



Clinical trial results:

Initially entitled: A Medical Research Council randomised trial to compare ASPIRIN versus HYDROXYUREA / ASPIRIN in 'INTERMEDIATE RISK' Primary Thrombocythaemia and HYDROXYUREA / ASPIRIN versus ANAGRELIDE / ASPIRIN in 'HIGH RISK' Primary Thrombocythaemia.

Following closure of the high risk arm: A randomised trial to compare ASPIRIN versus HYDROXYUREA/ASPIRIN in 'intermediate risk' primary thrombocythaemia and ASPIRIN only with observation in 'Low risk' primary thrombocythaemia.

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2004-000245-38 |
| Trial protocol | FR |
| Global end of trial date | 10 November 2016 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 12 July 2018 |
| First version publication date | 12 July 2018 |
| Summary attachment (see zip file) | Appendix 3 (Appendix 3 - PT1 EudraCT 2004-000245-38 SAE Listings.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-----|
| Sponsor protocol code | PT1 |
|-----------------------|-----|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | ISRCTN72251782 |
| ClinicalTrials.gov id (NCT number) | NCT00175838 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | R&D No.: A05033 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University of Cambridge & Cambridge University Hospitals NHS Foundation Trust |
| Sponsor organisation address | Addenbrookes Hospital, Hills Road, Cambridge, United Kingdom, CB2 0QQ |
| Public contact | Julia Cook, University of Cambridge, 44 01223 348091, julia.cook@addenbrookes.nhs.uk |
| Scientific contact | Prof. Anthony Green, University of Cambridge, 44 01223 762668, haem-pa2@cimr.cam.ac.uk |

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 | 31 May 2013 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 May 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 November 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- 1) In low risk patients (aged > or = 18 years and < 40 years, no high risk factors): What is the incidence of thrombosis and major haemorrhage while receiving aspirin only?
- 2) In intermediate risk patients (aged > or = 40 years and < 60 years, no high risk factors): Does hydroxyurea reduce thrombosis and major haemorrhage when added to aspirin?
- 3) In high risk patients (aged > or = 60, or other risk factors as defined below in this document): does anagrelide reduce vascular occlusive events as effectively as hydroxyurea?
- 4) In high risk patients (aged > or = 60, or other risk factors as defined below in this document): is anagrelide as effective as hydroxyurea in reducing elevated platelet counts?
- 5) What is the effect of the treatment modalities on quality of life?

Protection of trial subjects:

All treatments used on the study were already considered standard therapy for essential thrombocythaemia. Patients gave informed consent to enter the study and the collection of additional samples including blood and bone marrow were voluntary.

Background therapy:

Aspirin is an oral antiplatelet drug, used extensively worldwide in patients at risk of strokes and heart attacks. All patients were advised to take aspirin 75 mg daily (100 mg in Australia) or an alternative antiplatelet agent if aspirin was contraindicated. Aspirin is considered to be a background therapy for this trial as it was administered to each of the clinical trial subjects as standard care regardless of risk group or randomisation group.

Evidence for comparator:

Evidence from a randomised prospective study of 'high-risk' patients demonstrated that cytoreduction with hydroxyurea significantly reduced vascular occlusion. The observed reduction in this prospective study of 29 months median duration was from 24% for those not given cytoreductive treatment to 3.6% for those receiving hydroxyurea — approximately a six-fold reduction. In another prospective study where all patients received hydroxyurea, an incidence of major thrombotic events was 5.6%/year.

Anagrelide is a quinazolin compound developed as a potent inhibitor of platelet aggregation. It was additionally found to produce thrombocytopenia at lower plasma concentrations than required for its anti-aggregating effect and this has led to its use in patients with thrombocythaemia. Analysis of the bone marrow of patients receiving anagrelide has demonstrated a reduction in megakaryocyte size and ploidy, but not in number, suggesting inhibition of megakaryocyte maturation.

| | |
|---|--------------|
| Actual start date of recruitment | 21 July 1997 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|----------------------|
| Country: Number of subjects enrolled | France: 54 |
| Country: Number of subjects enrolled | Australia: 48 |
| Country: Number of subjects enrolled | Ireland: 3 |
| Country: Number of subjects enrolled | New Zealand: 37 |
| Country: Number of subjects enrolled | United Kingdom: 1317 |
| Worldwide total number of subjects | 1459 |
| EEA total number of subjects | 1374 |

Notes:

Subjects enrolled per age group

| | |
|---|------|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 1 |
| Adults (18-64 years) | 1109 |
| From 65 to 84 years | 345 |
| 85 years and over | 4 |

Subject disposition

Recruitment

Recruitment details:

198 centres in 5 countries entered patients. Republic of Ireland closed to all recruitment and follow up in May 2006 as no co-ordinating PI could be found for the country as required by the Irish Medicines Board. Recruitment closure dates in all other countries were:

Low risk: 30 Apr 2013

Intermediate risk: 31 Jul 2012

High risk: 15 Aug 2002

Pre-assignment

Screening details:

Patients with a diagnosis of Essential Thrombocythaemia were assessed for study inclusion according to standard diagnostic criteria (PVSG criteria). Medical history & physical exam including splenic size were performed to determine risk group. Blood samples, blood films, bone marrow aspirate & bone marrow trephines collected as appropriate.

Period 1

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

Arms

| | |
|------------------------------|------------------------|
| Are arms mutually exclusive? | No |
| Arm title | High Risk - Anagrelide |

Arm description:

Patients were classified as at high risk if they met one or more of the following criteria: an age of at least 60 years; current or previous platelet counts of 1 million per cubic millimeter or more; a history of ischemia, thrombosis, or embolism; hemorrhage caused by essential thrombocythemia; hypertension requiring therapy; and diabetes requiring the administration of a hypoglycemic agent.

Eligible patients were randomized to receive anagrelide and aspirin (in a 1:1 ratio vs hydroxycarbamide and aspirin). Minimization was used to ensure that equal numbers of patients were assigned to each group, both overall and within subgroups defined by previous treatment (no treatment or aspirin or cytoreductive therapy or both).

Patients who were identified to have the incorrect diagnosis or risk group after randomisation were ineligible and not included in the analysis.

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

Dosage and administration details:

The routine initial dosage of anagrelide should be 0.5mg b.d. (the formulation of anagrelide is in 0.5mg capsules). The count should be checked one week after starting therapy because occasional patients respond rapidly. If the platelet count is not falling after two weeks, the daily dose can be increased by 0.5mg/day every 1 - 2 weeks. The average dose of anagrelide required to control the platelet count adequately is between 2 and 2.5mg/day. The maximum dose of anagrelide should not exceed 10mg/day or 3mg in a single dose.

| | |
|------------------|------------------------------|
| Arm title | High Risk - Hydroxycarbamide |
|------------------|------------------------------|

Arm description:

Patients were classified as at high risk if they met one or more of the following criteria: an age of at least 60 years; current or previous platelet counts of 1 million per cubic millimeter or more; a history of ischemia, thrombosis, or embolism; hemorrhage caused by essential thrombocythemia; hypertension

requiring therapy; and diabetes requiring the administration of a hypoglycemic agent.

Eligible patients were randomized to receive hydroxycarbamide and aspirin (in a 1:1 ratio vs anagrelide and aspirin). Minimization was used to ensure that equal numbers of patients were assigned to each group, both overall and within subgroups defined by previous treatment (no treatment or aspirin or cytoreductive therapy or both).

Patients who were identified to have the incorrect diagnosis or risk group after randomisation were ineligible and not included in the analysis.

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Hydroxycarbamide |
| Investigational medicinal product code | |
| Other name | Hydroxyurea |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Patients assigned to hydroxycarbamide were treated with 0.5 to 2 g oral hydroxycarbamide daily, adjusted to maintain the platelet count within the range $200-400 \times 10^9/L$.

| | |
|------------------|--------------------------------------|
| Arm title | Intermediate Risk - Hydroxycarbamide |
|------------------|--------------------------------------|

Arm description:

Intermediate risk patients were aged 40 to ≤ 59 years with no high risk features.

Eligible patients were randomized to receive hydroxycarbamide and aspirin (in a 1:1 ratio vs aspirin alone). Minimization was used to ensure that equal numbers of patients were assigned to each group, both overall and within subgroups defined by previous treatment (no treatment or aspirin or cytoreductive therapy or both).

Patients who were identified to have the incorrect diagnosis or risk group after randomisation were ineligible and not included in the analysis.

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Hydroxycarbamide |
| Investigational medicinal product code | |
| Other name | Hydroxyurea |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Patients assigned to hydroxycarbamide were treated with 0.5 to 2 g oral hydroxycarbamide daily, adjusted to maintain the platelet count within the range $200-400 \times 10^9/L$.

| | |
|------------------|-------------------|
| Arm title | Intermediate Risk |
|------------------|-------------------|

Arm description:

Intermediate risk patients were aged 40 to ≤ 59 years with no high risk features.

Eligible patients were randomized to receive aspirin alone (in a 1:1 ratio vs hydroxycarbamide and aspirin). Minimization was used to ensure that equal numbers of patients were assigned to each group, both overall and within subgroups defined by previous treatment (no treatment or aspirin or cytoreductive therapy or both).

Patients who were identified to have the incorrect diagnosis or risk group after randomisation were ineligible and not included in the analysis.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Low Risk |

Arm description:

Low risk patients were aged 18 to ≤ 39 years with no high risk features

Patients who were identified to have the incorrect diagnosis or risk group after randomisation were ineligible and not included in the analysis.

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

| Number of subjects in period 1 | High Risk - Anagrelide | High Risk - Hydroxycarbamide | Intermediate Risk - Hydroxycarbamide |
|---------------------------------------|---------------------------|---------------------------------|---|
| Started | 408 | 407 | 192 |
| Completed | 405 | 404 | 182 |
| Not completed | 3 | 3 | 10 |
| Protocol deviation | 3 | 3 | 10 |

| Number of subjects in period 1 | Intermediate Risk | Low Risk |
|---------------------------------------|-------------------|----------|
| Started | 190 | 262 |
| Completed | 176 | 256 |
| Not completed | 14 | 6 |
| Protocol deviation | 14 | 6 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | High Risk - Anagrelide |
|-----------------------|------------------------|

Reporting group description:

Patients were classified as at high risk if they met one or more of the following criteria: an age of at least 60 years; current or previous platelet counts of 1 million per cubic millimeter or more; a history of ischemia, thrombosis, or embolism; hemorrhage caused by essential thrombocythemia; hypertension requiring therapy; and diabetes requiring the administration of a hypoglycemic agent.

Eligible patients were randomized to receive anagrelide and aspirin (in a 1:1 ratio vs hydroxycarbamide and aspirin). Minimization was used to ensure that equal numbers of patients were assigned to each group, both overall and within subgroups defined by previous treatment (no treatment or aspirin or cytoreductive therapy or both).

Patients who were identified to have the incorrect diagnosis or risk group after randomisation were ineligible and not included in the analysis.

| | |
|-----------------------|------------------------------|
| Reporting group title | High Risk - Hydroxycarbamide |
|-----------------------|------------------------------|

Reporting group description:

Patients were classified as at high risk if they met one or more of the following criteria: an age of at least 60 years; current or previous platelet counts of 1 million per cubic millimeter or more; a history of ischemia, thrombosis, or embolism; hemorrhage caused by essential thrombocythemia; hypertension requiring therapy; and diabetes requiring the administration of a hypoglycemic agent.

Eligible patients were randomized to receive hydroxycarbamide and aspirin (in a 1:1 ratio vs anagrelide and aspirin). Minimization was used to ensure that equal numbers of patients were assigned to each group, both overall and within subgroups defined by previous treatment (no treatment or aspirin or cytoreductive therapy or both).

Patients who were identified to have the incorrect diagnosis or risk group after randomisation were ineligible and not included in the analysis.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Intermediate Risk - Hydroxycarbamide |
|-----------------------|--------------------------------------|

Reporting group description:

Intermediate risk patients were aged 40 to \leq 59 years with no high risk features.

Eligible patients were randomized to receive hydroxycarbamide and aspirin (in a 1:1 ratio vs aspirin alone). Minimization was used to ensure that equal numbers of patients were assigned to each group, both overall and within subgroups defined by previous treatment (no treatment or aspirin or cytoreductive therapy or both).

Patients who were identified to have the incorrect diagnosis or risk group after randomisation were ineligible and not included in the analysis.

| | |
|-----------------------|-------------------|
| Reporting group title | Intermediate Risk |
|-----------------------|-------------------|

Reporting group description:

Intermediate risk patients were aged 40 to \leq 59 years with no high risk features.

Eligible patients were randomized to receive aspirin alone (in a 1:1 ratio vs hydroxycarbamide and aspirin). Minimization was used to ensure that equal numbers of patients were assigned to each group, both overall and within subgroups defined by previous treatment (no treatment or aspirin or cytoreductive therapy or both).

Patients who were identified to have the incorrect diagnosis or risk group after randomisation were ineligible and not included in the analysis.

| | |
|-----------------------|----------|
| Reporting group title | Low Risk |
|-----------------------|----------|

Reporting group description:

Low risk patients were aged 18 to \leq 39 years with no high risk features

Patients who were identified to have the incorrect diagnosis or risk group after randomisation were ineligible and not included in the analysis.

| Reporting group values | High Risk - Anagrelide | High Risk - Hydroxycarbamide | Intermediate Risk - Hydroxycarbamide |
|--|------------------------|------------------------------|--------------------------------------|
| Number of subjects | 408 | 407 | 192 |
| 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) | 240 | 228 | 191 |
| From 65-84 years | 165 | 178 | 1 |
| 85 years and over | 3 | 1 | 0 |
| Age continuous Units: years | | | |
| median | 61 | 62 | 52 |
| full range (min-max) | 23 to 88 | 21 to 88 | 40 to 75 |
| Gender categorical Units: Subjects | | | |
| Female | 243 | 225 | 126 |
| Male | 165 | 182 | 66 |

| Reporting group values | Intermediate Risk | Low Risk | Total |
|--|-------------------|----------|-------|
| Number of subjects | 190 | 262 | 1459 |
| 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 | 1 | 1 |
| Adults (18-64 years) | 189 | 261 | 1109 |
| From 65-84 years | 1 | 0 | 345 |
| 85 years and over | 0 | 0 | 4 |
| Age continuous Units: years | | | |
| median | 51 | 33 | |
| full range (min-max) | 26 to 74 | 17 to 40 | - |
| Gender categorical Units: Subjects | | | |
| Female | 102 | 192 | 888 |
| Male | 88 | 70 | 571 |

End points

End points reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | High Risk - Anagrelide |
|-----------------------|------------------------|

Reporting group description:

Patients were classified as at high risk if they met one or more of the following criteria: an age of at least 60 years; current or previous platelet counts of 1 million per cubic millimeter or more; a history of ischemia, thrombosis, or embolism; hemorrhage caused by essential thrombocythemia; hypertension requiring therapy; and diabetes requiring the administration of a hypoglycemic agent.

Eligible patients were randomized to receive anagrelide and aspirin (in a 1:1 ratio vs hydroxycarbamide and aspirin). Minimization was used to ensure that equal numbers of patients were assigned to each group, both overall and within subgroups defined by previous treatment (no treatment or aspirin or cytoreductive therapy or both).

Patients who were identified to have the incorrect diagnosis or risk group after randomisation were ineligible and not included in the analysis.

| | |
|-----------------------|------------------------------|
| Reporting group title | High Risk - Hydroxycarbamide |
|-----------------------|------------------------------|

Reporting group description:

Patients were classified as at high risk if they met one or more of the following criteria: an age of at least 60 years; current or previous platelet counts of 1 million per cubic millimeter or more; a history of ischemia, thrombosis, or embolism; hemorrhage caused by essential thrombocythemia; hypertension requiring therapy; and diabetes requiring the administration of a hypoglycemic agent.

Eligible patients were randomized to receive hydroxycarbamide and aspirin (in a 1:1 ratio vs anagrelide and aspirin). Minimization was used to ensure that equal numbers of patients were assigned to each group, both overall and within subgroups defined by previous treatment (no treatment or aspirin or cytoreductive therapy or both).

Patients who were identified to have the incorrect diagnosis or risk group after randomisation were ineligible and not included in the analysis.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Intermediate Risk - Hydroxycarbamide |
|-----------------------|--------------------------------------|

Reporting group description:

Intermediate risk patients were aged 40 to \leq 59 years with no high risk features.

Eligible patients were randomized to receive hydroxycarbamide and aspirin (in a 1:1 ratio vs aspirin alone). Minimization was used to ensure that equal numbers of patients were assigned to each group, both overall and within subgroups defined by previous treatment (no treatment or aspirin or cytoreductive therapy or both).

Patients who were identified to have the incorrect diagnosis or risk group after randomisation were ineligible and not included in the analysis.

| | |
|-----------------------|-------------------|
| Reporting group title | Intermediate Risk |
|-----------------------|-------------------|

Reporting group description:

Intermediate risk patients were aged 40 to \leq 59 years with no high risk features.

Eligible patients were randomized to receive aspirin alone (in a 1:1 ratio vs hydroxycarbamide and aspirin). Minimization was used to ensure that equal numbers of patients were assigned to each group, both overall and within subgroups defined by previous treatment (no treatment or aspirin or cytoreductive therapy or both).

Patients who were identified to have the incorrect diagnosis or risk group after randomisation were ineligible and not included in the analysis.

| | |
|-----------------------|----------|
| Reporting group title | Low Risk |
|-----------------------|----------|

Reporting group description:

Low risk patients were aged 18 to \leq 39 years with no high risk features

Patients who were identified to have the incorrect diagnosis or risk group after randomisation were ineligible and not included in the analysis.

Primary: Arterial or venous thrombosis, serious hemorrhage, or death from thrombosis or hemorrhage

| | |
|-----------------|---|
| End point title | Arterial or venous thrombosis, serious hemorrhage, or death from thrombosis or hemorrhage |
|-----------------|---|

End point description:

The composite primary end point was the time from randomization until the patient died from thrombosis or haemorrhage or had a serious hemorrhage or thrombotic event.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

All end points that occurred following randomization and were reported before July 31, 2004 in the high risk group and all end points that occurred following randomization to May 31, 2013 and were reported before October 31, 2013 in other groups.

| End point values | High Risk - Anagrelide | High Risk - Hydroxycarbamide | Intermediate Risk - Hydroxycarbamide | Intermediate Risk |
|-----------------------------|------------------------|------------------------------|--------------------------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 405 ^[1] | 404 ^[2] | 182 ^[3] | 176 ^[4] |
| Units: Events | 55 | 36 | 11 | 11 |

Notes:

[1] - Excludes ineligible patients

[2] - Excludes ineligible patients

[3] - Excludes ineligible patients

[4] - Excludes ineligible patients

| End point values | Low Risk | | | |
|-----------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 256 ^[5] | | | |
| Units: Events | 19 | | | |

Notes:

[5] - Excludes ineligible patients

Statistical analyses

| | |
|---|---|
| Statistical analysis title | High risk, primary endpoint |
| Comparison groups | High Risk - Anagrelide v High Risk - Hydroxycarbamide |
| Number of subjects included in analysis | 809 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.03 |
| Method | Logrank |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.04 |
| upper limit | 2.37 |

| | |
|---|--|
| Statistical analysis title | Intermediate risk, primary endpoint |
| Comparison groups | Intermediate Risk - Hydroxycarbamide v Intermediate Risk |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 1 |
| Method | Logrank |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.42 |
| upper limit | 2.25 |

Secondary: Patient survival

| | |
|--|------------------|
| End point title | Patient survival |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| All end points that occurred following randomization and were reported before July 31, 2004 in the high risk group and all end points that occurred following randomization to May 31, 2013 and were reported before October 31, 2013 in other groups. | |

| End point values | High Risk - Anagrelide | High Risk - Hydroxycarbamide | Intermediate Risk - Hydroxycarbamide | Intermediate Risk |
|-----------------------------|------------------------|------------------------------|--------------------------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 405 | 404 | 182 | 176 |
| Units: Events | 31 | 27 | 10 | 7 |

| End point values | Low Risk | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 256 | | | |
| Units: Events | 0 | | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | High risk, secondary endpoint, survival |
| Comparison groups | High Risk - Anagrelide v High Risk - Hydroxycarbamide |
| Number of subjects included in analysis | 809 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.6 ^[6] |
| Method | Logrank |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.93 |

Notes:

[6] - NS - not significant

| | |
|---|--|
| Statistical analysis title | Int risk, secondary endpoint, survival |
| Comparison groups | Intermediate Risk - Hydroxycarbamide v Intermediate Risk |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.5 |
| Method | Logrank |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 3.61 |

Secondary: Disease transformation to myelofibrosis, AML or myelodysplasia

| | |
|-----------------|---|
| End point title | Disease transformation to myelofibrosis, AML or myelodysplasia ^[7] |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

All end points that occurred following randomization to May 31, 2013 and were reported before October 31, 2013.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Statistics are not reported for the High Risk arms here as they are broken out into separate end points of myelofibrosis alone and AML + myelodysplasia as noted below.

| End point values | Intermediate Risk - Hydroxycarbamide | Intermediate Risk | Low Risk | |
|-----------------------------|--------------------------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 182 | 176 | 256 | |
| Units: Events | 5 | 6 | 1 | |

Statistical analyses

| Statistical analysis title | Int risk, secondary endpoint, transformation |
|---|--|
| Comparison groups | Intermediate Risk - Hydroxycarbamide v Intermediate Risk |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.7 |
| Method | Logrank |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.24 |
| upper limit | 2.58 |

Secondary: Disease transformation to myelofibrosis

| | |
|-----------------|--|
| End point title | Disease transformation to myelofibrosis ^[8] |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

All end points that occurred following randomization and were reported before July 31, 2004.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistics are not reported for the Intermediate Risk or Low Risk arms here as they are amalgamated into one end point of myelofibrosis + AML + myelodysplasia as noted above.

| End point values | High Risk - Anagrelide | High Risk - Hydroxycarbamide | | |
|-----------------------------|------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 405 | 404 | | |
| Units: Events | 16 | 5 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | High risk, secondary endpoint, transformation |
| Comparison groups | High Risk - Anagrelide v High Risk - Hydroxycarbamide |
| Number of subjects included in analysis | 809 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.01 |
| Method | Logrank |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.24 |
| upper limit | 6.86 |

Secondary: Disease transformation to AML or myelodysplasia

| | |
|-----------------|--|
| End point title | Disease transformation to AML or myelodysplasia ^[9] |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

All end points that occurred following randomization and were reported before July 31, 2004.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are not reported for the Intermediate Risk or Low Risk arms here as they are amalgamated into one end point of myelofibrosis + AML + myelodysplasia as noted above.

| End point values | High Risk - Anagrelide | High Risk - Hydroxycarbamide | | |
|-----------------------------|------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 405 | 404 | | |
| Units: Events | 4 | 6 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | High risk, secondary endpoint, transformation |
| Comparison groups | High Risk - Anagrelide v High Risk - Hydroxycarbamide |
| Number of subjects included in analysis | 809 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.5 ^[10] |
| Method | Logrank |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.67 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 2.33 |

Notes:

[10] - NS - not significant

Secondary: Disease transformation to polycythaemia vera

| | |
|-----------------|--|
| End point title | Disease transformation to polycythaemia vera |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

All end points that occurred following randomization and were reported before July 31, 2004 in the high risk group and all end points that occurred following randomization to May 31, 2013 and were reported before October 31, 2013 in other groups.

| End point values | High Risk - Anagrelide | High Risk - Hydroxycarbamide | Intermediate Risk - Hydroxycarbamide | Intermediate Risk |
|-----------------------------|------------------------|------------------------------|--------------------------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 405 | 404 | 182 | 176 |
| Units: Events | 1 | 1 | 0 | 6 |

| End point values | Low Risk | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 256 | | | |
| Units: Events | 2 | | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | High risk, secondary endpoint, transformation |
| Comparison groups | High Risk - Anagrelide v High Risk - Hydroxycarbamide |
| Number of subjects included in analysis | 809 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 1 [11] |
| Method | Logrank |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.06 |
| upper limit | 1.6 |

Notes:

[11] - NS - not significant

| | |
|---|--|
| Statistical analysis title | Int risk, secondary endpoint, transformation |
| Comparison groups | Intermediate Risk - Hydroxycarbamide v Intermediate Risk |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.01 |
| Method | Logrank |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0 |

Secondary: Quality of life

| | |
|-----------------|---------------------------------|
| End point title | Quality of life ^[12] |
|-----------------|---------------------------------|

End point description:

Quality of life (QL) was assessed using the EORTC QLQ-C30 version 2 questionnaire at randomization and yearly thereafter for five years. Scoring was according to guidelines provided by the EORTC QL Group with scores interpreted so that increased functional status indicates a benefit whereas increased symptoms indicate a poorer quality of life.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The first five years on the trial for patients in Intermediate risk group.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As specified in the protocol, this end point does not apply to all arms of the study.

| | | | | |
|-----------------------------|--------------------------------------|-------------------|--|--|
| End point values | Intermediate Risk - Hydroxycarbamide | Intermediate Risk | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[13] | 0 ^[14] | | |
| Units: Score | | | | |

Notes:

[13] - See attached figure (Appendix 1).

[14] - See attached figure (Appendix 1).

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Appendix 1/Appendix 1 - PT1 EudraCT 2004-000245-38 |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Platelet count control

| | |
|-----------------|--|
| End point title | Platelet count control ^[15] |
|-----------------|--|

End point description:

Data points were based on patients with a platelet count recorded within one month of each time point and remaining on their assigned treatment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Platelet counts were recorded at 3 monthly intervals from randomization to 24 months post entry.

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As specified in the protocol, this end point only applies to the treatment groups in the High Risk arm of the study.

| End point values | High Risk - Anagrelide | High Risk - Hydroxycarbamide | | |
|---|------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[16] | 0 ^[17] | | |
| Units: Platelet count (x10 ⁹ /L) | | | | |

Notes:

[16] - See attached graph (Appendix 2).

[17] - See attached graph (Appendix 2).

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Appendix 2/Appendix 2 - PT1 EudraCT 2004-000245-38 High |
|-----------------------------------|---|

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

AEs were recorded from study registration until the last follow up visit attended by the patient.

Adverse event reporting additional description:

Please see Appendix 3 attached.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|------|
| Dictionary name | None |
|-----------------|------|

| | |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: SAE listings provided as an attachment

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 09 May 2005 | The following changes were made to the protocol and patient documents: <ul style="list-style-type: none">- Due to the closure of the high risk arms all references to this group were removed.- The low and intermediate risk arms of the study were previously supported by the Medical Research Council, but are now supported by the NCRI.- Definition of low and intermediate risk groups was altered to include patients with platelet counts up to 1500x10⁹/l (those with platelet counts >1000x10⁹/l were originally deemed to be high risk).- Details of the additional Pregnancy in PT survey added to protocol- General updates in order to conform to the EU Directive 2001/20/EC including new details on serious adverse event reporting- Inclusion of a GP letter |
| 20 February 2008 | The protocol was updated in line with current regulations and reformatted to Sponsor's new template. Exemption from drug accountability and labelling requirements was requested. The majority of changes were regarding trial conduct; the science of the study and overall methodology, objectives and outcomes remained unchanged. In summary: <ul style="list-style-type: none">- Update of pharmacovigilance section including introduction of NCI grading of adverse events and a new SAE form- Increased information of study drug- UK only references removed to become international protocol- Clarification of procedures, objectives and assessments- Removal of pregnancy survey |
| 22 April 2009 | Addition of annual follow-up blood sample collection and annual buccal swab sample collection in order to monitor the natural progression of the disease and molecular changes over time. |
| 04 January 2010 | Changes were made to the protocol, patient information sheet and consent forms as outlined below: <ul style="list-style-type: none">- Transfer of data management and randomisation for the trial from the CTSU in Oxford to the CCTC in Cambridge.- Clarification on wording regarding the drug labelling exemption and the request for samples of constitutional DNA. |
| 09 August 2012 | Changes made to the end date of the trial. The protocol, patient information sheet and consent forms were updated to reflect the new information. In summary: <ul style="list-style-type: none">- Recruitment to the intermediate risk arm of the trial was extended to 31 July 2012.- Recruitment to the low risk arm of the trial was extended to 30 April 2014.- Removal of wording in the protocol regarding accrual into the intermediate risk arm.- Removal of wording in the protocol regarding hydroxycarbamide (hydroxyurea) as an IMP for the trial. |
| 20 January 2014 | Extension of follow up period for a further 10 years - end of study expected in April 2024. |
| 01 November 2016 | <ul style="list-style-type: none">- Follow up period reduced to end in 2016- Change to definition of End of Study- Changes to the locations where samples should be sent and where they will be stored |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/16000354>