on patients under dialysis indicated that febuxostat was effective and well tolerated in these patients (Horikoshi et al., 2013).

The ninth SOC in number of events was “Cardiac disorders” (n = 232, 70% of which serious), where the most represented PT was “Palpitations” (listed, n = 50, 9 of which serious). The PT gathering the greatest number of serious events was “Myocardial infarction” (unlisted, n = 38), followed by “Cardiac failure” (unlisted, n = 27). Again, cardiovascular diseases are a common background of gout and hyperuricaemia, as about 26% had history of ischaemic heart diseases including infarction and heart failure (Singh et al., 2011; Perez-Ruiz et al., 2014). Patients with gout are also predisposed to heart failure and infarction because: i) The presence of other cardiovascular comorbidities, and risk factors for myocardial infarction and heart failure in about 74% of patients (Singh et al., 2011); ii) previous history of infarction or heart failure (Thanassoulis et at., 2010); iii) gout/hyperuricemia is recognised as an independent risk factor for heart failure as gout patients had 2 to 3-fold higher incidence of heart failure or myocardial infarction, including events with fatal outcome (Perez-Ruiz et al., 2014), as compared with those without gout

(Krishnan et al, 2012). Therefore, these serious cardiac events are much more likely representing outcomes of gout rather than ADRs caused by febuxostat.

The tenth SOC in number of events was “Respiratory, thoracic and mediastinal disorders” (n = 172, 43% of which serious), where the most represented PT was “Dyspnoea” (listed, n = 60, 21 of which serious); “Dyspnoea” was also the PT gathering the greatest number of serious events, followed by “Pulmonary embolism” (unlisted, n = 10). As for other cardiovascular events, gout and hyperuricemia also represent risk factors for the development of pulmonary embolism (Yamada et al., 2010).

Overall the safety profile emerging from the post-marketing surveillance widely overlaps to that for allopurinol, being “Skin and subcutaneous tissue disorders”, “Investigations” (i.e., liver function), “Gastrointestinal disorders”, “Metabolism and nutrition disorders”, the most commonly affected SOCs for both drugs, thus confirming the findings of clinical trials whereas there is a clear evidence that all the above mentioned unlisted events (and also some of the listed ones, i.e., renal failure) are part of the natural history of the disease.

The safety profile which emerged from clinical studies was confirmed in the post-marketing experience, however some adverse drug reactions (ADRs) were exclusively collected in the postmarketing, probably because their frequency is rare enough to hinder the detection in clinical trials. Therefore skin/hypersensitivity reactions such as Anaphylactic reaction, Drug hypersensitivity, Toxic epidermal necrolysis, Stevens-Johnson syndrome, Angioedema, Drug reaction with eosinophilia and systemic symptoms, generalised rash and pruritic rash have been added as rare ADRs in the product information on the basis of the post-marketing experience. Likewise hepatic events such as Jaundice and Liver injury, renal events (Tubulointerstital nephritis), and musculoskeletal events (Rhabdomyolysis) were inserted as rare ADRs on the basis of the postmarketing experience.

Currently 3 safety topics have been considered important identified risks for febuxostat (Serious skin / hypersensitivity ADRs, rhabdomyolysis and drug-drug interaction between febuxostat and azathioprine / mercaptopurine), whereas 6 additional safety topics such as cardiovascular events, hepatic events, renal events, neurological events, haematological / bleeding events and thyroid events were considered potential risks.

The important identified risks overlap with known safety issues for allopurinol, likewise allopurinol can be associated with cardiovascular events, hepatic events, renal events, neurological events, haematological / bleeding events and thyroid events, although some of these safety issues are due co-morbidities of the target patient population. Overall the emerging safety profile overlaps with that of allopurinol, therefore all ADRs identified to be causally related to febuxostat can be considered as class effects of xanthine oxidase inhibitors.

2.5.1. Discussion on clinical safety

The most common TESSs reported in the treatment groups were anaemia, febrile neutropenia, leukopenia, neutropenia, thrombocytopenia, constipation, diarrhoea, nausea, vomiting, mucosal inflammation, pyrexia, decreased platelet count, hyperglycaemia, hyperphosphataemia and headache. Among these events, some imbalance between treatment groups occurred; in particular, the febuxostat group showed a higher incidence of anaemia, mucosal inflammation, pyrexia and headache, whereas the allopurinol treatment group showed a higher incidence of neutropenia. No other notable difference between treatment groups was detected for the remaining PTs mentioned above.

There were 3 new treatment-related TESSs observed in the febuxostat arm of the study: left bundle branch block, sinus tachycardia and haemorrhage. The MAH proposed to implement these new TESSs in the product information of febuxostat which was agreed by the CHMP.

A higher proportion of patients in the febuxostat group experienced moderate and severe TESSs (41.0% vs. 37.6% and 31.2% vs. 18.5% for moderate and severe TESSs in febuxostat and allopurinol group respectively) and also a higher proportion of patients in the febuxostat treatment group experienced serious TESSs (namely 12.1% vs. 3.5% in febuxostat and allopurinol group respectively), all of them were judged to be not treatment related in any treatment group by the investigator. The MAH provided a discussion regarding the imbalance of serious events, which occurred more frequently in the febuxostat group. It was explained that several factors have contributed to an imbalance in adverse events between treatment arms: bias caused by the imbalances in terms of types of HM and some other medical history conditions, the lack of restriction in terms of number of previous lines of chemotherapy and the chemotherapy regimens to be administered to the patients. The MAH also provided a detailed discussion about febrile neutropenia, pneumonia and infection which occurred with greater frequency in the febuxostat arm and mentioned that the same factors have contributed to an imbalance for these adverse events between treatment arms. The baseline imbalances between treatment groups were considered a plausible explanation by the CHMP.

A total of 6 (1.7%) patients experienced TESSs resulting in death and all were allocated to the febuxostat group, all of them were judged to be not treatment-related by the investigator. Based on the detailed analysis provided by the MAH of each fatal outcome in the FLORENCE study, a relation to the study treatment cannot be detected. However, currently a post marketing comparative cardiovascular safety study is ongoing (as described in the RMP) to clarify the cardiovascular risk profile of febuxostat vs. allopurinol (FAST). In view of the risk for cardiac arrhythmias and sudden death associated with TLS the CHMP requested as a precautionary measure cardiac monitoring as clinically appropriate during the therapy with febuxostat and the product information was updated accordingly.

Four patients in total experienced TESSs leading to dose reduction. These subjects were all allocated to febuxostat, whereas no TESSs leading to dose reduction occurred in allopurinol treatment group. In 3 patients, the event leading to the dose reduction was considered to be treatment-related as blood uric acid concentrations were excessively decreased for these 3 patients, thus reflecting the efficacy of the urate lowering treatment. The other events leading to dose reduction were tumour lysis syndrome, renal failure and hyperphosphataemia, all of which occurred in one patient. This was considered to be a special case of lack of drug effect by the sponsor. During the procedure, the MAH provided a detailed discussion about the patient with lack of drug effect. The MAH clarified that some prior or concomitant medications may have contributed to the development of the above conditions; therefore it is conceivable that several factors have led to their development. Particularly, the main contribution was likely given by some patient's baseline characteristics and conditions: elderly age, advanced stage DLCBL with bulky disease and high proliferative rate (as witnessed by the LDH level), generalized oedemas treated with intravenous diuretics and impaired renal function with reduced renal parenchymal reserve. Finally, it is also worth noting that the investigator decided (in blind condition) to continue the study treatment, thus confirming that the benefit/risk assessment was still in favour of continuing the urate-lowering treatment. Though it is acknowledged that sUA plays a key role in TLS and renal damage development, in some patients these complications may arise due to other factors which cannot be controlled with urate- lowering agents; nevertheless, as occurred for this patient, the maintenance of an adequate sUA control is essential to prevent further worsening in TLS and renal insufficiency. This rational was found acceptable by the CHMP.

No significant differences or changes from baseline were observed for any vital sign between febuxostat and allopurinol group.

Regarding the patients completing the study (339 out of 346 subjects completed the study), the number as well as the reason for the discontinuation were considered to be acceptable.

The SOCs with the highest number of spontaneous reported serious adverse events were renal and urinary disorders (197 ADRs), skin and subcutaneous tissue disorders (193 ADRs), general disorders and administration site conditions (183 ADRS) and investigations (169 ADRs).

Additional safety information from a completed clinical development program which has fully evaluated the safety and efficacy of Febuxostat 80 and 120 mg tablets for the chronic management of hyperuricemia in patients with gout and in addition, postmarketing safety information for Febuxostat was available. No new safety information can be identified from postmarketing experience which has not already been evaluated during former PSUR assessment procedures.

The MAH provided an assessment about interactions of febuxostat with cytotoxic chemotherapy which was based on already known febuxostat data and literature references available on anticancer drugs. No drug-drug interaction data of febuxostat with cytotoxic chemotherapy are available and possible interactions of febuxostat with any concomitantly administered cytotoxic drug cannot be excluded definitely. Therefore possible interactions of febuxostat with cytotoxic chemotherapy should be closely monitored in future PSURs (all cases including possible interactions should be reviewed and discussed). The RMP has also been updated accordingly. The MAH has also updated the wording in the PI as follows: “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”.

2.5.2. Conclusions on clinical safety

In the randomized, double-blind, Phase 3 pivotal FLORENCE study comparing febuxostat with allopurinol (in 346 patients undergoing chemotherapy for haematologic malignancies at intermediate-to-high risk of TLS), 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 febuxostat in gout, with the exception of the following three adverse reactions Left bundle branch block, sinus tachycardia and haemorrhage which were included in the product information. A total of 6 (1.7%) patients experienced TESSs resulting in death and all were allocated to the febuxostat group, all of them were judged to be not treatment-related by the investigator. Based on the detailed analysis provided by the MAH of each fatal outcome in the FLORENCE study, a relation to the study treatment cannot be detected. However, currently a post marketing comparative cardiovascular safety study is ongoing (as described in the RMP) to clarify the cardiovascular risk profile of febuxostat vs. allopurinol (FAST). In view of the known risk for cardiac arrhythmias and sudden death associated with TLS the CHMP requested as a precautionary measure cardiac monitoring as clinically appropriate during therapy with febuxostat and the product information was updated accordingly.

No interaction studies have been conducted by the MAH. The Florence study has not been designed to deliver information about interactions with cytotoxic chemotherapy and the product information has been updated accordingly. The MAH will closely monitor (as described in the RMP) the case reports of drug-drug interactions in the next PSURs. In addition, the MAH should submit the following safety data in the next PSUR:

- The MAH will closely monitor the case reports of drug-drug interactions in the next PSURs.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.2 could be acceptable if the MAH implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report. The PRAC endorsed PRAC Rapporteur assessment report is attached. The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 5.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	- Serious skin / hypersensitivity reactions - Rhabdomyolysis - Drug-drug interaction with azathioprine or mercaptopurine
Important potential risks	- Cardiovascular events - Hepatic events - Renal events - Neuropsychiatric events - Haematological / Bleeding events - Thyroid events - Off label use in the paediatric population (TLS specific)
Missing information	- Children and adolescents - Subjects in whom the rate of serum urate formation is greatly increased (eg, malignant disease and its treatment, Lesch-Nyhan syndrome) - Organ transplantation - Severe hepatic impairment - Pregnancy and lactation - Limited experience in: female patients, elderly patients, severe renal impairment, moderate hepatic impairment

	- Interaction with standard therapy of haematological malignancies (TLS specific) - Off label use in patients with solid tumors (TLS specific)

Pharmacovigilance plan

Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan.

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports (planned or actual)**
Febuxostat versus Allopurinol Streamlined Trial (FAST) A prospective, randomised, open-label, blinded endpoint (PROBE) clinical trial evaluating the long term cardiovascular safety of febuxostat in comparison with allopurinol in patients with chronic symptomatic hyperuricaemia (phase 4 study, category 1)	The primary objective is to compare the cardiovascular safety profile (in terms of Anti-Platelet Trialists' Collaboration, APTC events) of febuxostat versus allopurinol when taken for an average of 3 years in patients aged 60 years or older with chronic hyperuricaemia in conditions where urate deposition has already occurred. The secondary objectives are to evaluate other cardiovascular adverse events for both products.	Cardiovascular safety: the primary analysis will be based on the time from randomisation to the first occurrence of any adjudicated (by a blinded independent committee) event included in the APTC composite end point of: i) hospitalisation for non fatal myocardial infarction; ii) hospitalisation for non fatal stroke; iii) death due to a cardiovascular event.	Ongoing: 338 patients have been randomised out of 5,706 planned (status 07-Jan-2013)	31-Jan-2013 1st interim update 31-Jan-2014 2nd interim update 31-Jan-2015 3rd interim update 31-Jan-2016 4th interim update 30-Sep-2016 Final study report
Safety and drug-drug interaction study of cotreatment with febuxostat and low escalating doses of thiopurines in patients with inflammatory bowel diseases (study code MIOL/13/FEB+AZA-DDI/001) (phase 1 study, category 2)	The primary objective of this study is to evaluate the adjustment of thiopurine dose, during cotreatment with febuxostat, to maintain the efficacy and safety of	Drug drug interaction with azathioprine / mercaptopurine: The primary analysis will be based on: i) Thiopurine dose percentage reduction; ii) proportion of	Planned.	Protocol submitted along this report on 29-Jun-2013 (see Annex 8). Regulatory submission: December 2013.

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports (planned or actual)
	thiopurines in inflammatory bowel disease patients.	patients with 6-thioguanine nucleotide (6-TGN) levels in the acceptance range iii) 6-TGN concentrations determined in red blood cells.		Study start (first patient in): February 2014 Study finish (last patient out): January 2015 Study report: September 2015

In addition the following PhV-activity is planned

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Interaction with standard therapy of haematological malignancies (TLS)	Possible interactions of febuxostat with cytotoxic chemotherapy will be closely monitored in future PSURs (all cases including possible interactions will be reviewed and discussed). Routine pharmacovigilance.	Monitor the interaction with standard therapy of haematological malignancies and the patient safety

Risk minimisation measures

Summary of risk minimisation measures by safety concern

Safety concern	Pharmacovigilance Activities	Additional risk Minimisation Activities
Identified Risks		
Serious skin / hypersensitivity reactions	Routine Pharmacovigilance In vitro study for determining the extent of cross-reactivity of febuxostat on T cell clones sensitive to allopurinol and to characterise T cells from patients with Serious skin / hypersensitivity reactions to febuxostat when available	DHPC on Serious skin / hypersensitivity reactions (procedure RM2 018.1) submitted to EMA on 24-May-2012
Rhabdomyolysis	Routine	No additional risk minimisation measures

Safety concern	Pharmacovigilance Activities	Additional risk Minimisation Activities
	pharmacovigilance	are in place
Drug-drug interaction with azathioprine or mercaptopurine	Routine pharmacovigilance Clinical study MIOL/13/FEB+AZA-DDI/001	No additional risk minimisation measures are in place
Potential Risks		
Cardiovascular events	Routine Pharmacovigilance Clinical study FAST	No additional risk minimisation measures are in place
Hepatic events	Routine pharmacovigilance	No additional risk minimisation measures are in place
Renal events	Routine pharmacovigilance	No additional risk minimisation measures are in place
Neuropsychiatric events	Routine pharmacovigilance	No additional risk minimisation measures are in place
Haematological / Bleeding events	Routine pharmacovigilance	No additional risk minimisation measures are in place
Thyroid events	Routine pharmacovigilance	No additional risk minimisation measures are in place
Off label use in the paediatric population (TLS specific)	Routine pharmacovigilance	Medicinal product subjected to medical prescription
Missing Information		
Children and adolescents	Routine pharmacovigilance	No additional risk minimisation measures are in place
Subjects in whom the rate of serum urate formation is greatly increased (eg, malignant disease and its treatment, Lesch-Nyhan syndrome)	Routine pharmacovigilance	No additional risk minimisation measures are in place
Organ transplantation	Routine pharmacovigilance	No additional risk minimisation measures are in place
Severe hepatic impairment	Routine pharmacovigilance	No additional risk minimisation measures are in place
Pregnancy and lactation	Routine pharmacovigilance	No additional risk minimisation measures are in place
Limited experience in: female patients, elderly patients, severe renal impairment, moderate hepatic impairment.	Routine pharmacovigilance	No additional risk minimisation measures are in place
Interaction with standard therapy of haematological malignancies (TLS) *	Routine pharmacovigilance	No additional risk minimisation measures are in place

Safety concern	Pharmacovigilance Activities	Additional risk Minimisation Activities
Off-label use in patients with solid tumors (TLS specific)	Routine pharmacovigilance	Medicinal product subjected to medical prescription

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated. Particularly, a new warning with regard to the need to undergo cardiac examination has been added to the product information. The Package Leaflet has been updated accordingly.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The Phase III pivotal study showed that febuxostat is superior over allopurinol in terms of reduction of sUA (a well-established surrogate endpoint for TLS and renal impairment), in patients undergoing chemotherapy for haematological malignancies at intermediate to high risk of TLS. Moreover, results of this trial provide evidence that febuxostat is effective in preserving renal function.

The efficacy profile of febuxostat is maintained regardless of baseline hyperuricaemia (sUA level >7.5 mg/dL), creatinine level, type of HM, ECOG PS score and TLS risk grade as confirmed by the exploratory analyses performed in subpopulations of patients with different baseline characteristics.

A significantly higher sUA reduction compared to allopurinol is achieved after only 24 hours, which is a relevant factor in the prevention of urate-nephropathy, especially in patients in whom chemotherapy cannot be delayed.

On the whole, efficacy analyses provided clear evidence for a benefit of febuxostat over allopurinol in terms of control of sUA level throughout the whole treatment period while preserving renal function.

Furthermore, as the risk of TLS and renal events is known to increase for every mg/dl increase of sUA and febuxostat provided a mean sUA reduction of at least 1 mg/dL compared with allopurinol in the course of the trial, febuxostat is expected to provide a better control of sUA levels (and thereby lower the risk of TLS-consequences, e.g. renal damage) in patients undergoing chemotherapy, as compared to allopurinol.

Uncertainty in the knowledge about the beneficial effects

It has to be noted though, that in the submitted study (FLO-01), patients with only certain types of haematological malignancies (chronic lymphocytic leukaemia CLL, acute leukaemia AL and Lymphoma) were included. Therefore no data is available regarding other cytostatics and co-medications used in haematologic malignancies other than those involved in the study and possible interactions of these with Febuxostat, with the risk of having an impact on its efficacy, cannot be excluded at this point.
Regarding serum creatinine levels, no significant difference was found between the two treatment groups. This means that formally the co-primary efficacy endpoint of the trial was not met. This was due to the fact that renal function stayed equally stable over time on average in both treatment arms, and hence superiority of febuxostat over allopurinol (as postulated in the correspondingly planned statistical superiority test, SAP) could not be demonstrated. However, the CHMP is of the opinion that the demonstration of superiority versus allopurinol in terms of improved control of sUA levels that is seen as

a clinically well-established surrogate endpoint for TLS and renal impairment overrules this deficiency from a clinical perspective.

Risks

Unfavourable effects
In the FLORENCE study 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 Left bundle branch block, sinus tachycardia and haemorrhage which were included in the product information.

Uncertainty in the knowledge about the unfavourable effects
No interaction studies have been conducted by the MAH. The Florence study has not been designed to deliver information about interactions and the product information has been updated accordingly. The MAH will closely monitor the case reports of drug-drug interactions in the next PSURs. The product information and RMP have been updated accordingly.

A total of 6 (1.7%) patients experienced TESSs resulting in death and all were allocated to the febuxostat group, all of them were judged to be not treatment-related by the investigator. One of the fatal cases concerned a patient who died from myocardial ischaemia and acute cardiac failure, which was judged to be not treatment-related by the investigator. Based on the detailed analysis provided by the MAH of each fatal outcome in the FLORENCE study, a relation to the study treatment cannot be detected. However, currently a post marketing comparative cardiovascular safety study is ongoing (as described in the RMP) to clarify the cardiovascular risk profile of febuxostat vs. allopurinol (FAST). In view of the known risk for cardiac arrhythmias and sudden death associated with TLS the CHMP requested as a precautionary measure cardiac monitoring as clinically appropriate during therapy with febuxostat and the product information was updated accordingly.

Benefit-Risk Balance
Febuxostat at a dose of 120mg per day is an acceptable therapeutic option in the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of TLS.
It does not require dose-adjustments (i.e. for patients with renal impairment) as allopurinol does

In the submitted phase III study:

- AUC sUA1-8 was significantly lower in the febuxostat group in comparison with the allopurinol group P <0,0001 in the intermediate risk subgroup, p=0,0313 in the high risk group).

- A more rapid onset of action: sUA reduction through febuxostat begins on Day 2 (i.e. 24 hours after starting treatment vs. allopurinol requiring a minimum of 2 days), which could be beneficial for patients in whom chemotherapy administration cannot be delayed.

- A significant mean sUA reduction at each time point from Day 2 to Day 8, to an extent of 1 mg/dL and above, compared with allopurinol was maintained over time. It is known that for every milligram per decilitre (mg/dl)- increase in uric acid, the risk of TLS is increased 1.75-fold and the risk for renal events is increased 2.21-fold (Coiffier et alii, 2008).

- A lower rate of treatment failures (defined as presence of two or more consecutive values of sUA missing or > 7.5 mg/dL) was observed as compared to allopurinol (1.7 vs 4.0% respectively).

- A comparable safety-profile and no significant difference regarding mean change (%) of serum creatinine from baseline to Day 8 or at any time point, when compared with allopurinol.

- The oral administration of febuxostat, in contrast to rasburicase which is the standard therapy for patients at a high risk of TLS, but needs to be administered intravenously. Furthermore, rasburicase cannot be used in patients with G6PD deficiency.

Importance of favourable and unfavourable effects

As the risk of TLS and renal events is known to increase for every mg/dl increase of sUA and since febuxostat provided a mean sUA reduction of at least 1 mg/dL compared to allopurinol in the course of the trial, febuxostat is expected to provide better control of sUA levels (and thereby lower the risk of TLS-consequences, e.g. renal damage) in patients undergoing chemotherapy, as compared to allopurinol.

In the Florence study one of the fatal cases concerned a patient who died from myocardial ischaemia and acute cardiac failure, which was judged to be not treatment-related by the investigator A post marketing cardiovascular safety study (FAST) with febuxostat and allopurinol as comparator is being conducted to clarify the cardiovascular risk profile of Febuxostat vs. allopurinol (as described in the RMP). In view of the vulnerability of the new target population and the risk for cardiac arrhythmias and sudden death associated with TLS cardiac monitoring as clinically appropriate should be carried out during febuxostat treatment (as described in the product information).

Benefit-risk balance

Discussion on the Benefit-Risk Balance

The Phase III pivotal study showed that febuxostat was superior over allopurinol in terms of reduction of sUA (a well-established surrogate endpoint for TLS and renal impairment), in patients undergoing chemotherapy for Haematological Malignancies (HM) at intermediate to high risk of TLS. Moreover, results of this trial provide evidence that febuxostat is effective in preserving renal function.

The efficacy profile of febuxostat is maintained regardless of baseline hyperuricaemia (sUA level >7.5 mg/dL), creatinine level, type of HM, ECOG PS score and TLS risk grade as confirmed by the exploratory analyses performed in subpopulations of patients with different baseline characteristics. A significantly higher sUA reduction compared to allopurinol is achieved after only 24 hours, which is a relevant factor in the prevention of urate-nephropathy, especially in patients in whom chemotherapy cannot be delayed. On the whole, efficacy analyses provided clear evidence for a benefit of febuxostat over allopurinol in terms of control of sUA level throughout the whole treatment period while preserving renal function. Furthermore, as the risk of TLS and renal events is known to increase for every mg/dl increase of sUA and since febuxostat provided a mean sUA reduction of at least 1 mg/dL compared to allopurinol in the course of the trial, febuxostat is expected to provide better control of sUA levels (and thereby lower the risk of TLS-consequences, e.g. renal damage) in patients with intermediate and high risk TLS undergoing chemotherapy, as compared to allopurinol.

The CHMP concluded that the efficacy profile of febuxostat is maintained in terms of reduction of sUA in both, patients with intermediate and high risk of TLS. The reduction of sUA is deemed to be an established surrogate endpoint for TLS. Looking at the creatinine levels, it can also be concluded that the renal function in patients undergoing chemotherapy for haematological malignancies is preserved in both, patients with intermediate and high risk of TLS. 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 Left bundle branch block, sinus tachycardia and haemorrhage which were included in the product information.

The benefit-risk balance of febuxostat for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome is considered positive.
In addition, the CHMP considered that the MAH should submit the following safety data in the next PSUR:

- The MAH will closely monitor the case reports of drug-drug interactions in the next PSURs.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) accepted		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II

Extension of Indication to include the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Additional data exclusivity / market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet is updated in accordance.

Summary

Please refer to the scientific discussion Adenuric-H-C-777-II-37.