Clinical trial results:
A multicentre, randomised, double-blind, parallel group study on the therapeutic efficacy and safety of Febuxostat (taken once daily) and the therapeutic efficacy and safety of Allopurinol on serum urate concentration in subjects suffering from hyperuricemia and gout.

Summary

EudraCT number	2012-001858-25
Trial protocol	GR IT ES BG
Global end of trial date	02 July 2015

Results information

Result version number	v1 (current)
This version publication date	21 March 2018
First version publication date	21 March 2018

Trial information

Trial identification

Sponsor protocol code	MEIN/11/FEB-GOU/001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Menarini International Operations Luxemburg S.A.
Sponsor organisation address	1, Avenue de la Gare, Luxembourg, Luxembourg, L-1611
Public contact	Medical Scientific Management, Menarini International Operations Luxemburg S.A., 00352 264976,
Scientific contact	Menarini Corporate Medical Department, A. Menarini Industrie Farmaceutiche Riunite S.A., 0039 05556801,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 July 2015
Global end of trial reached?	Yes
Global end of trial date	02 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary study objective is to determine whether Febuxostat 80 mg, given once a day, is better than Allopurinol 300 mg/die considering the proportion of subjects, at visit 1 (week 4), whose serum urate concentrations will be below 6 mg/dL (357 µmol/L).

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinky, Good Clinical Practice (GCP) guidelines and local law requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2013
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	Poland: 37
Country: Number of subjects enrolled	Spain: 44
Country: Number of subjects enrolled	Bulgaria: 115
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Romania: 62
Country: Number of subjects enrolled	Italy: 70
Worldwide total number of subjects	330
EEA total number of subjects	330

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)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	249
From 65 to 84 years	77
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 59 investigational study sites in 6 European countries (16 in Italy, 13 in Bulgaria, 13 in Romania, 9 in Poland, 7 in Spain and 1 in Greece).
FPI: 04 June 2013 - LPO: 02 July 2015
Phase IV
Treatment duration 24 weeks

Pre-assignment

Screening details:

Eligible subjects underwent a 14-day run-in/wash-out period with placebo to evaluate subjects compliance. Subjects with placebo compliance below 60% were not to be randomised. Qualified subjects were randomised to Febuxostat 80 mg or Allopurinol 300 mg.

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The blinding procedure is performed by the over encapsulation technique, that will guarantee the maintenance of blind conditions. The tablets of the study drug or the comparator will be placed in hard gelatine capsules in order to obtain that the three pharmaceutical dosage forms will have the same appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Febuxostat 80 mg

Arm description:

Febuxostat 80 mg given once a day. Dosage form is Oral capsules as result of the over encapsulation of the 80 mg oral tablets. Treatment period of 4 weeks +/- 4 days.

Arm type	Experimental
Investigational medicinal product name	Febuxostat 80 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Coated tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage 80 mg once a day. Coated tablets administered over encapsulated by a hard gelatin capsule as result of the blinding treatment.

Arm title	Allopurinol 300 mg

Arm description:

Allopurinol 300 mg given once a day. Dosage form is Oral capsules as result of the over encapsulation of three 100 mg oral tablets. Treatment period of 4 weeks +/- 4 days.

Arm type	Active comparator
Investigational medicinal product name	Allopurinol 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage 300 mg once a day. Three oral tablets of 100 mg administered over encapsulated by a hard gelatin capsule as result of the blinding treatment.

Number of subjects in period 1	Febuxostat 80 mg	Allopurinol 300 mg
Started	167	163
Completed	143	140
Not completed	24	23
non compliance treatment	1	1
Adverse event, serious fatal	1	2
Consent withdrawn by subject	2	2
death	1	-
Protocol deviation	16	16
not specified	3	2

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The blinding procedure is performed by the over encapsulation technique, that will guarantee the maintenance of blind conditions. The tablets of the study drug or the comparator will be placed in hard gelatine capsules in order to obtain that the three pharmaceutical dosage forms will have the same appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Febuxostat 80 mg/Febuxostat 80 mg

Arm description:

Patients coming from Period 1 (4 weeks of Febuxostat 80 mg) and with serum urate < di 6 mg/dl, continue same treatment for further 4 weeks +/- 4 days. Febuxostat 80 mg given once a day. Dosage form is Oral capsules as result of the over encapsulation of the 80 mg oral tablets.

Arm type	Experimental
Investigational medicinal product name	Febuxostat 80mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Coated tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage 80 mg once a day. Coated tablets administered over encapsulated by a hard gelatin capsule as result of the blinding treatment.

Arm title	Febuxostat 80 mg/Febuxostat 120 mg

Arm description:

Patients coming from Period 1 (4 weeks of Febuxostat 80 mg) and with serum urate >= di 6 mg/dl, shift treatment to Febuxostat 120mg for further 4 weeks +/- 4 days. Febuxostat 120 mg is given once a day. Dosage form is oral capsules as result of the over encapsulation of the 120 mg oral tablets.

Arm type	not a pure line
Investigational medicinal product name	Febuxostat 120 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Coated tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage 120 mg once a day. Coated tablets administered over encapsulated by a hard gelatin capsule as result of the blinding treatment.

Investigational medicinal product name	Febuxostat 80 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet, Capsule, hard
Routes of administration	Buccal use

Dosage and administration details:

Dosage 80 mg once a day. Coated tablets administered over encapsulated by a hard gelatin capsule as result of the blinding treatment.

Arm title	Allopurinol 300 mg/Allopurinol 300 mg

Arm description:

Patients coming from Period 1 (4 weeks of Allopurinol 300 mg) and with serum urate < di 6 mg/dl, continue treatment with Allopurinol 300 mg for further 4 weeks +/- 4 days.Allopurinol 300 mg is given once a day. Dosage form is oral capsules as result of the over encapsulation of three 100 mg oral tablets. Treatment period of 4 weeks +/- 4 days.

Arm type	Active comparator
Investigational medicinal product name	Allopurinol 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage 300 mg once a day. Three oral tablets of 100 mg administered over encapsulated by a hard gelatin capsule as result of the blinding treatment.

Arm title	Allopurinol 300 mg/Febuxostat 80 mg

Arm description:

Patients coming from Period 1 (4 weeks of Allopurinol 300 mg) and with serum urate >= di 6 mg/dl, shift treatment to Febuxostat 80 mg for further 4 weeks +/- 4 days. Febuxosta 80 mg given once a day. Dosage form is oral capsules as result of the over encapsulation of 80 mg oral tablets.

Arm type	not a pure line

Investigational medicinal product name	Febuxostat 80 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Coated tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage 80 mg once a day. Coated tablets administered over encapsulated by a hard gelatin capsule as result of the blinding treatment.

Investigational medicinal product name	Allopurinol 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage 300 mg once a day. Three oral tablets of 100 mg administered over encapsulated by a hard gelatin capsule as result of the blinding treatment.

Number of subjects in period 2	Febuxostat 80 mg/Febuxostat 80 mg	Febuxostat 80 mg/Febuxostat 120 mg	Allopurinol 300 mg/Allopurinol 300 mg
Started	97	46	90
Completed	94	43	87
Not completed	3	3	3
non compliance treatment	1	-	-
Adverse event, serious fatal	-	1	1
Consent withdrawn by subject	-	1	-
Lost to follow-up	1	-	1
Protocol deviation	1	-	1
not specified	-	1	-

Number of subjects in period 2	Allopurinol 300 mg/Febuxostat 80 mg
Started	50
Completed	49
Not completed	1
non compliance treatment	-
Adverse event, serious fatal	1
Consent withdrawn by subject	-
Lost to follow-up	-
Protocol deviation	-
not specified	-

Period 3

Period 3 title	Period 3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The blinding procedure is performed by the over encapsulation technique, that will guarantee the maintenance of blind conditions. The tablets of the study drug or the comparator will be placed in hard gelatine capsules in order to obtain that the three pharmaceutical dosage forms will have the same appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Febuxostat 80 mg pure line

Arm description:

Patients in this arm have always taken Febuxostat 80 mg during the previous 8 weeks of treatment and are randomized to take the same treatment in the next 16 weeks till the end of the study. Febuxostat 80 mg given once a day. Dosage form are oral capsules as results of the over encapsulation of the 80 mg oral tablets.

Arm type	Experimental
Investigational medicinal product name	Febuxostat 80 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Coated tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage 80 mg once a day. Coated tablets administered over encapsulated by a hard gelatin capsule as result of the blinding treatment.

Arm title	Febuxostat 80 mg/Febuxostat 120 mg

Arm description:

Patients have previously taken during the study Febuxostat 80 mg (4 weeks) and Febuxostat 120 mg (4 weeks). They are now randomized to continue Febuxostat 120 mg treatment for 16 weeks, till the end of the study. Febuxostat 120 mg is given once a day. Dosage form is oral capsules as result of the over encapsulation of the 120 mg oral tablets.

Arm type	not a pure line
Investigational medicinal product name	Febuxostat 80 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Coated tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage 80 mg once a day. Coated tablets administered over encapsulated by a hard gelatin capsule as result of the blinding treatment.

Investigational medicinal product name	Febuxostat 120 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Coated tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage 120 mg once a day. Coated tablets administered over encapsulated by hard gelatin capsule as result of the blinding treatment

Arm title	Allopurinol 300 pure line

Arm description:

Patients in this arm have always taken Allopurinol 300 mg during the previous 8 weeks of treatment and are randomized to take the same treatment in the next 16 weeks till the end of the study. Allopurinol 300 mg given once a day. Dosage form are oral capsules as results of the over encapsulation of three 100 mg oral tablets.

Arm type	Active comparator
Investigational medicinal product name	Allopurinol 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage 300 mg once a day. Three oral tablets of 100 mg administered over encapsulated by a hard gelatin capsule as result of the blinding treatment.

Arm title	Allopurinol 300 mg/Febuxostat 80 mg

Arm description:

Patients have previously taken during the study Allopurinol 300 mg (4 weeks) and Febuxostat 80 mg (4 weeks). If their serum urate is < 6 mg/dl, they are now randomized to continue Febuxostat 80 mg treatment for 16 weeks, till the end of the study. Febuxostat 80 mg is given once a day. Dosage form is oral capsules as result of the over encapsulation of the 80 mg oral tablets.

Arm type	not a pure line
Investigational medicinal product name	Febuxostat 80 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet, Capsule, hard
Routes of administration	Buccal use

Dosage and administration details:

Dosage 80 mg once a day. Coated tablets administered over encapsulated by a hard gelatin capsule as result of the blinding treatment.

Investigational medicinal product name	Allopurinol 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage 300 mg once a day. Three oral tablets of 100 mg administered over encapsulated by a hard gelatin capsule as result of the blinding treatment.

Arm title	Allopurinol 300 mg/Febuxostat 80 mg/Febuxostat 120

Arm description:

Patients have previously taken during the study Allopurinol 300 mg (4 weeks) and Febuxostat 80 mg (4 weeks). If their serum urate is >= 6 mg/dl, they shift treatment to Febuxostat 120 mg for 16 weeks, till the end of the study. Febuxostat 120 mg is given once a day. Dosage form is oral capsules as result of the over encapsulation of the 120 mg oral tablets.

Arm type	not a pure line
Investigational medicinal product name	Allopurinol 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage 300 mg once a day. Three oral tablets of 100 mg administered over encapsulated by a hard gelatin capsule as result of the blinding treatment.

Investigational medicinal product name	Febuxostat 80 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Coated tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage 80 mg once a day. Coated tablets administered over encapsulated by a hard gelatin capsule as result of the blinding treatment.

Investigational medicinal product name	Febuxostat 120 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Coated tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage 120 mg once a day. Coated tablets administered over encapsulated by hard gelatin capsule as result of the blinding treatment

Number of subjects in period 3	Febuxostat 80 mg pure line	Febuxostat 80 mg/Febuxostat 120 mg	Allopurinol 300 pure line
Started	94	43	87
Completed	94	43	87

Number of subjects in period 3	Allopurinol 300 mg/Febuxostat 80 mg	Allopurinol 300 mg/Febuxostat 80 mg/Febuxostat 120
Started	27	22
Completed	27	22

Baseline characteristics

Reporting groups	
Reporting group title	Febuxostat 80 mg

Reporting group description:

Febuxostat 80 mg given once a day. Dosage form is Oral capsules as result of the over encapsulation of the 80 mg oral tablets. Treatment period of 4 weeks +/- 4 days.

Reporting group title	Allopurinol 300 mg

Reporting group description:

Allopurinol 300 mg given once a day. Dosage form is Oral capsules as result of the over encapsulation of three 100 mg oral tablets. Treatment period of 4 weeks +/- 4 days.

Reporting group values	Febuxostat 80 mg	Allopurinol 300 mg	Total
Number of subjects	167	163	330
Age categorical Units: Subjects			
Adults (18-64 years)	128	121	249
From 65-84 years	38	39	77
85 years and over	1	3	4
Age continuous Units: years			
arithmetic mean	56.17	57.42	
standard deviation	± 11.49	± 12.29	-
Gender categorical Units: Subjects			
Female	151	145	296
Male	16	18	34

Subject analysis sets	
Subject analysis set title	Modified Safety/Febuxostat 80 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Modified Safety population includes all enrolled subjects who received at least one dose of placebo treatment during the run in/wash out period and took at least a dose of double-blind, randomized treatment.

Subject analysis set title	Modified Safety/Allopurinol 300 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Modified Safety population includes all enrolled subjects who received at least one dose of placebo treatment during the run in/wash out period and took at least a dose of double-blind, randomized treatment.

Subject analysis set title	Full Analysis Set/Febuxostat 80 mg
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS population includes all randomized subjects, who received at least one dose of study medication (including placebo) and with at least one assessment after visit 0 (Day 0) of serum urate.

Subject analysis set title	Full Analysis Set/Allopurinol 300 mg
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS population includes all randomized subjects, who received at least one dose of study medication (including placebo) and with at least one assessment after visit 0 (Day 0) of serum urate.

Subject analysis set title	PP Population/Febuxostat 80 mg
Subject analysis set type	Per protocol

Subject analysis set description:

Include all subjects in the FAS population without any major protocol violation.

Subject analysis set title	PP Population/Allopurinol 300 mg
Subject analysis set type	Per protocol

Subject analysis set description:

Include all subjects in the FAS population without any major protocol violation.

Reporting group values	Modified Safety/Febuxostat 80 mg	Modified Safety/Allopurinol 300 mg	Full Analysis Set/Febuxostat 80 mg
Number of subjects	167	162	150
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	 56.17 ± 11.49	 57.34 ± 12.28	 55.59 ± 11.20
Gender categorical Units: Subjects			
Female Male	16 151	18 144	11 139

Reporting group values	Full Analysis Set/Allopurinol 300 mg	PP Population/Febuxostat 80 mg	PP Population/Allopurinol 300 mg
Number of subjects	148	139	137
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	 57.14 ± 12.21	 55.08 ± 11.20	 57.02 ± 12.22
Gender categorical Units: Subjects			
Female Male	14 134	9 130	12 125

End points

End points reporting groups

Reporting group title	Febuxostat 80 mg

Reporting group description:

Febuxostat 80 mg given once a day. Dosage form is Oral capsules as result of the over encapsulation of the 80 mg oral tablets. Treatment period of 4 weeks +/- 4 days.

Reporting group title	Allopurinol 300 mg

Reporting group description:

Allopurinol 300 mg given once a day. Dosage form is Oral capsules as result of the over encapsulation of three 100 mg oral tablets. Treatment period of 4 weeks +/- 4 days.

Reporting group title	Febuxostat 80 mg/Febuxostat 80 mg

Reporting group description:

Patients coming from Period 1 (4 weeks of Febuxostat 80 mg) and with serum urate < di 6 mg/dl, continue same treatment for further 4 weeks +/- 4 days. Febuxostat 80 mg given once a day. Dosage form is Oral capsules as result of the over encapsulation of the 80 mg oral tablets.

Reporting group title	Febuxostat 80 mg/Febuxostat 120 mg

Reporting group description:

Patients coming from Period 1 (4 weeks of Febuxostat 80 mg) and with serum urate >= di 6 mg/dl, shift treatment to Febuxostat 120mg for further 4 weeks +/- 4 days. Febuxostat 120 mg is given once a day. Dosage form is oral capsules as result of the over encapsulation of the 120 mg oral tablets.

Reporting group title	Allopurinol 300 mg/Allopurinol 300 mg

Reporting group description:

Patients coming from Period 1 (4 weeks of Allopurinol 300 mg) and with serum urate < di 6 mg/dl, continue treatment with Allopurinol 300 mg for further 4 weeks +/- 4 days.Allopurinol 300 mg is given once a day. Dosage form is oral capsules as result of the over encapsulation of three 100 mg oral tablets. Treatment period of 4 weeks +/- 4 days.

Reporting group title	Allopurinol 300 mg/Febuxostat 80 mg

Reporting group description:

Patients coming from Period 1 (4 weeks of Allopurinol 300 mg) and with serum urate >= di 6 mg/dl, shift treatment to Febuxostat 80 mg for further 4 weeks +/- 4 days. Febuxosta 80 mg given once a day. Dosage form is oral capsules as result of the over encapsulation of 80 mg oral tablets.

Reporting group title	Febuxostat 80 mg pure line

Reporting group description:

Patients in this arm have always taken Febuxostat 80 mg during the previous 8 weeks of treatment and are randomized to take the same treatment in the next 16 weeks till the end of the study. Febuxostat 80 mg given once a day. Dosage form are oral capsules as results of the over encapsulation of the 80 mg oral tablets.

Reporting group title	Febuxostat 80 mg/Febuxostat 120 mg

Reporting group description:

Patients have previously taken during the study Febuxostat 80 mg (4 weeks) and Febuxostat 120 mg (4 weeks). They are now randomized to continue Febuxostat 120 mg treatment for 16 weeks, till the end of the study. Febuxostat 120 mg is given once a day. Dosage form is oral capsules as result of the over encapsulation of the 120 mg oral tablets.

Reporting group title	Allopurinol 300 pure line

Reporting group description:

Patients in this arm have always taken Allopurinol 300 mg during the previous 8 weeks of treatment and are randomized to take the same treatment in the next 16 weeks till the end of the study. Allopurinol 300 mg given once a day. Dosage form are oral capsules as results of the over encapsulation of three 100 mg oral tablets.

Reporting group title	Allopurinol 300 mg/Febuxostat 80 mg

Reporting group description:

Patients have previously taken during the study Allopurinol 300 mg (4 weeks) and Febuxostat 80 mg (4 weeks). If their serum urate is < 6 mg/dl, they are now randomized to continue Febuxostat 80 mg treatment for 16 weeks, till the end of the study. Febuxostat 80 mg is given once a day. Dosage form is

oral capsules as result of the over encapsulation of the 80 mg oral tablets.

Reporting group title	Allopurinol 300 mg/Febuxostat 80 mg/Febuxostat 120

Reporting group description:

Patients have previously taken during the study Allopurinol 300 mg (4 weeks) and Febuxostat 80 mg (4 weeks). If their serum urate is >= 6 mg/dl, they shift treatment to Febuxostat 120 mg for 16 weeks, till the end of the study. Febuxostat 120 mg is given once a day. Dosage form is oral capsules as result of the over encapsulation of the 120 mg oral tablets.

Subject analysis set title	Modified Safety/Febuxostat 80 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Modified Safety population includes all enrolled subjects who received at least one dose of placebo treatment during the run in/wash out period and took at least a dose of double-blind, randomized treatment.

Subject analysis set title	Modified Safety/Allopurinol 300 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Modified Safety population includes all enrolled subjects who received at least one dose of placebo treatment during the run in/wash out period and took at least a dose of double-blind, randomized treatment.

Subject analysis set title	Full Analysis Set/Febuxostat 80 mg
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS population includes all randomized subjects, who received at least one dose of study medication (including placebo) and with at least one assessment after visit 0 (Day 0) of serum urate.

Subject analysis set title	Full Analysis Set/Allopurinol 300 mg
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS population includes all randomized subjects, who received at least one dose of study medication (including placebo) and with at least one assessment after visit 0 (Day 0) of serum urate.

Subject analysis set title	PP Population/Febuxostat 80 mg
Subject analysis set type	Per protocol

Subject analysis set description:

Include all subjects in the FAS population without any major protocol violation.

Subject analysis set title	PP Population/Allopurinol 300 mg
Subject analysis set type	Per protocol

Subject analysis set description:

Include all subjects in the FAS population without any major protocol violation.

Primary: Percentage of subjects with sUA < 6 mg/dL after 4 week treatment

End point title	Percentage of subjects with sUA < 6 mg/dL after 4 week treatment

End point description:

The primary objective of the study was to determine whether Febuxostat 80 mg, given once a day, was more effective than Allopurinol 300 mg/day considering the proportion of subjects, at visit 1 (week 4), whose serum urate concentrations was below 6 mg/dl (357 µmol/L).

End point type	Primary

End point timeframe:

4 weeks of treatment, from Visit 0 (randomization visit) to Visit 1 (4 weeks +/- 4 days).

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg	PP Population/Febuxostat 80 mg	PP Population/Allopurinol 300 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	150	148	139	137
Units: number of patients SUA < 6	102	94	98	91

Statistical analyses

Statistical analysis title	Febuxostat 80mg vs Allopurinol300 mg FAS populatio

Statistical analysis description:

Difference between number of patients taking Febuxostat 80 mg and patient taking Allopurinol 300 mg and with Sua levels < 6.0 mg/dl after 4 weeks treatment. Analysis performed in the FAS population

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.414 [1]
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	4.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.28
upper limit	15.25

Notes:

[1] - Not statistically significant (p>0.05)

Statistical analysis title	Febuxostat 80mg vs Allopurinol 300mg PP population

Statistical analysis description:

Difference between number of patients taking Febuxostat 80 mg and patient taking Allopurinol 300 mg and with Sua levels < 6.o mg/dl after 4 weeks treatment. Analysis performed in the PP population

Comparison groups	PP Population/Allopurinol 300 mg v PP Population/Febuxostat 80 mg
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.465 [2]
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	4.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.28
upper limit	15.04

Notes:

[2] - Not statistically significant (p>0.05)

Secondary: Percentage of subjects with sUA level <6 mg/dL after 8 weeks treatment

End point title	Percentage of subjects with sUA level <6 mg/dL after 8 weeks treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day vs Allopurinol 300 mg/day, given after a four-week treatment, in lowering serum urate concentration below 6 mg/dl at visit 2 (week 8 after randomization).

End point type	Secondary

End point timeframe:

8 weeks of treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	90		
Units: number of patients	83	71		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Difference between number of patients taking Febuxostat 80 mg and patient taking Allopurinol 300 mg and with SUA levels < 6.0 mg/dl after 8 weeks of treatment.

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.231 [3]
Method	Fisher exact

Notes:

[3] - Not statistically significant (p>0.05)

Secondary: Percentage of subjects with sUA < 6 mg/dL after 12 week treatment

End point title	Percentage of subjects with sUA < 6 mg/dL after 12 week treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day vs Allopurinol 300 mg/day in lowering serum urate concentration below 6 mg/dl at visit 3 (12 weeks after randomization).

End point type	Secondary

End point timeframe:

12 weeks treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: number of patients	77	66		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg
Statistical analysis description:	
Difference between number of patients taking Febuxostat 80 mg and patient taking Allopurinol 300 mg and with SUA levels < 6.0 mg/dl after 12 weeks of treatment.	
Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.317 [4]
Method	Fisher exact

Notes:

[4] - Not statistically significant (p>0.05)

Secondary: Percentage of subjects with sUA < 6 mg/dL after 16 week treatment

End point title	Percentage of subjects with sUA < 6 mg/dL after 16 week treatment
End point description:	
To evaluate the efficacy of Febuxostat 80 mg/day vs Allopurinol 300 mg/day in lowering serum urate concentration below 6 mg/dl at visit 4 (16 weeks after randomization).	
End point type	Secondary
End point timeframe:	
16 week of treatment	

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: number of patients	79	66		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Difference between number of patients taking Febuxostat 80 mg and patient taking Allopurinol 300 mg and with SUA levels < 6.0 mg/dl after 16 weeks of treatment.

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.168 [5]
Method	Fisher exact

Notes:

[5] - Not statistically significant (p>0.05)

Secondary: Percentage of subjects with sUA < 6 mg/dL after 20 weeks treatment

End point title	Percentage of subjects with sUA < 6 mg/dL after 20 weeks treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day vs Allopurinol 300 mg/day in lowering serum urate concentration below 6 mg/dl at visit 5 (20 weeks after randomization).

End point type	Secondary

End point timeframe:

20 weeks of treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: number of patients	75	64		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Difference between number of patients taking Febuxostat 80 mg and patient taking Allopurinol 300 mg and with SUA levels < 6.0 mg/dl after 20 weeks of treatment.

Comparison groups	Full Analysis Set/Allopurinol 300 mg v Full Analysis Set/Febuxostat 80 mg
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.321 [6]
Method	Fisher exact

Notes:

[6] - Not statistically significant (p>0.05)

Secondary: Percentage of subjects with sUA < 6 mg/dL after 24 week treatment

End point title	Percentage of subjects with sUA < 6 mg/dL after 24 week treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day vs Allopurinol 300 mg/day in lowering serum urate concentration below 6 mg/dl at visit 6 (24 weeks after randomization).

End point type	Secondary

End point timeframe:

24 week of treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: number of patients	75	65		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Difference between number of patients taking Febuxostat 80 mg and patient taking Allopurinol 300 mg and with SUA levels < 6.0 mg/dl after 24 weeks of treatment.

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.415 [7]
Method	Fisher exact

Notes:

[7] - Not statistically significant (p>0.05)

Secondary: Percentage of patients with last 3 SUA levels < 6 mg/dl at 16,20 and 24 weeks

End point title	Percentage of patients with last 3 SUA levels < 6 mg/dl at 16,20 and 24 weeks

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day versus Allopurinol 300 mg/day considering the number of subjects with at least 3 serum urate levels (at 16, 20 and 24 weeks from the treatment start) < 6.0 mg/dl within each of the three subgroups of subjects defined by baseline urate concentration (< 9.0 mg/dl, >= 9.0 mg/dl but < 10 mg/dl, >= 10 mg/dl)

End point type	Secondary

End point timeframe:

From 16 weeks to 24 weeks after randomization (Visit 0). A total of 8 weeks of timeframe evaluation

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	78		
Units: number of patients				
Baseline SUA levels < 9 mg/dl	31	22		
Baseline SUA levels >= 9 and < 10 mg/dl	23	12		
Baseline SUA levels >= 10	9	13		

Statistical analyses

Statistical analysis title	Febuxostat vs Allopurinol with SUA < 9 mg/dl

Statistical analysis description:

Difference between number of patients taking Febuxostat 80 mg and patient taking Allopurinol 300 mg having both SUA levels < 9 mg/dl at baseline and at least 3 SUA levels < 6.0 mg/dl at 16,20 and 24 weeks.

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.061 [8]
Method	Fisher exact

Notes:

[8] - Not statistically significant (p>0.05)

Statistical analysis title	Feb vs Allo with SUA >= 9 and <10 mg/dl

Statistical analysis description:

Difference between number of patients taking Febuxostat 80 mg and patient taking Allopurinol 300 mg having both SUA levels >= 9 and < 10 mg/dl at baseline and at least 3 SUA levels < 6.0 mg/dl at 16,20 and 24 weeks.

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27 [9]
Method	Fisher exact

Notes:

[9] - Not statistically significant (p>0.05)

Statistical analysis title	Febuxostat vs Allopurinol with SUA >= 10 mg/dl

Statistical analysis description:

Difference between number of patients taking Febuxostat 80 mg and patient taking Allopurinol 300 mg having both SUA levels >= 10 mg/dl at baseline and at least 3 SUA levels < 6.0 mg/dl at 16,20 and 24 weeks.

Comparison groups	Full Analysis Set/Allopurinol 300 mg v Full Analysis Set/Febuxostat 80 mg

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.525 [10]
Method	Fisher exact

Notes:

[10] - Not statistically significant (p>0.05)

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg overall

Statistical analysis description:

Difference between number of patients taking Febuxostat 80 mg and patient taking Allopurinol 300 mg having at least 3 SUA levels < 6.0 mg/dl at 16,20 and 24 weeks.

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.152 [11]
Method	Fisher exact

Notes:

[11] - Not statistically significant (p>0.05)

Secondary: Mean values reduction from baseline in SUA levels after 4 weeks treatment

End point title	Mean values reduction from baseline in SUA levels after 4 weeks treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day versus Allopurinol 300 mg/day considering, for each treatment arm, the mean decrease from baseline of serum urate levels after 4 weeks (Visit 1) of drug intake.

End point type	Secondary

End point timeframe:

4 weeks of treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150	148		
Units: mg/dl				
arithmetic mean (standard deviation)	-4.36 (± 1.72)	-3.66 (± 1.65)		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Comparison between Febuxostat 80 mg and Allopurinol 300 mg in the mean change from baseline values of Sua levels after 4 weelks treatment

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [12]
Method	ANCOVA

Notes:

[12] - Statistically significant (p<0.05)

Secondary: Mean values reduction from baseline in SUA levels after 8 weeks treatment

End point title	Mean values reduction from baseline in SUA levels after 8 weeks treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day versus Allopurinol 300 mg/day considering, for each treatment arm, the mean decrease from baseline of serum urate levels after 8 weeks (Visit 2) of drug intake.

End point type	Secondary

End point timeframe:

8 weeks of treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	90		
Units: mg/dl				
arithmetic mean (standard deviation)	-4.66 (± 1.541)	-4.26 (± 1.542)		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Comparison between Febuxostat 80 mg and Allopurinol 300 mg in the mean change from baseline values of Sua levels after 8 weelks treatment

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025 [13]
Method	ANCOVA

Notes:

[13] - Statistically significant (p<0.05)

Secondary: Mean values reduction from baseline in SUA levels after 12 weeks treatment

End point title	Mean values reduction from baseline in SUA levels after 12 weeks treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day versus Allopurinol 300 mg/day considering, for each treatment arm, the mean decrease from baseline of serum urate levels after 12 weeks (Visit 3) of drug intake.

End point type	Secondary

End point timeframe:

12 weeks of treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: mg/dl				
arithmetic mean (standard deviation)	-4.79 (± 1.461)	-4.14 (± 1.636)		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Comparison between Febuxostat 80 mg and Allopurinol 300 mg in the mean change from baseline values of Sua levels after 12 weeks treatment

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [14]
Method	ANCOVA

Notes:

[14] - Statistically significant ($p<0.05$)

Secondary: Mean values reduction from baseline in SUA levels after 16 weeks treatment

End point title	Mean values reduction from baseline in SUA levels after 16 weeks treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day versus Allopurinol 300 mg/day considering, for each treatment arm, the mean decrease from baseline of serum urate levels after 16 weeks (Visit 4) of drug intake.

End point type	Secondary

End point timeframe:

16 weeks of treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: mg/dl				
arithmetic mean (standard deviation)	-4.75 (± 1.523)	-4.12 (± 1.66)		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Comparison between Febuxostat 80 mg and Allopurinol 300 mg in the mean change from baseline values of Sua levels after 16 weeks treatment

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [15]
Method	ANCOVA

Notes:

[15] - Statistically significant (p<0.05)

Secondary: Mean values reduction from baseline in SUA levels after 20 weeks treatment

End point title	Mean values reduction from baseline in SUA levels after 20 weeks treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day versus Allopurinol 300 mg/day considering, for each treatment arm, the mean decrease from baseline of serum urate levels after 20 weeks (Visit 5) of drug intake.

End point type	Secondary

End point timeframe:

20 weeks of treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: mg/dl				
arithmetic mean (standard deviation)	-4.49 (± 1.867)	-4.09 (± 1.655)		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Comparison between Febuxostat 80 mg and Allopurinol 300 mg in the mean change from baseline values of Sua levels after 20 weeks treatment

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.075 [16]
Method	ANCOVA

Notes:

[16] - Not statistically significant (p>0.05)

Secondary: Mean values reduction from baseline in SUA levels after 24 weeks treatment

End point title	Mean values reduction from baseline in SUA levels after 24 weeks treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day versus Allopurinol 300 mg/day considering, for each treatment arm, the mean decrease from baseline of serum urate levels after 24 weeks (Visit 6) of drug intake.

End point type	Secondary

End point timeframe:

24 weeks of treatment (end of study)

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: mg/dl				
arithmetic mean (standard deviation)	-4.46 (± 1.97)	-4.03 (± 1.764)		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Comparison between Febuxostat 80 mg and Allopurinol 300 mg in the mean change from baseline

values of Sua levels after 24 weeks treatment

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.083 [17]
Method	ANCOVA

Notes:

[17] - Not statistically significant (p>0.05)

Secondary: Mean percentage reduction from baseline in SUA levels after 4 weeks treatment

End point title	Mean percentage reduction from baseline in SUA levels after 4 weeks treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day versus Allopurinol 300 mg/day considering, for each treatment arm, the mean percentage decrease from baseline of serum urate levels after 4 weeks (Visit 1) of drug intake.

End point type	Secondary

End point timeframe:

4 week of treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150	148		
Units: percent change				
arithmetic mean (standard deviation)	-45.50 (± 17.50)	-38.49 (± 15.45)		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Comparison between Febuxostat 80 mg and Allopurinol 300 mg in the mean percent change from baseline values of Sua levels after 4 weelks treatment

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [18]
Method	ANOVA

Notes:

[18] - Statistically significant (p<0.05)

Secondary: Mean percentage reduction from baseline in SUA levels after 8 weeks treatment

End point title	Mean percentage reduction from baseline in SUA levels after 8 weeks treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day versus Allopurinol 300 mg/day considering, for each treatment arm, the mean percentage decrease from baseline of serum urate levels after 8 weeks (Visit 2) of drug intake.

End point type	Secondary

End point timeframe:

8 weeks of treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	90		
Units: percent change				
arithmetic mean (standard deviation)	-49.75 (± 15.317)	-44.94 (± 13.715)		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Comparison between Febuxostat 80 mg and Allopurinol 300 mg in the mean percent change from baseline values of Sua levels after 8 weeks treatment

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017 [19]
Method	ANOVA

Notes:

[19] - Statistically significant (p<0.05)

Secondary: Mean percentage reduction from baseline in SUA levels after 12 weeks treatment

End point title	Mean percentage reduction from baseline in SUA levels after 12 weeks treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day versus Allopurinol 300 mg/day considering, for each treatment arm, the mean percentage decrease from baseline of serum urate levels after 12 weeks (Visit 3) of drug intake.

End point type	Secondary

End point timeframe:

12 weeks treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: percent change				
arithmetic mean (standard deviation)	-51.49 (± 14.911)	-43.43 (± 14.938)		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Comparison between Febuxostat 80 mg and Allopurinol 300 mg in the mean percent change from baseline values of Sua levels after 12 weeks treatment

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [20]
Method	ANOVA

Notes:

[20] - Statistically significant (p<0.05)

Secondary: Mean percentage reduction from baseline in SUA levels after 16 weeks treatment

End point title	Mean percentage reduction from baseline in SUA levels after 16 weeks treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day versus Allopurinol 300 mg/day considering, for each treatment arm, the mean percentage decrease from baseline of serum urate levels after 16 weeks (Visit 4) of drug intake.

End point type	Secondary

End point timeframe:

16 weeks treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: percent change				
arithmetic mean (standard deviation)	-51.13 (± 15.695)	-43.45 (± 15.244)		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Comparison between Febuxostat 80 mg and Allopurinol 300 mg in the mean percent change from baseline values of Sua levels after 16 weeks treatment

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [21]
Method	ANOVA

Notes:

[21] - Statistically significant (p<0.05)

Secondary: Mean percentage reduction from baseline in SUA levels after 20 weeks treatment

End point title	Mean percentage reduction from baseline in SUA levels after 20 weeks treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day versus Allopurinol 300 mg/day considering, for each treatment arm, the mean percentage decrease from baseline of serum urate levels after 20 weeks (Visit 5) of drug intake.

End point type	Secondary

End point timeframe:

20 weeks treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: percent change				
arithmetic mean (standard deviation)	-48.24 (± 19.041)	-42.97 (± 15.036)		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Comparison between Febuxostat 80 mg and Allopurinol 300 mg in the mean percent change from

baseline values of Sua levels after 20 weeks treatment

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047 [22]
Method	ANOVA

Notes:

[22] - Statistically significant (p<0.05)

Secondary: Mean percentage reduction from baseline in SUA levels after 24 weeks treatment

End point title	Mean percentage reduction from baseline in SUA levels after 24 weeks treatment

End point description:

To evaluate the efficacy of Febuxostat 80 mg/day versus Allopurinol 300 mg/day considering, for each treatment arm, the mean percentage decrease from baseline of serum urate levels after 24 weeks (Visit 6) of drug intake.

End point type	Secondary

End point timeframe:

24 weeks of treatment (end of study)

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: percent change				
arithmetic mean (standard deviation)	-48.06 (± 20.163)	-42.37 (± 16.136)		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Comparison between Febuxostat 80 mg and Allopurinol 300 mg in the mean percent change from baseline values of Sua levels after 24 weeks treatment

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045 [23]
Method	ANOVA

Notes:

[23] - Statistically significant (p<0.05)

Post-hoc: Percentage of subjects with sUA < 5 mg/dL after 4 week treatment	
End point title	Percentage of subjects with sUA < 5 mg/dL after 4 week treatment

End point description:

To determine whether Febuxostat 80 mg/day, was more effective than Allopurinol 300 mg/day considering the proportion of subjects, at visit 1 (week 4), whose serum urate concentrations was below 5 mg/dl.

End point type	Post-hoc

End point timeframe:

4 weeks treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	143	141		
Units: number of patients SUA < 5	66	33		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Percentage of patients with serum urate levels <5 mg/dl after 4 weeks of treatment

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	284
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.0001 [24]
Method	Fisher exact

Notes:

[24] - Statistically significant (p<0.005)

Post-hoc: Percentage of subjects with sUA < 5 mg/dL after 8 week treatment	
End point title	Percentage of subjects with sUA < 5 mg/dL after 8 week treatment

End point description:

To determine whether Febuxostat 80 mg/day, was more effective than Allopurinol 300 mg/day considering the proportion of subjects, at visit 2 (week 8), whose serum urate concentrations was below 5 mg/dl.

End point type	Post-hoc

End point timeframe:

8 weeks treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	90		
Units: number of patients SUA < 5	62	41		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg
Statistical analysis description: Percentage of subjects with sUA < 5 mg/dL after 8 week treatment	
Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	187
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0117 [25]
Method	Fisher exact

Notes:

[25] - Statistically significant (p<0.05)

Post-hoc: Percentage of subjects with sUA < 5 mg/dL after 12 week treatment

End point title	Percentage of subjects with sUA < 5 mg/dL after 12 week treatment
End point description: To determine whether Febuxostat 80 mg/day, was more effective than Allopurinol 300 mg/day considering the proportion of subjects, at visit 3 (week 12), whose serum urate concentrations was below 5 mg/dl.	
End point type	Post-hoc
End point timeframe: 12 weeks of treatment	

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: number of patients SUA < 5	62	39		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg
Statistical analysis description: Percentage of patients with serum urate levels <5 mg/dl after 12 weeks of treatment	
Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis

	Set/Allopurinol 300 mg
Number of subjects included in analysis	181
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0042 [26]
Method	Fisher exact

Notes:

[26] - Statistically significant (p<0.05)

Post-hoc: Percentage of patients with Sua levels <5 mg/dl after 16 weeks of treatment

End point title	Percentage of patients with Sua levels <5 mg/dl after 16 weeks of treatment

End point description:

To determine whether Febuxostat 80 mg/day, was more effective than Allopurinol 300 mg/day considering the proportion of subjects, at visit 4 (week 16), whose serum urate concentrations was below 5 mg/dl.

End point type	Post-hoc

End point timeframe:

16 weeks treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: number of patients SUA < 5	63	40		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Percentage of patients with serum urate levels <5 mg/dl after 16 weeks of treatment

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	181
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0043 [27]
Method	Fisher exact

Notes:

[27] - Statistically significant (p<0.05)

Post-hoc: Percentage of patients with Sua levels <5 mg/dl after 20 weeks of treatment

End point title	Percentage of patients with Sua levels <5 mg/dl after 20 weeks of treatment

End point description:

To determine whether Febuxostat 80 mg/day, was more effective than Allopurinol 300 mg/day considering the proportion of subjects, at visit 5 (week 20), whose serum urate concentrations was below 5 mg/dl.

End point type	Post-hoc

End point timeframe:

20 weeks of treatment

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: number of patients SUA < 5	54	37		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg

Statistical analysis description:

Percentage of patients with serum urate levels <5 mg/dl after 4 weeks of treatment

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	181
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0449 [28]
Method	Fisher exact

Notes:

[28] - Statistically significant (p<0.05)

Post-hoc: Percentage of subjects with sUA < 5 mg/dL after 24 week treatment

End point title	Percentage of subjects with sUA < 5 mg/dL after 24 week treatment

End point description:

To determine whether Febuxostat 80 mg/day, was more effective than Allopurinol 300 mg/day considering the proportion of subjects, at visit 6 (week 24), whose serum urate concentrations was below 5 mg/dl.

End point type	Post-hoc

End point timeframe:

24 weeks treatment (end of study).

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	87		
Units: number of patients SUA < 5	61	32		

Statistical analyses

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg
Statistical analysis description: Percentage of subjects with sUA < 5 mg/dL after 24 week treatment	
Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	181
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0002 [29]
Method	Fisher exact

Notes:

[29] - Statistically significant (p<0.05)

Post-hoc: Percentage of patients with last 3 SUA levels < 5 mg/dl at 16,20 and 24 weeks

End point title	Percentage of patients with last 3 SUA levels < 5 mg/dl at 16,20 and 24 weeks
End point description: To evaluate the efficacy of Febuxostat 80 mg/day versus Allopurinol 300 mg/day considering the number of subjects with at least 3 serum urate levels (at 16, 20 and 24 weeks from the treatment start) < 5.0 mg/dl within each of the three subgroups of subjects defined by baseline urate concentration (< 9.0 mg/dl, >= 9.0 mg/dl but < 10 mg/dl, >= 10 mg/dl).	
End point type	Post-hoc
End point timeframe: From 16 weeks to 24 weeks after randomization (Visit 0). A total of 8 weeks of timeframe evaluation	

End point values	Full Analysis Set/Febuxostat 80 mg	Full Analysis Set/Allopurinol 300 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	78		
Units: number of patients SUA < 5				
Baseline Sua levels < 9 mg/dl	22	9		
Baseline SUA levels >= 9 and < 10 mg/dl	15	7		
Baseline SUA levels >= 10	6	4		

Statistical analyses

Statistical analysis title	Febuxostat vs Allopurinol with SUA < 9 mg/dl

Statistical analysis description:

Difference between number of patients taking Febuxostat 80 mg and patient taking Allopurinol 300 mg having both SUA levels < 9 mg/dl at baseline and at least 3 SUA levels < 5.0 mg/dl at 16,20 and 24 weeks

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	167
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0047 [30]
Method	Fisher exact

Notes:

[30] - Statistically significant (p<0.05)

Statistical analysis title	Feb vs Allo with SUA >= 9 and <10 mg/dl

Statistical analysis description:

Difference between number of patients taking Febuxostat 80 mg and patient taking Allopurinol 300 mg having both SUA levels >= 9 and < 10 mg/dl at baseline and at least 3 SUA levels < 5.0 mg/dl at 16,20 and 24 weeks.

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	167
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4032 [31]
Method	Fisher exact

Notes:

[31] - Not statistically significant (p>0.05)

Statistical analysis title	Febuxostat vs Allopurinol with SUA >= 10 mg/dl

Statistical analysis description:

Difference between number of patients taking Febuxostat 80 mg and patient taking Allopurinol 300 mg having both SUA levels >= 10 mg/dl at baseline and at least 3 SUA levels < 5.0 mg/dl at 16,20 and 24 weeks.

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg
Number of subjects included in analysis	167
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4727 [32]
Method	Fisher exact

Notes:

[32] - Not statistically significant (p>0.05)

Statistical analysis title	Febuxostat 80 mg vs Allopurinol 300 mg overall

Statistical analysis description:

Difference between number of patients taking Febuxostat 80 mg and patient taking Allopurinol 300 mg having at least 3 SUA levels < 5.0 mg/dl at 16,20 and 24 weeks.

Comparison groups	Full Analysis Set/Febuxostat 80 mg v Full Analysis Set/Allopurinol 300 mg

Number of subjects included in analysis	167
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0026 [33]
Method	Fisher exact

Notes:

[33] - Statistically significant (p<0.05)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent at Visit -1 (2 weeks before treatment phase) to follow-up period of 2 weeks after the administration of the last treatment dose. Treatment duration was of 24 weeks.

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Febuxostat 80 mg Modified Safety Poulation

Reporting group description:

Febuxostat 80 mg given once a day. Dosage form is Oral capsules as result of the over encapsulation of the 80 mg oral tablets. Treatment period of 4 weeks +/- 4 days.

Reporting group title	Febuxostat 120 mg Modified Safety Population

Reporting group description: -

Reporting group title	Allopurinol 300 mg Modified Safety Population

Reporting group description: -

Serious adverse events	Febuxostat 80 mg Modified Safety Poulation	Febuxostat 120 mg Modified Safety Population	Allopurinol 300 mg Modified Safety Population
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 218 (2.29%)	3 / 68 (4.41%)	3 / 162 (1.85%)
number of deaths (all causes)	1	2	0
number of deaths resulting from adverse events	1	2	0
Investigations			
Blood triglycerides increased			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Myocardial infarction			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sudden death			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Parkinsonism			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
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			
Pyrexia			
subjects affected / exposed	2 / 218 (0.92%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			

subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Tonsillitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Febuxostat 80 mg Modified Safety Poulation	Febuxostat 120 mg Modified Safety Population	Allopurinol 300 mg Modified Safety Population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	205 / 218 (94.04%)	66 / 68 (97.06%)	153 / 162 (94.44%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Parathyroid cyst			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Renal cyst			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Synovial cyst			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Contusion			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Diastolic hypertension			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	1	0	1
Hypertension			
subjects affected / exposed	2 / 218 (0.92%)	2 / 68 (2.94%)	2 / 162 (1.23%)
occurrences (all)	2	2	3
Hypertensive crisis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Systolic hypertension			

subjects affected / exposed	3 / 218 (1.38%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	3	1	0
Thrombophlebitis superficial			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Surgical and medical procedures			
Tophus removal operation			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Weight loss diet			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	2 / 162 (1.23%)
occurrences (all)	0	0	2
Influenza like illness			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Sense of oppression			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Nasopharyngitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Psychiatric disorders			

Libido decreased			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase decreased			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	62 / 218 (28.44%)	18 / 68 (26.47%)	55 / 162 (33.95%)
occurrences (all)	68	23	66
Albumin urine present			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	41 / 218 (18.81%)	18 / 68 (26.47%)	34 / 162 (20.99%)
occurrences (all)	45	26	38
B-lymphocyte count decreased			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Bacterial test			
subjects affected / exposed	1 / 218 (0.46%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	1	2	1
Bacterial test positive			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	1	0	1
Band neutrophil percentage decreased			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Basophil count decreased			
subjects affected / exposed	3 / 218 (1.38%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	3	2	2
Basophil count increased			
subjects affected / exposed	8 / 218 (3.67%)	6 / 68 (8.82%)	8 / 162 (4.94%)
occurrences (all)	8	6	11
Basophil percentage decreased			

subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Basophil percentage increased			
subjects affected / exposed	7 / 218 (3.21%)	5 / 68 (7.35%)	9 / 162 (5.56%)
occurrences (all)	7	7	13
Bilirubin conjugated			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	0	1	1
Bilirubin conjugated increased			
subjects affected / exposed	37 / 218 (16.97%)	16 / 68 (23.53%)	31 / 162 (19.14%)
occurrences (all)	45	21	36
Bilirubin urine			
subjects affected / exposed	3 / 218 (1.38%)	1 / 68 (1.47%)	2 / 162 (1.23%)
occurrences (all)	3	1	2
Blood albumin decreased			
subjects affected / exposed	6 / 218 (2.75%)	2 / 68 (2.94%)	5 / 162 (3.09%)
occurrences (all)	6	2	6
Blood albumin increased			
subjects affected / exposed	17 / 218 (7.80%)	6 / 68 (8.82%)	11 / 162 (6.79%)
occurrences (all)	19	6	14
Blood alkaline phosphatase			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase decreased			
subjects affected / exposed	4 / 218 (1.83%)	1 / 68 (1.47%)	2 / 162 (1.23%)
occurrences (all)	5	1	3
Blood alkaline phosphatase increased			
subjects affected / exposed	14 / 218 (6.42%)	5 / 68 (7.35%)	10 / 162 (6.17%)
occurrences (all)	17	5	13
Blood bilirubin			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	0	1	1
Blood bilirubin decreased			
subjects affected / exposed	4 / 218 (1.83%)	0 / 68 (0.00%)	2 / 162 (1.23%)
occurrences (all)	6	0	2

Blood bilirubin increased			
subjects affected / exposed	19 / 218 (8.72%)	10 / 68 (14.71%)	13 / 162 (8.02%)
occurrences (all)	22	15	15
Blood bilirubin unconjugated increased			
subjects affected / exposed	2 / 218 (0.92%)	8 / 68 (11.76%)	3 / 162 (1.85%)
occurrences (all)	2	10	3
Blood calcium decreased			
subjects affected / exposed	8 / 218 (3.67%)	6 / 68 (8.82%)	5 / 162 (3.09%)
occurrences (all)	9	7	6
Blood calcium increased			
subjects affected / exposed	33 / 218 (15.14%)	14 / 68 (20.59%)	17 / 162 (10.49%)
occurrences (all)	42	17	21
Blood chloride decreased			
subjects affected / exposed	26 / 218 (11.93%)	9 / 68 (13.24%)	18 / 162 (11.11%)
occurrences (all)	28	12	21
Blood chloride increased			
subjects affected / exposed	32 / 218 (14.68%)	16 / 68 (23.53%)	25 / 162 (15.43%)
occurrences (all)	34	20	30
Blood cholesterol increased			
subjects affected / exposed	2 / 218 (0.92%)	0 / 68 (0.00%)	2 / 162 (1.23%)
occurrences (all)	2	0	2
Blood creatine increased			
subjects affected / exposed	3 / 218 (1.38%)	4 / 68 (5.88%)	7 / 162 (4.32%)
occurrences (all)	4	5	8
Blood creatine phosphokinase			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Blood creatine phosphokinase MB increased			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	0	1	1
Blood creatine phosphokinase decreased			
subjects affected / exposed	1 / 218 (0.46%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	1	1	1
Blood creatine phosphokinase increased			

subjects affected / exposed	32 / 218 (14.68%)	9 / 68 (13.24%)	31 / 162 (19.14%)
occurrences (all)	34	9	37
Blood creatinine decreased			
subjects affected / exposed	3 / 218 (1.38%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	3	1	1
Blood creatinine increased			
subjects affected / exposed	34 / 218 (15.60%)	14 / 68 (20.59%)	23 / 162 (14.20%)
occurrences (all)	45	16	32
Blood glucose			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Blood glucose decreased			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Blood glucose increased			
subjects affected / exposed	58 / 218 (26.61%)	24 / 68 (35.29%)	48 / 162 (29.63%)
occurrences (all)	72	25	65
Blood lactate dehydrogenase decreased			
subjects affected / exposed	6 / 218 (2.75%)	0 / 68 (0.00%)	4 / 162 (2.47%)
occurrences (all)	7	0	8
Blood lactate dehydrogenase increased			
subjects affected / exposed	22 / 218 (10.09%)	11 / 68 (16.18%)	20 / 162 (12.35%)
occurrences (all)	28	13	24
Blood phosphorus increased			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Blood potassium abnormal			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Blood potassium decreased			
subjects affected / exposed	7 / 218 (3.21%)	3 / 68 (4.41%)	6 / 162 (3.70%)
occurrences (all)	7	3	8
Blood potassium increased			

subjects affected / exposed	29 / 218 (13.30%)	14 / 68 (20.59%)	15 / 162 (9.26%)
occurrences (all)	32	14	25
Blood pressure ambulatory increased			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	1	0	1
Blood pressure diastolic increased			
subjects affected / exposed	3 / 218 (1.38%)	2 / 68 (2.94%)	2 / 162 (1.23%)
occurrences (all)	4	3	2
Blood pressure increased			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	1	0	1
Blood pressure systolic increased			
subjects affected / exposed	6 / 218 (2.75%)	4 / 68 (5.88%)	2 / 162 (1.23%)
occurrences (all)	6	5	2
Blood sodium decreased			
subjects affected / exposed	15 / 218 (6.88%)	8 / 68 (11.76%)	19 / 162 (11.73%)
occurrences (all)	15	11	21
Blood sodium increased			
subjects affected / exposed	26 / 218 (11.93%)	17 / 68 (25.00%)	23 / 162 (14.20%)
occurrences (all)	30	18	25
Blood thrombin increased			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	7 / 218 (3.21%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	7	1	1
Blood thyroid stimulating hormone increased			
subjects affected / exposed	15 / 218 (6.88%)	4 / 68 (5.88%)	12 / 162 (7.41%)
occurrences (all)	17	4	15
Blood triglycerides increased			
subjects affected / exposed	52 / 218 (23.85%)	16 / 68 (23.53%)	41 / 162 (25.31%)
occurrences (all)	69	18	58
Blood uric acid decreased			

subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Blood uric acid increased			
subjects affected / exposed	1 / 218 (0.46%)	3 / 68 (4.41%)	1 / 162 (0.62%)
occurrences (all)	1	3	1
Blood urine			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Blood urine present			
subjects affected / exposed	21 / 218 (9.63%)	15 / 68 (22.06%)	20 / 162 (12.35%)
occurrences (all)	25	17	27
C-reactive protein increased			
subjects affected / exposed	75 / 218 (34.40%)	27 / 68 (39.71%)	57 / 162 (35.19%)
occurrences (all)	88	31	75
CD4 lymphocytes decreased			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	2
Calcium ionised increased			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Cells in urine			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Coagulation test abnormal			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Coagulation time shortened			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	1	0	1
Creatinine renal clearance decreased			
subjects affected / exposed	37 / 218 (16.97%)	18 / 68 (26.47%)	26 / 162 (16.05%)
occurrences (all)	44	22	35
Creatinine renal clearance increased			
subjects affected / exposed	21 / 218 (9.63%)	6 / 68 (8.82%)	20 / 162 (12.35%)
occurrences (all)	26	6	30
Crystal urine			

subjects affected / exposed	1 / 218 (0.46%)	2 / 68 (2.94%)	5 / 162 (3.09%)
occurrences (all)	1	2	6
Crystal urine present			
subjects affected / exposed	10 / 218 (4.59%)	8 / 68 (11.76%)	10 / 162 (6.17%)
occurrences (all)	11	8	12
Electrocardiogram T wave abnormal			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Eosinophil count			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	2 / 162 (1.23%)
occurrences (all)	0	0	2
Eosinophil count decreased			
subjects affected / exposed	5 / 218 (2.29%)	3 / 68 (4.41%)	4 / 162 (2.47%)
occurrences (all)	5	3	4
Eosinophil count increased			
subjects affected / exposed	25 / 218 (11.47%)	9 / 68 (13.24%)	17 / 162 (10.49%)
occurrences (all)	28	10	23
Eosinophil percentage decreased			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	2	0
Eosinophil percentage increased			
subjects affected / exposed	12 / 218 (5.50%)	5 / 68 (7.35%)	10 / 162 (6.17%)
occurrences (all)	13	5	12
Gamma-glutamyltransferase increased			
subjects affected / exposed	42 / 218 (19.27%)	20 / 68 (29.41%)	41 / 162 (25.31%)
occurrences (all)	54	23	52
Glucose urine			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	1	0	1
Glucose urine present			
subjects affected / exposed	2 / 218 (0.92%)	3 / 68 (4.41%)	3 / 162 (1.85%)
occurrences (all)	2	3	3
Haematocrit abnormal			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1

Haematocrit decreased			
subjects affected / exposed	10 / 218 (4.59%)	4 / 68 (5.88%)	21 / 162 (12.96%)
occurrences (all)	12	4	26
Haematocrit increased			
subjects affected / exposed	21 / 218 (9.63%)	6 / 68 (8.82%)	14 / 162 (8.64%)
occurrences (all)	26	7	15
Haemoglobin abnormal			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	2 / 218 (0.92%)	0 / 68 (0.00%)	10 / 162 (6.17%)
occurrences (all)	4	0	16
Haemoglobin increased			
subjects affected / exposed	10 / 218 (4.59%)	4 / 68 (5.88%)	8 / 162 (4.94%)
occurrences (all)	12	4	9
Haemoglobin urine			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	2 / 162 (1.23%)
occurrences (all)	0	1	2
Haemoglobin urine present			
subjects affected / exposed	9 / 218 (4.13%)	3 / 68 (4.41%)	7 / 162 (4.32%)
occurrences (all)	10	3	7
High density lipoprotein decreased			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
International normalised ratio decreased			
subjects affected / exposed	16 / 218 (7.34%)	5 / 68 (7.35%)	12 / 162 (7.41%)
occurrences (all)	18	6	15
International normalised ratio increased			
subjects affected / exposed	5 / 218 (2.29%)	5 / 68 (7.35%)	5 / 162 (3.09%)
occurrences (all)	5	6	7
LDL/HDL ratio increased			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Laboratory test abnormal			

subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	0	1	2
Low density lipoprotein increased			
subjects affected / exposed	44 / 218 (20.18%)	22 / 68 (32.35%)	29 / 162 (17.90%)
occurrences (all)	51	23	40
Lymphocyte count			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Lymphocyte count abnormal			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Lymphocyte count decreased			
subjects affected / exposed	6 / 218 (2.75%)	0 / 68 (0.00%)	5 / 162 (3.09%)
occurrences (all)	6	0	6
Lymphocyte count increased			
subjects affected / exposed	9 / 218 (4.13%)	5 / 68 (7.35%)	11 / 162 (6.79%)
occurrences (all)	11	5	11
Lymphocyte percentage decreased			
subjects affected / exposed	2 / 218 (0.92%)	2 / 68 (2.94%)	3 / 162 (1.85%)
occurrences (all)	2	2	3
Lymphocyte percentage increased			
subjects affected / exposed	3 / 218 (1.38%)	0 / 68 (0.00%)	3 / 162 (1.85%)
occurrences (all)	4	0	4
Mean cell volume decreased			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Monocyte count			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Monocyte count decreased			
subjects affected / exposed	2 / 218 (0.92%)	0 / 68 (0.00%)	6 / 162 (3.70%)
occurrences (all)	2	0	6
Monocyte count increased			
subjects affected / exposed	33 / 218 (15.14%)	11 / 68 (16.18%)	29 / 162 (17.90%)
occurrences (all)	42	12	31
Monocyte percentage decreased			

subjects affected / exposed	1 / 218 (0.46%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	1	1	0
Monocyte percentage increased			
subjects affected / exposed	5 / 218 (2.29%)	6 / 68 (8.82%)	8 / 162 (4.94%)
occurrences (all)	6	7	8
Neutrophil count decreased			
subjects affected / exposed	12 / 218 (5.50%)	3 / 68 (4.41%)	7 / 162 (4.32%)
occurrences (all)	16	4	8
Neutrophil count increased			
subjects affected / exposed	18 / 218 (8.26%)	5 / 68 (7.35%)	7 / 162 (4.32%)
occurrences (all)	20	5	8
Neutrophil percentage decreased			
subjects affected / exposed	4 / 218 (1.83%)	2 / 68 (2.94%)	4 / 162 (2.47%)
occurrences (all)	6	2	8
Neutrophil percentage increased			
subjects affected / exposed	2 / 218 (0.92%)	3 / 68 (4.41%)	3 / 162 (1.85%)
occurrences (all)	2	3	3
Nitrite urine present			
subjects affected / exposed	4 / 218 (1.83%)	1 / 68 (1.47%)	4 / 162 (2.47%)
occurrences (all)	5	1	4
Platelet count decreased			
subjects affected / exposed	4 / 218 (1.83%)	1 / 68 (1.47%)	5 / 162 (3.09%)
occurrences (all)	5	1	5
Platelet count increased			
subjects affected / exposed	10 / 218 (4.59%)	1 / 68 (1.47%)	5 / 162 (3.09%)
occurrences (all)	11	1	7
Protein C increased			
subjects affected / exposed	0 / 218 (0.00%)	2 / 68 (2.94%)	2 / 162 (1.23%)
occurrences (all)	0	2	2
Protein total abnormal			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Protein total decreased			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Protein urine			

subjects affected / exposed	1 / 218 (0.46%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	1	1	1
Protein urine present			
subjects affected / exposed	17 / 218 (7.80%)	12 / 68 (17.65%)	13 / 162 (8.02%)
occurrences (all)	17	12	16
Prothrombin level decreased			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	2 / 162 (1.23%)
occurrences (all)	1	0	2
Prothrombin level increased			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Prothrombin time prolonged			
subjects affected / exposed	5 / 218 (2.29%)	1 / 68 (1.47%)	2 / 162 (1.23%)
occurrences (all)	5	1	2
Prothrombin time shortened			
subjects affected / exposed	0 / 218 (0.00%)	2 / 68 (2.94%)	1 / 162 (0.62%)
occurrences (all)	0	2	1
Red blood cell count decreased			
subjects affected / exposed	20 / 218 (9.17%)	13 / 68 (19.12%)	20 / 162 (12.35%)
occurrences (all)	25	15	24
Red blood cell count increased			
subjects affected / exposed	15 / 218 (6.88%)	6 / 68 (8.82%)	10 / 162 (6.17%)
occurrences (all)	16	7	10
Red blood cell sedimentation rate increased			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Red blood cells urine			
subjects affected / exposed	6 / 218 (2.75%)	1 / 68 (1.47%)	4 / 162 (2.47%)
occurrences (all)	6	1	4
Red blood cells urine positive			
subjects affected / exposed	19 / 218 (8.72%)	11 / 68 (16.18%)	20 / 162 (12.35%)
occurrences (all)	23	11	24
Renal function test abnormal			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0

Specific gravity urine abnormal			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Specific gravity urine decreased			
subjects affected / exposed	52 / 218 (23.85%)	26 / 68 (38.24%)	38 / 162 (23.46%)
occurrences (all)	60	28	49
Specific gravity urine increased			
subjects affected / exposed	34 / 218 (15.60%)	21 / 68 (30.88%)	25 / 162 (15.43%)
occurrences (all)	44	24	27
Transaminases increased			
subjects affected / exposed	2 / 218 (0.92%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	3	0	1
Urinary casts present			
subjects affected / exposed	1 / 218 (0.46%)	3 / 68 (4.41%)	4 / 162 (2.47%)
occurrences (all)	2	5	4
Urinary sediment present			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	2 / 162 (1.23%)
occurrences (all)	1	0	3
Urine analysis abnormal			
subjects affected / exposed	6 / 218 (2.75%)	4 / 68 (5.88%)	7 / 162 (4.32%)
occurrences (all)	8	4	7
Urine bilirubin increased			
subjects affected / exposed	8 / 218 (3.67%)	5 / 68 (7.35%)	5 / 162 (3.09%)
occurrences (all)	8	5	6
Urine ketone body			
subjects affected / exposed	1 / 218 (0.46%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	1	1	0
Urine ketone body present			
subjects affected / exposed	15 / 218 (6.88%)	13 / 68 (19.12%)	5 / 162 (3.09%)
occurrences (all)	16	14	7
Urine leukocyte esterase			
subjects affected / exposed	3 / 218 (1.38%)	5 / 68 (7.35%)	1 / 162 (0.62%)
occurrences (all)	3	6	1
Urine leukocyte esterase positive			
subjects affected / exposed	10 / 218 (4.59%)	6 / 68 (8.82%)	13 / 162 (8.02%)
occurrences (all)	11	6	15

Urine osmolarity decreased			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	2 / 162 (1.23%)
occurrences (all)	0	0	2
Urine output decreased			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Urine oxalate			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	1	0	1
Urine protein, quantitative			
subjects affected / exposed	2 / 218 (0.92%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	2	1	1
Urine protein/creatinine ratio increased			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Urine transitional cells present			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	0	1	1
Urobilinogen urine			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	2 / 162 (1.23%)
occurrences (all)	0	1	2
Urobilinogen urine increased			
subjects affected / exposed	10 / 218 (4.59%)	3 / 68 (4.41%)	5 / 162 (3.09%)
occurrences (all)	12	3	5
Weight decreased			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
White blood cell agglutination present			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	1	0	1
White blood cell analysis abnormal			

subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	5 / 162 (3.09%)
occurrences (all)	1	0	5
White blood cell count decreased			
subjects affected / exposed	9 / 218 (4.13%)	4 / 68 (5.88%)	4 / 162 (2.47%)
occurrences (all)	11	4	5
White blood cells urine			
subjects affected / exposed	2 / 218 (0.92%)	0 / 68 (0.00%)	2 / 162 (1.23%)
occurrences (all)	2	0	2
White blood cells urine positive			
subjects affected / exposed	27 / 218 (12.39%)	12 / 68 (17.65%)	21 / 162 (12.96%)
occurrences (all)	37	15	31
Wound healing normal			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
pH urine decreased			
subjects affected / exposed	67 / 218 (30.73%)	31 / 68 (45.59%)	49 / 162 (30.25%)
occurrences (all)	92	42	57
pH urine increased			
subjects affected / exposed	8 / 218 (3.67%)	0 / 68 (0.00%)	2 / 162 (1.23%)
occurrences (all)	9	0	2
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Joint injury			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	2
Atrial fibrillation			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Atrial flutter			

subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Bradycardia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Extrasystoles			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Sinus bradycardia			
subjects affected / exposed	1 / 218 (0.46%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	1	1	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Polyneuropathy			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 218 (0.46%)	2 / 68 (2.94%)	3 / 162 (1.85%)
occurrences (all)	1	2	4
Haemoglobinaemia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Leukocytosis			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	0	1	1
Leukopenia			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Lymphocytosis			

subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	2 / 218 (0.92%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	4	0	1
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Polycythaemia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
White blood cell disorder			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 218 (0.92%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	3	1	1
Abdominal pain lower			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	12 / 218 (5.50%)	0 / 68 (0.00%)	6 / 162 (3.70%)
occurrences (all)	13	0	6
Dry mouth			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Gastritis			

subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	1	0	1
Gastroenteritis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Mouth cyst			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Biliary cyst			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Hepatic steatosis			
subjects affected / exposed	2 / 218 (0.92%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	2	1	1
Liver disorder			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Rash generalised			

subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Nodule			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Bacteriuria			
subjects affected / exposed	1 / 218 (0.46%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	1	1	0
Bilirubinuria			
subjects affected / exposed	4 / 218 (1.83%)	2 / 68 (2.94%)	8 / 162 (4.94%)
occurrences (all)	4	3	9
Bladder dysfunction			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Crystalluria			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	2 / 162 (1.23%)
occurrences (all)	0	1	3
Haematuria			
subjects affected / exposed	3 / 218 (1.38%)	0 / 68 (0.00%)	5 / 162 (3.09%)
occurrences (all)	3	0	6
Haemoglobinuria			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Ketonuria			
subjects affected / exposed	6 / 218 (2.75%)	3 / 68 (4.41%)	4 / 162 (2.47%)
occurrences (all)	6	3	4
Leukocyturia			
subjects affected / exposed	6 / 218 (2.75%)	3 / 68 (4.41%)	3 / 162 (1.85%)
occurrences (all)	7	3	3
Nephrolithiasis			
subjects affected / exposed	1 / 218 (0.46%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	1	1	1
Proteinuria			
subjects affected / exposed	14 / 218 (6.42%)	8 / 68 (11.76%)	11 / 162 (6.79%)
occurrences (all)	16	9	12

Renal colic			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Strangury			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Urine abnormality			
subjects affected / exposed	4 / 218 (1.83%)	3 / 68 (4.41%)	4 / 162 (2.47%)
occurrences (all)	4	3	5
Endocrine disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Glucose tolerance impaired			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Goitre			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	2 / 162 (1.23%)
occurrences (all)	0	0	2
Impaired fasting glucose			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Thyroid cyst			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 218 (2.29%)	0 / 68 (0.00%)	2 / 162 (1.23%)
occurrences (all)	7	0	2
Back pain			

subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Gout			
subjects affected / exposed	6 / 218 (2.75%)	1 / 68 (1.47%)	7 / 162 (4.32%)
occurrences (all)	8	1	8
Gouty arthritis			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Joint ankylosis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Lower limb fracture			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Meniscal degeneration			
subjects affected / exposed	2 / 218 (0.92%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	2	0	0
Metatarsalgia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Pain in extremity			

subjects affected / exposed	2 / 218 (0.92%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	2	0	1
Rotator cuff syndrome			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Spondylitis			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Tendonitis			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Laryngitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Mastitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 218 (0.92%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	2	1	1
Otitis media acute			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	2
Pharyngitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0

Sinusitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	1	0	1
Tracheitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 218 (0.46%)	1 / 68 (1.47%)	2 / 162 (1.23%)
occurrences (all)	1	1	2
Urinary tract infection			
subjects affected / exposed	2 / 218 (0.92%)	0 / 68 (0.00%)	3 / 162 (1.85%)
occurrences (all)	2	0	3
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	3	0	0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Dyslipidaemia			
subjects affected / exposed	2 / 218 (0.92%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	2	0	1
Glucose tolerance impaired			
subjects affected / exposed	2 / 218 (0.92%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	2	0	0
Gout			
subjects affected / exposed	10 / 218 (4.59%)	7 / 68 (10.29%)	10 / 162 (6.17%)
occurrences (all)	18	14	16
Gouty tophus			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Hyperalbuminaemia			
subjects affected / exposed	1 / 218 (0.46%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	1	1	1
Hypercalcaemia			

subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	2 / 162 (1.23%)
occurrences (all)	0	0	2
Hyperchloraemia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	1	0	1
Hypercholesterolaemia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	2 / 162 (1.23%)
occurrences (all)	1	0	2
Hyperkalaemia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Hypernatraemia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Hypertriglyceridaemia			
subjects affected / exposed	6 / 218 (2.75%)	1 / 68 (1.47%)	1 / 162 (0.62%)
occurrences (all)	6	1	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 68 (1.47%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Osteopenia			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Overweight			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Sodium retention			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Type 2 diabetes mellitus			

subjects affected / exposed	1 / 218 (0.46%)	0 / 68 (0.00%)	0 / 162 (0.00%)
occurrences (all)	1	0	0
Type I hyperlipidaemia			
subjects affected / exposed	0 / 218 (0.00%)	0 / 68 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 February 2013	Changes introduced were the following: -CPK and C-reactive protein were added among the blood chemistry parameters -Clarifications on procedures for reporting gout flares as AEs were given; -Clarifications on the definition of SUSAR were given; -The specification of the baseline visit for the inclusion criterion of serum uric acid ≥ 8.0mg/dl was removed; -The procedures for the criteria for eligibility at the end of the 2-week run-in period relative to gout flares and availability of the results of laboratory tests at Visit 0 were better clarified; -The requirement for the availability of the results of laboratory tests at Visits 1 and 2 was better clarified; -The study flow-chart, the description of visit plan and the study design diagram were modified according to the changes in procedures for the management of gout flares and the availability of the results of laboratory tests; -A clarification of the time of definition of the baseline time point was given; -The two distinctive sets for the analysis of efficacy endpoints were defined; -The dosage of Allopurinol was better clarified.
21 March 2014	Changes introduced were the following: -Names of responsible persons of the sponsor and CRO were changed; -Following an EMA request, a form was introduced for collecting additional information in case of serious hepatic and cutaneous reactions; -The sample size was recalculated according to changes in statistical power; -The study timelines were prolonged; -The inclusion criterion of the American Rheumatism Association for the classification of the acute arthritis of primary gout was applied to medical history; -The exclusion criterion on lactose intolerance was clarified as a required known criterion; -The method of calculation of creatinine clearance (Cockroft-Gault formula) was specified; -Procedures for the repetition of laboratory tests in case the randomization visit was postponed due to gout flare were given; -Procedures to be followed in case of study discontinuation were better clarified; -Methods of calculation of compliance for prophylaxis therapy were added; -The timelines required between Visit -1 and Visit 0 were modified; -The blood sample and urine collection at Visit 0 were deleted, except in case the visit was postponed due to gout flare; -The baseline time point for safety and efficacy evaluations was redefined and was better clarified; -The safety population was redefined as inclusive of all enrolled subjects (not only randomised subjects); -The reference person of the sponsor in charge of keeping the copies of the randomization envelopes for emergency unblinding was changed from the medical expert to a generic sponsor personnel.

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.

No limitations or caveats are applicable to this summary

Notes: