Clinical trial results:
A phase III randomized, multicenter, double-blind, active controlled study to compare the efficacy and safety of two different anagrelide formulations in patients with Essential Thrombocythemia (TEAM-ET 2.0)

Summary

EudraCT number	2013-003410-41
Trial protocol	AT LT BG PL
Global end of trial date	14 April 2015

Results information

Result version number	v1 (current)
This version publication date	18 February 2017
First version publication date	18 February 2017

Trial information

Trial identification

Sponsor protocol code	AOP18007

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, Wien, Austria, 1160
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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	04 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2015
Global end of trial reached?	Yes
Global end of trial date	14 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine whether Anagrelide Retard is non-inferior to Thromboreductin® in terms of mean platelet count measured by a central laboratory/centralized method at three time points during the maintenance period.

Protection of trial subjects:

An IDMC was established, responsible for safeguarding the interests of trial participants, assessing the safety of the interventions during the trial. The DMC met quarterly from the time of first patient randomization until last patient's study finalization.

Protection with regards to reducing individual health risks:
Any prophylactic medications to reduce the risk of thrombotic events other than alternative cytoreductive treatments or any medication to control or treat disease related symptoms/adverse events are permitted throughout the study (e.g. paracetamol, Aspirin®). No drugs with an effect to reduce platelet counts are permitted during the whole study.
In case of palpitations, a low dose beta-blocker should be used, if clinically indicated. Paracetamol is the preferred drug to treat anagrelide related headache. Standard locally available therapy is to be used in case of diarrhoea (for example loperamide).

Background therapy:

At the discretion of the investigator, any therapy reducing the risk of thrombotic events was allowed, except for cytoreductive drugs.

Evidence for comparator:

According to the EMA 'Points to consider on the clinical requirements of modified release products submitted as a line extension of an existing marketing authorization' (CPMP/EWP/1875/03/Final), demonstration of non-inferiority of a modified-release formulation is considered sufficient, unless efficacy and safety of a drug are closely related, or the effect of the product is bi-directional. Therefore, Thromboreductin® was chosen as the comparator.

Actual start date of recruitment	26 March 2014
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	Poland: 27
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Bulgaria: 25
Country: Number of subjects enrolled	Lithuania: 8
Country: Number of subjects enrolled	Russian Federation: 37
Worldwide total number of subjects	112
EEA total number of subjects	75

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)	72
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 112 subjects were screened at 18 centers in Austria (3), Bulgaria (2), Lithuania (2), Poland (5) and Russia (6). 6 of these subjects were screening failures. One subject was randomized but did not receive treatment and was classified as screening failure. 107 subjects were randomized and 106 subjects were included in the Safety Set.

Pre-assignment

Screening details:

Patients with confirmed diagnosis of ET at high risk (age ≥ 60 years, platelet counts ≥ 1000 G/L, increase of platelet count ≥ 300 G/L within 3 months, severe thrombohemorrhagic/ ischemic symptoms) of experiencing ET-related events, being currently treated or (ET treatment or Anagrelide) naïve.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Anagrelide Retard

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Analgrelide Retard 2mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Optimal dosing (increase to achieve the target platelet level, decrease in case of toxicity following the SmPC specifications of dosing rules for Thromboreductin were applied to each patient to reduce (for ANA-naive subjects) or maintain platelets (for anagrelide pre-treated subjects) (tbc) the platelet count ≤400 G/L or, in cases in which further dose up-titration was not possible due to poor tolerability, at least below 600 G/L.

Arm title	Thromboreductin

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Thromboreductin® 0.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Optimal dosing (increase to achieve the target platelet level, decrease in case of toxicity following the SmPC specifications of Thromboreductin® were applied to each patient to reduce (for ANA-naive subjects) or maintain (tbc) platelets (for anagrelide pre-treated subjects) the platelet count ≤400 G/L or, in cases in which further dose up-titration was not possible due to poor tolerability, at least below 600 G/L.

Number of subjects in period 1[1]	Anagrelide Retard	Thromboreductin
Started	52	54
Completed	52	54

Notes:

[1] - 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: 6 of the 112 subjects were screening failures and were subsequently not included.

Period 2

Period 2 title	Overall trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Anagrelide Retard

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Analgrelide Retard 2mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Titration Phase: The dose was adjusted weekly up to 12 weeks in order to achieve a "stable platelet count" on two consecutive measurements (main criterion: between 150 and 400 G/L, but further criteria also applied using fluctuation criteria).
ANA-naive patients started with dose level 2 (i.e. 2 mg Anagrelide Retard per day). ANA-treated patients were switched to the dose level which was closest to the pre-study anagrelide dose at study start, followed by weekly adjustments if required (platelet response, toxicity). Weekly titration was done in 1 mg with Anagrelide Retard steps with a maximum daily dose of 10 mg.
Maintenance Phase: Patients reaching the desired response stable platelet count, were switched to a 4-week maintenance phase at the dose determined. Depending on dose level, IMPs were to be taken once (morning) or twice daily (every 12 hours) after meal intake. From dose level 2 onwards, total daily dose was split in two as near as possible equivalent doses.

Arm title	Thromboreductin

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Thromboreductin® 0.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Titration Phase: The dose was adjusted weekly up to 12 weeks in order to achieve a "stable platelet count" (main criterion defined as between 150 and 400 G/L, but further criteria were also applied using fluctuation criteria) on two consecutive measurements.
ANA-naive patients started with dose level 2 (i.e. 2 mg Anagrelide Retard per day). ANA-treated patients were switched to the dose level which was closest to the pre-study anagrelide dose at study start, followed by weekly adjustments if required, according to the platelet response and toxicity. Weekly titration was done in 0.5 mg with Thromboreductin steps. The maximum daily dose was 5 mg

Thromboreductin.
Maintenance Phase: see Anagrelide retard

Number of subjects in period 2	Anagrelide Retard	Thromboreductin
Started	52	54
Completed	43	48
Not completed	9	6
Adverse event, serious fatal	1	-
Consent withdrawn by subject	3	1
Adverse event, non-fatal	3	4
unrelated medical condition	1	-
non-compliance	1	-
failure to achieve the target platelet level	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Anagrelide Retard
Reporting group description: -	
Reporting group title	Thromboreductin
Reporting group description: -	

Reporting group values	Anagrelide Retard	Thromboreductin	Total
Number of subjects	52	54	106
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	56.3	54.7	
standard deviation	± 15.31	± 16.93	-
Gender categorical Units: Subjects			
Female	37	35	72
Male	15	19	34
Diagnostic criteria for initial diagnosis Units: Subjects			
PVSG	3	3	6
WHO 2001 criteria for ET	4	6	10
WHO 2008 criteria for ET	43	43	86
Other	2	2	4
Demonstration of JAK2V61F Units: Subjects			
NEGATIVE	28	25	53
POSITIVE	24	29	53
Demonstration of other clonal marker Units: Subjects			
No	51	52	103
Yes	0	2	2
Missing	1	0	1
Specification of other clonal marker Units: Subjects			
Calreticulin	0	1	1
Calreticulin Mutation	0	1	1
Missing	52	52	104
ANA-pretreatment status (3 classes)			
Category "Missing Anagrelide-naïve" means: Missing Anagrelide-naïve using other cytoreductive treatment than Anagrelide			
Units: Subjects			
Anagrelide-treated	7	8	15
Anagrelide-truly naïve	23	26	49
Missing Anagrelide-naïve	22	20	42

End points

End points reporting groups

Reporting group title	Anagrelide Retard
Reporting group description: -	
Reporting group title	Thromboreductin
Reporting group description: -	
Reporting group title	Anagrelide Retard
Reporting group description: -	
Reporting group title	Thromboreductin
Reporting group description: -	
Subject analysis set title	Safety analysis (SA) set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who were randomized and received at least one dose of one of the IMPs.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects of the SA set with at least one measurement of platelet count following at least one dose of IMP.	
Subject analysis set title	Per Protocol (PP) set
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects of the FAS, who entered the maintenance phase, had three valid platelet results and for whom no relevant protocol deviations were documented.	

Primary: Mean platelet count based on three measurements during the maintenance phase

End point title	Mean platelet count based on three measurements during the maintenance phase
End point description:	
End point type	Primary
End point timeframe:	
Visit M1 (day 0 of maintenance phase), Visit M3 (day 14 of maintenance phase), Visit M5 (day 28 of maintenance phase)	

End point values	Anagrelide Retard	Thromboreductin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	46		
Units: G/L				
least squares mean (standard error)	280.7731 (± 1.0525)	305.0135 (± 1.0507)		

Statistical analyses

Statistical analysis title	Primary analysis of the main endpoint based on PPS

Statistical analysis description:

The primary efficacy endpoint was analysed by means of a repeated measurement analysis using a mixed model (MMRM).

Comparison groups	Anagrelide Retard v Thromboreductin
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Ratio of means
Point estimate	0.9205
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	1.037

Notes:

[1] - The mixed model included the factors treatment group, time, cross factor time*treatment group, stratification variable treatment status before titration phase and covariates age and cardiovascular medical history. Non-inferiority was concluded if the upper limit of the one-sided 97.5% confidence interval of the treatment difference between Anagrelide and Thromboreductin® did not exceed 1.3 in the ratio of mean platelet count of three measurements of the maintenance phase.

Statistical analysis title	Supportive analysis using the FAS population

Statistical analysis description:

The supportive analysis used the same model as applied for the primary analysis (repeated measurement analysis using a mixed model (MMRM)).

Comparison groups	Thromboreductin v Anagrelide Retard
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Ratio of means
Point estimate	0.8956
Confidence interval	
level	95 %
sides	1-sided
upper limit	1.008

Notes:

[2] - see main analysis of primary endpoint for PP

Secondary: Response definition 1 (D1): Achievement of mean platelet level <600 G/L during maintenance phase

End point title	Response definition 1 (D1): Achievement of mean platelet level <600 G/L during maintenance phase

End point description:

Response is evaluated taking the mean of three platelet counts from central laboratory.

End point type	Secondary

End point timeframe:

Visits M1, M3 and M5

End point values	Anagrelide Retard	Thromboreductin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	46		
Units: Number of patients within this category				
Responder D1=no	2	0		
Responder D1=yes	39	46		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis based on FAS

Statistical analysis description:

Comparison of responder rates between treatment groups using Fisher's exact test (5% significance level) and unconditional two-sided 95% exact confidence intervals for the difference in rates (Anagrelide – Thromboreductin®).

Comparison groups	Anagrelide Retard v Thromboreductin
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.219
Method	Fisher exact
Parameter estimate	Risk diff. and confidence interval in %
Point estimate	-4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.5
upper limit	16.2

Secondary: Response definition 2 (D2): Achievement of increase in platelet level ≤ 300 G/L during maintenance phase

End point title	Response definition 2 (D2): Achievement of increase in platelet level ≤ 300 G/L during maintenance phase

End point description:

Response was evaluated comparing the change from M1. Platelet measurements were taken from the central laboratory.

End point type	Secondary

End point timeframe:

Visits M1 M3 and M5

End point values	Anagrelide Retard	Thromboreductin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	50		
Units: Number of patients within this category				
Responder D2=no	2	1		
Responder D2=yes	44	49		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis based on FAS

Statistical analysis description:

Comparison of responder rates between treatment groups using Fisher's exact test (5% significance level) and unconditional two-sided 95% exact confidence intervals for the difference in rates (Anagrelide – Thromboreductin).

Comparison groups	Anagrelide Retard v Thromboreductin
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.606
Method	Fisher exact
Parameter estimate	Risk diff. and confidence interval in %
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.4
upper limit	17.8

Secondary: Response definition 3 (D3): Platelet level during maintenance period ≤ 1000 G/L

End point title	Response definition 3 (D3): Platelet level during maintenance period ≤ 1000 G/L

End point description:

Platelet measurements were taken from the central laboratory.

End point type	Secondary

End point timeframe:

Visits M1, M3 and M5

End point values	Anagrelide Retard	Thromboreductin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	50		
Units: Number of patients within this category				
Responder D3=no	0	1		
Responder D3=yes	46	49		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis based on FAS

Statistical analysis description:

Comparison of responder rates between treatment groups using Fisher's exact test (5% significance level) and unconditional two-sided 95% exact confidence intervals for the difference in rates (Anagrelide – Thromboreductin®).

Comparison groups	Thromboreductin v Anagrelide Retard
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.999
Method	Fisher exact
Parameter estimate	Risk diff. and confidence interval in %
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.2
upper limit	22

Secondary: Response definition 4 (D4): Platelet level between 150 G/L and 400 G/L during maintenance phase

End point title	Response definition 4 (D4): Platelet level between 150 G/L and 400 G/L during maintenance phase

End point description:

Platelet count had to be within 150 G/L and 400 G/L during the whole maintenance phase. Platelet measurements were taken from the central laboratory.

End point type	Secondary

End point timeframe:

Visits M1, M3 and M5

End point values	Anagrelide Retard	Thromboreductin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	50		
Units: Number of patients within this category				
Responder D4=no	20	25		
Responder D4=yes	26	25		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis based on FAS

Statistical analysis description:

Comparison of responder rates between treatment groups using Fisher's exact test (5% significance level) and unconditional two-sided 95% exact confidence intervals for the difference in rates (Anagrelide – Thromboreductin®).

Comparison groups	Anagrelide Retard v Thromboreductin
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.546
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.7
upper limit	26.4

Secondary: Time from randomization until entrance in the maintenance phase

End point title	Time from randomization until entrance in the maintenance phase

End point description:

End point type	Secondary

End point timeframe:

Whole observational period.

End point values	Anagrelide Retard	Thromboreductin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: days				
arithmetic mean (standard error)	46.7 (± 2.86)	43.4 (± 2.67)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis based on FAS
Comparison groups	Anagrelide Retard v Thromboreductin
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.4073
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.28

Notes:

[3] - The Cox model used the factors treatment group and the covariates pre-treated/naive subjects, presence of cardiovascular disease and age as a dichotomous variable. Two-sided p-value of the logrank, hazard ratio and corresponding 95% CIs for hazard ratio were included.

Secondary: Time from randomization until withdrawal

End point title	Time from randomization until withdrawal

End point description:

End point type	Secondary

End point timeframe:

whole observational period.

End point values	Anagrelide Retard	Thromboreductin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: days				
arithmetic mean (standard error)	109.1 (± 4.82)	106.3 (± 2.8)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis based on FAS

Statistical analysis description:

See analysis description for endpoint ‘Time from randomization until entrance in the maintenance phase’

Comparison groups	Anagrelide Retard v Thromboreductin
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.5013 [5]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	4.05

Notes:

[4] - Analysis description for endpoint 'Time from randomization until entrance in the maintenance phase'
[5] - p-value from log-rank test

Secondary: Number of titrations in the titration and maintenance phase

End point title	Number of titrations in the titration and maintenance phase

End point description:

End point type	Secondary

End point timeframe:

Titration period

End point values	Anagrelide Retard	Thromboreductin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: number of titrations				
arithmetic mean (standard deviation)	2.5 (± 1.86)	2.3 (± 1.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maintenance dose

End point title	Maintenance dose

End point description:

Maintenance dose, as taken at entry to maintenance period dose in mg used during maintenance phase

End point type	Secondary

End point timeframe:

Maintenance period

End point values	Anagrelide Retard	Thromboreductin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	48		
Units: mg				
Dose level 1 (1mg/0.5mg)	4	1		
Dose level 2 (2mg/1mg)	10	4		
Dose level 3 (3mg/1.5mg)	11	18		
Dose level 4 (4mg/2mg)	9	8		
Dose level 5 (5mg/2.5mg)	8	10		
Dose level 6 (6mg/3mg)	1	4		
Dose level 7 (7mg/3.5mg)	1	2		
Dose level 8 (8mg/4mg)	0	1		
Dose level 9 (9mg/4.5mg)	0	0		
Dose level 10 (10mg/5mg)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life EQ-5D-3L - Weighted Index Score T1

End point title	Quality of Life EQ-5D-3L - Weighted Index Score T1

End point description:

End point type	Secondary

End point timeframe:

Titration period T1

End point values	Anagrelide Retard	Thromboreductin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: G/L				
arithmetic mean (standard deviation)	0.811 (± 0.1639)	0.853 (± 0.157)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life EQ-5D-3L - Weighted Index Score M1

End point title	Quality of Life EQ-5D-3L - Weighted Index Score M1

End point description:

End point type	Secondary

End point timeframe:

Maintenance phase M1

End point values	Anagrelide Retard	Thromboreductin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: G/L				
arithmetic mean (standard deviation)	0.847 (± 0.1847)	0.87 (± 0.1607)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life EQ-5D-3L - Weighted Index Score M5

End point title	Quality of Life EQ-5D-3L - Weighted Index Score M5

End point description:

End point type	Secondary

End point timeframe:

Maintenance phase M5

End point values	Anagrelide Retard	Thromboreductin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	52		
Units: G/L				
arithmetic mean (standard deviation)	0.847 (± 0.1649)	0.875 (± 0.1509)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean platelet count during titration phase

End point title	Mean platelet count during titration phase

End point description:

Mean platelet value for each time point during titration phase. Time points during titration phase run from T2 to T12 (weekly) at maximum. Results are referring to local laboratory.

End point type	Secondary

End point timeframe:

Titration period

End point values	Anagrelide Retard	Thromboreductin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: G/L				
least squares mean (confidence interval 95%)				
T2	639.2564 (568.1331 to 719.2834)	618.4118 (553.4826 to 690.9578)		
T3	429.3448 (345.9588 to 532.8293)	461.3066 (375.978 to 566.0006)		
T4	425.3496 (329.0591 to 549.8171)	414.2949 (323.5496 to 530.4912)		
T5	381.3893 (289.9106 to 501.7333)	391.4326 (301.5132 to 508.1683)		
T6	378.8447 (278.8502 to 514.6967)	352.0067 (266.1607 to 465.5411)		
T7	403.3565 (259.9157 to 625.9587)	388.8185 (261.7483 to 577.5769)		
T8	371.3544 (252.7565 to 545.6005)	383.545 (278.3144 to 528.5632)		
T9	501.6619 (230.9258 to 1089.807)	458.0205 (199.8996 to 1049.44)		
T10	392.7461 (230.705 to 668.6008)	333.4875 (208.7979 to 532.6389)		
T11	746.2463 (475.585 to 1170.944)	414.6818 (294.1042 to 584.6941)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis based on FAS T2

Statistical analysis description:

The change from baseline in platelet counts at each visit during titration was analyzed using an ANCOVA model of the original log-transformed data of absolute platelet count with the same covariates as used for the analysis of the primary efficacy parameter including the log-transformed baseline platelet value in addition and excluding the factor visit. ANCOVAs were run for each visit.

Comparison groups	Anagrelide Retard v Thromboreductin

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.5451
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.0337
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9275
upper limit	1.152

Notes:

[6] - Least square estimates of each treatment group and the difference thereof and corresponding standard deviations, two-sided 95% CIs and corresponding p-values for the treatment difference and covariates were derived. Data from local laboratory were taken for this kind of analysis.

Statistical analysis title	Secondary endpoint analysis based on FAS T3

Statistical analysis description:

The change from baseline in platelet counts at each visit during titration was analyzed using an ANCOVA model of the original log-transformed data of absolute platelet count with the same covariates as used for the analysis of the primary efficacy parameter including the log-transformed baseline platelet value in addition and excluding the factor visit. ANCOVAs were run for each visit.

Comparison groups	Anagrelide Retard v Thromboreductin
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.4854
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.9307
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7592
upper limit	1.1409

Notes:

[7] - Least square estimates of each treatment group and the difference thereof and corresponding standard deviations, two-sided 95% CIs and corresponding p-values for the treatment difference and covariates were derived. Data from local laboratory were taken for this kind of analysis.

Statistical analysis title	Secondary endpoint analysis based on FAS T4

Statistical analysis description:

The change from baseline in platelet counts at each visit during titration was analyzed using an ANCOVA model of the original log-transformed data of absolute platelet count with the same covariates as used for the analysis of the primary efficacy parameter including the log-transformed baseline platelet value in addition and excluding the factor visit. ANCOVAs were run for each visit.

Comparison groups	Anagrelide Retard v Thromboreductin
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.8308
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.0267

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8039
upper limit	1.3112

Notes:

[8] - Least square estimates of each treatment group and the difference thereof and corresponding standard deviations, two-sided 95% CIs and corresponding p-values for the treatment difference and covariates were derived. Data from local laboratory were taken for this kind of analysis.

Statistical analysis title	Secondary endpoint analysis based on FAS T6

Statistical analysis description:

The change from baseline in platelet counts at each visit during titration was analyzed using an ANCOVA model of the original log-transformed data of absolute platelet count with the same covariates as used for the analysis of the primary efficacy parameter including the log-transformed baseline platelet value in addition and excluding the factor visit. ANCOVAs were run for each visit.

Comparison groups	Anagrelide Retard v Thromboreductin
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.63
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.0762
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7938
upper limit	1.4593

Notes:

[9] - Least square estimates of each treatment group and the difference thereof and corresponding standard deviations, two-sided 95% CIs and corresponding p-values for the treatment difference and covariates were derived. Data from local laboratory were taken for this kind of analysis.

Statistical analysis title	Secondary endpoint analysis based on FAS T7

Statistical analysis description:

The change from baseline in platelet counts at each visit during titration was analyzed using an ANCOVA model of the original log-transformed data of absolute platelet count with the same covariates as used for the analysis of the primary efficacy parameter including the log-transformed baseline platelet value in addition and excluding the factor visit. ANCOVAs were run for each visit.

Comparison groups	Anagrelide Retard v Thromboreductin
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.8506
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.0374
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6999
upper limit	1.5376

Notes:

[10] - Least square estimates of each treatment group and the difference thereof and corresponding standard deviations, two-sided 95% CIs and corresponding p-values for the treatment difference and covariates were derived. Data from local laboratory were taken for this kind of analysis.

Statistical analysis title	Secondary endpoint analysis based on FAS T8

Statistical analysis description:

The change from baseline in platelet counts at each visit during titration was analyzed using an ANCOVA model of the original log-transformed data of absolute platelet count with the same covariates as used for the analysis of the primary efficacy parameter including the log-transformed baseline platelet value in addition and excluding the factor visit. ANCOVAs were run for each visit.

Comparison groups	Anagrelide Retard v Thromboreductin
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.8463
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.9682
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.3586

Notes:

[11] - Least square estimates of each treatment group and the difference thereof and corresponding standard deviations, two-sided 95% CIs and corresponding p-values for the treatment difference and covariates were derived. Data from local laboratory were taken for this kind of analysis.

Statistical analysis title	Secondary endpoint analysis based on FAS T9

Statistical analysis description:

The change from baseline in platelet counts at each visit during titration was analyzed using an ANCOVA model of the original log-transformed data of absolute platelet count with the same covariates as used for the analysis of the primary efficacy parameter including the log-transformed baseline platelet value in addition and excluding the factor visit. ANCOVAs were run for each visit.

Comparison groups	Anagrelide Retard v Thromboreductin
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.6921
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.0953
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.7642

Notes:

[12] - Least square estimates of each treatment group and the difference thereof and corresponding standard deviations, two-sided 95% CIs and corresponding p-values for the treatment difference and covariates were derived. Data from local laboratory were taken for this kind of analysis.

Statistical analysis title	Secondary endpoint analysis based on FAS T10

Statistical analysis description:

The change from baseline in platelet counts at each visit during titration was analyzed using an ANCOVA

model of the original log-transformed data of absolute platelet count with the same covariates as used for the analysis of the primary efficacy parameter including the log-transformed baseline platelet value in addition and excluding the factor visit. ANCOVAs were run for each visit.

Comparison groups	Anagrelide Retard v Thromboreductin
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.6261
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.1777
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5703
upper limit	2.432

Notes:

[13] - Least square estimates of each treatment group and the difference thereof and corresponding standard deviations, two-sided 95% CIs and corresponding p-values for the treatment difference and covariates were derived. Data from local laboratory were taken for this kind of analysis.

Statistical analysis title	Secondary endpoint analysis based on FAS T5

Statistical analysis description:

The change from baseline in platelet counts at each visit during titration was analyzed using an ANCOVA model of the original log-transformed data of absolute platelet count with the same covariates as used for the analysis of the primary efficacy parameter including the log-transformed baseline platelet value in addition and excluding the factor visit. ANCOVAs were run for each visit.

Comparison groups	Anagrelide Retard v Thromboreductin
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.8496
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.9743
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7417
upper limit	1.2799

Notes:

[14] - Least square estimates of each treatment group and the difference thereof and corresponding standard deviations, two-sided 95% CIs and corresponding p-values for the treatment difference and covariates were derived. Data from local laboratory were taken for this kind of analysis.

Statistical analysis title	Secondary endpoint analysis based on FAS T11

Statistical analysis description:

The change from baseline in platelet counts at each visit during titration was analyzed using an ANCOVA model of the original log-transformed data of absolute platelet count with the same covariates as used for the analysis of the primary efficacy parameter including the log-transformed baseline platelet value in addition and excluding the factor visit. ANCOVAs were run for each visit.

Comparison groups	Anagrelide Retard v Thromboreductin

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.0447
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.7996
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.0208
upper limit	3.1723

Notes:

[15] - Least square estimates of each treatment group and the difference thereof and corresponding standard deviations, two-sided 95% CIs and corresponding p-values for the treatment difference and covariates were derived. Data from local laboratory were taken for this kind of analysis.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening Period: V 1, d -7 to -1
Titration Period: V 2, d 1
V 3, d 8
V 4, d 15
V 5, d 22
V 6, d 29
V 7 up to V 13, d 36 up to 78
Maintenance Period: V 14, d 85
V 15, d 92
V 16, d 99
V 17, d 106
V 18, d 113
V 19, 28d after V 18

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Anagrelide Retard
Reporting group description: -	
Reporting group title	Thromboreductin

Reporting group description: -

Serious adverse events	Anagrelide Retard	Thromboreductin	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 52 (21.15%)	1 / 54 (1.85%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastrointestinal Stromal Tumour			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
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			
Head injury			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			

subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic thrombosis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemorrhagic anaemia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden hearing loss			

subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	2 / 52 (3.85%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric artery thrombosis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 52 (1.92%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (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			
Lobar pneumonia			

subjects affected / exposed	2 / 52 (3.85%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
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	Anagrelide Retard	Thromboreductin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 52 (80.77%)	42 / 54 (77.78%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibroma			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 52 (9.62%)	4 / 54 (7.41%)	
occurrences (all)	6	6	
Hypotension			
subjects affected / exposed	3 / 52 (5.77%)	1 / 54 (1.85%)	
occurrences (all)	6	1	
Haematoma			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Phlebitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Surgical and medical procedures			

Dental implantation			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 52 (5.77%)	3 / 54 (5.56%)	
occurrences (all)	4	3	
Peripheral swelling			
subjects affected / exposed	4 / 52 (7.69%)	1 / 54 (1.85%)	
occurrences (all)	4	1	
Fatigue			
subjects affected / exposed	2 / 52 (3.85%)	2 / 54 (3.70%)	
occurrences (all)	3	2	
Pyrexia			
subjects affected / exposed	3 / 52 (5.77%)	1 / 54 (1.85%)	
occurrences (all)	3	1	
Asthenia			
subjects affected / exposed	2 / 52 (3.85%)	1 / 54 (1.85%)	
occurrences (all)	2	1	
Adverse drug reaction			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Condition aggravated			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	4	0	
Pain			

subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Breast cyst			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Erectile dysfunction			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 52 (1.92%)	2 / 54 (3.70%)	
occurrences (all)	1	2	
Dyspnoea exertional			
subjects affected / exposed	0 / 52 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
Epistaxis			
subjects affected / exposed	2 / 52 (3.85%)	0 / 54 (0.00%)	
occurrences (all)	3	0	
Catarrh			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Obstructive airways disorder			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 52 (3.85%)	2 / 54 (3.70%)	
occurrences (all)	4	3	
Agitation			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Depression			

subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Investigations			
Platelet count decreased			
subjects affected / exposed	2 / 52 (3.85%)	1 / 54 (1.85%)	
occurrences (all)	3	1	
Blood creatine increased			
subjects affected / exposed	0 / 52 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
C-reactive protein increased			
subjects affected / exposed	1 / 52 (1.92%)	1 / 54 (1.85%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 52 (1.92%)	1 / 54 (1.85%)	
occurrences (all)	1	3	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Blood glucose increased			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Blood iron decreased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Blood urea increased			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	2	
Brain natriuretic peptide increased			

subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Eosinophil count increased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Joint injury			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Overdose			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	3	
Cardiac disorders			
Palpitations			
subjects affected / exposed	16 / 52 (30.77%)	15 / 54 (27.78%)	
occurrences (all)	33	31	
Tachycardia			
subjects affected / exposed	5 / 52 (9.62%)	2 / 54 (3.70%)	
occurrences (all)	7	15	
Sinus bradycardia			
subjects affected / exposed	0 / 52 (0.00%)	5 / 54 (9.26%)	
occurrences (all)	0	6	
Left ventricular hypertrophy			
subjects affected / exposed	0 / 52 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
Atrial flutter			

subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Atrioventricular block first degree			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Bradycardia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Coronary artery disease			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Defect conduction intraventricular			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Extrasystoles			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Myocardial ischaemia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Right ventricular failure			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Supraventricular extrasystoles			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 52 (36.54%)	19 / 54 (35.19%)	
occurrences (all)	62	56	
Dizziness			
subjects affected / exposed	5 / 52 (9.62%)	3 / 54 (5.56%)	
occurrences (all)	5	5	
Paraesthesia			
subjects affected / exposed	2 / 52 (3.85%)	0 / 54 (0.00%)	
occurrences (all)	2	0	

Hypoaesthesia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	7	0	
Somnolence			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	3 / 52 (5.77%)	1 / 54 (1.85%)	
occurrences (all)	3	3	
Anaemia			
subjects affected / exposed	2 / 52 (3.85%)	0 / 54 (0.00%)	
occurrences (all)	3	0	
Lymphadenopathy			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	3	0	
Pancytopenia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 52 (1.92%)	1 / 54 (1.85%)	
occurrences (all)	1	1	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Eye haemorrhage			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Eye oedema			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Visual acuity reduced			

subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	2	
Visual impairment			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	10 / 52 (19.23%)	3 / 54 (5.56%)	
occurrences (all)	13	3	
Abdominal pain			
subjects affected / exposed	5 / 52 (9.62%)	5 / 54 (9.26%)	
occurrences (all)	7	5	
Diarrhoea			
subjects affected / exposed	5 / 52 (9.62%)	5 / 54 (9.26%)	
occurrences (all)	5	5	
Nausea			
subjects affected / exposed	5 / 52 (9.62%)	4 / 54 (7.41%)	
occurrences (all)	5	8	
Dyspepsia			
subjects affected / exposed	4 / 52 (7.69%)	2 / 54 (3.70%)	
occurrences (all)	4	2	
Vomiting			
subjects affected / exposed	4 / 52 (7.69%)	0 / 54 (0.00%)	
occurrences (all)	4	0	
Constipation			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Eructation			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Food poisoning			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	

Gastritis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	2	0	
Hepatocellular injury			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 52 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
Dry skin			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Rash generalised			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Skin irritation			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Nocturia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Renal impairment			

subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 52 (5.77%)	3 / 54 (5.56%)	
occurrences (all)	4	3	
Pain in extremity			
subjects affected / exposed	5 / 52 (9.62%)	0 / 54 (0.00%)	
occurrences (all)	6	0	
Back pain			
subjects affected / exposed	2 / 52 (3.85%)	0 / 54 (0.00%)	
occurrences (all)	2	0	
Myalgia			
subjects affected / exposed	1 / 52 (1.92%)	1 / 54 (1.85%)	
occurrences (all)	2	1	
Arthritis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Bursitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Joint swelling			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Muscle swelling			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Muscular weakness			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Neck pain			

subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Osteoarthritis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 52 (5.77%)	1 / 54 (1.85%)	
occurrences (all)	4	1	
Ear infection			
subjects affected / exposed	1 / 52 (1.92%)	1 / 54 (1.85%)	
occurrences (all)	1	1	
Oral herpes			
subjects affected / exposed	0 / 52 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
Upper respiratory tract infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	2	
Cystitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Dermatophytosis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Gingivitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	

Hordeolum			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 52 (1.92%)	1 / 54 (1.85%)	
occurrences (all)	1	1	
Hypokalaemia			
subjects affected / exposed	1 / 52 (1.92%)	1 / 54 (1.85%)	
occurrences (all)	1	2	
Decreased appetite			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Gout			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	3	0	
Hypermagnesaemia			

subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Iron deficiency			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2014	- an exclusion criterion was updated to add electrolyte imbalance - subjects were to be monitored for evidence of cardiovascular effects during treatment. - subjects who benefited from the study treatment could be further treated with an anagrelide formulation instead as previously stated Thromboreductin after the end of the study. - changes to the protocol-specified analyses • statistical model and main hypothesis • definition of response rates • change to baseline of platelet count • extent of exposure • adverse events

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported