



## Clinical trial results:

### Febuxostat for Tumor Lysis Syndrome Prevention in Hematologic Malignancies: a Randomized, Double Blind, Phase III Study versus Allopurinol

#### Summary

EudraCT number	2012-000776-42
Trial protocol	DE ES CZ HU IT PL
Global end of trial date	11 October 2013

#### Results information

Result version number	v1 (current)
This version publication date	04 November 2018
First version publication date	04 November 2018

#### Trial information

##### Trial identification

Sponsor protocol code	FLO-01
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01724528
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Menarini Ricerche S.p.A
Sponsor organisation address	Via Sette Santi 1, Florence, Italy, 50131
Public contact	Direzione Ricerca Clinica, Menarini Ricerche S.p.A, 0039 055 5680 9933, ACapriati@menarini-ricerche.it
Scientific contact	Direzione Ricerca Clinica, Menarini Ricerche S.p.A, 0039 055 5680 9933, ACapriati@menarini-ricerche.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	28 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 October 2013
Global end of trial reached?	Yes
Global end of trial date	11 October 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

In order to minimize patients' discomfort and avoid unnecessary blood sampling, the protocol sections dealing with the description of the study procedures to be done at Screening were amended to specify that safety lab tests, urinalysis or 12 lead ECG at Screening Visit not needed to be done if they have been performed in the preceding 24 hours at investigative site for the standard care of the patients (Amendment N.1 dated 15 February 2013).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2012
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: 10
Country: Number of subjects enrolled	Spain: 48
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Hungary: 54
Country: Number of subjects enrolled	Italy: 32
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Croatia: 9
Country: Number of subjects enrolled	Romania: 20
Country: Number of subjects enrolled	Russian Federation: 82
Country: Number of subjects enrolled	Serbia: 17
Country: Number of subjects enrolled	Ukraine: 53
Worldwide total number of subjects	346
EEA total number of subjects	193

Notes:

<b>Subjects enrolled per age group</b>	
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)	230
From 65 to 84 years	113
85 years and over	3

## Subject disposition

### Recruitment

Recruitment details:

First patient in (screening) 01 Oct 2012, last patient out 11 Oct 2013. At 79 sites across 11 European countries (Croatia, Czech Republic, Germany, Hungary, Italy, Poland, Romania, Russia, Serbia, Spain and Ukraine) and Brazil

### Pre-assignment

Screening details:

Subjects complying with inclusion/exclusion criteria were to be randomised to receive (blinded) standard, low or high dose of study treatment as per investigator's assessment (mainly based on renal function). Randomization was balanced by TLS risk and serum uric acid levels ( $\leq$  or  $>$  7.5 mg/dL)

### Period 1

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

Blinding implementation details:

As the size and the shape of the Allopurinol 100 mg and Febuxostat 120 mg tablets differ as well as the posologic scheme of Allopurinol high dosage, double blind condition were secured by encapsulation of treatment tablets. Differences in weight were compensated by adequate filling material, so that capsules match in weight and appearance.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Febuxostat

Arm description:

Febuxostat for 7-9 days.

Febuxostat: standard dose PO (per os) from day 1 to day 7 (can be continued up to day 9 at investigator's discretion)

Arm type	Experimental
Investigational medicinal product name	Febuxostat
Investigational medicinal product code	
Other name	Adenuric
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

120 mg/day

<b>Arm title</b>	Allopurinol
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Arm description:

Allopurinol for 7-9 days

Allopurinol: Standard dose, low dose or high dose (as per investigator's judgement at the time of randomization) from day 1 to day 7 (can be continued up to day 9 at investigator's discretion).

Arm type	Active comparator
Investigational medicinal product name	Allopurinol
Investigational medicinal product code	
Other name	Zyloric
Pharmaceutical forms	Capsule
Routes of administration	Oral use

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**Dosage and administration details:**

300 mg/day (standard dose), 300 mg b.i.d./day (high dose), 200 mg/day (low dose)

<b>Number of subjects in period 1</b>	Febuxostat	Allopurinol
Started	173	173
Completed	169	170
Not completed	4	3
Adverse event, serious fatal	3	-
Consent withdrawn by subject	-	2
Patient refused to attend last visit	1	-
Protocol deviation	-	1

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**Period 2**

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

**Blinding implementation details:**

Treatment blinding was kept for the entire study duration up to the closure of database performed after last patient last visit.

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**Arms**

<b>Arm title</b>	Either Febuxostat or Allopurinol
Arm description:	
Final safety Follow up/End of Study Visit performed two weeks after after the randomization.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 2</b>	Either Febuxostat or Allopurinol
Started	339
Completed	339

## Baseline characteristics

### Reporting groups

Reporting group title	Febuxostat
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Reporting group description:

Febuxostat for 7-9 days.

Febuxostat: standard dose PO (per os) from day 1 to day 7 (can be continued up to day 9 at investigator's discretion)

Reporting group title	Allopurinol
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Reporting group description:

Allopurinol for 7-9 days

Allopurinol: Standard dose, low dose or high dose (as per investigator's judgement at the time of randomization) from day 1 to day 7 (can be continued up to day 9 at investigator's discretion).

Reporting group values	Febuxostat	Allopurinol	Total
Number of subjects	173	173	346
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	112	118	230
From 65-84 years	60	53	113
85 years and over	1	2	3
Age continuous			
Units: years			
geometric mean	58.5	58.3	
standard deviation	± 14.26	± 13.26	-
Gender categorical			
Units: Subjects			
Female	65	67	132
Male	108	106	214
serum uric acid (sUA)			
Units: Subjects			
< or = 7.5 mg/dL	151	152	303
> 7.5 mg/dL	22	21	43
TLS risk			
Units: Subjects			
Intermediate	143	141	284
High	30	32	62
Type of Hematologic Malignancy			
Units: Subjects			
Acute leukemia	34	25	59
Chronic lymphocytic leukemia	80	94	174

Lymphoma	59	54	113
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## End points

### End points reporting groups

Reporting group title	Febuxostat
Reporting group description: Febuxostat for 7-9 days.	
Febuxostat: standard dose PO (per os) from day 1 to day 7 (can be continued up to day 9 at investigator's discretion)	
Reporting group title	Allopurinol
Reporting group description: Allopurinol for 7-9 days	
Allopurinol: Standard dose, low dose or high dose (as per investigator's judgement at the time of randomization) from day 1 to day 7 (can be continued up to day 9 at investigator's discretion).	
Reporting group title	Either Febuxostat or Allopurinol
Reporting group description: Final safety Follow up/End of Study Visit performed two weeks after after the randomization.	

### Primary: Serum Uric Acid (sUA) Level Control

End point title	Serum Uric Acid (sUA) Level Control
End point description: Area under the curve of sUA from baseline (Day 1) to the evaluation visit (Day 8)	
End point type	Primary
End point timeframe: 8 days	

End point values	Febuxostat	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	172		
Units: Mg x hour/dL				
arithmetic mean (standard deviation)	514 (± 225.71)	708.0 (± 234.42)		

### Statistical analyses

Statistical analysis title	Superior test
Comparison groups	Febuxostat v Allopurinol
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

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**Primary: Preservation of Renal Function**

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End point title	Preservation of Renal Function
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End point description:

Change in serum creatinine level from baseline (Day 1) to the evaluation visit (Day 8)

End point type	Primary
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End point timeframe:

8 days

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End point values	Febuxostat	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	171		
Units: mg/dl				
arithmetic mean (standard deviation)	-0.03 (± 0.352)	-0.05 (± 0.171)		

**Statistical analyses**

Statistical analysis title	Superior test
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Comparison groups	Febuxostat v Allopurinol
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Number of subjects included in analysis	344
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.0903
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Method	ANCOVA
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**Secondary: Treatment Responder Rate**

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End point title	Treatment Responder Rate
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End point description:

Assessment of treatment responder rate, where treatment response is defined as the maintenance of SUA ≤ 7.5 mg/dL from Day 3 to Day 8

End point type	Secondary
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End point timeframe:

6 days

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End point values	Febuxostat	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	173		
Units: subjects	3	7		

## Statistical analyses

Statistical analysis title	Superior test
Comparison groups	Febuxostat v Allopurinol
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1993
Method	Wilson's confidence interval

## Secondary: Assessment of Laboratory Tumor Lysis Syndrome (LTLS)

End point title	Assessment of Laboratory Tumor Lysis Syndrome (LTLS)
End point description:	
Assessment of LTLS, from Day 3 to Day 8. According to Cairo-Bishop definition LTLS is defined by the presence of 2 or more laboratory abnormalities including: a 25% increase or levels above normal for serum uric acid, potassium, and phosphate or a 25% decrease or levels below normal for calcium.	
End point type	Secondary
End point timeframe:	
6 days	

End point values	Febuxostat	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	173		
Units: subjects	14	16		

## Statistical analyses

Statistical analysis title	Superior test
Comparison groups	Allopurinol v Febuxostat
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8488
Method	Chi-squared

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**Secondary: Assessment of Clinical Tumor Lysis Syndrome (CTLS)**

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End point title	Assessment of Clinical Tumor Lysis Syndrome (CTLS)
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End point description:

Assessment of CTLS, from Day 3 to Day 8. According to Cairo-Bishop definition, CTLS is defined by the presence of LTLS in addition to 1 or more of the following significant clinical complications: renal insufficiency, cardiac arrhythmias, sudden death and seizures. The grade of CTLS is defined by the maximal grade of the clinical manifestation

End point type	Secondary
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End point timeframe:

6 days

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End point values	Febuxostat	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	173		
Units: subjects	3	2		

**Statistical analyses**

Statistical analysis title	Superior test
Comparison groups	Febuxostat v Allopurinol
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Chi-squared

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

14 ± 2 days

Adverse event reporting additional description:

Analysed for the Safety Population (all patients who received the study drug)

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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### Reporting groups

Reporting group title	Febuxostat
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Reporting group description:

Febuxostat for 7-9 days.

Febuxostat: standard dose PO (per os) from day 1 to day 7 (can be continued up to day 9 at investigator's discretion)

Reporting group title	Allopurinol
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Reporting group description:

Allopurinol for 7-9 days

Allopurinol: Standard dose, low dose or high dose (as per investigator's judgement at the time of randomization) from day 1 to day 7 (can be continued up to day 9 at investigator's discretion).

Serious adverse events	Febuxostat	Allopurinol	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 173 (12.14%)	6 / 173 (3.47%)	
number of deaths (all causes)	6	0	
number of deaths resulting from adverse events	6	0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 173 (0.58%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			

subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 173 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	2 / 173 (1.16%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 173 (1.16%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 173 (1.73%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 173 (1.16%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 173 (0.58%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 173 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure			
subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 173 (2.89%)	2 / 173 (1.16%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 0	
Sepsis			
subjects affected / exposed	3 / 173 (1.73%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Septic shock			
subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			



Hypokalaemia			
subjects affected / exposed	0 / 173 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 173 (0.58%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Febuxostat	Allopurinol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	116 / 173 (67.05%)	112 / 173 (64.74%)	
Investigations			
Platelet count decreased			
subjects affected / exposed	9 / 173 (5.20%)	6 / 173 (3.47%)	
occurrences (all)	9	6	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 173 (7.51%)	5 / 173 (2.89%)	
occurrences (all)	14	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	38 / 173 (21.97%)	25 / 173 (14.45%)	
occurrences (all)	48	31	
Leukopenia			
subjects affected / exposed	25 / 173 (14.45%)	27 / 173 (15.61%)	
occurrences (all)	26	27	
Neutropenia			
subjects affected / exposed	30 / 173 (17.34%)	40 / 173 (23.12%)	
occurrences (all)	32	42	

Thrombocytopenia subjects affected / exposed occurrences (all)	25 / 173 (14.45%) 28	19 / 173 (10.98%) 20	
General disorders and administration site conditions			
Mucosal inflammation subjects affected / exposed occurrences (all)	11 / 173 (6.36%) 11	3 / 173 (1.73%) 3	
Pyrexia subjects affected / exposed occurrences (all)	23 / 173 (13.29%) 25	18 / 173 (10.40%) 21	
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	14 / 173 (8.09%) 16	11 / 173 (6.36%) 12	
Diarrhoea subjects affected / exposed occurrences (all)	16 / 173 (9.25%) 21	11 / 173 (6.36%) 13	
Nausea subjects affected / exposed occurrences (all)	22 / 173 (12.72%) 25	21 / 173 (12.14%) 23	
Vomiting subjects affected / exposed occurrences (all)	10 / 173 (5.78%) 11	12 / 173 (6.94%) 12	
Metabolism and nutrition disorders			
Hyperglycaemia subjects affected / exposed occurrences (all)	6 / 173 (3.47%) 7	9 / 173 (5.20%) 10	
Hyperphosphataemia subjects affected / exposed occurrences (all)	9 / 173 (5.20%) 9	4 / 173 (2.31%) 4	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2013	<p>Amendment No.1 specifically deals with the following changes:</p> <ol style="list-style-type: none"><li>1. In order to minimize patients' discomfort and avoid unnecessary blood sampling, the protocol sections dealing with the description of the study procedures to be done at Screening are amended to specify that safety lab tests, urinalysis or 12 lead ECG at Screening Visit do not need to be done if they have been performed in the preceding 24 hours at investigative site for the standard care of the patients.</li><li>2. In order to clarify the exclusion criterion relative to patients with diagnosis of ischemic heart disease or congestive heart failure, the protocol sections dealing with the exclusion criteria are amended to specify that only patients with uncontrolled ischemic heart disease or congestive heart failure cannot participate to the study.</li><li>3. In order to include the new EU SMPCs of ADENURIC® 120 MG film-coated tablets (20 December 2012) and minor clarifications and administrative changes.</li></ol>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported