



Clinical trial results:

A randomized, open-label, multicenter, controlled, parallel arm, phase III study assessing the efficacy and safety of AOP2014 vs. Hydroxyurea in patients with Polycythemia Vera

Summary

EudraCT number	2012-005259-18
Trial protocol	HU CZ IT SK AT BG DE PL ES BE
Global end of trial date	08 April 2016

Results information

Result version number	v1 (current)
This version publication date	11 March 2018
First version publication date	11 March 2018

Trial information

Trial identification

Sponsor protocol code	PROUD-PV
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AOP Orphan Pharmaceuticals AG
Sponsor organisation address	Wilhelminenstrasse 91/II f/B4, Vienna, Austria, 1160
Public contact	Head of Clinical Operations, AOP Orphan Pharmaceuticals AG, 43 015037224446, michael.zoerer@aoporphan.com
Scientific contact	Head of Clinical Operations, AOP Orphan Pharmaceuticals AG, 43 015037224446, michael.zoerer@aoporphan.com

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	24 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 April 2016
Global end of trial reached?	Yes
Global end of trial date	08 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of AOP2014 vs. Hydroxyurea in terms of disease response rate in both Hydroxyurea naïve and currently treated patients, diagnosed with Polycythemia Vera.

Protection of trial subjects:

An independent DMC was established that reviewed accumulated data on safety as well as efficacy in an open-label manner in regular intervals. Following the meetings the DMC advised the sponsor in writing on outcomes and findings of the meeting. Per the signed DMC charter the DMC took responsibility for continued safety as well as efficacy oversight.

Background therapy:

Low dose aspirin (acetylsalicylic acid) (100 mg/day) was given to patients in both groups, during the 12 months of study treatment, unless contraindicated.

Evidence for comparator:

Hydroxyurea is an established first-line treatment option currently approved in several European countries for Polycythemia Vera (PV) patients requiring a cytoreductive therapy. Clinical trials have shown that Hydroxyurea is an effective drug for preventing thrombosis in PV compared to phlebotomy. Major concerns of a long term treatment with Hydroxyurea is development of intolerance or resistance in a significant proportion of patients, and its potential leukemogenic risk, based on the mechanism of action.

Actual start date of recruitment	17 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 10
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Austria: 19
Country: Number of subjects enrolled	Bulgaria: 45
Country: Number of subjects enrolled	Czech Republic: 27
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hungary: 35
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Russian Federation: 33
Country: Number of subjects enrolled	Ukraine: 30

Country: Number of subjects enrolled	Romania: 9
Worldwide total number of subjects	257
EEA total number of subjects	194

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)	177
From 65 to 84 years	79
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients meeting the inclusion criteria were contacted and asked for their interest in participating in the study. All patients who agreed to participate in the study provided written informed consent before any study specific assessments or procedures were performed.

Pre-assignment

Screening details:

Patients diagnosed with Polycythemia Vera, either Hydroxyurea naïve or currently being treated with Hydroxyurea, and fulfilling other eligibility criteria were randomized. Patients considered for study entry, but who failed to meet one or more of the eligibility criteria, were reported in the eCRF detailing the reason for ineligibility.

Period 1

Period 1 title	Enrollment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AOP2014

Arm description:

Patients planned to be treated with AOP2014

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Hydroxyurea

Arm description:

Patients planned to be treated with Hydroxyurea

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	AOP2014	Hydroxyurea
Started	127	130
Completed	127	127
Not completed	0	3
Consent withdrawn by subject	-	3

Period 2

Period 2 title	Treatment period
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	AOP2014
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Arm description:

Patients treated with AOP2014. During the initial treatment phase (first 12 weeks following randomization), the dose of AOP2014 was adjusted to the dose which delivered the optimal disease response.

Arm type	Experimental
Investigational medicinal product name	AOP2014
Investigational medicinal product code	AOP2014
Other name	Peg-P-IFN- α -2b
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

AOP2014 was administered at the starting dose of 100 μ g every 2 weeks for up to 12 months of treatment. During the initial treatment phase (first 12 weeks following randomization), the dose of AOP2014 was adjusted to the dose which delivered the optimal disease response (Hematocrit [Hct] <45%, platelets <400 x 10⁹/L and leukocytes <10 x 10⁹/L). If no complete response was achieved, patients were treated at the individual highest tolerable dose, which had been achieved and kept during the maintenance treatment phase.

Investigational medicinal product name	Hydroxyurea
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

For the patients concurrently receiving Hydroxyurea at the time of screening but randomized to AOP2014 was the initial phase of the trial (up to week 12) a transition from Hydroxyurea to AOP2014. Hydroxyurea dose was decreased every two weeks and discontinued after week 12.

Arm title	Hydroxyurea
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Arm description:

Patients treated with Hydroxyurea. During the initial treatment phase (first 12 weeks following randomization), the dose of Hydroxyurea was adjusted to the dose which delivered the optimal disease response.

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

Dosage and administration details:

Hydroxyurea was administered per os at the starting dose of 500 mg daily for up to 12 months of treatment. During the initial treatment phase (first 12 weeks following randomization), the dose of Hydroxyurea was adjusted to the dose which delivered the optimal disease response (Hematocrit [Hct] <45%, platelets <400 x 10⁹/L and leukocytes <10 x 10⁹/L). If no complete response was achieved, patients were treated at the individual highest tolerable dose, which had been achieved and kept during the maintenance treatment phase.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: No analysis was done on all enrolled patients, full analysis set (e.g. patients who started treatment) was used.

Number of subjects in period 2^[2]	AOP2014	Hydroxyurea
Started	127	127
Week 12 Assessment visit	125	122
Completed	106	111
Not completed	21	16
Consent withdrawn by subject	6	5
Adverse event, non-fatal	11	3
Positive/Elevated TPOab	-	2
Administrative reasons	4	1
Lack of efficacy	-	2
Non-compliance with the protocol	-	3

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Three subjects were enrolled and randomized, but never received the treatment as they withdrew their consent before first administration.

Baseline characteristics

Reporting groups

Reporting group title	AOP2014
Reporting group description:	
Patients treated with AOP2014. During the initial treatment phase (first 12 weeks following randomization), the dose of AOP2014 was adjusted to the dose which delivered the optimal disease response.	
Reporting group title	Hydroxyurea
Reporting group description:	
Patients treated with Hydroxyurea. During the initial treatment phase (first 12 weeks following randomization), the dose of Hydroxyurea was adjusted to the dose which delivered the optimal disease response.	

Reporting group values	AOP2014	Hydroxyurea	Total
Number of subjects	127	127	254
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)	90	84	174
From 65-84 years	36	43	79
85 years and over	1	0	1
Age continuous			
Units: years			
arithmetic mean	58.5	57.9	
standard deviation	± 10.81	± 13.1	-
Gender categorical			
Units: Subjects			
Female	68	67	135
Male	59	60	119
Race			
Units: Subjects			
White	127	127	254
Durration of Polycythemia Vera			
Units: month(s)			
arithmetic mean	12.6	15.7	
standard deviation	± 24.7	± 25.65	-

Subject analysis sets

Subject analysis set title	AOP2014 PPS
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set (PPS) consisted of patients included in the Full Analysis Set who completed a certain pre-specified minimal exposure to the treatment regimen, had all measurements needed for assessment of the primary endpoint available and did not violate the study protocol in major concerns. The PPS was used for efficacy sensitivity analysis.

Subject analysis set title	Hydroxyurea PPS
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set (PPS) consisted of patients included in the Full Analysis Set who completed a certain pre-specified minimal exposure to the treatment regimen, had all measurements needed for assessment of the primary endpoint available and did not violate the study protocol in major concerns. The PPS was used for efficacy sensitivity analysis.

Reporting group values	AOP2014 PPS	Hydroxyurea PPS	
Number of subjects	115	114	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	84	74	
From 65-84 years	30	40	
85 years and over	1	0	
Age continuous			
Units: years			
arithmetic mean	58	58.4	
standard deviation	± 10.67	± 13.09	
Gender categorical			
Units: Subjects			
Female	60	59	
Male	55	55	
Race			
Units: Subjects			
White	115	114	
Durration of Polycythemia Vera			
Units: month(s)			
arithmetic mean	12.6	14.9	
standard deviation	± 25.56	± 24.52	

End points

End points reporting groups

Reporting group title	AOP2014
Reporting group description:	
Patients planned to be treated with AOP2014	
Reporting group title	Hydroxyurea
Reporting group description:	
Patients planned to be treated with Hydroxyurea	
Reporting group title	AOP2014
Reporting group description:	
Patients treated with AOP2014. During the initial treatment phase (first 12 weeks following randomization), the dose of AOP2014 was adjusted to the dose which delivered the optimal disease response.	
Reporting group title	Hydroxyurea
Reporting group description:	
Patients treated with Hydroxyurea. During the initial treatment phase (first 12 weeks following randomization), the dose of Hydroxyurea was adjusted to the dose which delivered the optimal disease response.	
Subject analysis set title	AOP2014 PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol Set (PPS) consisted of patients included in the Full Analysis Set who completed a certain pre-specified minimal exposure to the treatment regimen, had all measurements needed for assessment of the primary endpoint available and did not violate the study protocol in major concerns. The PPS was used for efficacy sensitivity analysis.	
Subject analysis set title	Hydroxyurea PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol Set (PPS) consisted of patients included in the Full Analysis Set who completed a certain pre-specified minimal exposure to the treatment regimen, had all measurements needed for assessment of the primary endpoint available and did not violate the study protocol in major concerns. The PPS was used for efficacy sensitivity analysis.	

Primary: Disease response rate

End point title	Disease response rate
End point description:	
The disease response rate was defined by the rate of patients who met all criteria after 12 months of AOP2014 or Hydroxyurea treatment:	
• Haematocrit < 45% without phlebotomy (at least 3 month since last phlebotomy) • Platelets < 400 x 10⁹/L • Leukocytes < 10 x 10⁹/L • Spleen size normality defined as spleen length ≤ 12cm for females/≤ 13 cm for males (by imaging)	
Patients who discontinued the study were considered as non-responders.	
End point type	Primary
End point timeframe:	
The disease response rate at 12 months of treatment (Week 52 assessment visit).	

End point values	AOP2014	Hydroxyurea	AOP2014 PPS	Hydroxyurea PPS
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	122	123	115	114
Units: subjects				
Responder	26	34	26	33
Non-responder	96	89	89	81

Statistical analyses

Statistical analysis title	Evaluation of non-inferiority, full analysis set
Statistical analysis description:	
The analysis of the primary efficacy endpoint was defined as disease response rate after one year, testing non-inferiority of AOP2014 to Hydroxyurea using a weighted Cochran-Mantel-Haenszel method (adjusted for the stratification groups) to calculate the confidence interval.	
Comparison groups	Hydroxyurea v AOP2014
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	= 0.2233 ^[2]
Method	Wald test
Parameter estimate	Difference in percentages
Point estimate	-6.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.23
upper limit	4.09

Notes:

[1] - Non-inferiority is concluded if the lower limit of the 95% two-sided CI of the Mantel-Haenszel common estimate of response rate difference exceeds -10.5% for the Full Analysis Set and the Per Protocol Analysis Set.

[2] - The Wald test for testing the non-inferiority of AOP2014 versus Hydroxyurea was not adjusted for the stratification groups.

Statistical analysis title	Evaluation of non-inferiority, per-protocol set
Statistical analysis description:	
The analysis of the primary efficacy endpoint was defined as disease response rate after one year, testing non-inferiority of AOP2014 to Hydroxyurea using a weighted Cochran-Mantel-Haenszel method (adjusted for the stratification groups) to calculate the confidence interval.	
Comparison groups	Hydroxyurea PPS v AOP2014 PPS
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
P-value	= 0.2353 ^[4]
Method	Wald test
Parameter estimate	Difference in percentages
Point estimate	-6.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.49
upper limit	4.92

Notes:

[3] - Non-inferiority is concluded if the lower limit of the 95% two-sided CI of the Mantel-Haenszel common estimate of response rate difference exceeds -10.5% for the Full Analysis Set and the Per Protocol Analysis Set.

[4] - The Wald test for testing the non-inferiority of AOP2014 versus Hydroxyurea was not adjusted for the stratification groups.

Secondary: Complete haematological response

End point title	Complete haematological response
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End point description:

The disease response (without spleen size normality) i.e. the complete haematological response was defined as:

- Haematocrit < 45% without phlebotomy (at least 3 month since last phlebotomy)
- Platelets < 400 x 10⁹/L
- Leukocytes < 10 x 10⁹/L

End point type	Secondary
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End point timeframe:

Complete haematological response at 12 months of treatment (Week 52 assessment visit).

End point values	AOP2014	Hydroxyurea	AOP2014 PPS	Hydroxyurea PPS
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	123	125	113	114
Units: subjects				
Responder	53	57	50	53
Non-responder	70	68	63	61

Statistical analyses

Statistical analysis title	Evaluation of non-inferiority, full analysis set
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Statistical analysis description:

Complete haematological response after one year, testing non-inferiority of AOP2014 to Hydroxyurea using a weighted Cochran-Mantel-Haenszel method (adjusted for the stratification groups) to calculate the confidence interval.

Comparison groups	AOP2014 v Hydroxyurea
Number of subjects included in analysis	248
Analysis specification	Post-hoc
Analysis type	non-inferiority ^[5]
P-value	= 0.0028 ^[6]
Method	Wald test
Parameter estimate	Difference in percentages
Point estimate	-3.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.55
upper limit	9.52

Notes:

[5] - Non-inferiority is concluded if the lower limit of the 95% two-sided CI of the Mantel-Haenszel common estimate of response rate difference exceeds - 20.0% for the Full Analysis Set and the Per Protocol Analysis Set.

[6] - The Wald test for testing the non-inferiority of AOP2014 versus Hydroxyurea was not adjusted for the stratification groups.

Statistical analysis title	Evaluation of non-inferiority, per-protocol set
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Statistical analysis description:

Complete haematological response after one year, testing non-inferiority of AOP2014 to Hydroxyurea using a weighted Cochran-Mantel-Haenszel method (adjusted for the stratification groups) to calculate the confidence interval.

Comparison groups	AOP2014 PPS v Hydroxyurea PPS
Number of subjects included in analysis	227
Analysis specification	Post-hoc
Analysis type	non-inferiority ^[7]
P-value	= 0.0036 ^[8]
Method	Wald test
Parameter estimate	Difference in percentages
Point estimate	-2.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.76
upper limit	10.49

Notes:

[7] - Non-inferiority is concluded if the lower limit of the 95% two-sided CI of the Mantel-Haenszel common estimate of response rate difference exceeds - 20.0% for the Full Analysis Set and the Per Protocol Analysis Set.

[8] - The Wald test for testing the non-inferiority of AOP2014 versus Hydroxyurea was not adjusted for the stratification groups.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first study treatment administration onwards through the observational phase until the last safety follow-up visit.

Adverse event reporting additional description:

Subjects were queried about adverse events at each visit (approximately every two weeks).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Hydroxyurea
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Reporting group description:

Patients treated with Hydroxyurea

Reporting group title	AOP2014
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Reporting group description:

Patients treated with AOP2014

Serious adverse events	Hydroxyurea	AOP2014	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 127 (8.66%)	14 / 127 (11.02%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 127 (1.57%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spermatocytic seminoma			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Embolism			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Aortic valve replacement			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid endarterectomy			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst excision			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
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			
Multi-organ failure			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine polyp			

subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
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			
Subcutaneous haematoma			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 127 (1.57%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Supraventricular tachycardia subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhagic transformation stroke subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			

subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (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: 0 %

Non-serious adverse events	Hydroxyurea	AOP2014	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 127 (87.40%)	100 / 127 (78.74%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma			

subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Angiolipoma			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Benign neoplasm of thyroid gland			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Blepharal papilloma			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Fibrous histiocytoma			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	2	0	
Primary myelofibrosis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Blood pressure fluctuation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Circulatory collapse			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Erythromelalgia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Femoral artery occlusion			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Haematoma			
subjects affected / exposed	3 / 127 (2.36%)	1 / 127 (0.79%)	
occurrences (all)	4	1	

Hypertension			
subjects affected / exposed	7 / 127 (5.51%)	4 / 127 (3.15%)	
occurrences (all)	7	5	
Hypertensive crisis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Peripheral circulatory failure			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Peripheral coldness			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Phlebitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Raynaud's phenomenon			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Subclavian steal syndrome			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Varicose vein			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Vascular pain			
subjects affected / exposed	2 / 127 (1.57%)	0 / 127 (0.00%)	
occurrences (all)	2	0	
Surgical and medical procedures			
Cataract operation			

subjects affected / exposed	3 / 127 (2.36%)	0 / 127 (0.00%)	
occurrences (all)	3	0	
Endocervical curettage			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Eye operation			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Intraocular lens implant			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Maxillofacial operation			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Ovarian cystectomy			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 127 (3.94%)	7 / 127 (5.51%)	
occurrences (all)	7	14	
Axillary pain			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	1 / 127 (0.79%)	2 / 127 (1.57%)	
occurrences (all)	1	2	
Chills			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Drug intolerance			

subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Fatigue		
subjects affected / exposed	17 / 127 (13.39%)	16 / 127 (12.60%)
occurrences (all)	21	43
Feeling cold		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	3	0
Impaired healing		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	2
Inflammation		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Influenza like illness		
subjects affected / exposed	2 / 127 (1.57%)	7 / 127 (5.51%)
occurrences (all)	2	7
Injection site erythema		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Injection site pain		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	2
Injection site pruritus		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	2
Mucosal inflammation		
subjects affected / exposed	1 / 127 (0.79%)	2 / 127 (1.57%)
occurrences (all)	2	2
Oedema peripheral		
subjects affected / exposed	1 / 127 (0.79%)	3 / 127 (2.36%)
occurrences (all)	1	3
Pain		
subjects affected / exposed	4 / 127 (3.15%)	1 / 127 (0.79%)
occurrences (all)	5	1
Puncture site pain		

subjects affected / exposed occurrences (all)	1 / 127 (0.79%) 1	0 / 127 (0.00%) 0	
Pyrexia subjects affected / exposed occurrences (all)	2 / 127 (1.57%) 3	7 / 127 (5.51%) 11	
Sensation of foreign body subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Soft tissue inflammation subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	1 / 127 (0.79%) 1	0 / 127 (0.00%) 0	
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Social circumstances Stress at work subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Breast pain subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Endometrial dysplasia subjects affected / exposed occurrences (all)	1 / 127 (0.79%) 1	0 / 127 (0.00%) 0	
Erectile dysfunction subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Fibrocystic breast disease			

subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Metrorrhagia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Ovarian cyst			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Uterine cervical erosion			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Uterine haemorrhage			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 127 (3.94%)	7 / 127 (5.51%)	
occurrences (all)	6	7	
Dyspnoea			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Dyspnoea exertional			
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Epistaxis			
subjects affected / exposed	2 / 127 (1.57%)	2 / 127 (1.57%)	
occurrences (all)	2	3	
Increased bronchial secretion			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	3 / 127 (2.36%)	3 / 127 (2.36%)	
occurrences (all)	3	5	
Pneumonitis			

subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Pulmonary hypertension subjects affected / exposed occurrences (all)	2 / 127 (1.57%) 2	0 / 127 (0.00%) 0	
Rhinitis allergic subjects affected / exposed occurrences (all)	2 / 127 (1.57%) 2	0 / 127 (0.00%) 0	
Sneezing subjects affected / exposed occurrences (all)	1 / 127 (0.79%) 1	0 / 127 (0.00%) 0	
Throat irritation subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Psychiatric disorders			
Affective disorder subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Agitation subjects affected / exposed occurrences (all)	1 / 127 (0.79%) 1	0 / 127 (0.00%) 0	
Anxiety subjects affected / exposed occurrences (all)	3 / 127 (2.36%) 3	4 / 127 (3.15%) 4	
Anxiety disorder subjects affected / exposed occurrences (all)	1 / 127 (0.79%) 1	0 / 127 (0.00%) 0	
Apathy subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Depressed mood subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Depression subjects affected / exposed occurrences (all)	1 / 127 (0.79%) 1	2 / 127 (1.57%) 2	

Emotional distress			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Hallucination			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	5 / 127 (3.94%)	4 / 127 (3.15%)	
occurrences (all)	7	4	
Mood altered			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Mood swings			
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Nervousness			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Panic attack			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Restlessness			
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Sleep disorder			
subjects affected / exposed	1 / 127 (0.79%)	3 / 127 (2.36%)	
occurrences (all)	1	3	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Cholelithiasis			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Gallbladder disorder			

subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Hepatic cyst			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Hepatic steatosis			
subjects affected / exposed	1 / 127 (0.79%)	2 / 127 (1.57%)	
occurrences (all)	1	2	
Hepatomegaly			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Liver disorder			
subjects affected / exposed	1 / 127 (0.79%)	2 / 127 (1.57%)	
occurrences (all)	1	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 127 (0.79%)	9 / 127 (7.09%)	
occurrences (all)	1	10	
Anti-thyroid antibody positive			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 127 (0.79%)	8 / 127 (6.30%)	
occurrences (all)	1	9	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	4	
Blood bilirubin increased			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Blood fibrinogen decreased			

subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	2	0
Blood glucose increased		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Blood iron decreased		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Blood lactate dehydrogenase increased		
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Blood phosphorus decreased		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Blood potassium decreased		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Blood potassium increased		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Blood pressure abnormal		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Blood pressure systolic increased		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Blood thyroid stimulating hormone increased		
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Blood urea increased		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Blood uric acid increased		

subjects affected / exposed	1 / 127 (0.79%)	2 / 127 (1.57%)
occurrences (all)	1	2
Body temperature decreased		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Body temperature increased		
subjects affected / exposed	1 / 127 (0.79%)	3 / 127 (2.36%)
occurrences (all)	1	3
Ejection fraction decreased		
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Electrocardiogram PR prolongation		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Electrocardiogram QT interval abnormal		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Gamma-glutamyltransferase increased		
subjects affected / exposed	1 / 127 (0.79%)	18 / 127 (14.17%)
occurrences (all)	1	24
Haematocrit decreased		
subjects affected / exposed	4 / 127 (3.15%)	0 / 127 (0.00%)
occurrences (all)	5	0
Haematocrit increased		
subjects affected / exposed	1 / 127 (0.79%)	6 / 127 (4.72%)
occurrences (all)	1	10
Haemoglobin decreased		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Hepatic enzyme increased		
subjects affected / exposed	0 / 127 (0.00%)	7 / 127 (5.51%)
occurrences (all)	0	9
Mean cell volume increased		

subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Nitrite urine present			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	8 / 127 (6.30%)	2 / 127 (1.57%)	
occurrences (all)	14	2	
Platelet count increased			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Transferrin decreased			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Visual acuity tests abnormal			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
White blood cell count decreased			
subjects affected / exposed	4 / 127 (3.15%)	3 / 127 (2.36%)	
occurrences (all)	8	8	
White blood cell count increased			
subjects affected / exposed	2 / 127 (1.57%)	0 / 127 (0.00%)	
occurrences (all)	2	0	
White blood cells urine positive			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Contrast media reaction			

subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	2 / 127 (1.57%)	1 / 127 (0.79%)	
occurrences (all)	2	1	
Foot fracture			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Forearm fracture			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Gastrointestinal disorder postoperative			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Limb injury			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Overdose			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Subcutaneous haematoma			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Traumatic haematoma			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			

Cataract congenital subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Marfan's syndrome subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Cardiac disorders			
Aortic valve calcification subjects affected / exposed occurrences (all)	3 / 127 (2.36%) 3	0 / 127 (0.00%) 0	
Arrhythmia subjects affected / exposed occurrences (all)	1 / 127 (0.79%) 1	0 / 127 (0.00%) 0	
Atrial fibrillation subjects affected / exposed occurrences (all)	2 / 127 (1.57%) 10	2 / 127 (1.57%) 2	
Atrial flutter subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Atrioventricular block second degree subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Bradycardia subjects affected / exposed occurrences (all)	1 / 127 (0.79%) 1	0 / 127 (0.00%) 0	
Bundle branch block left subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Cardiac failure subjects affected / exposed occurrences (all)	1 / 127 (0.79%) 1	0 / 127 (0.00%) 0	
Cyanosis subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1	
Dilatation ventricular			

subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Intracardiac thrombus			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Mitral valve calcification			
subjects affected / exposed	2 / 127 (1.57%)	0 / 127 (0.00%)	
occurrences (all)	2	0	
Mitral valve incompetence			
subjects affected / exposed	2 / 127 (1.57%)	1 / 127 (0.79%)	
occurrences (all)	2	1	
Palpitations			
subjects affected / exposed	1 / 127 (0.79%)	2 / 127 (1.57%)	
occurrences (all)	1	3	
Sinoatrial block			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Sinus tachycardia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Supraventricular extrasystoles			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	1 / 127 (0.79%)	3 / 127 (2.36%)	
occurrences (all)	2	3	
Ventricular extrasystoles			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Nervous system disorders			
Burning sensation			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	2	0	
Dizziness			
subjects affected / exposed	10 / 127 (7.87%)	12 / 127 (9.45%)	
occurrences (all)	14	15	

Dysgeusia		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Head discomfort		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Headache		
subjects affected / exposed	11 / 127 (8.66%)	12 / 127 (9.45%)
occurrences (all)	16	26
Hypoaesthesia		
subjects affected / exposed	0 / 127 (0.00%)	3 / 127 (2.36%)
occurrences (all)	0	5
Intercostal neuralgia		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Lumbar radiculopathy		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	2	0
Migraine		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Migraine with aura		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Neuralgia		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Neuropathy peripheral		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Paraesthesia		
subjects affected / exposed	4 / 127 (3.15%)	0 / 127 (0.00%)
occurrences (all)	4	0
Peripheral nerve lesion		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1

Radiculopathy			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Sinus headache			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Trigeminal neuritis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	31 / 127 (24.41%)	8 / 127 (6.30%)	
occurrences (all)	50	9	
Granulocytopenia			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Cytopenia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	27 / 127 (21.26%)	11 / 127 (8.66%)	
occurrences (all)	53	27	
Lymphadenopathy			
subjects affected / exposed	2 / 127 (1.57%)	0 / 127 (0.00%)	
occurrences (all)	2	0	
Neutropenia			
subjects affected / exposed	5 / 127 (3.94%)	2 / 127 (1.57%)	
occurrences (all)	11	2	
Polycythaemia			

subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Splenic infarction			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Splenomegaly			
subjects affected / exposed	3 / 127 (2.36%)	5 / 127 (3.94%)	
occurrences (all)	3	5	
Thrombocytopenia			
subjects affected / exposed	36 / 127 (28.35%)	19 / 127 (14.96%)	
occurrences (all)	99	35	
Thrombocytosis			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Ear discomfort			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Tinnitus			
subjects affected / exposed	0 / 127 (0.00%)	3 / 127 (2.36%)	
occurrences (all)	0	8	
Vertigo			
subjects affected / exposed	7 / 127 (5.51%)	4 / 127 (3.15%)	
occurrences (all)	7	4	
Eye disorders			
Age-related macular degeneration			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Asthenopia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Blepharitis			

subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)
occurrences (all)	1	1
Blepharochalasis		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Cataract		
subjects affected / exposed	3 / 127 (2.36%)	6 / 127 (4.72%)
occurrences (all)	3	6
Chalazion		
subjects affected / exposed	2 / 127 (1.57%)	0 / 127 (0.00%)
occurrences (all)	2	0
Conjunctival haemorrhage		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Corneal opacity		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Diabetic retinopathy		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Dry eye		
subjects affected / exposed	2 / 127 (1.57%)	4 / 127 (3.15%)
occurrences (all)	2	4
Eye inflammation		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Eye irritation		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Eye pain		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Keratopathy		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Maculopathy		

subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Myopia			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Posterior capsule opacification			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Presbyopia			
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Retinopathy			
subjects affected / exposed	1 / 127 (0.79%)	2 / 127 (1.57%)	
occurrences (all)	1	2	
Retinopathy hypertensive			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Visual acuity reduced			
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 127 (1.57%)	0 / 127 (0.00%)	
occurrences (all)	2	0	
Abdominal distension			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	2	1	
Abdominal pain			
subjects affected / exposed	7 / 127 (5.51%)	7 / 127 (5.51%)	
occurrences (all)	11	7	
Abdominal pain upper			
subjects affected / exposed	6 / 127 (4.72%)	2 / 127 (1.57%)	
occurrences (all)	11	3	

Abdominal wall disorder		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Aphthous ulcer		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Burning mouth syndrome		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Constipation		
subjects affected / exposed	6 / 127 (4.72%)	3 / 127 (2.36%)
occurrences (all)	6	5
Diarrhoea		
subjects affected / exposed	10 / 127 (7.87%)	8 / 127 (6.30%)
occurrences (all)	20	15
Diverticulum intestinal		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Dry mouth		
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)
occurrences (all)	1	1
Dyspepsia		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Epigastric discomfort		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Flatulence		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Gastric disorder		
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)
occurrences (all)	2	1
Gastritis		
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2

Gastrointestinal pain		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Gastrooesophageal reflux disease		
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)
occurrences (all)	1	1
Gingival bleeding		
subjects affected / exposed	2 / 127 (1.57%)	1 / 127 (0.79%)
occurrences (all)	2	1
Gingival pain		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Haematemesis		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Haemorrhoidal haemorrhage		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Irritable bowel syndrome		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Nausea		
subjects affected / exposed	15 / 127 (11.81%)	3 / 127 (2.36%)
occurrences (all)	19	4
Oesophagitis		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Paraesthesia oral		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Rectal haemorrhage		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Reflux gastritis		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1

Stomatitis			
subjects affected / exposed	2 / 127 (1.57%)	2 / 127 (1.57%)	
occurrences (all)	5	2	
Truncus coeliacus thrombosis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	5 / 127 (3.94%)	3 / 127 (2.36%)	
occurrences (all)	6	3	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 127 (0.00%)	6 / 127 (4.72%)	
occurrences (all)	0	9	
Blood blister			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Dermatitis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	4 / 127 (3.15%)	0 / 127 (0.00%)	
occurrences (all)	4	0	
Eczema			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	6	
Erythema			
subjects affected / exposed	1 / 127 (0.79%)	3 / 127 (2.36%)	
occurrences (all)	1	4	
Hyperhidrosis			
subjects affected / exposed	0 / 127 (0.00%)	3 / 127 (2.36%)	
occurrences (all)	0	3	
Night sweats			
subjects affected / exposed	3 / 127 (2.36%)	2 / 127 (1.57%)	
occurrences (all)	3	2	
Photosensitivity reaction			

subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	8 / 127 (6.30%)	10 / 127 (7.87%)	
occurrences (all)	9	41	
Pruritus generalised			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	2	
Psoriasis			
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Rash			
subjects affected / exposed	4 / 127 (3.15%)	3 / 127 (2.36%)	
occurrences (all)	5	3	
Rash erythematous			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Rosacea			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Skin exfoliation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Skin hyperpigmentation			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Xeroderma			
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	

Dysuria			
subjects affected / exposed	2 / 127 (1.57%)	0 / 127 (0.00%)	
occurrences (all)	2	0	
Leukocyturia			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Micturition urgency			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Nephrolithiasis			
subjects affected / exposed	2 / 127 (1.57%)	0 / 127 (0.00%)	
occurrences (all)	2	0	
Nephroptosis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Nocturia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Pyelocaliectasis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Renal colic			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Renal cyst			
subjects affected / exposed	2 / 127 (1.57%)	2 / 127 (1.57%)	
occurrences (all)	2	2	
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Hyperthyroidism			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Hypothyroidism			

subjects affected / exposed	1 / 127 (0.79%)	3 / 127 (2.36%)	
occurrences (all)	1	3	
Thyroiditis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 127 (3.15%)	12 / 127 (9.45%)	
occurrences (all)	5	24	
Arthritis reactive			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	4 / 127 (3.15%)	9 / 127 (7.09%)	
occurrences (all)	5	9	
Bone pain			
subjects affected / exposed	1 / 127 (0.79%)	2 / 127 (1.57%)	
occurrences (all)	1	2	
Gouty arthritis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Groin pain			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	1 / 127 (0.79%)	3 / 127 (2.36%)	
occurrences (all)	1	3	
Muscular weakness			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			

subjects affected / exposed	1 / 127 (0.79%)	3 / 127 (2.36%)	
occurrences (all)	1	8	
Musculoskeletal pain			
subjects affected / exposed	0 / 127 (0.00%)	5 / 127 (3.94%)	
occurrences (all)	0	14	
Myalgia			
subjects affected / exposed	3 / 127 (2.36%)	11 / 127 (8.66%)	
occurrences (all)	3	13	
Neck pain			
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Osteoarthritis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Osteochondrosis			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Osteoporosis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	3 / 127 (2.36%)	9 / 127 (7.09%)	
occurrences (all)	3	12	
Spinal pain			
subjects affected / exposed	2 / 127 (1.57%)	3 / 127 (2.36%)	
occurrences (all)	2	3	
Tendonitis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	2 / 127 (1.57%)	0 / 127 (0.00%)	
occurrences (all)	2	0	
Alveolar osteitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	

Bronchitis		
subjects affected / exposed	6 / 127 (4.72%)	3 / 127 (2.36%)
occurrences (all)	6	3
Conjunctivitis		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Cystitis		
subjects affected / exposed	1 / 127 (0.79%)	2 / 127 (1.57%)
occurrences (all)	1	2
Erysipelas		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Folliculitis		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	2	0
Fungal infection		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Fungal skin infection		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	3
Gastrointestinal viral infection		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Herpes zoster		
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)
occurrences (all)	1	1
Infection		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Influenza		
subjects affected / exposed	10 / 127 (7.87%)	2 / 127 (1.57%)
occurrences (all)	10	2
Laryngitis		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1

Lower respiratory tract infection subjects affected / exposed occurrences (all)	1 / 127 (0.79%) 1	0 / 127 (0.00%) 0
Lyme disease subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	8 / 127 (6.30%) 10	4 / 127 (3.15%) 8
Oesophageal candidiasis subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1
Onychomycosis subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1
Oral herpes subjects affected / exposed occurrences (all)	2 / 127 (1.57%) 3	1 / 127 (0.79%) 1
Oral infection subjects affected / exposed occurrences (all)	1 / 127 (0.79%) 1	0 / 127 (0.00%) 0
Parainfluenzae virus infection subjects affected / exposed occurrences (all)	1 / 127 (0.79%) 1	0 / 127 (0.00%) 0
Paronychia subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	1 / 127 (0.79%) 1
Pharyngitis subjects affected / exposed occurrences (all)	2 / 127 (1.57%) 2	0 / 127 (0.00%) 0
Respiratory tract infection subjects affected / exposed occurrences (all)	3 / 127 (2.36%) 3	2 / 127 (1.57%) 2
Rhinitis subjects affected / exposed occurrences (all)	2 / 127 (1.57%) 3	3 / 127 (2.36%) 3

Sinusitis			
subjects affected / exposed	3 / 127 (2.36%)	1 / 127 (0.79%)	
occurrences (all)	4	1	
Tonsillitis			
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Tooth infection			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	5 / 127 (3.94%)	5 / 127 (3.94%)	
occurrences (all)	6	7	
Urinary tract infection			
subjects affected / exposed	5 / 127 (3.94%)	4 / 127 (3.15%)	
occurrences (all)	6	5	
Viraemia			
subjects affected / exposed	2 / 127 (1.57%)	0 / 127 (0.00%)	
occurrences (all)	2	0	
Viral infection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 127 (1.57%)	0 / 127 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 127 (0.00%)	3 / 127 (2.36%)	
occurrences (all)	0	3	
Dehydration			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Gout			

subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Hyperkalaemia		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	2	0
Hyperuricaemia		
subjects affected / exposed	0 / 127 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Hypocalcaemia		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Hypoglycaemia		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Hypokalaemia		
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)
occurrences (all)	1	2
Hyponatraemia		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Iron deficiency		
subjects affected / exposed	4 / 127 (3.15%)	5 / 127 (3.94%)
occurrences (all)	5	7
Type 2 diabetes mellitus		
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences (all)	1	0
Vitamin D deficiency		
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2014	Following the discussions with the U.S. FDA, the secondary endpoint "Durable disease response" was added. The amended study protocol states that the endpoint "Durable disease response" was to be analysed as the primary one for study submission in the U.S.; however, for study submission in Europe the primary endpoint "disease response at 12 months" remained unchanged. In order to avoid confusion, a separate US Specific SAP was written for submission in the U.S. All endpoints as per study protocol were included in both SAPs (for the European and for the U.S submission). The statistical methods and sample size justification are consistent in both SAPs. In addition, the power calculation for "Durable disease response" is presented in the separate US specific SAP.
12 February 2016	According to EMA advice letter dated 12-Feb-2016, the protocol amendment was added on 15-Jun-2016. Primary objective was changed from "To demonstrate superiority of AOP2014 vs. Hydroxyurea in terms of disease response rate in both Hydroxyurea naïve and currently treated patients, diagnosed with Polycythemia Vera." to "To demonstrate non-inferiority of AOP2014 vs. Hydroxyurea in terms of disease response rate in both Hydroxyurea naïve and currently treated patients, diagnosed with Polycythemia Vera."

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported