Clinical trial results:
Open label, multi-centre, parallel group study to compare the pharmacokinetics (PK), pharmacodynamics (PD) and safety of febuxostat between pediatric patients (>=6<18 years of age) and adults.

Summary

EudraCT number	2016-001445-61
Trial protocol	IT HU ES BG
Global end of trial date	25 July 2018

Results information

Result version number	v1 (current)
This version publication date	14 February 2019
First version publication date	14 February 2019

Trial information

Trial identification

Sponsor protocol code	FLO-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03605212
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Menarini Ricerche S.p.A.
Sponsor organisation address	Via Sette Santi 1, Florence, Italy, 50131
Public contact	Corporate Director of Clinical Sciences, Menarini Ricerche S.p.A., +39 055 56809990, ACapriati@menarini-ricerche.it
Scientific contact	Corporate Director of Clinical Sciences, Menarini Ricerche S.p.A., +39 055 56809990, ACapriati@menarini-ricerche.it

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001417-PIP01-12
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 July 2018
Global end of trial reached?	Yes
Global end of trial date	25 July 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

If any event(s) related to the conduct of the study or the development of the IMP affected the safety of the study participants, the Sponsor and the Investigator were to take appropriate urgent safety measures to protect the patients against any immediate hazard. The CAs and IRB/IECs were to be informed forthwith about these new events and the measures taken.
For patients participating in the study, Menarini Ricerche S.p.A. had stipulated an insurance policy in accordance with local regulatory requirements.

Background therapy:

First cycle of cytotoxic chemotherapy for the treatment of the underlying disease (hematological malignancy) starting 2 days after start of study drug treatment.

Evidence for comparator: -

Actual start date of recruitment	27 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Italy: 11
Worldwide total number of subjects	30
EEA total number of subjects	30

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	3
Adolescents (12-17 years)	3
Adults (18-64 years)	14
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was screened and enrolled on 27 Feb 2017. The last patient completed the study on 16 Jul 2018. The study was conducted at 17 sites in 4 European countries.

Pre-assignment

Screening details:

A total of 31 patients was screened, of whom 30 were enrolled and 28 completed the study regularly. Two enrolled patients were withdrawn from study drug treatment.

Period 1

Period 1 title	Day 1
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1_Cohort 2_Children

Arm description:

Children: DAY 1 before first febuxostat dosing.

Arm type	Cohort 1_Cohort 2_Children
Investigational medicinal product name	not applicable
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Not applicable for baseline period.

Arm title	Cohort 3_Cohort 4_Adolescents

Arm description:

Adolescents: DAY 1 before first febuxostat dosing.

Arm type	Cohort 3_Cohort 4_Adolescents
Investigational medicinal product name	not applicable
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Not applicable for baseline period.

Arm title	Adults

Arm description:

Adults: DAY 1 before first febuxostat dosing.

Arm type	Adults

Investigational medicinal product name	not applicable
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Not applicable for baseline period.

Number of subjects in period 1	Cohort 1_Cohort 2_Children	Cohort 3_Cohort 4_Adolescents	Adults
Started	3	3	24
Completed	3	3	24

Period 2

Period 2 title	Treatment Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1_Cohort 2_Children

Arm description:

Children (aged ≥6 - <12).

Arm type	Experimental
Investigational medicinal product name	Febuxostat 40 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cohort 1: 2x20 mg QD.
Minimum treatment duration was for 7 days starting from Visit 1 (Day 1), which should have occurred 2 days prior to the planned start of first chemotherapy cycle. The Investigator was given the possibility to prolong the treatment duration up to 9 days on the basis of the chemotherapy regimen administered to the patient.

Investigational medicinal product name	Febuxostat 60 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cohort 2: 3x20 mg QD.
Minimum treatment duration was for 7 days starting from Visit 1 (Day 1), which should have occurred 2 days prior to the planned start of first chemotherapy cycle. The Investigator was given the possibility to prolong the treatment duration up to 9 days on the basis of the chemotherapy regimen administered to the patient.

Arm title	Cohort 3_Cohort 4_Adolescents

Arm description:

Adolescents (aged ≥12 - <18).

Arm type	Experimental
Investigational medicinal product name	Febuxostat 80 mg
Investigational medicinal product code	
Other name	ADENURIC® 80 mg
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cohort 3: 1x80 mg QD.
Minimum treatment duration was for 7 days starting from Visit 1 (Day 1), which should have occurred 2 days prior to the planned start of first chemotherapy cycle. The Investigator was given the possibility to prolong the treatment duration up to 9 days on the basis of the chemotherapy regimen administered to the patient.

Investigational medicinal product name	Febuxostat 120 mg
Investigational medicinal product code	
Other name	ADENURIC® 120 mg
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cohort 4: 1x120mg QD.
Minimum treatment duration was for 7 days starting from Visit 1 (Day 1), which should have occurred 2 days prior to the planned start of first chemotherapy cycle. The Investigator was given the possibility to prolong the treatment duration up to 9 days on the basis of the chemotherapy regimen administered to the patient.

Arm title	Adults

Arm description:

Adults

Arm type	Experimental
Investigational medicinal product name	Febuxostat 120 mg
Investigational medicinal product code	
Other name	ADENURIC® 120 mg
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1x120 mg QD.
Minimum treatment duration was for 7 days starting from Visit 1 (Day 1), which should have occurred 2 days prior to the planned start of first chemotherapy cycle. The Investigator was given the possibility to prolong the treatment duration up to 9 days on the basis of the chemotherapy regimen administered to the patient.

Number of subjects in period 2	Cohort 1_Cohort 2_Children	Cohort 3_Cohort 4_Adolescents	Adults
Started	3	3	24
Completed	2	3	23
Not completed	1	0	1
Physician decision	-	-	1
Adverse event, non-fatal	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1_Cohort 2_Children
Reporting group description:	
Children: DAY 1 before first febuxostat dosing.	
Reporting group title	Cohort 3_Cohort 4_Adolescents
Reporting group description:	
Adolescents: DAY 1 before first febuxostat dosing.	
Reporting group title	Adults
Reporting group description:	
Adults: DAY 1 before first febuxostat dosing.	

Reporting group values	Cohort 1_Cohort 2_Children	Cohort 3_Cohort 4_Adolescents	Adults
Number of subjects	3	3	24
Age categorical Units: Subjects			
Children (2-11 years)	3	0	0
Adolescents (12-17 years)	0	3	0
Adults (18-64 years)	0	0	14
From 65-84 years	0	0	10
Age continuous Units: years			
arithmetic mean	7.33	14.00	60.21
standard deviation	± 1.528	± 1.000	± 15.376
Gender categorical Units: Subjects			
Female	1	2	11
Male	2	1	13
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	3	2	24
Race Units: Subjects			
White	3	2	23
other	0	1	1
Weight Units: kg			
arithmetic mean	26.13	60.47	75.60
standard deviation	± 2.043	± 19.747	± 15.469

Reporting group values	Total		
Number of subjects	30		
Age categorical Units: Subjects			
Children (2-11 years)	3		
Adolescents (12-17 years)	3		

Adults (18-64 years)	14		
From 65-84 years	10		

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	14		
Male	16		
Ethnicity Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	29		
Race Units: Subjects			
White	28		
other	2		
Weight Units: kg arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Cohort 1_Cohort 2_Children
Reporting group description: Children: DAY 1 before first febuxostat dosing.	
Reporting group title	Cohort 3_Cohort 4_Adolescents
Reporting group description: Adolescents: DAY 1 before first febuxostat dosing.	
Reporting group title	Adults
Reporting group description: Adults: DAY 1 before first febuxostat dosing.	
Reporting group title	Cohort 1_Cohort 2_Children
Reporting group description: Children (aged ≥6 - <12).	
Reporting group title	Cohort 3_Cohort 4_Adolescents
Reporting group description: Adolescents (aged ≥12 - <18).	
Reporting group title	Adults
Reporting group description: Adults	

Primary: Pharmacokinetic parameter: CL/F

End point title	Pharmacokinetic parameter: CL/F[1]
End point description:	
End point type	Primary
End point timeframe: At Day 8.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the paucity of data in the minor patient population and in agreement with EMA, there was no statistical analysis. All safety data available were presented until the date of Last Patient Last Visit.

End point values	Cohort 1_Cohort 2_Children	Cohort 3_Cohort 4_Adolescents	Adults	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: volume/time				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[2] - This study was prematurely terminated. No statistical analyses have been performed.

[3] - This study was prematurely terminated. No statistical analyses have been performed.

[4] - This study was prematurely terminated. No statistical analyses have been performed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected during Screening, i.e. after ICF signature until DAY 1, Visit 1 before first IMP intake and specifically Treatment Emergent Signs and Symptoms (TESSs) occurring from first IMP intake at Visit 1, DAY 1 until Visit 10, DAY 14.

Adverse event reporting additional description:

The safety analysis was run on the safety population (all patients who had received at least one dose of study drug). Safety variables included TESS, namely any reported AE occurred or worsened after first study drug intake or any clinically relevant change in safety laboratory parameters, physical examination, PS, 12-Lead ECG and vital signs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Cohort 1 (40mg)

Reporting group description:

Cohort 1, Children (≥6 - <12) receiving 40 mg febuxostat (2 tablets á 20 mg)

Reporting group title	Cohort 3 (80mg)

Reporting group description:

Cohort 3, Adolescents (≥12 - <18) receiving 80 mg febuxostat (1 tablet Adenuric® 80 mg)

Reporting group title	Adults (120mg)

Reporting group description:

Adults (≥18) receiving 120 mg febuxostat (1 tablet Adenuric® 120 mg)

Reporting group title	Overall

Reporting group description:

Overall

Serious adverse events	Cohort 1 (40mg)	Cohort 3 (80mg)	Adults (120mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	5 / 24 (20.83%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Enterobacter test positive			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Septic shock			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 30 (20.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Enterobacter test positive			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Proctitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Septic shock			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Staphylococcal infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort 1 (40mg)	Cohort 3 (80mg)	Adults (120mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	20 / 24 (83.33%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Thrombophlebitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Facial pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Inflammation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Mucosal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Oedema peripheral			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Pain			

subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	3 / 24 (12.50%)
occurrences (all)	1	0	3
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	3	0	1
Hiccups			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Hallucination			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Investigations			
ALT increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
AST increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
BP increased			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Blood triglycerides increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Hemoglobin decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Neutrophil count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
White blood cell (WBC) count decreased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 24 (8.33%)
occurrences (all)	1	1	2
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Extrasystoles			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	4 / 24 (16.67%)
occurrences (all)	1	2	4
Language disorder			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	4 / 24 (16.67%)
occurrences (all)	2	0	4
Lymphopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 24 (12.50%)
occurrences (all)	0	0	3
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	4 / 24 (16.67%)
occurrences (all)	2	0	4
Abdominal pain upper			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Abdominal rigidity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Anorectal discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Aphthous ulcer			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Constipation			

subjects affected / exposed	1 / 3 (33.33%)	3 / 3 (100.00%)	4 / 24 (16.67%)
occurrences (all)	1	3	5
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	4 / 24 (16.67%)
occurrences (all)	0	0	5
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Faeces soft			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Gingival swelling			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Hematemesis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Hematochezia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Lip pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	4	0	2
Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0

Rash			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Skin discolouration			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Limb discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Temporomandibular joint syndrome			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Oral herpes			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Fluid retention			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Hyperglycaemia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	1 / 24 (4.17%)
occurrences (all)	1	2	1

Hyperkalaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Hypo HDL cholesterolaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Hypocalcaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 30 (86.67%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Thrombophlebitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Facial pain			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Inflammation			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		
Hiccups			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Wheezing			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hallucination			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Investigations			
ALT increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
AST increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
BP increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Blood triglycerides increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hemoglobin decreased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
Neutrophil count decreased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
White blood cell (WBC) count decreased			

subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 4		
Cardiac disorders Arrhythmia subjects affected / exposed occurrences (all) Extrasystoles subjects affected / exposed occurrences (all)	 1 / 30 (3.33%) 1 1 / 30 (3.33%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Language disorder subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	 1 / 30 (3.33%) 1 6 / 30 (20.00%) 7 1 / 30 (3.33%) 1 1 / 30 (3.33%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 6 / 30 (20.00%) 6 1 / 30 (3.33%) 1 3 / 30 (10.00%) 3 2 / 30 (6.67%) 2		
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	6 / 30 (20.00%) 6			
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 2			
Abdominal rigidity subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1			
Anorectal discomfort subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1			
Aphthous ulcer subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1			
Constipation subjects affected / exposed occurrences (all)	8 / 30 (26.67%) 9			
Diarrhoea subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 5			
Dyspepsia subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1			
Faeces soft subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1			
Gingival swelling subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1			
Hematemesis subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1			
Hematochezia subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1			

Lip pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Skin discolouration			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Limb discomfort			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Temporomandibular joint syndrome			

subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Infections and infestations			
Oral herpes			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Fluid retention			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Hyperkalaemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hyperphosphataemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hypo HDL cholesterolaemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Hypokalaemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2017	Besides others, clarification that UA analyses in blood sample safety tests could be done in both specimen, serum or plasma, with the same normal reference ranges.
03 February 2017	Country specific Protocol Amendment for Hungary clarifying that the exclusion or withdrawal of adult and pediatric patients with severe renal dysfunction will be based on the cut off of the CLcr < 30 mL/min and < 60 mL/min/1.73 m2, respectively.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Per EMA waiver, the Sponsor early stopped the study on 25July2018 because febuxostat was of no benefit in TLS prevention in minors over existing treatments. Adverse Events are reported, primary endpoint data are not reported due to paucity of data.

Notes: