



## 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 during Final 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:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 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 <sup>[1]</sup>              |
| 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                   |
| <b>Arm title</b>                       | 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.

|                    |         |
|--------------------|---------|
| <b>Arm title</b>   | 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.

| <b>Number of subjects in period 1</b>             | Anagrelide retard | Placebo |
|---------------------------------------------------|-------------------|---------|
| Started                                           | 77                | 69      |
| Completed                                         | 60                | 52      |
| Not completed                                     | 17                | 17      |
| Adverse event, serious fatal                      | 1                 | 1       |
| sponsor decision                                  | -                 | 1       |
| Consent withdrawn by subject                      | 1                 | 4       |
| Lack of efficacy: AE that constitutes ET-related  | 4                 | 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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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 | ±       |

| <b>Reporting group values</b>                      | 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 |

| <b>Reporting group values</b>                         | Per-protocol Set 1<br>(PP1) - Placebo | Per-protocol Set 2<br>(PP2) - Placebo |  |
|-------------------------------------------------------|---------------------------------------|---------------------------------------|--|
| Number of subjects                                    | 47                                    | 33                                    |  |
| Age categorical                                       |                                       |                                       |  |
| Units: Subjects                                       |                                       |                                       |  |
| In utero                                              | 0                                     | 0                                     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                                     | 0                                     |  |
| Newborns (0-27 days)                                  | 0                                     | 0                                     |  |
| Infants and toddlers (28 days-23<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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 platelet 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              |

|                                         |                                                                                   |
|-----------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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                                                                              |

|                                         |                                                                                   |
|-----------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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                                                                                |

|                                         |                                                                                   |
|-----------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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                                                                              |

|                                         |                                                                                   |
|-----------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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                                                                                                                                                                                                                                                                               |                                                               |

| <b>End point values</b>                   | 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)                  |

| <b>End point values</b>                   | 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

| <b>Statistical analysis title</b>       | 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                                                                                |

| <b>Statistical analysis title</b> | 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              |

|                                         |                                                                                                                                  |
|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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                                                                              |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | 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

| <b>End point values</b>                   | 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)                 |

| <b>End point values</b>                   | 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

| <b>Statistical analysis title</b>       | 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                                                                                |

| <b>Statistical analysis title</b> | 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 <sup>[1]</sup>                             | 53 <sup>[2]</sup>                            | 42 <sup>[3]</sup>                            | 69 <sup>[4]</sup>                   |
| 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<br>Set 1 (PP1) -<br>Placebo | Per-protocol<br>Set 2 (PP2) -<br>Placebo |  |  |
|--------------------------------------|------------------------------------------|------------------------------------------|--|--|
| Subject group type                   | Subject analysis set                     | Subject analysis set                     |  |  |
| Number of subjects analysed          | 47 <sup>[5]</sup>                        | 33 <sup>[6]</sup>                        |  |  |
| Units: G/L                           |                                          |                                          |  |  |
| arithmetic mean (standard deviation) |                                          |                                          |  |  |
| Day 7                                | 136.5971 (±<br>77.0207)                  | -3.545 (±<br>82.7825)                    |  |  |
| Day 14                               | -32.702 (±<br>86.1442)                   | -30.884 (±<br>92.6846)                   |  |  |
| Day 21                               | -27.15 (±<br>80.6909)                    | -35.031 (±<br>90.279)                    |  |  |
| Day 28                               | -27.489 (±<br>88.7393)                   | -12.281 (±<br>80.6755)                   |  |  |
| Month 3                              | -59.489 (±<br>106.3604)                  | -45.156 (±<br>103.879)                   |  |  |
| Month 6                              | -29.452 (±<br>109.099)                   | -16.61 (±<br>91.453)                     |  |  |
| Month 9                              | -42.334 (±<br>127.5186)                  | -29.472 (±<br>130.4681)                  |  |  |
| Month 12                             | -17.282 (±<br>139.7283)                  | -8.926 (±<br>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

|                                         |                                                                                     |
|-----------------------------------------|-------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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                                                                        |

|                                         |                                                                                   |
|-----------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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                                                                      |

|                                         |                                                                                     |
|-----------------------------------------|-------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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                                                                        |

|                                         |                                                                                   |
|-----------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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                                                                      |

|                                         |                                                                                     |
|-----------------------------------------|-------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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                                                                        |

|                                                                                                                                                                                           |                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| <b>Secondary: Number of subjects changing risk status to high risk</b>                                                                                                                    |                                                      |
| End point title                                                                                                                                                                           | Number of subjects changing risk status to high risk |
| End point description:<br>Change to high risk status (platelets $\geq$ 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:<br>overall study                                                                                                                                                     |                                                      |

| <b>End point values</b>     | 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                                   |

| <b>End point values</b>     | 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

| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                 | 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                                                                              |

| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                 | 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                                                                            |

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[7]</sup>                             | 53 <sup>[8]</sup>                            | 42 <sup>[9]</sup>                            | 69 <sup>[10]</sup>                  |
| 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 <sup>[11]</sup>                 | 33 <sup>[12]</sup>                 |  |  |
| 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 month 12

## 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:<br>change to baseline (visit 2, day 0)<br>score 0-100 |                                                        |
| End point type                                                               | Secondary                                              |
| End point timeframe:<br>Visit 2, day 0<br>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 <sup>[13]</sup> |
| Method                                  | Wilcoxon (Mann-Whitney) |

Notes:

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

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[14]</sup>                                                             |
| Method                                  | Wilcoxon (Mann-Whitney)                                                             |

Notes:

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

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[15]</sup>                                                             |
| Method                                  | Wilcoxon (Mann-Whitney)                                                             |

Notes:

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

|                                   |                          |
|-----------------------------------|--------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[16]</sup>                                                             |
| Method                                  | Wilcoxon (Mann-Whitney)                                                             |

Notes:

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

|                                                                                                                                                                                                                                                                                                                                                |                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Mental Health ITT Verum                                                             |
| Statistical analysis description:<br>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 <sup>[17]</sup>                                                             |
| Method                                                                                                                                                                                                                                                                                                                                         | Wilcoxon (Mann-Whitney)                                                             |

Notes:

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

|                                                                                                                                                                                                                                                                                                                                                |                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Mental Health ITT Verum Placebo     |
| Statistical analysis description:<br>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 <sup>[18]</sup>             |
| Method                                                                                                                                                                                                                                                                                                                                         | Wilcoxon (Mann-Whitney)             |

Notes:

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

|                                                                                                                                                                                                                                                                                                                                                |                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Physical functioning ITT Placebo    |
| Statistical analysis description:<br>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 <sup>[19]</sup>             |
| Method                                                                                                                                                                                                                                                                                                                                         | Wilcoxon (Mann-Whitney)             |

Notes:

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

|                                                                                                                                                                                                                                                                                                                                                |                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Physical functioning ITT Verum                                    |
| Statistical analysis description:<br>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 <sup>[20]</sup> |
| Method                                  | Wilcoxon (Mann-Whitney) |

Notes:

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

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[21]</sup>                                                             |
| Method                                  | Wilcoxon (Mann-Whitney)                                                             |

Notes:

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

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[22]</sup>                                                               |
| Method                                  | Wilcoxon (Mann-Whitney)                                                             |

Notes:

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

|                                   |                                 |
|-----------------------------------|---------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[23]</sup>  |
| Method                                  | Wilcoxon (Mann-Whitney) |

Notes:

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

|                                   |                               |
|-----------------------------------|-------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[24]</sup>                                                             |
| Method                                  | Wilcoxon (Mann-Whitney)                                                             |

Notes:

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

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[25]</sup>                                                             |
| Method                                  | Wilcoxon (Mann-Whitney)                                                             |

Notes:

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

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[26]</sup>                                                             |
| Method                                  | Wilcoxon (Mann-Whitney)                                                             |

Notes:

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

|                                                                                                                                                                                                                                                                                                                                                |                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Vitality ITT Placebo                                                                |
| Statistical analysis description:<br>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)

|                                                                                                                                                                                                                                                                                                                                                |                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Vitality ITT Verum                                                                  |
| Statistical analysis description:<br>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)

|                                                                                                                                                                                                                                                                                                                                                |                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Bodily Pain PP1 Verum                                                             |
| Statistical analysis description:<br>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)

|                                                                                                                                                                                                                                                      |                         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                    | Bodily Pain PP1 Placebo |
| Statistical analysis description:<br>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 |                         |

|                                         |                                                                                   |
|-----------------------------------------|-----------------------------------------------------------------------------------|
| 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 <sup>[30]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                   |                          |
|-----------------------------------|--------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[31]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[32]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[33]</sup> |
| Method                                  | Wilcoxon (Mann-Whitney) |

Notes:

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

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[34]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[35]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[36]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                                                                                                                                                                                                                                                                                                                                |                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Limitation emotional PP1 Placebo                                                  |
| Statistical analysis description:<br>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 <sup>[37]</sup>                                                           |
| Method                                                                                                                                                                                                                                                                                                                                         | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                                                                                                                                                                                                                                                                                                                                |                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Limitation emotional PP1 Verum                                                    |
| Statistical analysis description:<br>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 <sup>[38]</sup>                                                           |
| Method                                                                                                                                                                                                                                                                                                                                         | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                                                                                                                                                                                                                                                                                                                                |                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Limitation physical PP1 Verum                                                     |
| Statistical analysis description:<br>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 <sup>[39]</sup>                                                           |
| Method                                                                                                                                                                                                                                                                                                                                         | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                                                                                                                                                                                                                                      |                                 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                    | Limitation physical PP1 Placebo |
| Statistical analysis description:<br>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 |                                 |

|                                         |                                                                                   |
|-----------------------------------------|-----------------------------------------------------------------------------------|
| 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 <sup>[40]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[41]</sup>                                                            |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[42]</sup>                      |
| Method                                  | Wilcoxon (Mann-Whitney)                      |

Notes:

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

|                                   |                    |
|-----------------------------------|--------------------|
| <b>Statistical analysis title</b> | 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 <sup>[43]</sup>  |
| Method                                  | Wilcoxon (Mann-Whitney) |

Notes:

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

|                                   |                      |
|-----------------------------------|----------------------|
| <b>Statistical analysis title</b> | 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 <sup>[44]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[45]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[46]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                                                                                                                                                                                                                                                                                                                                |                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | General Health PP2 Verum                                                          |
| Statistical analysis description:<br>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 <sup>[47]</sup>                                                            |
| Method                                                                                                                                                                                                                                                                                                                                         | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                                                                                                                                                                                                                                                                                                                                |                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Mental Health PP2 Verum                                                           |
| Statistical analysis description:<br>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 <sup>[48]</sup>                                                           |
| Method                                                                                                                                                                                                                                                                                                                                         | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                                                                                                                                                                                                                                                                                                                                |                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Mental Health PP2 Placebo                                                         |
| Statistical analysis description:<br>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 <sup>[49]</sup>                                                           |
| Method                                                                                                                                                                                                                                                                                                                                         | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                                                                                                                                                                                                                                      |                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                    | Physical functioning PP2 Placebo |
| Statistical analysis description:<br>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 |                                  |

|                                         |                                                                                   |
|-----------------------------------------|-----------------------------------------------------------------------------------|
| 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 <sup>[50]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[51]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[52]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[53]</sup> |
| Method                                  | Wilcoxon (Mann-Whitney) |

Notes:

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

|                                   |                                 |
|-----------------------------------|---------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[54]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                   |                               |
|-----------------------------------|-------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[55]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[56]</sup>                                                           |
| Method                                  | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                                                                                                                                                                                                                                                                                                                                |                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Social functioning PP2 Placebo                                                    |
| Statistical analysis description:<br>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 <sup>[57]</sup>                                                           |
| Method                                                                                                                                                                                                                                                                                                                                         | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                                                                                                                                                                                                                                                                                                                                |                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Vitality PP2 Placebo                                                              |
| Statistical analysis description:<br>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 <sup>[58]</sup>                                                           |
| Method                                                                                                                                                                                                                                                                                                                                         | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                                                                                                                                                                                                                                                                                                                                |                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Vitality PP2 Verum                                                                |
| Statistical analysis description:<br>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 <sup>[59]</sup>                                                           |
| Method                                                                                                                                                                                                                                                                                                                                         | Wilcoxon (Mann-Whitney)                                                           |

Notes:

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

|                                                                                                                                                                                                                                                      |                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                    | Bodily Pain PP2 Verum |
| Statistical analysis description:<br>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 |                       |

|                                         |                                                                                   |
|-----------------------------------------|-----------------------------------------------------------------------------------|
| 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 <sup>[60]</sup>                                                           |
| 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<br>subjects affected / exposed<br>occurrences (all)            | 1 / 77 (1.30%)<br>1   | 0 / 69 (0.00%)<br>0 |  |
| Vascular disorders                                                               |                       |                     |  |
| Hot flush<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 77 (1.30%)<br>1   | 0 / 69 (0.00%)<br>0 |  |
| Pallor<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 77 (1.30%)<br>1   | 0 / 69 (0.00%)<br>0 |  |
| Vascular pain<br>subjects affected / exposed<br>occurrences (all)                | 0 / 77 (0.00%)<br>0   | 1 / 69 (1.45%)<br>1 |  |
| Vasodilatation<br>subjects affected / exposed<br>occurrences (all)               | 1 / 77 (1.30%)<br>1   | 0 / 69 (0.00%)<br>0 |  |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 77 (2.60%)<br>2   | 0 / 69 (0.00%)<br>0 |  |
| Flushing<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 77 (2.60%)<br>2   | 0 / 69 (0.00%)<br>0 |  |
| Erythromelalgia<br>subjects affected / exposed<br>occurrences (all)              | 0 / 77 (0.00%)<br>0   | 2 / 69 (2.90%)<br>3 |  |
| Peripheral vascular disorder<br>subjects affected / exposed<br>occurrences (all) | 1 / 77 (1.30%)<br>1   | 2 / 69 (2.90%)<br>5 |  |
| Haematoma<br>subjects affected / exposed<br>occurrences (all)                    | 2 / 77 (2.60%)<br>2   | 2 / 69 (2.90%)<br>3 |  |
| Surgical and medical procedures                                                  |                       |                     |  |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                 | 8 / 77 (10.39%)<br>11 | 6 / 69 (8.70%)<br>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<br>occurrences (all)             | 1 / 77 (1.30%)<br>2 | 0 / 69 (0.00%)<br>0 |  |
| Investigations                                               |                     |                     |  |
| Platelet count increased                                     |                     |                     |  |
| subjects affected / exposed                                  | 1 / 77 (1.30%)      | 6 / 69 (8.70%)      |  |
| occurrences (all)                                            | 1                   | 6                   |  |
| N-terminal prohormone brain<br>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<br>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<br>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<br>occurrences (all)                                         | 0 / 77 (0.00%)<br>0    | 1 / 69 (1.45%)<br>1   |  |
| Haemoglobin decreased<br>subjects affected / exposed<br>occurrences (all)                | 1 / 77 (1.30%)<br>1    | 0 / 69 (0.00%)<br>0   |  |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)             | 1 / 77 (1.30%)<br>1    | 0 / 69 (0.00%)<br>0   |  |
| Injury, poisoning and procedural complications                                           |                        |                       |  |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                            | 2 / 77 (2.60%)<br>2    | 2 / 69 (2.90%)<br>2   |  |
| Injury<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 77 (0.00%)<br>0    | 1 / 69 (1.45%)<br>1   |  |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 77 (0.00%)<br>0    | 1 / 69 (1.45%)<br>1   |  |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 77 (1.30%)<br>1    | 0 / 69 (0.00%)<br>0   |  |
| Cardiac disorders                                                                        |                        |                       |  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                         | 23 / 77 (29.87%)<br>39 | 9 / 69 (13.04%)<br>15 |  |
| Acute myocardial infarction<br>subjects affected / exposed<br>occurrences (all)          | 1 / 77 (1.30%)<br>1    | 0 / 69 (0.00%)<br>0   |  |
| Arrhythmia<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 77 (1.30%)<br>1    | 0 / 69 (0.00%)<br>0   |  |
| Atrioventricular block second degree<br>subjects affected / exposed<br>occurrences (all) | 0 / 77 (0.00%)<br>0    | 1 / 69 (1.45%)<br>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<br>subjects affected / exposed<br>occurrences (all)             | 0 / 77 (0.00%)<br>0  | 1 / 69 (1.45%)<br>1 |  |
| Syncope<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 77 (0.00%)<br>0  | 1 / 69 (1.45%)<br>1 |  |
| VIIIth nerve paralysis<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 77 (0.00%)<br>0  | 1 / 69 (1.45%)<br>1 |  |
| Blood and lymphatic system disorders                                                          |                      |                     |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                                   | 5 / 77 (6.49%)<br>7  | 2 / 69 (2.90%)<br>3 |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                          | 7 / 77 (9.09%)<br>12 | 0 / 69 (0.00%)<br>0 |  |
| Thrombocytosis<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 77 (1.30%)<br>1  | 4 / 69 (5.80%)<br>4 |  |
| Iron deficiency anaemia<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 77 (2.60%)<br>3  | 0 / 69 (0.00%)<br>0 |  |
| Anaemia folate deficiency<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 77 (1.30%)<br>1  | 0 / 69 (0.00%)<br>0 |  |
| Disseminated intravascular<br>coagulation<br>subjects affected / exposed<br>occurrences (all) | 0 / 77 (0.00%)<br>0  | 1 / 69 (1.45%)<br>1 |  |
| Polycythaemia<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 77 (1.30%)<br>1  | 0 / 69 (0.00%)<br>0 |  |
| Splenomegaly<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 77 (1.30%)<br>1  | 0 / 69 (0.00%)<br>0 |  |
| Ear and labyrinth disorders                                                                   |                      |                     |  |

|                                                                             |                      |                      |  |
|-----------------------------------------------------------------------------|----------------------|----------------------|--|
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                 | 7 / 77 (9.09%)<br>7  | 3 / 69 (4.35%)<br>3  |  |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)                | 1 / 77 (1.30%)<br>1  | 1 / 69 (1.45%)<br>1  |  |
| Eye disorders                                                               |                      |                      |  |
| Visual impairment<br>subjects affected / exposed<br>occurrences (all)       | 2 / 77 (2.60%)<br>2  | 2 / 69 (2.90%)<br>2  |  |
| Conjunctivitis allergic<br>subjects affected / exposed<br>occurrences (all) | 0 / 77 (0.00%)<br>0  | 1 / 69 (1.45%)<br>1  |  |
| Eye oedema<br>subjects affected / exposed<br>occurrences (all)              | 0 / 77 (0.00%)<br>0  | 1 / 69 (1.45%)<br>1  |  |
| Scintillating scotoma<br>subjects affected / exposed<br>occurrences (all)   | 1 / 77 (1.30%)<br>1  | 0 / 69 (0.00%)<br>0  |  |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)          | 0 / 77 (0.00%)<br>0  | 1 / 69 (1.45%)<br>1  |  |
| Gastrointestinal disorders                                                  |                      |                      |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                  | 7 / 77 (9.09%)<br>8  | 5 / 69 (7.25%)<br>10 |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)    | 7 / 77 (9.09%)<br>13 | 2 / 69 (2.90%)<br>8  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)               | 6 / 77 (7.79%)<br>7  | 2 / 69 (2.90%)<br>5  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                | 5 / 77 (6.49%)<br>6  | 1 / 69 (1.45%)<br>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<br>subjects affected / exposed<br>occurrences (all) | 0 / 77 (0.00%)<br>0 | 1 / 69 (1.45%)<br>1 |  |
| Hepatomegaly<br>subjects affected / exposed<br>occurrences (all)          | 1 / 77 (1.30%)<br>1 | 0 / 69 (0.00%)<br>0 |  |
| Skin and subcutaneous tissue disorders                                    |                     |                     |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)              | 4 / 77 (5.19%)<br>5 | 1 / 69 (1.45%)<br>1 |  |
| Night sweats<br>subjects affected / exposed<br>occurrences (all)          | 1 / 77 (1.30%)<br>1 | 3 / 69 (4.35%)<br>3 |  |
| Hyperhidrosis<br>subjects affected / exposed<br>occurrences (all)         | 2 / 77 (2.60%)<br>3 | 1 / 69 (1.45%)<br>1 |  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)              | 1 / 77 (1.30%)<br>1 | 1 / 69 (1.45%)<br>1 |  |
| Dermatitis allergic<br>subjects affected / exposed<br>occurrences (all)   | 1 / 77 (1.30%)<br>1 | 1 / 69 (1.45%)<br>2 |  |
| Erythema<br>subjects affected / exposed<br>occurrences (all)              | 1 / 77 (1.30%)<br>2 | 1 / 69 (1.45%)<br>1 |  |
| Skin depigmentation<br>subjects affected / exposed<br>occurrences (all)   | 2 / 77 (2.60%)<br>2 | 0 / 69 (0.00%)<br>0 |  |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)            | 0 / 77 (0.00%)<br>0 | 1 / 69 (1.45%)<br>1 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 77 (1.30%)<br>1 | 0 / 69 (0.00%)<br>0 |  |
| Telangiectasia                                                            |                     |                     |  |

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 23 August 2010 | <ul style="list-style-type: none"> <li>-Investigator was not blinded since a platelet reduction by Anagrelide retard could have a potential unblinding effect. The Sponsor was blinded.</li> <li>-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.</li> <li>- EAC was established. The treatment allocation status was blinded for the subject, but open for the primary site investigators.</li> <li>- 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.</li> <li>- 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.</li> <li>- The exclusion criterion "diabetes mellitus" was modified to "poorly controlled" diabetes mellitus</li> <li>- 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.</li> <li>- Blinded AEs/ SAEs management, including blinded SUSARs reporting was added.</li> <li>-subjects to be treated for a maximum of 3 years as long as they do not experience their 1st clinically significant ET-related event.</li> <li>- Laboratory tests were split into local and central.</li> <li>- Use of version of the Declaration of Helsinki of October 1996.</li> <li>- The causality assessment for drug-event relationship was changed to "Yes, related/ No, unrelated" judgment.</li> <li>- References added: ARETA Study Working Guideline for idv staff, ARETA Study Working Guideline for Harrison, DMC and EAC Charter.</li> <li>- Measurement of prothrombin time and NT-proBNP.</li> </ul> |
| 11 March 2014  | <ol style="list-style-type: none"> <li>1) Introduction of the analysis based on the CALR and MPL mutational status as potentially relevant to predict disease prognosis and treatment outcomes.</li> <li>2) Inclusion of progressive thrombocytosis as a risk changing event into the ET-related event definitions as the primary endpoint (i.e. platelet criterion)</li> <li>3) Intensification of the ECG monitoring schedule in the study (additional ECGs scheduled at months 1, 3, 6 and 9.</li> <li>4) Magnesium was included into the list of biochemical parameters to be measured at regular intervals.</li> <li>5) Early withdrawal visits were preponed for all active subjects in case of study completion after stage I analysis at the earliest date possible.</li> <li>6) Specification on post study care (after study completion) for subjects, who received active drug during the study.</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported