Clinical trial results:
A phase III, randomized, multicenter, subject- and sponsor-blinded, placebo controlled study to compare the efficacy and safety of “Anagrelide retard” versus placebo in “at risk” subjects with Essential Thrombocythaemia

Summary

EudraCT number	2009-017095-24
Trial protocol	AT SK SI LT BG
Global end of trial date	12 January 2015

Results information

Result version number	v1 (current)
This version publication date	27 May 2021
First version publication date	27 May 2021

Trial information

Trial identification

Sponsor protocol code	AOP13007

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/IIf, Vienna, Austria,
Public contact	Dr. Michael Zörer, AOP Orphan Pharmaceuticals AG, 0043 1503 72 44 46, michael.zoerer@aoporphan.com
Scientific contact	Dr. Michael Zörer, AOP Orphan Pharmaceuticals AG, 0043 1503 72 44 46, michael.zoerer@aoporphan.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2015
Global end of trial reached?	Yes
Global end of trial date	12 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether "Anagrelide retard" compared to placebo will reduce the rate of ET-related complications in subjects with potential risk for ET-related Events

Protection of trial subjects:

Clinical significant deviations from physical examination, vital signs, ECG, ECHO, laboratory parameters as well as therapy tolerance and adverse events will be evaluated by the investigator for the assessment of subject’s safety. Patients should be monitored during treatment for evidence of cardiovascular effects that may require further cardiovascular examination and investigation. Hypokalaemia or hypomagnesaemia must be corrected prior to Anagrelide administration and should be monitored periodically duringFinal therapy. Furthermore, serum calcium should be monitored periodically on treatment.

Careful evaluation of the subject’s diaries by the investigator on every visit will help to detect unreported adverse events.

For evaluation of Quality of Life (QoL) under test drug as compared to placebo, the SF-36 Questionnaire will be used.

Written informed consent was obtained from all subjects prior to entry into the study. The investigator explained to each subject, orally and in writing (subject information sheet), the nature, significance, risks and implications of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 March 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Austria: 12
Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	Lithuania: 5
Country: Number of subjects enrolled	Ukraine: 11
Country: Number of subjects enrolled	Russian Federation: 59

Country: Number of subjects enrolled	Croatia: 4
Worldwide total number of subjects	146
EEA total number of subjects	76

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)	146
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects who enter into the screening period of the study (defined as the point at which the subject signs the informed consent) will receive a unique screening no before any study procedures are performed. This no will be used to identify the subject throughout the entire trial and must be used on all study documentation related that subject.

Period 1

Period 1 title	Main Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Subject, Monitor, Data analyst, Assessor

Blinding implementation details:

This was a subject and sponsor-blinded clinical study, the investigator was not blinded to treatment. The sponsor functions (including medical monitor, pharmacovigilance manager, clinical project manager, trial data manager and trial statistician) were blinded until after the database lock. Randomization scheme was prepared by an independent statistician (not otherwise involved in the study), and was stored securely with no access to it by the sponsor functions mentioned above.

Arms

Are arms mutually exclusive?	Yes
Arm title	Anagrelide retard

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Anagrelide retard 2mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Titration Phase (Visit 2 – Visit 6, i.e. 4 weeks):
Week 1:
1x1 tablet/d of "Anagrelide retard" (1 tablet = 2mg; total dose = 2mg/d) or placebo was administered in week 1.
Week 2
"Anagrelide retard":
Dosing was titrated up according to response (platelet reduction) to 4 mg/day (= 2x1 tablet) in week 2.
Week 3 – Week 4
"Anagrelide retard"
In week 3 and 4, dose was either increased or decreased to maintain platelets in the normal or close to normal range. The maximum dose was 4 tablets (= 8mg Anagrelide retard) per day.
Maintenance Phase (Visit 7 – Visit 10, i.e. up to 11 months)
"Anagrelide retard"
During maintenance phase (month 2 – month 12) doses of treatment were adjusted to the highest tolerated level which was able to maintain the platelet count within the normal range.

Arm title	Placebo

Arm description: -

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Titration Phase (Visit 2 – Visit 6, i.e. 4 weeks)
Week 1:
1x1 tablet/d of placebo was administered in week 1.
Week 2
2x1 tablet/d of placebo was administered in week 2.
Week 3 – Week 4
In week 3 and week 4 the maximum dose was 4 tablets per day.
Maintenance Phase (Visit 7 – Visit 10, i.e. up to 11 months)
In order to guarantee blinding of subjects, the number of placebo tablets to be taken by the subject varied during maintenance period:
month 2 - month 3: 2x1 tablet/d
month 3 - month 6: 3x1 tablet/d
month 6 - month 9: 4x1 tablet/d
month 9 - month 12: 4x1 tablet/d
Tablets were taken once daily after a high-fat meal intake (breakfast or lunch).The subjects were given dietary advice about high fat meals.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: This was a subject and sponsor-blinded clinical study, the investigator was not blinded to treatment. The sponsor functions (including medical monitor, pharmacovigilance manager, clinical project manager, trial data manager and trial statistician) were blinded until after the database lock. Randomization scheme was prepared by an independent statistician (not otherwise involved in the study), and was stored securely with no access to it by the sponsor functions mentioned above.

Number of subjects in period 1	Anagrelide retard	Placebo
Started	77	69
Completed	60	52
Not completed	17	17
Adverse event, serious fatal	1	1
sponsor decision	-	1
Lack of efficacy: AE that constitutes ET-related	4	4
Consent withdrawn by subject	1	4
Adverse event, non-fatal	3	-
Administrative reasons	2	-
Pregnancy	1	-
patient relocated to another country	-	1
unstable platelet count	1	-
Lost to follow-up	2	-
Lack of efficacy: insufficient platelet reduction	2	6

Baseline characteristics

Reporting groups	
Reporting group title	Anagrelide retard
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Anagrelide retard	Placebo	Total
Number of subjects	77	69	146
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	77	69	146
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
SA			
Units: years			
arithmetic mean	40.9	45.2	
standard deviation	± 11.25	± 10.57	-
Gender categorical Units: Subjects			
Female	57	51	108
Male	20	18	38
JAK2 status			
Day 0, ITT			
Units: Subjects			
positive	47	44	91
negative	28	25	53
not recorded	2	0	2
Body Mass Index Units: kilogram(s)/square meter			
arithmetic mean	24.68	26.036	
standard deviation	± 4.6444	± 4.5731	-
Duration of ET			
SA			
Units: Days			
median	75	78	
standard deviation	± 577.36	± 510.39	-

Subject analysis sets

Subject analysis set title	Safety Set (SA) - Anagrelide Retard
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Set (SA): All subjects who had at least one dose of treatment and one contact with the investigator afterwards are analyzed for safety. - Anagrelide Retard

Subject analysis set title	Intent-to-Treat Set (ITT) - Anagrelide retard
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intent-to-Treat Set (ITT): all subjects who had at least one dose of treatment and also at least one observation visit with efficacy assessment under medication were evaluated as the 'intention to treat' (ITT) population. Subjects were excluded from the ITT population if a severe protocol violation occurred (e.g. true diagnosis was not ET). - Anagrelide retard

Subject analysis set title	Per-protocol Set 1 (PP1) - Anagrelide Retard
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol Set 1 (PP1): Subjects who were included in the ITT population and completed the study without showing major protocol deviations were included in the per protocol population (PP1). Note that subjects who discontinued due to lack of efficacy (increase of platelets and/or ET-related event were not excluded from the PP1 population even if other major protocol deviations occurred. - Anagrelide Retard

Subject analysis set title	Per-protocol Set 2 (PP2) - Anagrelide retard
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol Set 2 (PP2): An additional PP data set for exploratory purposes (PP2) that in addition to PP1 specifications excluded those subjects who had central laboratory bone marrow biopsy findings that suggested a diagnosis differing from ET. - Anagrelide retard

Subject analysis set title	Safety Set (SA) - Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Set (SA): All subjects who had at least one dose of treatment and one contact with the investigator afterwards are analyzed for safety. - Placebo

Subject analysis set title	Intent-to-Treat Set (ITT) - Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intent-to-Treat Set (ITT): all subjects who had at least one dose of treatment and also at least one observation visit with efficacy assessment under medication were evaluated as the 'intention to treat' (ITT) population. Subjects were excluded from the ITT population if a severe protocol violation occurred (e.g. true diagnosis was not ET). - Placebo

Subject analysis set title	Per-protocol Set 1 (PP1) - Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol Set 1 (PP1) - Placebo

Subject analysis set title	Per-protocol Set 2 (PP2) - Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol Set 2 (PP2): An additional PP data set for exploratory purposes (PP2) that in addition to PP1 specifications excluded those subjects who had central laboratory bone marrow biopsy findings that suggested a diagnosis differing from ET. - Placebo

Reporting group values	Safety Set (SA) - Anagrelide Retard	Intent-to-Treat Set (ITT) - Anagrelide retard	Per-protocol Set 1 (PP1) - Anagrelide Retard
Number of subjects	77	77	53
Age categorical Units: Subjects			
In utero	0	0	0

Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	77	77	53
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
SA			
Units: years			
arithmetic mean	40.9		42.6
standard deviation	± 11.25	±	± 11.53
Gender categorical			
Units: Subjects			
Female	57	57	40
Male	20	20	13
JAK2 status			
Day 0, ITT			
Units: Subjects			
positive	47	47	32
negative	28	28	19
not recorded	2	2	2
Body Mass Index			
Units: kilogram(s)/square meter			
arithmetic mean	24.68	24.68	
standard deviation	± 4.6444	± 4.6444	±
Duration of ET			
SA			
Units: Days			
median	75	75	
standard deviation	± 577.36	± 577.36	±

Reporting group values	Per-protocol Set 2 (PP2) - Anagrelide retard	Safety Set (SA) - Placebo	Intent-to-Treat Set (ITT) - Placebo
Number of subjects	42	69	69
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	42	69	69
From 65-84 years	0	0	0
85 years and over	0	0	0

Age continuous			
SA			
Units: years			
arithmetic mean	42	45.2	
standard deviation	± 11.48	± 10.57	±
Gender categorical			
Units: Subjects			
Female	32	51	51
Male	10	18	18
JAK2 status			
Day 0, ITT			
Units: Subjects			
positive	26	44	44
negative	14	25	25
not recorded	2	0	0
Body Mass Index			
Units: kilogram(s)/square meter			
arithmetic mean		26.036	26.036
standard deviation	±	± 4.5731	± 4.5731
Duration of ET			
SA			
Units: Days			
median		78	78
standard deviation	±	± 510.39	± 510.39

Reporting group values	Per-protocol Set 1 (PP1) - Placebo	Per-protocol Set 2 (PP2) - Placebo	
Number of subjects	47	33	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	47	33	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
SA			
Units: years			
arithmetic mean	46.6	46.4	
standard deviation	± 10.24	± 10.17	
Gender categorical			
Units: Subjects			
Female	39	28	
Male	8	5	

JAK2 status			
Day 0, ITT			
Units: Subjects			
positive	27	18	
negative	20	15	
not recorded	0	0	
Body Mass Index Units: kilogram(s)/square meter arithmetic mean standard deviation	±	±	
Duration of ET			
SA			
Units: Days median standard deviation	±	±	

End points

End points reporting groups

Reporting group title	Anagrelide retard
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Safety Set (SA) - Anagrelide Retard
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Set (SA): All subjects who had at least one dose of treatment and one contact with the investigator afterwards are analyzed for safety. - Anagrelide Retard	
Subject analysis set title	Intent-to-Treat Set (ITT) - Anagrelide retard
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intent-to-Treat Set (ITT): all subjects who had at least one dose of treatment and also at least one observation visit with efficacy assessment under medication were evaluated as the 'intention to treat' (ITT) population. Subjects were excluded from the ITT population if a severe protocol violation occurred (e.g. true diagnosis was not ET). - Anagrelide retard	
Subject analysis set title	Per-protocol Set 1 (PP1) - Anagrelide Retard
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-protocol Set 1 (PP1): Subjects who were included in the ITT population and completed the study without showing major protocol deviations were included in the per protocol population (PP1). Note that subjects who discontinued due to lack of efficacy (increase of platelets and/or ET-related event were not excluded from the PP1 population even if other major protocol deviations occurred. - Anagrelide Retard	
Subject analysis set title	Per-protocol Set 2 (PP2) - Anagrelide retard
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-protocol Set 2 (PP2): An additional PP data set for exploratory purposes (PP2) that in addition to PP1 specifications excluded those subjects who had central laboratory bone marrow biopsy findings that suggested a diagnosis differing from ET. - Anagrelide retard	
Subject analysis set title	Safety Set (SA) - Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Set (SA): All subjects who had at least one dose of treatment and one contact with the investigator afterwards are analyzed for safety. - Placebo	
Subject analysis set title	Intent-to-Treat Set (ITT) - Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intent-to-Treat Set (ITT): all subjects who had at least one dose of treatment and also at least one observation visit with efficacy assessment under medication were evaluated as the 'intention to treat' (ITT) population. Subjects were excluded from the ITT population if a severe protocol violation occurred (e.g. true diagnosis was not ET). - Placebo	
Subject analysis set title	Per-protocol Set 1 (PP1) - Placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-protocol Set 1 (PP1) - Placebo	
Subject analysis set title	Per-protocol Set 2 (PP2) - Placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-protocol Set 2 (PP2): An additional PP data set for exploratory purposes (PP2) that in addition to PP1 specifications excluded those subjects who had central laboratory bone marrow biopsy findings that suggested a diagnosis differing from ET. - Placebo	

Primary: Time to first ET-related event assessed by EAC adjudication and platelet criteria

End point title	Time to first ET-related event assessed by EAC adjudication and platelet criteria

End point description:

Following platelet related will be considered as events for the confirmatory analysis of the study:
platelet counts > 1000 G/l as ET-related events together with the following additional specifications:
- One single platelet count above 1000 G/l will suffice to qualify as ET related event.
- Platelet counts > 1000 G/l will be considered irrespectively of the patient's platelet count when entering the study.
- Platelet counts > 1000 G/l will also qualify as ET-related event when having occurred in the titration phase.
Increase of platelet count > 300 G/L within 3 months together with all the following additional specifications
- the highest value following the increase is above the upper limit of normal (400 G/L)
- the increased platelet value should be maintained during the subsequent visit to indicate durability of the increase and not a temporary phenomenon during dose adaptation, where the subsequent visit does not need to be within 3 months where the increase was observed

End point type	Primary

End point timeframe:

overall study

End point values	Intent-to-Treat Set (ITT) - Anagrelide retard	Per-protocol Set 1 (PP1) - Anagrelide Retard	Per-protocol Set 2 (PP2) - Anagrelide retard	Intent-to-Treat Set (ITT) - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77	53	42	69
Units: Ratio				
arithmetic mean (confidence interval 95%)	0.87 (0.74 to 0.94)	0.89 (0.73 to 0.95)	0.85 (0.67 to 0.94)	0.69 (0.16 to 0.79)

End point values	Per-protocol Set 1 (PP1) - Placebo	Per-protocol Set 2 (PP2) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	33		
Units: Ratio				
arithmetic mean (confidence interval 95%)	0.65 (0.45 to 0.78)	0.62 (0.39 to 0.79)		

Statistical analyses

Statistical analysis title	KM model with re-assessed pletelet criteria ITT
Comparison groups	Intent-to-Treat Set (ITT) - Anagrelide retard v Intent-to-Treat Set (ITT) - Placebo

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.79

Statistical analysis title	KM model with re-assessed platelet criteria PP1
Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard v Per-protocol Set 1 (PP1) - Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.71

Statistical analysis title	KM model with re-assessed platelet criteria PP2
Comparison groups	Per-protocol Set 2 (PP2) - Placebo v Per-protocol Set 2 (PP2) - Anagrelide retard
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0029
Method	Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	0.88

Primary: Time to first ET-related event by EAC and platelet criteria (as originally planned)

End point title	Time to first ET-related event by EAC and platelet criteria (as originally planned)
End point description:	
End point type	Primary
End point timeframe: overall study	

End point values	Intent-to-Treat Set (ITT) - Anagrelide retard	Per-protocol Set 1 (PP1) - Anagrelide Retard	Per-protocol Set 2 (PP2) - Anagrelide retard	Intent-to-Treat Set (ITT) - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77	53	42	69
Units: Ratio				
arithmetic mean (confidence interval 95%)	0.79 (0.65 to 0.88)	0.79 (0.62 to 0.89)	0.76 (0.56 to 0.88)	0.66 (0.5 to 0.78)

End point values	Per-protocol Set 1 (PP1) - Placebo	Per-protocol Set 2 (PP2) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	33		
Units: Ratio				
arithmetic mean (confidence interval 95%)	0.62 (0.43 to 0.77)	0.59 (0.36 to 0.76)		

Statistical analyses

Statistical analysis title	Kaplan-Meier model-ITT
Comparison groups	Intent-to-Treat Set (ITT) - Anagrelide retard v Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0124
Method	Fisher exact
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.03

Statistical analysis title	Kaplan-Meier model-PP1
Comparison groups	Per-protocol Set 1 (PP1) - Placebo v Per-protocol Set 1 (PP1) - Anagrelide Retard
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0153
Method	Fisher exact
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	1.07

Statistical analysis title	Kaplan-Meier model-PP2
Comparison groups	Per-protocol Set 2 (PP2) - Placebo v Per-protocol Set 2 (PP2) - Anagrelide retard
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0404
Method	Fisher exact
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	1.24

Secondary: Time to 1st ET-related event assessed by the EAC adjudication	
End point title	Time to 1st ET-related event assessed by the EAC adjudication

End point description:

Information on ET-related events will be taken from the EAC adjudication only, without considering the platelet criteria. The
censoring mechanism will therefore include all patients being EAC adjudicated as having an ET-related event as failures; all other patients will be censored.

End point type	Secondary

End point timeframe:

overall study

End point values	Intent-to-Treat Set (ITT) - Anagrelide retard	Per-protocol Set 1 (PP1) - Anagrelide Retard	Per-protocol Set 2 (PP2) - Anagrelide retard	Intent-to-Treat Set (ITT) - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77	53	42	69
Units: Ratio				
arithmetic mean (confidence interval 95%)	0.88 (0.78 to 0.94)	0.89 (0.76 to 0.95)	0.85 (0.7 to 0.93)	0.82 (0.71 to 0.9)

End point values	Per-protocol Set 1 (PP1) - Placebo	Per-protocol Set 2 (PP2) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	33		
Units: Ratio				
arithmetic mean (confidence interval 95%)	0.78 (0.63 to 0.87)	0.78 (0.59 to 0.89)		

Statistical analyses

Statistical analysis title	Kaplan-Meier model ITT
Comparison groups	Intent-to-Treat Set (ITT) - Anagrelide retard v Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1089
Method	Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.35

Statistical analysis title	Kaplan-Meier model PP1
Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard v Per-protocol Set 1 (PP1) - Placebo

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0585
Method	Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.21

Statistical analysis title	Kaplan-Meier model PP2
Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard v Per-protocol Set 2 (PP2) - Placebo v Per-protocol Set 2 (PP2) - Anagrelide retard
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2179
Method	Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	1.81

Secondary: Time to 1st ET-related event by re-assessed platelet criteria

End point title	Time to 1st ET-related event by re-assessed platelet criteria

End point description:

Time to 1st ET-related event using platelet criteria will be analyzed using the same models as for the primary efficacy parameter. Information on ET-related events will be taken from the two platelet criteria, whichever comes first; whereas neglecting the EAC
adjudication. The censoring mechanism will therefore include all patients as having an ET-related event if one of the platelet criteria has been fulfilled as failures, all other patients will be censored.

End point type	Secondary

End point timeframe:

overall study

End point values	Intent-to-Treat Set (ITT) - Anagrelide retard	Per-protocol Set 1 (PP1) - Anagrelide Retard	Per-protocol Set 2 (PP2) - Anagrelide retard	Intent-to-Treat Set (ITT) - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77	53	42	69
Units: Ratio				
arithmetic mean (confidence interval 95%)	0.98 (0.89 to 1)	1 (1 to 1)	1 (1 to 1)	0.82 (0.7 to 0.9)

End point values	Per-protocol Set 1 (PP1) - Placebo	Per-protocol Set 2 (PP2) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	33		
Units: Ratio				
arithmetic mean (confidence interval 95%)	0.81 (0.66 to 0.9)	0.8 (0.6 to 0.91)		

Statistical analyses

Statistical analysis title	Kaplan-Meier model ITT

Statistical analysis description:

Information on ET-related events will be taken from the two platelet criteria, whichever comes first; whereas neglecting the EAC
adjudication. The censoring mechanism will therefore include all patients as having an ET-related event if one of the platelet criteria has been fulfilled as failures, all other patients will be censored.

Comparison groups	Intent-to-Treat Set (ITT) - Anagrelide retard v Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 2.5
Method	Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.4

Statistical analysis title	Kaplan-Meier model PP1

Statistical analysis description:

Information on ET-related events will be taken from the two platelet criteria, whichever comes first; whereas neglecting the EAC
adjudication. The censoring mechanism will therefore include all patients as having an ET-related event if one of the platelet criteria has been fulfilled as failures, all other patients will be censored.

Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard v Per-protocol Set 1 (PP1) - Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.42

Statistical analysis title	Kaplan-Meier model PP2

Statistical analysis description:

Information on ET-related events will be taken from the two platelet criteria, whichever comes first; whereas neglecting the EAC
adjudication. The censoring mechanism will therefore include all patients as having an ET-related event if one of the platelet criteria has been fulfilled as failures, all other patients will be censored.

Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard v Per-protocol Set 2 (PP2) - Placebo v Per-protocol Set 2 (PP2) - Anagrelide retard
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.44

Secondary: Time to 1st ET-related event by Investigator and re-assessed platelet criteria

End point title	Time to 1st ET-related event by Investigator and re-assessed platelet criteria

End point description:

Time to 1st ET-related event using both investigator adjudication and platelet criteria will be analyzed using the same models as for the primary efficacy parameter. Information on ET-related events will be taken from the CRF entries made by the investigators and the two platelet criteria, whichever comes first. The censoring mechanism will therefore include all patients as having an ET-related event if determined by the investigator as such or if one of the platelet criteria has been fulfilled as failures, all other patients will be censored.

End point type	Secondary

End point timeframe:

overall study

End point values	Intent-to-Treat Set (ITT) - Anagrelide retard	Per-protocol Set 1 (PP1) - Anagrelide Retard	Per-protocol Set 2 (PP2) - Anagrelide retard	Intent-to-Treat Set (ITT) - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77	53	42	69
Units: Ratio				
arithmetic mean (confidence interval 95%)	0.86 (0.75 to 0.92)	0.88 (0.76 to 0.95)	0.85 (0.7 to 0.93)	0.74 (0.61 to 0.83)

End point values	Per-protocol Set 1 (PP1) - Placebo	Per-protocol Set 2 (PP2) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	33		
Units: Ratio				
arithmetic mean (confidence interval 95%)	0.69 (0.53 to 0.81)	0.69 (0.5 to 0.82)		

Statistical analyses

Statistical analysis title	Kaplan-Meier model ITT
Comparison groups	Intent-to-Treat Set (ITT) - Anagrelide retard v Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0044
Method	Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.81

Statistical analysis title	Kaplan-Meier model PP1
Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard v Per-protocol Set 1 (PP1) - Placebo

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009
Method	Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.65

Secondary: Change to baseline of platelet count

End point title	Change to baseline of platelet count

End point description:

The results at regular Visit 2 = Day 0 serve as baseline; if not available, the results of regular Visit 1 = Screening are used.

End point type	Secondary

End point timeframe:

screening to month 12

End point values	Intent-to-Treat Set (ITT) - Anagrelide retard	Per-protocol Set 1 (PP1) - Anagrelide Retard	Per-protocol Set 2 (PP2) - Anagrelide retard	Intent-to-Treat Set (ITT) - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77[1]	53[2]	42[3]	69[4]
Units: G/L				
arithmetic mean (standard deviation)				
Day 7	-218.836 (± 154.9862)	-234.117 (± 136.5971)	-226.814 (± 145.3837)	-6.116 (± 72.3912)
Day 14	-388.965 (± 229.0479)	-421.809 (± 198.5606)	-418.283 (± 212.708)	-25.372 (± 87.8962)
Day 21	-324.161 (± 229.4759)	-345.728 (± 213.9435)	-349.11 (± 220.5995)	-23.362 (± 78.8303)
Day 28	-387.251 (± 205.521)	-407.345 (± 174.4643)	-418.817 (± 160.4846)	-21.219 (± 91.5135)
Month 3	-394.381 (± 198.0757)	741.404 (± 148.5678)	-395.756 (± 163.3204)	-38.254 (± 113.6795)
Month 6	-399.519 (± 196.2274)	-386.506 (± 175.8822)	-386.174 (± 186.9479)	-18.282 (± 103.8526)
Month 9	-393.844 (± 203.91)	-383.657 (± 198.313)	-393.505 (± 211.5138)	-24.388 (± 120.7491)
Month 12	-356.641 (± 229.7164)	-377.404 (± 207.4387)	-394.205 (± 203.8863)	-10.942 (± 129.3443)

Notes:

[1] - n day 7: 76
n day 14: 75
n day 21 and 28: 74
n month 3: 69

n month 6: 63
n month 9 + 12 : 61

[2] - n month 3: 52
n month 6, 9 + 12 : 49

[3] - n month 3: 41
n month 6: 39
n month 9 + 12 : 38

[4] - n day 14: 68
n day 21:66
n day 28:64
n month 3: 63
n month 6: 60
n month 9: 56
n month 12: 52

End point values	Per-protocol Set 1 (PP1) - Placebo	Per-protocol Set 2 (PP2) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47[5]	33[6]		
Units: G/L				
arithmetic mean (standard deviation)				
Day 7	136.5971 (± 77.0207)	-3.545 (± 82.7825)		
Day 14	-32.702 (± 86.1442)	-30.884 (± 92.6846)		
Day 21	-27.15 (± 80.6909)	-35.031 (± 90.279)		
Day 28	-27.489 (± 88.7393)	-12.281 (± 80.6755)		
Month 3	-59.489 (± 106.3604)	-45.156 (± 103.879)		
Month 6	-29.452 (± 109.099)	-16.61 (± 91.453)		
Month 9	-42.334 (± 127.5186)	-29.472 (± 130.4681)		
Month 12	-17.282 (± 139.7283)	-8.926 (± 128.9752)		

Notes:

[5] - n day 14 and 21: 46
n day 28: 45
n month 3: 45
n month 6: 44
n month 9: 41
n month 12: 39

[6] - n day 14, 21, 28: 32
n month 3: 32
n month 6: 31
n month 9: 29
n month 12: 27

Statistical analyses

No statistical analyses for this end point

Secondary: Maintaining of best individual response by best individual response

End point title	Maintaining of best individual response by best individual response

End point description:

Complete response is defined as platelet count < 400 G/L in absence of ET-related events (EAC rated)

during the previous 3 months (90 days)
Partial response is defined as platelet count < 600 G/L OR platelet count reduction of more than 200 G/L from baseline value
No response is defined as any response that does not satisfy complete or partial response
The results at regular Visit 2 = Day 0 serve as baseline; if not available, the results of regular Visit 1 = Screening are used
Maintaining if BIR is defined as presence of BIR at the last documented visit in the study, if BIR was achieved before the last documented visit in the study

End point type	Secondary

End point timeframe:

overall study

End point values	Intent-to-Treat Set (ITT) - Anagrelide retard	Per-protocol Set 1 (PP1) - Anagrelide Retard	Intent-to-Treat Set (ITT) - Placebo	Per-protocol Set 1 (PP1) - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77	53	69	47
Units: Number of Patients				
Complete Response no	24	18	6	2
Complete Response yes	38	30	6	1
Partial Response no	4	2	17	14
Partial Response yes	5	2	6	5
No response no	4	0	2	1
No Response yes	0	0	34	24

Statistical analyses

Statistical analysis title	Descriptive statistics ITT Complete response
Comparison groups	Intent-to-Treat Set (ITT) - Anagrelide retard v Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.066
Method	Fisher exact

Statistical analysis title	Descriptive statistics PP1 Complete response
Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard v Per-protocol Set 1 (PP1) - Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.553
Method	Fisher exact

Statistical analysis title	Descriptive statistics ITT Partial res...
Comparison groups	Intent-to-Treat Set (ITT) - Anagrelide retard v Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.213
Method	Fisher exact

Statistical analysis title	Descriptive statistics PP1 Partial res...
Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard v Per-protocol Set 1 (PP1) - Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.289
Method	Fisher exact

Statistical analysis title	Descriptive statistics ITT No res...
Comparison groups	Intent-to-Treat Set (ITT) - Anagrelide retard v Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Secondary: Number of subjects changing risk status to high risk	
End point title	Number of subjects changing risk status to high risk
End point description:	
Change to high risk status (platelets >= 1.000 G/L, increase of platelets > 300 G/L, or occurrence of any ET-related event) as assessed by the investigator	
End point type	Secondary
End point timeframe:	
overall study	

End point values	Intent-to-Treat Set (ITT) - Anagrelide retard	Per-protocol Set 1 (PP1) - Anagrelide Retard	Per-protocol Set 2 (PP2) - Anagrelide retard	Intent-to-Treat Set (ITT) - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77	53	42	69
Units: Number of subjects				
no	68	47	36	51
yes	9	6	6	8

End point values	Per-protocol Set 1 (PP1) - Placebo	Per-protocol Set 2 (PP2) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	33		
Units: Number of subjects				
no	32	22		
yes	25	11		

Statistical analyses

Statistical analysis title	Change in risk status ITT

Statistical analysis description:

Number of patients changing at least once the risk status to high risk according to the criteria above will be presented with counts and percentages for each treatment group. Rates between treatment groups will be compared using Fisher’s exact test, odds ratios
and the two-sided 95% confidence intervals for odds ratios.

Comparison groups	Intent-to-Treat Set (ITT) - Anagrelide retard v Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	2.6667
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1076
upper limit	6.4205

Statistical analysis title	Change in risk status PP1

Statistical analysis description:

Number of patients changing at least once the risk status to high risk according to the criteria above will be presented with counts and percentages for each treatment group. Rates between treatment groups will be compared using Fisher’s exact test, odds ratios
and the two-sided 95% confidence intervals for odds ratios.

Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard v Per-protocol Set 1 (PP1) - Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	3.6719
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2876
upper limit	10.471

Statistical analysis title	Change in risk status PP2

Statistical analysis description:

Number of patients changing at least once the risk status to high risk according to the criteria above will be presented with counts and percentages for each treatment group. Rates between treatment groups will be compared using Fisher's exact test, odds ratios
and the two-sided 95% confidence intervals for odds ratios.

Comparison groups	Per-protocol Set 2 (PP2) - Anagrelide retard v Per-protocol Set 2 (PP2) - Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9717
upper limit	9.2618

Secondary: JAK2 mutational status by visit

End point title	JAK2 mutational status by visit

End point description:

JAK status according to results from central laboratory

End point type	Secondary

End point timeframe:

Day 0 to months 12

End point values	Intent-to-Treat Set (ITT) - Anagrelide retard	Per-protocol Set 1 (PP1) - Anagrelide Retard	Per-protocol Set 2 (PP2) - Anagrelide retard	Intent-to-Treat Set (ITT) - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77[7]	53[8]	42[9]	69[10]
Units: Number of patients				
Day 0 negative	28	19	14	25
Day 0 positive	47	32	26	44
Month 12/WD negative	27	18	14	21
Month 12/WD positive	43	32	25	40

Notes:

[7] - n = 70 at month 12

[8] - n = 50 at month 12

[9] - n = 39 at month 12

[10] - n = 61 at month 12

End point values	Per-protocol Set 1 (PP1) - Placebo	Per-protocol Set 2 (PP2) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47[11]	33[12]		
Units: Number of patients				
Day 0 negative	20	15		
Day 0 positive	27	18		
Month 12/WD negative	17	14		
Month 12/WD positive	27	18		

Notes:

[11] - n = 44 at month 12

[12] - n = 32 at month12

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life measured by the SF-36v2® questionnaire

End point title	Quality of life measured by the SF-36v2® questionnaire
End point description:	
change to baseline (visit 2, day 0) score 0-100	
End point type	Secondary
End point timeframe:	
Visit 2, day 0 Visit 8, month 6	

End point values	Intent-to-Treat Set (ITT) - Anagrelide retard	Per-protocol Set 1 (PP1) - Anagrelide Retard	Per-protocol Set 2 (PP2) - Anagrelide retard	Intent-to-Treat Set (ITT) - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77	53	42	69
Units: QoL-Score				

arithmetic mean (standard deviation)				
General health	0.65 (± 16.048)	0.04 (± 15.782)	0.73 (± 14.047)	-0.2 (± 13.471)
mental health	3.03 (± 16.132)	4.27 (± 16.535)	3.92 (± 17.084)	0.58 (± 15.128)
physical functioning	15.128 (± 13.731)	1.82 (± 14.491)	0.12 (± 9.832)	0.82 (± 9.698)
Role limitation emotional	4.37 (± 22.184)	6.42 (± 23.835)	6.53 (± 25.62)	0.95 (± 15.729)
Role limitation physical	1.47 (± 20.615)	1.35 (± 21.61)	1.75 (± 20.761)	0.56 (± 17.241)
Social functioning	1.23 (± 16.41)	0.52 (± 16.901)	3.38 (± 17.091)	-0.66 (± 17.266)
Vitality	3.42 (± 18.297)	3.39 (± 19.38)	3.04 (± 19.073)	1.97 (± 17.875)
bodily pain	4.79 (± 21.146)	4.67 (± 22.028)	5.15 (± 19.638)	-1.02 (± 18.925)

End point values	Per-protocol Set 1 (PP1) - Placebo	Per-protocol Set 2 (PP2) - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	33		
Units: QoL-Score				
arithmetic mean (standard deviation)				
General health	0.02 (± 11.063)	-1.25 (± 10.451)		
mental health	2.31 (± 14.09)	0.36 (± 11.049)		
physical functioning	2 (± 7.274)	1.47 (± 6.798)		
Role limitation emotional	2.13 (± 14.998)	-0.14 (± 12.324)		
Role limitation physical	6.16 (± 16.377)	2.46 (± 15.529)		
Social functioning	2.13 (± 15.027)	3.02 (± 12.789)		
Vitality	2.34 (± 16.608)	-0.22 (± 13.659)		
bodily pain	1.05 (± 17.073)	0.69 (± 13.411)		

Statistical analyses

Statistical analysis title	Bodily pain ITT Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Placebo v Intent-to-Treat Set (ITT) - Anagrelide retard

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.115 [13]
Method	Wilcoxon (Mann-Whitney)

Notes:

[13] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Bodily pain ITT Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Placebo v Intent-to-Treat Set (ITT) - Anagrelide retard
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.693 [14]
Method	Wilcoxon (Mann-Whitney)

Notes:

[14] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	General Health ITT Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Anagrelide retard v Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.979 [15]
Method	Wilcoxon (Mann-Whitney)

Notes:

[15] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	General Health ITT Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Anagrelide retard v Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.541 [16]
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Mental Health ITT Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Anagrelide retard v Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.047 [17]
Method	Wilcoxon (Mann-Whitney)

Notes:

[17] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Mental Health ITT Verum Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.656 [18]
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Physical functioning ITT Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.439 [19]
Method	Wilcoxon (Mann-Whitney)

Notes:

[19] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Physical functioning ITT Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Placebo v Intent-to-Treat Set (ITT) -

	Anagrelide retard
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.422 [20]
Method	Wilcoxon (Mann-Whitney)

Notes:

[20] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Limitation Emotional ITT Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Placebo v Intent-to-Treat Set (ITT) - Anagrelide retard
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.072 [21]
Method	Wilcoxon (Mann-Whitney)

Notes:

[21] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Limitation Emotional ITT Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Placebo v Intent-to-Treat Set (ITT) - Anagrelide retard
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7 [22]
Method	Wilcoxon (Mann-Whitney)

Notes:

[22] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Limitation Physical ITT Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Placebo v Intent-to-Treat Set (ITT) - Anagrelide retard

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.71 [23]
Method	Wilcoxon (Mann-Whitney)

Notes:

[23] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Limitation Physical ITT Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Anagrelide retard v Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.374 [24]
Method	Wilcoxon (Mann-Whitney)

Notes:

[24] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Social functioning ITT Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Anagrelide retard v Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.528 [25]
Method	Wilcoxon (Mann-Whitney)

Notes:

[25] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Social functioning ITT Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Placebo v Intent-to-Treat Set (ITT) - Anagrelide retard
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.964 [26]
Method	Wilcoxon (Mann-Whitney)

Notes:

[26] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Vitality ITT Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Placebo v Intent-to-Treat Set (ITT) - Anagrelide retard
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.341 [27]
Method	Wilcoxon (Mann-Whitney)

Notes:

[27] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Vitality ITT Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Intent-to-Treat Set (ITT) - Anagrelide retard v Intent-to-Treat Set (ITT) - Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.097 [28]
Method	Wilcoxon (Mann-Whitney)

Notes:

[28] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Bodily Pain PP1 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard v Per-protocol Set 1 (PP1) - Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.214 [29]
Method	Wilcoxon (Mann-Whitney)

Notes:

[29] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Bodily Pain PP1 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's

manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Placebo v Per-protocol Set 1 (PP1) - Anagrelide Retard
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.734 [30]
Method	Wilcoxon (Mann-Whitney)

Notes:

[30] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	General Health PP1 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard v Per-protocol Set 1 (PP1) - Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.592 [31]
Method	Wilcoxon (Mann-Whitney)

Notes:

[31] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	General Health PP1 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Placebo v Per-protocol Set 1 (PP1) - Anagrelide Retard
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.962 [32]
Method	Wilcoxon (Mann-Whitney)

Notes:

[32] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Mental Health PP1 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Placebo v Per-protocol Set 1 (PP1) - Anagrelide Retard

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.361 [33]
Method	Wilcoxon (Mann-Whitney)

Notes:

[33] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Mental Health PP1 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard v Per-protocol Set 1 (PP1) - Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.016 [34]
Method	Wilcoxon (Mann-Whitney)

Notes:

[34] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Physical functioning PP1 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard v Per-protocol Set 1 (PP1) - Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.415 [35]
Method	Wilcoxon (Mann-Whitney)

Notes:

[35] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Physical functioning PP1 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Placebo v Per-protocol Set 1 (PP1) - Anagrelide Retard
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.098 [36]
Method	Wilcoxon (Mann-Whitney)

Notes:

[36] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Limitation emotional PP1 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Placebo v Per-protocol Set 1 (PP1) - Anagrelide Retard
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.387 [37]
Method	Wilcoxon (Mann-Whitney)

Notes:

[37] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Limitation emotional PP1 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard v Per-protocol Set 1 (PP1) - Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.028 [38]
Method	Wilcoxon (Mann-Whitney)

Notes:

[38] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Limitation physical PP1 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard v Per-protocol Set 1 (PP1) - Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.374 [39]
Method	Wilcoxon (Mann-Whitney)

Notes:

[39] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Limitation physical PP1 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's

manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Placebo v Per-protocol Set 1 (PP1) - Anagrelide Retard
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.019 [40]
Method	Wilcoxon (Mann-Whitney)

Notes:

[40] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Social functioning PP1 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Placebo v Per-protocol Set 1 (PP1) - Anagrelide Retard
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.43 [41]
Method	Wilcoxon (Mann-Whitney)

Notes:

[41] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Social functioning PP1 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.854 [42]
Method	Wilcoxon (Mann-Whitney)

Notes:

[42] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Vitality PP1 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Anagrelide Retard

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.17 [43]
Method	Wilcoxon (Mann-Whitney)

Notes:

[43] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Vitality PP1 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 1 (PP1) - Placebo v Per-protocol Set 1 (PP1) - Anagrelide Retard
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.626 [44]
Method	Wilcoxon (Mann-Whitney)

Notes:

[44] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Bodily Pain PP2 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Placebo v Per-protocol Set 2 (PP2) - Anagrelide retard
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.719 [45]
Method	Wilcoxon (Mann-Whitney)

Notes:

[45] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	General Health PP2 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Placebo v Per-protocol Set 2 (PP2) - Anagrelide retard
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.543 [46]
Method	Wilcoxon (Mann-Whitney)

Notes:

[46] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	General Health PP2 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Anagrelide retard v Per-protocol Set 2 (PP2) - Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.52 [47]
Method	Wilcoxon (Mann-Whitney)

Notes:

[47] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Mental Health PP2 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Anagrelide retard v Per-protocol Set 2 (PP2) - Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.036 [48]
Method	Wilcoxon (Mann-Whitney)

Notes:

[48] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Mental Health PP2 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Placebo v Per-protocol Set 2 (PP2) - Anagrelide retard
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.959 [49]
Method	Wilcoxon (Mann-Whitney)

Notes:

[49] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Physical functioning PP2 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's

manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Placebo v Per-protocol Set 2 (PP2) - Anagrelide retard
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.345 [50]
Method	Wilcoxon (Mann-Whitney)

Notes:

[50] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Physical functioning PP2 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Anagrelide retard v Per-protocol Set 2 (PP2) - Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.962 [51]
Method	Wilcoxon (Mann-Whitney)

Notes:

[51] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Limitation emotional PP2 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Anagrelide retard v Per-protocol Set 2 (PP2) - Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.093 [52]
Method	Wilcoxon (Mann-Whitney)

Notes:

[52] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Limitation emotional PP2 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Placebo v Per-protocol Set 2 (PP2) - Anagrelide retard

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.807 [53]
Method	Wilcoxon (Mann-Whitney)

Notes:

[53] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Limitation physical PP2 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Placebo v Per-protocol Set 2 (PP2) - Anagrelide retard
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.193 [54]
Method	Wilcoxon (Mann-Whitney)

Notes:

[54] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Limitation physical PP2 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Anagrelide retard v Per-protocol Set 2 (PP2) - Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.323 [55]
Method	Wilcoxon (Mann-Whitney)

Notes:

[55] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Social functioning PP2 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Anagrelide retard v Per-protocol Set 2 (PP2) - Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.228 [56]
Method	Wilcoxon (Mann-Whitney)

Notes:

[56] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Social functioning PP2 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Placebo v Per-protocol Set 2 (PP2) - Anagrelide retard
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.253 [57]
Method	Wilcoxon (Mann-Whitney)

Notes:

[57] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Vitality PP2 Placebo

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Placebo v Per-protocol Set 2 (PP2) - Anagrelide retard
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.554 [58]
Method	Wilcoxon (Mann-Whitney)

Notes:

[58] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Vitality PP2 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Anagrelide retard v Per-protocol Set 2 (PP2) - Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.222 [59]
Method	Wilcoxon (Mann-Whitney)

Notes:

[59] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Statistical analysis title	Bodily Pain PP2 Verum

Statistical analysis description:

The SF-36v2® health questionnaire will be analysed following the instructions as described in Ware, J. E., Jr., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2007). User's

manual for the SF-36v2® Health Survey (2nd ed.). Lincoln, RI: QualityMetric Incorporated.

Comparison groups	Per-protocol Set 2 (PP2) - Anagrelide retard v Per-protocol Set 2 (PP2) - Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.248 [60]
Method	Wilcoxon (Mann-Whitney)

Notes:

[60] - p-value of paired Wilcoxon signed rank test for paired differences (two-sided)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: main and safety extension	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17

Reporting groups	
Reporting group title	Anagrelide retard
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Anagrelide retard	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 77 (11.69%)	4 / 69 (5.80%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Clear cell renal cell carcinoma			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma	Additional description: Lung adenocarcinoma		
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Burns second degree			

subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Appendicectomy			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Prostatic operation			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Volvulus			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (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			
Appendicitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
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	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 77 (88.31%)	48 / 69 (69.57%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Uterine leiomyoma			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Pallor			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Vascular pain			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Vasodilatation			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	2 / 77 (2.60%)	0 / 69 (0.00%)	
occurrences (all)	2	0	
Flushing			
subjects affected / exposed	2 / 77 (2.60%)	0 / 69 (0.00%)	
occurrences (all)	2	0	
Erythromelalgia			
subjects affected / exposed	0 / 77 (0.00%)	2 / 69 (2.90%)	
occurrences (all)	0	3	
Peripheral vascular disorder			
subjects affected / exposed	1 / 77 (1.30%)	2 / 69 (2.90%)	
occurrences (all)	1	5	
Haematoma			
subjects affected / exposed	2 / 77 (2.60%)	2 / 69 (2.90%)	
occurrences (all)	2	3	
Surgical and medical procedures			
Hypertension			
subjects affected / exposed	8 / 77 (10.39%)	6 / 69 (8.70%)	
occurrences (all)	11	6	
Prostatic operation			

subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Eyelid operation			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Knee arthroplasty			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Tooth extraction			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 77 (6.49%)	4 / 69 (5.80%)	
occurrences (all)	6	7	
Asthenia			
subjects affected / exposed	6 / 77 (7.79%)	2 / 69 (2.90%)	
occurrences (all)	9	3	
Chest pain			
subjects affected / exposed	4 / 77 (5.19%)	2 / 69 (2.90%)	
occurrences (all)	4	2	
Oedema peripheral			
subjects affected / exposed	2 / 77 (2.60%)	2 / 69 (2.90%)	
occurrences (all)	3	2	
Influenza like illness			
subjects affected / exposed	1 / 77 (1.30%)	2 / 69 (2.90%)	
occurrences (all)	1	2	
Pyrexia			
subjects affected / exposed	3 / 77 (3.90%)	0 / 69 (0.00%)	
occurrences (all)	3	0	
Chills			
subjects affected / exposed	1 / 77 (1.30%)	1 / 69 (1.45%)	
occurrences (all)	1	2	
Oedema			

subjects affected / exposed	2 / 77 (2.60%)	0 / 69 (0.00%)	
occurrences (all)	3	0	
Exercise tolerance decreased			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Feeling hot			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	2 / 77 (2.60%)	0 / 69 (0.00%)	
occurrences (all)	3	0	
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Menopausal symptoms			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Menorrhagia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Sexual dysfunction			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	3 / 77 (3.90%)	0 / 69 (0.00%)	
occurrences (all)	5	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 77 (1.30%)	1 / 69 (1.45%)	
occurrences (all)	1	1	
Dyspnoea			
subjects affected / exposed	2 / 77 (2.60%)	0 / 69 (0.00%)	
occurrences (all)	2	0	
Dyspnoea exertional			
subjects affected / exposed	1 / 77 (1.30%)	1 / 69 (1.45%)	
occurrences (all)	1	1	
Dysphonia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Nasal oedema			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Pleurisy			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Apathy			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			

subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	2	0	
Investigations			
Platelet count increased			
subjects affected / exposed	1 / 77 (1.30%)	6 / 69 (8.70%)	
occurrences (all)	1	6	
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	4 / 77 (5.19%)	0 / 69 (0.00%)	
occurrences (all)	4	0	
Platelet count decreased			
subjects affected / exposed	4 / 77 (5.19%)	0 / 69 (0.00%)	
occurrences (all)	5	0	
Ejection fraction decreased			
subjects affected / exposed	1 / 77 (1.30%)	1 / 69 (1.45%)	
occurrences (all)	1	2	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Breath sounds			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Carotid pulse increased			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	2	0	
Electrocardiogram PQ interval shortened			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Haematocrit increased			

subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Haemoglobin decreased			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 77 (2.60%)	2 / 69 (2.90%)	
occurrences (all)	2	2	
Injury			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	23 / 77 (29.87%)	9 / 69 (13.04%)	
occurrences (all)	39	15	
Acute myocardial infarction			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Arrhythmia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Extrasystoles			

subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	36 / 77 (46.75%)	21 / 69 (30.43%)	
occurrences (all)	82	66	
Dizziness			
subjects affected / exposed	6 / 77 (7.79%)	4 / 69 (5.80%)	
occurrences (all)	8	7	
Hypoaesthesia			
subjects affected / exposed	5 / 77 (6.49%)	2 / 69 (2.90%)	
occurrences (all)	14	2	
Paraesthesia			
subjects affected / exposed	1 / 77 (1.30%)	3 / 69 (4.35%)	
occurrences (all)	1	5	
Somnolence			
subjects affected / exposed	3 / 77 (3.90%)	1 / 69 (1.45%)	
occurrences (all)	4	2	
Transient ischaemic attack			
subjects affected / exposed	1 / 77 (1.30%)	2 / 69 (2.90%)	
occurrences (all)	1	2	
Migraine			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Head discomfort			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Dystonia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Encephalopathy			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Neuritis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	

Peripheral sensory neuropathy			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
VIIIth nerve paralysis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 77 (6.49%)	2 / 69 (2.90%)	
occurrences (all)	7	3	
Thrombocytopenia			
subjects affected / exposed	7 / 77 (9.09%)	0 / 69 (0.00%)	
occurrences (all)	12	0	
Thrombocytosis			
subjects affected / exposed	1 / 77 (1.30%)	4 / 69 (5.80%)	
occurrences (all)	1	4	
Iron deficiency anaemia			
subjects affected / exposed	2 / 77 (2.60%)	0 / 69 (0.00%)	
occurrences (all)	3	0	
Anaemia folate deficiency			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Polycythaemia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Splenomegaly			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	7 / 77 (9.09%)	3 / 69 (4.35%)	
occurrences (all)	7	3	
Tinnitus			
subjects affected / exposed	1 / 77 (1.30%)	1 / 69 (1.45%)	
occurrences (all)	1	1	
Eye disorders			
Visual impairment			
subjects affected / exposed	2 / 77 (2.60%)	2 / 69 (2.90%)	
occurrences (all)	2	2	
Conjunctivitis allergic			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Eye oedema			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Scintillating scotoma			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 77 (9.09%)	5 / 69 (7.25%)	
occurrences (all)	8	10	
Abdominal pain upper			
subjects affected / exposed	7 / 77 (9.09%)	2 / 69 (2.90%)	
occurrences (all)	13	8	
Diarrhoea			
subjects affected / exposed	6 / 77 (7.79%)	2 / 69 (2.90%)	
occurrences (all)	7	5	
Vomiting			
subjects affected / exposed	5 / 77 (6.49%)	1 / 69 (1.45%)	
occurrences (all)	6	4	
Abdominal pain			

subjects affected / exposed	3 / 77 (3.90%)	2 / 69 (2.90%)	
occurrences (all)	15	2	
Gastrointestinal disorder			
subjects affected / exposed	3 / 77 (3.90%)	0 / 69 (0.00%)	
occurrences (all)	6	0	
Abdominal distension			
subjects affected / exposed	2 / 77 (2.60%)	0 / 69 (0.00%)	
occurrences (all)	2	0	
Dyspepsia			
subjects affected / exposed	1 / 77 (1.30%)	1 / 69 (1.45%)	
occurrences (all)	1	1	
Abdominal discomfort			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Epigastric discomfort			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Gastric ulcer			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Gingival bleeding			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	

Hepatocellular injury			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Hepatomegaly			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 77 (5.19%)	1 / 69 (1.45%)	
occurrences (all)	5	1	
Night sweats			
subjects affected / exposed	1 / 77 (1.30%)	3 / 69 (4.35%)	
occurrences (all)	1	3	
Hyperhidrosis			
subjects affected / exposed	2 / 77 (2.60%)	1 / 69 (1.45%)	
occurrences (all)	3	1	
Alopecia			
subjects affected / exposed	1 / 77 (1.30%)	1 / 69 (1.45%)	
occurrences (all)	1	1	
Dermatitis allergic			
subjects affected / exposed	1 / 77 (1.30%)	1 / 69 (1.45%)	
occurrences (all)	1	2	
Erythema			
subjects affected / exposed	1 / 77 (1.30%)	1 / 69 (1.45%)	
occurrences (all)	2	1	
Skin depigmentation			
subjects affected / exposed	2 / 77 (2.60%)	0 / 69 (0.00%)	
occurrences (all)	2	0	
Dermatitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Telangiectasia			

subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Nephrolithiasis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Urinary bladder haemorrhage			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	3 / 77 (3.90%)	4 / 69 (5.80%)	
occurrences (all)	8	4	
Myalgia			
subjects affected / exposed	4 / 77 (5.19%)	1 / 69 (1.45%)	
occurrences (all)	6	4	
Arthralgia			
subjects affected / exposed	1 / 77 (1.30%)	3 / 69 (4.35%)	
occurrences (all)	1	20	
Back pain			
subjects affected / exposed	3 / 77 (3.90%)	1 / 69 (1.45%)	
occurrences (all)	6	1	
Joint swelling			
subjects affected / exposed	1 / 77 (1.30%)	1 / 69 (1.45%)	
occurrences (all)	1	2	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 77 (1.30%)	1 / 69 (1.45%)	
occurrences (all)	2	4	
Bone pain			

subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Costochondritis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	2	0	
Pain in jaw			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	3	
Plantar fasciitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 77 (5.19%)	5 / 69 (7.25%)	
occurrences (all)	4	10	
Urinary tract infection			
subjects affected / exposed	1 / 77 (1.30%)	3 / 69 (4.35%)	
occurrences (all)	3	4	
Bronchitis			
subjects affected / exposed	2 / 77 (2.60%)	1 / 69 (1.45%)	
occurrences (all)	2	1	
Pharyngitis			
subjects affected / exposed	2 / 77 (2.60%)	1 / 69 (1.45%)	
occurrences (all)	3	1	
Tracheitis			
subjects affected / exposed	1 / 77 (1.30%)	2 / 69 (2.90%)	
occurrences (all)	1	2	
Upper respiratory tract infection			
subjects affected / exposed	1 / 77 (1.30%)	2 / 69 (2.90%)	
occurrences (all)	2	2	
Cystitis			
subjects affected / exposed	1 / 77 (1.30%)	1 / 69 (1.45%)	
occurrences (all)	5	1	

Rhinitis			
subjects affected / exposed	1 / 77 (1.30%)	1 / 69 (1.45%)	
occurrences (all)	2	1	
Acute tonsillitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Gingivitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Onychomycosis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Pulpitis dental			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Scarlet fever			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Subcutaneous abscess			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	

Muscle strain			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	2 / 77 (2.60%)	1 / 69 (1.45%)	
occurrences (all)	2	1	
Hypokalaemia			
subjects affected / exposed	2 / 77 (2.60%)	1 / 69 (1.45%)	
occurrences (all)	3	2	
Hypophosphataemia			
subjects affected / exposed	1 / 77 (1.30%)	2 / 69 (2.90%)	
occurrences (all)	1	4	
Hypercholesterolaemia			
subjects affected / exposed	1 / 77 (1.30%)	1 / 69 (1.45%)	
occurrences (all)	1	1	
Hyperkalaemia			
subjects affected / exposed	2 / 77 (2.60%)	0 / 69 (0.00%)	
occurrences (all)	2	0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 77 (1.30%)	1 / 69 (1.45%)	
occurrences (all)	1	1	
Hyperglycaemia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Hyperuricosuria			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Hypocalcaemia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 69 (1.45%)	
occurrences (all)	0	1	
Hypoproteinaemia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 69 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency			

subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 69 (1.45%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 August 2010	-Investigator was not blinded since a platelet reduction by Anagrelide retard could have a potential unblinding effect. The Sponsor was blinded. -Stratified randomization of the subjects according to their JAK2 mutational status. Hypothesis: JAK2 mutation positivity may be an independent risk factor for thrombosis in myeloproliferative. - EAC was established. The treatment allocation status was blinded for the subject, but open for the primary site investigators. - DMC had to review the unblinded cumulating data, advises the sponsor regarding safety of current and future participants. DMC responsible for monitoring safety data, reviewing AEs. The DMC was responsible for the interim safety review and the study conduct. - Risk factors at inclusion criteria were modified: "essential hypertension" replaced the hypertension definition of WHO grades and hormone replacement therapy and hormonal contraception were added. - The exclusion criterion "diabetes mellitus" was modified to "poorly controlled" diabetes mellitus - Definition of the primary endpoint relevant ET-related event was modified. A clinically significant ET-related event was defined as a disease-related event which implied a change of the subject risk status to the high risk group. - Blinded AEs/ SAEs management, including blinded SUSARs reporting was added. -subjects to be treated for a maximum of 3 years as long as they do not experience their 1st clinically significant ET-related event. - Laboratory tests were split into local and central. - Use of version of the Declaration of Helsinki of October 1996. - The causality assessment for drug-event relationship was changed to "Yes, related/ No, unrelated" judgment. - References added: ARETA Study Working Guideline for idv staff, ARETA Study Working Guideline for Harrison, DMC and EAC Charter. - Measurement of prothrombin time and NT-proBNP.
11 March 2014	1) Introduction of the analysis based on the CALR and MPL mutational status as potentially relevant to predict disease prognosis and treatment outcomes. 2) Inclusion of progressive thrombocytosis as a risk changing event into the ET-related event definitions as the primary endpoint (i.e. platelet criterion) 3) Intensification of the ECG monitoring schedule in the study (additional ECGs scheduled at months 1, 3, 6 and 9. 4) Magnesium was included into the list of biochemical parameters to be measured at regular intervals. 5) Early withdrawal visits were preponed for all active subjects in case of study completion after stage I analysis at the earliest date possible. 6) Specification on post study care (after study completion) for subjects, who received active drug during the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported