Clinical trial results:
The Effect of Intensive Urate Lowering Therapy (ULT) with Febuxostat in Comparison with Allopurinol on Cardiovascular Risk in Patients with Gout Using Surrogate Markers: a Randomized, Controlled Trial (Acronym: the FORWARD Trial)

Summary

EudraCT number	2014-005567-33
Trial protocol	NL DE PL HR IT
Global end of trial date	10 May 2017

Results information

Result version number	v1 (current)
This version publication date	19 August 2018
First version publication date	19 August 2018

Trial information

Trial identification

Sponsor protocol code	MEIN/14/FEB-PWV/001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02500641
WHO universal trial number (UTN)	-
Other trial identifiers	the FORWARD trial: MEIN/14/FEB-PWV/001

Notes:

Sponsors

Sponsor organisation name	Menarini International Operations Luxembourg S.A
Sponsor organisation address	1, Avenue de la Gare, Luxembourg, Luxembourg, L-1611
Public contact	Medical Scientific Management, Menarini International Operations Luxembourg S.A, 00352 264976, reception@menarini.lu
Scientific contact	Paolo Fabrizzi, Menarini, +39 0555680459, PFabrizzi@menarini.it

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	10 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 May 2017
Global end of trial reached?	Yes
Global end of trial date	10 May 2017
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 daily 80-120 mg is better than Allopurinol daily 100-600 mg in inducing positive changes in Pulse Wave Velocity (PWV) after 36 weeks of treatment. PVW is considered a valid surrogate endpoint with clearly established relevance to predict CV clinical outcome.

Protection of trial subjects:

This study has been carried out in compliance with the study protocol, the recommendations on biomedical research on human subjects of the Declaration of Helsinki, International Conference of Harmonisation – Good Clinical Practice (ICH-GCP) Guidelines, EU-Directive 2001/20 of April 4, 2001, and national requirements of the participating countries.

Background therapy:

To prevent flares in the initial stages of treatment, patients will be treated for at least 6 months with colchicine 0.5 - 1 mg QD or in case of colchicine intolerance, Naproxen 550 mg BID with Omeprazole (20-40 mg once daily), if indicated to be used.

Evidence for comparator: -

Actual start date of recruitment	24 August 2015
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	Netherlands: 1
Country: Number of subjects enrolled	Poland: 90
Country: Number of subjects enrolled	Romania: 52
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Serbia: 32
Worldwide total number of subjects	196
EEA total number of subjects	164

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)	128
From 65 to 84 years	68
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 29 Investigational study sites present in 5 European countries (11 in Poland, 6 in Romania, 4 in Italy, 1 in Germany, 1 in the Netherlands) and in a non European country (6 in Serbia).
FPI: 24 August 2015 - LPO: 10 May 2017. Phase IV.
Treatment duration: 36 weeks
Safety follow up: 2 weeks

Pre-assignment

Screening details:

Screening period was from 7 days to up to 30 days according to possibility of re-testing sUA level.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Evaluator of PWV/PWA was blinded to the treatment received by the subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Febuxostat 80/120

Arm description:

Febuxostat 80 mg or 120 mg once daily (120 mg daily, if serum urate was >6 mg/dL after 2 weeks of treatment at 80 mg daily).

Arm type	Experimental
Investigational medicinal product name	Febuxostat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Febuxostat 80 mg or 120 mg once daily (120 mg daily, if serum urate was >6 mg/dL after 2 weeks of treatment at 80 mg daily).

Arm title	Allopurinol 100/600 mg

Arm description:

Allopurinol 100 mg once daily (up to a maximum dose of 600 mg daily escalated in 100 mg increments every 2 weeks, if serum urate was >6 mg/dL after 2 weeks of treatment at the previous dose).

Arm type	Active comparator
Investigational medicinal product name	Allopurinol 100-600 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Allopurinol 100 mg once daily (up to a maximum dose of 600 mg daily escalated in 100 mg increments every 2 weeks, if serum urate was >6 mg/dL after 2 weeks of treatment at the previous dose).

Number of subjects in period 1	Febuxostat 80/120	Allopurinol 100/600 mg
Started	98	98
Completed	88	86
Not completed	10	12
Consent withdrawn by subject	4	5
Study terminated by Sponsor	1	-
Adverse event, non-fatal	-	2
not specificied	-	2
Lost to follow-up	1	-
Protocol deviation	1	2
not specified	3	-
non compliance study drug	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	196	196	
Age categorical Units: Subjects			
Adults (18-64 years)	128	128	
From 65-84 years	68	68	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	59.59		
standard deviation	± 10.6	-	
Gender categorical Units: Subjects			
Female	35	35	
Male	161	161	

Subject analysis sets

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

Subject analysis set description:

All randomised subjects who had taken at least one dose of study drug specified by treatment group and performed at least one primary efficacy assessment (PWV) after randomisation.

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

Subject analysis set description:

All randomised subjects who had taken at least one dose of study drug specified by treatment group and performed at least one primary efficacy assessment (PWV) after randomisation.

Reporting group values	Full Analysis Set/Febuxostat	Full Analysis Set/Allopurinol	
Number of subjects	92	90	
Age categorical Units: Subjects			
Adults (18-64 years)	66	58	
From 65-84 years	26	32	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	58.26	59.83	
standard deviation	± 10.97	± 9.96	
Gender categorical Units: Subjects			
Female	15	15	

Male	77	75	

End points

End points reporting groups

Reporting group title	Febuxostat 80/120
Reporting group description:	
Febuxostat 80 mg or 120 mg once daily (120 mg daily, if serum urate was >6 mg/dL after 2 weeks of treatment at 80 mg daily).	
Reporting group title	Allopurinol 100/600 mg
Reporting group description:	
Allopurinol 100 mg once daily (up to a maximum dose of 600 mg daily escalated in 100 mg increments every 2 weeks, if serum urate was >6 mg/dL after 2 weeks of treatment at the previous dose).	
Subject analysis set title	Full Analysis Set/Febuxostat
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised subjects who had taken at least one dose of study drug specified by treatment group and performed at least one primary efficacy assessment (PWV) after randomisation.	
Subject analysis set title	Full Analysis Set/Allopurinol
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised subjects who had taken at least one dose of study drug specified by treatment group and performed at least one primary efficacy assessment (PWV) after randomisation.	

Primary: Change in PWV after 36 weeks of treatment

End point title	Change in PWV after 36 weeks of treatment
End point description:	
To determine whether Febuxostat daily 80-120 mg was better than Allopurinol daily 100-600 mg in inducing positive changes in Pulse Wave Velocity (PWV) after 36 weeks of treatment.	
End point type	Primary
End point timeframe:	
36 weeks of treatment. From Visit 0 (randomization visit) to Visit 4 (36 weeks +/- 4 days).	

End point values	Full Analysis Set/Febuxostat	Full Analysis Set/Allopurinol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	90		
Units: Velocity m/s				
arithmetic mean (standard deviation)	9.0 (± 2.04)	9.05 (± 1.99)		

Statistical analyses

Statistical analysis title	Febuxostat vs Allopurinolo
Comparison groups	Full Analysis Set/Febuxostat v Full Analysis Set/Allopurinol

Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5298 [1]
Method	ANCOVA

Notes:

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent at Visit -1 (from 7 to 30 days before treatment phase in case of re-testing) to follow-up period of 2 weeks after the administration of the last treatment dose. Treatment duration was of 36 weeks.

Adverse event reporting additional description:

AE's were considered abnormalities in laboratory analyses (newly occurring after IMP administration or worsening of previously known abnormalities) considered clinically relevant by the Principal investigator (values significantly above or under normal range or requiring an intervention or diagnostic tests, or may result in the IMP discontinuation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Febuxostat 80/120 mg in Safety population

Reporting group description:

Initial daily dose is Febuxostat 80 mg given once a day. In case patient has sUA > 6 mg/dl after 2 weeks of treatment, then Febuxostat was up tritrated to 120 mg once a day and, if tolerated, maintained for the study duration.

Reporting group title	Allopurinol 100-600 mg in Safety Population

Reporting group description:

The initial daily dose is 100 mg , to be increased by 100 mg every 2 weeks in patients with sUA > 6 mg/dl. Maximum daily dose achievable in the study will depend on kidney function and tolerability, but will not exceed 600 mg.

Serious adverse events	Febuxostat 80/120 mg in Safety population	Allopurinol 100-600 mg in Safety Population	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 98 (10.20%)	8 / 98 (8.16%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Surgical and medical procedures			
Adhesiolysis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicectomy			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colectomy			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery bypass			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric bypass			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine operation			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraocular lens implant			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Asthma-chronic obstructive pulmonary disease overlap syndrome			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood triglycerides increased			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Large intestinal obstruction			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal adhesions			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Febuxostat 80/120 mg in Safety population	Allopurinol 100-600 mg in Safety Population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 98 (51.02%)	61 / 98 (62.24%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 98 (1.02%)	3 / 98 (3.06%)	
occurrences (all)	1	3	
Arteriosclerosis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 98 (2.04%)	3 / 98 (3.06%)	
occurrences (all)	2	3	
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Asthma-chronic obstructive pulmonary disease overlap syndrome			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	2	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Pulmonary mass			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Loss of libido			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 98 (4.08%)	1 / 98 (1.02%)	
occurrences (all)	4	1	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 98 (2.04%)	1 / 98 (1.02%)	
occurrences (all)	2	1	
Blood creatine phosphokinase increased			

subjects affected / exposed	3 / 98 (3.06%)	0 / 98 (0.00%)	
occurrences (all)	3	0	
Blood glucose increased			
subjects affected / exposed	3 / 98 (3.06%)	4 / 98 (4.08%)	
occurrences (all)	3	4	
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences (all)	2	0	
Blood pressure increased			
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences (all)	1	2	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences (all)	2	0	
Blood triglycerides increased			
subjects affected / exposed	2 / 98 (2.04%)	3 / 98 (3.06%)	
occurrences (all)	2	3	
Blood uric acid increased			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
C-reactive protein increased			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Eosinophil count decreased			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 98 (1.02%)	3 / 98 (3.06%)	
occurrences (all)	1	3	
Haemoglobin decreased			
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences (all)	1	2	
Hepatic enzyme increased			

subjects affected / exposed	4 / 98 (4.08%)	1 / 98 (1.02%)	
occurrences (all)	4	1	
Laboratory test abnormal			
subjects affected / exposed	2 / 98 (2.04%)	2 / 98 (2.04%)	
occurrences (all)	2	2	
Blood insulin increased			
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences (all)	0	2	
Blood potassium decreased			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Blood pressure abnormal			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
International normalised ratio increased			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Prothrombin time shortened			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Epicondylitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Forearm fracture			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Skin injury			

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Wound			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Adenomatous polyposis coli			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Type V hyperlipidaemia			
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences (all)	0	2	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences (all)	1	2	
Sciatica			
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences (all)	1	1	
Paraesthesia			
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences (all)	0	2	
Restless legs syndrome			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	

Thrombocytopenia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences (all)	1	3	
Diarrhoea			
subjects affected / exposed	2 / 98 (2.04%)	8 / 98 (8.16%)	
occurrences (all)	2	8	
Diverticulum intestinal			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences (all)	1	2	
Frequent bowel movements			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia oral			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	0 / 98 (0.00%)	4 / 98 (4.08%)	
occurrences (all)	0	4	
Nausea			
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences (all)	1	2	
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Hepatocellular injury			

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Alcoholic liver disease			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Liver disorder			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Pain of skin			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences (all)	1	2	
Skin disorder			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Nephropathy			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Renal impairment			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 98 (10.20%)	9 / 98 (9.18%)	
occurrences (all)	18	15	
Back pain			

subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences (all)	1	2	
Pain in extremity			
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences (all)	1	2	
Tendonitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	3	0	
Enthesopathy			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Intervertebral disc disorder			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Musculoskeletal discomfort			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	2	
Myopathy			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Spinal pain			
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences (all)	0	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences (all)	1	2	
Ear infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	

Laryngitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 98 (1.02%)	7 / 98 (7.14%)	
occurrences (all)	1	7	
Urinary tract infection			
subjects affected / exposed	2 / 98 (2.04%)	1 / 98 (1.02%)	
occurrences (all)	2	1	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Asymptomatic bacteriuria			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 98 (0.00%)	3 / 98 (3.06%)	
occurrences (all)	0	3	
Sinusitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Gout			
subjects affected / exposed	10 / 98 (10.20%)	15 / 98 (15.31%)	
occurrences (all)	25	27	
Metabolic syndrome			

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Dyslipidaemia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Hypercholesterolaemia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 98 (0.00%)	4 / 98 (4.08%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 April 2015	Changes introduced were the following: - Definition on exclusion criteria No.6 of basalioma skin cancer as minor skin cancer not to be excluded from trial participation. - Re-definition of contraception criteria accepted in the trial (exclusion criteria No.17) - Better explanation of dose modification of Allopurinol in case of significant renal function worsening. - Correction of allowed colchicine dosage. - Change of responsibility persons - Specification within secondary endpoint related to percentage of gout patients that serum urate concentration can be less than, or equal to 6 mg/dl after 12, 24 and 36 weeks of treatment. - Added section 10.4.1 "Management of laboratory abnormalities" - Deletion of ESR analysis from laboratory safety parameter in the Study Synopsis - Change of Country, number of sites and study duration - Introduction and definition of re-screening as new study procedure and consequent extension of the screening period from 7 days to period up to 30 days - Wording added on exclusion criteria 21 to better clarify the significant conditions which may result in a inadequate PWV/PWA measurement. - Added wording to confirm that within IMP/NIMP dispensed, treatment for flares is also included - Removal of triglycerides and LDL from safety laboratory evaluation as already present in central lab analysis. - Description of severe intensity of AE was slightly modified from „significant" to „important" abnormality: - Email reporting of SAEs is accepted as well as the fax reporting - Addition of safety section 10.4.1 "Management of laboratory abnormalities" containing additional wording on reporting of AEs and on laboratory parameters measured in central laboratory. - Addition of pregnancy of patient's partner (in case of male patients). - Other minor changes and corrections of typo error

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: