



Clinical trial results:

A Phase IIIb, randomised, open label study to compare the safety, efficacy and tolerability of anagrelide hydrochloride versus hydroxyurea in high-risk essential thrombocythaemia patients.

Summary

EudraCT number	2004-004061-15
Trial protocol	BE IE ES IT SK CZ SI BG PL
Global end of trial date	15 December 2015

Results information

Result version number	v1 (current)
This version publication date	29 October 2016
First version publication date	29 October 2016

Trial information

Trial identification

Sponsor protocol code	SPD422-403
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00202644
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Pharmaceutical Development Ltd
Sponsor organisation address	Hampshire International Business Park, Chineham, Basingstoke, Hampshire, United Kingdom, RG24 8EP
Public contact	Study Physician, Shire, +1 866-842-5335,
Scientific contact	Study Physician, Shire, +1 866-842-5335,

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	15 December 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to compare the safety of anagrelide and hydroxyurea in short and long term usage of up to three years with particular reference to cardiovascular safety (as assessed by echocardiography).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) of Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and other applicable local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 34
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Serbia: 18
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Spain: 7
Worldwide total number of subjects	146
EEA total number of subjects	128

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)	111
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 183 subjects were screened, 149 subjects were randomized at 29 sites across 10 countries. Four (4) subjects randomized but withdrawn prior to treatment and 1 subject not randomized but treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Anagrelide

Arm description:

Subjects received Anagrelide hydrochloride 1.0 milligram (mg) per day administered orally as 0.5 mg capsule twice daily (bid) for 1 week. Then the dose was titrated such that the total daily dose is incremented by no more than 0.5 mg in any 1 week and the recommended maximum single dose could not exceed 2.5 mg as required depending on platelet reduction versus adverse event profile. Total daily dosage was not exceed 10 mg. Subjects followed for up to 3 years.

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

Dosage and administration details:

Subjects received Anagrelide hydrochloride 1.0 milligram (mg) per day administered orally as 0.5 mg capsule twice daily (bid) for 1 week. Then the dose was titrated such that the total daily dose is incremented by no more than 0.5 mg in any 1 week and the recommended maximum single dose could not exceed 2.5 mg as required depending on platelet reduction versus adverse event profile. Total daily dosage was not exceed 10 mg. Subjects followed for up to 3 years.

Arm title	Hydroxyurea
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Arm description:

Subjects received Hydroxyurea as 1000 mg per day administered orally as 500 mg capsule twice daily and dose titrated to effect to achieve a response. Subjects followed for up to 3 years.

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

Dosage and administration details:

Subjects received Hydroxyurea as 1000 mg per day administered orally as 500 mg capsule twice daily and dose titrated to effect to achieve a response. Subjects followed for up to 3 years.

Number of subjects in period 1	Anagrelide	Hydroxyurea
Started	76	70
Completed	41	43
Not completed	35	27
Consent withdrawn by subject	8	6
Adverse event, non-fatal	12	13
Unspecified	9	1
Lost to follow-up	-	1
Lack of efficacy	6	6

Baseline characteristics

Reporting groups

Reporting group title	Anagrelide
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Reporting group description:

Subjects received Anagrelide hydrochloride 1.0 milligram (mg) per day administered orally as 0.5 mg capsule twice daily (bid) for 1 week. Then the dose was titrated such that the total daily dose is incremented by no more than 0.5 mg in any 1 week and the recommended maximum single dose could not exceed 2.5 mg as required depending on platelet reduction versus adverse event profile. Total daily dosage was not exceed 10 mg. Subjects followed for up to 3 years.

Reporting group title	Hydroxyurea
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Reporting group description:

Subjects received Hydroxyurea as 1000 mg per day administered orally as 500 mg capsule twice daily and dose titrated to effect to achieve a response. Subjects followed for up to 3 years.

Reporting group values	Anagrelide	Hydroxyurea	Total
Number of subjects	76	70	146
Age categorical			
Units: Subjects			
Adults (18-64 years)	58	53	111
From 65-84 years	18	17	35
Age Continuous			
Units: years			
arithmetic mean	52.1	52.9	
standard deviation	± 16.1	± 15.8	-
Gender, Male/Female			
The safety population was defined as all subjects who received at least 1 dose of study medication.			
Units: subjects			
Female	56	45	101
Male	20	25	45

End points

End points reporting groups

Reporting group title	Anagrelide
Reporting group description:	
Subjects received Anagrelide hydrochloride 1.0 milligram (mg) per day administered orally as 0.5 mg capsule twice daily (bid) for 1 week. Then the dose was titrated such that the total daily dose is incremented by no more than 0.5 mg in any 1 week and the recommended maximum single dose could not exceed 2.5 mg as required depending on platelet reduction versus adverse event profile. Total daily dosage was not exceed 10 mg. Subjects followed for up to 3 years.	
Reporting group title	Hydroxyurea
Reporting group description:	
Subjects received Hydroxyurea as 1000 mg per day administered orally as 500 mg capsule twice daily and dose titrated to effect to achieve a response. Subjects followed for up to 3 years.	

Primary: Change From Baseline in Left Ventricular Ejection Fraction (LVEF) Over Time

End point title	Change From Baseline in Left Ventricular Ejection Fraction (LVEF) Over Time ^[1]
End point description:	
The LVEF was considered a sufficiently sensitive measure to evaluate any changes in cardiac function. The Full Analysis Set (FAS) population included all randomized subjects who received at least 1 dose of study medication and who had a pretreatment and at least 1 post baseline LVEF measurement recorded. Here, n = Number of subjects analyzed for specified category at the specified time points in each arm respectively.	
End point type	Primary
End point timeframe:	
Baseline and Month 1, 2, 3, 6, 9, 12, 18, 24, 30 and 36	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No inferential statistical analysis was planned for this end-point.

End point values	Anagrelide	Hydroxyurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	68		
Units: percentage of ejection fraction				
arithmetic mean (standard deviation)				
Baseline (n=73,68)	66.4 (± 4.81)	66.9 (± 4.59)		
Change at Month 1 (n=71,64)	0.5 (± 4.68)	-1.1 (± 4.73)		
Change at Month 2 (n=68,63)	1.2 (± 5.8)	0 (± 5.03)		
Change at Month 3 (n=67,62)	0.1 (± 5.31)	-0.4 (± 3.94)		
Change at Month 6 (n=59,60)	-0.5 (± 5.68)	-0.6 (± 3.95)		
Change at Month 9 (n=52,52)	-0.8 (± 4.78)	-1.5 (± 5.15)		
Change at Month 12 (n=45,52)	-0.8 (± 6.61)	-0.6 (± 5.67)		
Change at Month 18 (n=41,48)	-2 (± 5.54)	-1.2 (± 4.84)		
Change at Month 24 (n=40,49)	-1.8 (± 6.81)	-1.7 (± 6.17)		
Change at Month 30 (n=40,45)	-1.8 (± 5.84)	-0.2 (± 5.38)		
Change at Month 36 (n=40,44)	-1.7 (± 6.55)	-0.6 (± 5.46)		

Statistical analyses

No statistical analyses for this end point

Primary: Platelet Count at Month 6

End point title	Platelet Count at Month 6
End point description:	
Platelet count was evaluated. The FAS population included all randomized subjects who received at least 1 dose of study medication and who had a pretreatment and at least 1 post baseline LVEF measurement recorded. Here, N = Number of subjects analyzed in each arm for this endpoint.	
End point type	Primary
End point timeframe:	
Month 6	

End point values	Anagrelide	Hydroxyurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: 10 ⁹ per liter				
arithmetic mean (standard deviation)	418.6 (± 135.96)	396 (± 144.07)		

Statistical analyses

Statistical analysis title	Anagrelide Vs Hydroxyurea
Comparison groups	Hydroxyurea v Anagrelide
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Parameter estimate	Least Square Mean
Point estimate	-100.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-179.42
upper limit	-21.49
Variability estimate	Standard error of the mean
Dispersion value	39.93

Notes:

[2] - Non-inferiority of anagrelide could be concluded if lower limit of 95% Confidence Interval for the difference between treatment groups (Hydroxyurea - Anagrelide) was > -100 x 10⁹/Liter.

Secondary: Change From Baseline in Platelet Counts at Month 3 and 36

End point title	Change From Baseline in Platelet Counts at Month 3 and 36
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End point description:

Platelet count was evaluated throughout the study. The FAS population included all randomized participants who received at least 1 dose of study medication and who had a pretreatment and at least 1 post baseline LVEF measurement recorded with last observation carried forward (LOCF). Here, n=number of subjects analysed for specified category at specified time points in each arm respectively.

End point type	Secondary
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End point timeframe:

Baseline and Month 3 and 36

End point values	Anagrelide	Hydroxyurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	68		
Units: 10 ⁹ per liter				
arithmetic mean (standard deviation)				
Change at Month 3 (n=73, 68)	575.3 (± 36.11)	462.2 (± 37.54)		
Change at Month 36 (n=73, 68)	531 (± 42.14)	462.8 (± 43.81)		

Statistical analyses

Statistical analysis title	Anagrelide Vs Hydroxyurea: Month 3
Comparison groups	Anagrelide v Hydroxyurea
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
Parameter estimate	Least Square Mean
Point estimate	-113.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-187.4
upper limit	-38.83
Variability estimate	Standard error of the mean
Dispersion value	37.56

Notes:

[3] - Non-inferiority of anagrelide could be concluded if lower limit of 95% Confidence Interval for the difference between treatment groups (Hydroxyurea - Anagrelide) was > -100 x 10⁹/Liter.

Statistical analysis title	Anagrelide Vs Hydroxyurea: Month 36
Comparison groups	Anagrelide v Hydroxyurea

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
Parameter estimate	Least Square Mean
Point estimate	-68.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-154.95
upper limit	18.43
Variability estimate	Standard error of the mean
Dispersion value	43.83

Notes:

[4] - Non-inferiority of anagrelide could be concluded if lower limit of 95% Confidence Interval for the difference between treatment groups (Hydroxyurea - Anagrelide) was $> -100 \times 10^9/\text{Liter}$.

Secondary: Percentage of Subjects With Complete Response

End point title	Percentage of Subjects With Complete Response
End point description:	
A complete response was defined as a platelet count of less than ($<$) $400 \times 10^9/\text{Liter}$ which was confirmed over 2 consecutive visits at least 28 days apart. The FAS population included all randomized subjects who received at least 1 dose of study medication and who had a pretreatment and at least 1 post baseline LVEF measurement recorded.	
End point type	Secondary
End point timeframe:	
Baseline up to Month 36	

End point values	Anagrelide	Hydroxyurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	68		
Units: percentage of subjects				
number (not applicable)	58.9	58.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Partial Response

End point title	Percentage of Subjects With Partial Response
End point description:	
A partial response is defined as a platelet count of $400\text{--}600 \times 10^9/\text{Liter}$ and a reduction in platelet count of at least $200 \times 10^9/\text{Liter}$ from baseline which was confirmed over 2 consecutive visits at least 28 days apart. The FAS population included all randomized subjects who received at least 1 dose of study medication and who had a pretreatment and at least 1 post baseline LVEF measurement recorded.	
End point type	Secondary
End point timeframe:	
Baseline up to Month 36	

End point values	Anagrelide	Hydroxyurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	68		
Units: percentage of subjects				
number (not applicable)	21.9	27.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Response

End point title	Time to Complete Response
End point description: Time in days from the date of the first dose of study medication to the date of the first visit at which response was classified. If a subject did not achieve response then they were censored at their last visit in the study (Month 36 or withdrawal). The FAS population included all randomized subjects who received at least 1 dose of study medication and who had a pretreatment and at least 1 post baseline LVEF measurement recorded.	
End point type	Secondary
End point timeframe: Baseline up to Month 36	

End point values	Anagrelide	Hydroxyurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	68		
Units: days				
median (confidence interval 95%)	177 (129 to 548)	123 (90 to 554)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Partial Response

End point title	Time to Partial Response
End point description: Time in days from the date of the first dose of study medication to the date of the first visit at which response was classified. If a subject did not achieve response then they were censored at their last visit in the study (Month 36 or withdrawal). The FAS population included all randomized subjects who received at least 1 dose of study medication and who had a pretreatment and at least 1 post baseline LVEF measurement recorded.	
End point type	Secondary

End point timeframe:
Baseline up to Month 36

End point values	Anagrelide	Hydroxyurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	68		
Units: days				
median (confidence interval 95%)	61 (43 to 85)	47 (41 to 57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Thrombotic and Haemorrhagic Events

End point title	Number of Subjects With Thrombotic and Haemorrhagic Events
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End point description:

Thrombohaemorrhagic events are a well-known complication of the underlying essential thrombocythemia (ET) and disease progression. Events such as arterial and venous thrombosis, serious haemorrhage (including gastrointestinal haemorrhage), and death from vascular causes have been reported in subjects who received cytoreductive treatment. The FAS population included all randomized subjects who received at least 1 dose of study medication and who had a pretreatment and at least 1 post baseline LVEF measurement recorded.

End point type	Secondary
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End point timeframe:

From the signing of informed consent until the last study-related visit (Month 36)

End point values	Anagrelide	Hydroxyurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	68		
Units: subjects				
number (not applicable)	30	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in White Blood Cell Count Over Time

End point title	Change From Baseline in White Blood Cell Count Over Time
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End point description:

White blood cell count was evaluated throughout the study. The FAS population included all randomized subjects who received at least 1 dose of study medication and who had a pretreatment and at least 1 post baseline LVEF measurement recorded. Here, n = Number of subjects analyzed for specified

category at the specified time points in each arm respectively.

End point type	Secondary
End point timeframe:	
Baseline and Month 6, 12, 18, 24, 30 and 36	

End point values	Anagrelide	Hydroxyurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	68		
Units: 10 ⁹ per liter				
arithmetic mean (standard deviation)				
Baseline (n=73,68)	9.13 (± 2.159)	10.2 (± 3.491)		
Change at Month 6 (n=60,58)	-0.38 (± 4.257)	-5.02 (± 2.525)		
Change at Month 12 (n=45,51)	-1 (± 2.001)	-4.79 (± 2.779)		
Change at Month 18 (n=42,49)	-1.18 (± 2.184)	-4.46 (± 2.664)		
Change at Month 24 (n=40,49)	-1.24 (± 2.283)	-4.82 (± 2.692)		
Change at Month 30 (n=40,45)	-1 (± 2.316)	-4.59 (± 3.391)		
Change at Month 36 (n=40,43)	-1.63 (± 2.234)	-4.46 (± 3.312)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Red Blood Cell Count Over Time

End point title	Change From Baseline in Red Blood Cell Count Over Time
End point description:	
Red blood cell count was evaluated throughout the study. The FAS population included all randomized subjects who received at least 1 dose of study medication and who had a pretreatment and at least 1 post baseline LVEF measurement recorded. Here, n = Number of subjects analyzed for specified category at the specified time points in each arm respectively.	
End point type	Secondary
End point timeframe:	
Baseline and Month 6, 12, 18, 24, 30 and 36	

End point values	Anagrelide	Hydroxyurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	68		
Units: 10 ¹² per liter				
arithmetic mean (standard deviation)				
Baseline (n=73,68)	4.757 (± 0.5897)	4.787 (± 0.6002)		

Change at Month 6 (n=60,58)	-0.227 (± 0.4134)	-1.467 (± 0.6563)		
Change at Month 12 (n=45,51)	-0.246 (± 0.4292)	-1.398 (± 0.5744)		
Change at Month 18 (n=42,49)	-0.225 (± 0.4224)	-1.323 (± 0.7278)		
Change at Month 24 (n=40,49)	-0.299 (± 0.5811)	-1.281 (± 0.7219)		
Change at Month 30 (n=40,45)	-0.295 (± 0.5713)	-1.339 (± 0.6509)		
Change at Month 36 (n=40,43)	-0.366 (± 0.4328)	-1.362 (± 0.6586)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signing of informed consent until the last study-related visit (Month 36)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Hydroxyurea
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Reporting group description:

Subjects received Hydroxyurea as 1000 mg per day administered orally as 500 mg capsule twice daily and dose titrated to effect to achieve a response. Subjects followed for up to 3 years.

Reporting group title	Anagrelide
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Reporting group description:

Subjects received Anagrelide hydrochloride 1.0 milligram (mg) per day administered orally as 0.5 mg capsule twice daily (bid) for 1 week. Then the dose was titrated such that the total daily dose is incremented by no more than 0.5 mg in any 1 week and the recommended maximum single dose could not exceed 2.5 mg as required depending on platelet reduction versus adverse event profile. Total daily dosage was not exceed 10 mg. Subjects followed for up to 3 years.

Serious adverse events	Hydroxyurea	Anagrelide	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 70 (18.57%)	17 / 76 (22.37%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenoid cystic carcinoma			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 70 (1.43%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malignant melanoma			
subjects affected / exposed	1 / 70 (1.43%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral nerve sheath tumour malignant			
subjects affected / exposed	1 / 70 (1.43%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
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			
Asthenia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Reproductive system and breast disorders			
Ovarian cyst			

subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 70 (1.43%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
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			
Foot fracture			
subjects affected / exposed	1 / 70 (1.43%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic amputation			
subjects affected / exposed	1 / 70 (1.43%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			

subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 70 (0.00%)	3 / 76 (3.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neurological decompensation			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis cerebral			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			

subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal fistula			
subjects affected / exposed	1 / 70 (1.43%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 70 (1.43%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Scleroderma			
subjects affected / exposed	1 / 70 (1.43%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tendon calcification			
subjects affected / exposed	1 / 70 (1.43%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Ear infection			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 70 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Hydroxyurea	Anagrelide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 70 (38.57%)	46 / 76 (60.53%)	
Vascular disorders			
Hypertension			

subjects affected / exposed occurrences (all)	1 / 70 (1.43%) 1	9 / 76 (11.84%) 12	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 70 (0.00%) 0	18 / 76 (23.68%) 29	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 70 (1.43%) 1	19 / 76 (25.00%) 33	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	8 / 70 (11.43%) 9 7 / 70 (10.00%) 7 5 / 70 (7.14%) 8	4 / 76 (5.26%) 6 1 / 76 (1.32%) 1 0 / 76 (0.00%) 0	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all)	4 / 70 (5.71%) 6 1 / 70 (1.43%) 1	5 / 76 (6.58%) 6 4 / 76 (5.26%) 7	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 70 (0.00%) 0	5 / 76 (6.58%) 5	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	3 / 70 (4.29%) 3	6 / 76 (7.89%) 7	
Respiratory, thoracic and mediastinal disorders			

Epistaxis subjects affected / exposed occurrences (all)	2 / 70 (2.86%) 2	4 / 76 (5.26%) 5	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 70 (2.86%) 2	6 / 76 (7.89%) 7	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	5 / 70 (7.14%) 8 6 / 70 (8.57%) 8 1 / 70 (1.43%) 1 2 / 70 (2.86%) 2	2 / 76 (2.63%) 2 2 / 76 (2.63%) 2 4 / 76 (5.26%) 4 4 / 76 (5.26%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2005	1. Details of the Medical Toxicology Unit Information Services were added to the emergency contact list. 2. Administrative changes were made to address inconsistency between synopsis and main text. 3. The requirement to formally document drug compliance in the electronic case report form (eCRF) was removed. 4. The serious adverse events (SAE) reporting requirements were clarified.
03 November 2005	1. The principal investigator, project physician, and study manager were changed. 2. The exclusion criterion related to renal and hepatic impairment was updated to exclude not only subjects with severe renal or hepatic impairment but also those with moderate impairment. 3. New participating countries were added. 4. Requirements for subject identification were updated to comply with local requirements.
08 August 2006	1. The contract research organization (CRO) and respective contact details were changed. 2. The emergency contact details were changed. 3. The responsible Shire Project Physician was changed. 4. Listed participating countries were deleted and recruitment expanded to other European Union (EU) territories.
11 February 2008	1. Holter monitoring to diagnose cardiac symptoms which may indicate arrhythmia was added. 2. The CRO conducting and reading echocardiographs was changed. 3. The sample subject information and consent form and information for subjects requiring bone marrow biopsy or aspiration was removed from the appendix. 4. Drug accountability records were clarified.
20 April 2009	1. The principal coordinating investigator was changed. 2. Shire staff contact information on Emergency Contact Information page was updated. 3. Study Design was updated to state that overall study duration was estimated to be at least 7 years. 4. Number and Source of Subjects was updated to state that 184 high-risk essential thrombocythemia (ET) subjects would be enrolled across 50 sites. 5. The cross reference was removed from the heading to after the statement diagnosis of ET. 6. The sentence "Subjects may however participate in study SPD422-403 whilst still enrolled in this study." was removed. 7. The following sentence was added Withdrawal of Subjects: "Subjects who withdraw from the study will return to the routine clinical care of their physician. 8. The following text regarding hydroxycarbamide capsules was added to Investigational Product[s]: "There are 10 capsules per blister pack and 10 blister packs are provided in a carton." 9. The following text was deleted in Labeling, Packaging, Storage, and Handling: "provided that the blind of the study is not compromised". 10. Echocardiogram and Holter Monitoring to Diagnose Cardiovascular Symptoms were updated to include the name of the CRO, the central reader of the Echocardiograms and Echocardiographs. 11. The following sentence was added to Serious Adverse Event Procedures: "The reference for safety information for this study is the current Investigator Brochure." 12. The appendices were updated to include CRO vendors for Bone Marrow Biopsy Review and Interactive Voice Response System (IVRS). 13. The reference for European Union (EU) Clinical Trial Directive 2001/20/EC was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported