



Clinical trial results:

A Phase II Study of Dasatinib Therapy in Children and Adolescents with Ph+ Leukemia with Resistance or Intolerance to Imatinib.

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2008-002260-33 |
| Trial protocol | IT ES FR NL GB DE Outside EU/EEA |
| Global end of trial date | |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 30 December 2017 |
| First version publication date | 30 December 2017 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | CA180-226 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00777036 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussée de la Hulpe 185, Brussels, Belgium, 1170 |
| Public contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com |
| Scientific contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000567-PIP01-09 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 01 September 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 September 2016 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine whether dasatinib is safe and effective in children and adolescents with newly diagnosed chronic myeloid leukemia (CML), or in children with Ph+ acute lymphoblastic leukemia (ALL), accelerated or blast phases CML who relapse after imatinib or who are resistant or intolerant to imatinib. The side effects of this oral investigational drug in children and adolescents will be evaluated

Protection of trial subjects:

The study was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 20 March 2009 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 1 |
| Country: Number of subjects enrolled | Australia: 3 |
| Country: Number of subjects enrolled | Brazil: 15 |
| Country: Number of subjects enrolled | Canada: 6 |
| Country: Number of subjects enrolled | France: 10 |
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | India: 19 |
| Country: Number of subjects enrolled | Italy: 8 |
| Country: Number of subjects enrolled | Mexico: 14 |
| Country: Number of subjects enrolled | Netherlands: 3 |
| Country: Number of subjects enrolled | Romania: 3 |
| Country: Number of subjects enrolled | Singapore: 2 |
| Country: Number of subjects enrolled | South Africa: 5 |
| Country: Number of subjects enrolled | Spain: 3 |
| Country: Number of subjects enrolled | United States: 23 |
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Country: Number of subjects enrolled | Russian Federation: 9 |
| Country: Number of subjects enrolled | Korea, Republic of: 15 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 145 |
| EEA total number of subjects | 33 |

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) | 3 |
| Children (2-11 years) | 63 |
| Adolescents (12-17 years) | 77 |
| Adults (18-64 years) | 2 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 80 sites (Argentina, Australia, Brazil, Canada, France, Germany, Great Britain, India, Italy, Korea, Mexico, Netherlands, Romania, Russia, Singapore, South Africa, Spain, and USA).

Pre-assignment

Screening details:

A total of 145 Subjects were enrolled and 130 Subjects were treated in the study. Reasons for non-treatment include 2 withdrew consent, 1 died, 11 failed to meet study criteria, and 1 other non-specified.

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | On Treatment |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 1 |

Arm description:

Children and adolescents with CP-CML who were resistant or intolerant to imatinib received dasatinib tablets at 60 mg/m² QD on a continuous oral regimen.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Dasatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dasatinib tablets at 60 mg/m² QD, with a maximum dose of 100 mg QD for subjects with high BSA

| | |
|------------------|----------|
| Arm title | Cohort 2 |
|------------------|----------|

Arm description:

Children and adolescents with Ph+ ALL, AP-CML or BP-CML who were resistant or intolerant to, or relapsed after imatinib therapy received dasatinib tablets at a dose schedule of 80 mg/m² QD on a continuous oral regimen.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Dasatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dasatinib tablets at dose schedule of 80 mg/m² QD, with a maximum dose of 140 mg QD for subjects with high BSA

| | |
|------------------|----------|
| Arm title | Cohort 3 |
|------------------|----------|

Arm description:

Children and adolescents with CP-CML who were treatment-naïve received dasatinib tablets at 60 mg/m² QD or powder for oral suspension (PFOS) at 72 mg/m² QD on a continuous oral regimen.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|----------------------------|
| Investigational medicinal product name | Dasatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Dasatinib powder for oral suspension (PFOS) at 72 mg/m² QD on a continuous oral regimen.

| | |
|--|--------------------|
| Investigational medicinal product name | Dasatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dasatinib tablets at 60 mg/m² QD, with a maximum dose of 100 mg QD for subjects with high BSA

| Number of subjects in period 1 ^[1] | Cohort 1 | Cohort 2 | Cohort 3 |
|---|----------|----------|----------|
| Started | 29 | 17 | 84 |
| Completed | 14 | 1 | 61 |
| Not completed | 15 | 16 | 23 |
| Adverse event, serious fatal | - | 2 | - |
| Non-compliance with Study Drug | 1 | - | - |
| Consent withdrawn by subject | 3 | 2 | 3 |
| Reason Not Specified | 4 | 7 | 12 |
| Progressive Disease | 5 | 4 | 6 |
| Maximum Clinical Benefit | 2 | - | 1 |
| Failure to Meet Study Criteria | - | 1 | - |
| Study Drug Toxicity | - | - | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 145 subjects were enrolled and 130 subjects were treated in the study and included in the baseline period. Reasons for non-treatment include 2 withdrew consent, 1 died, 11 failed to meet study criteria, and 1 other non-specified.

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | Follow-Up |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|--|--------------------|
| Arm title | Cohort 1 |
| Arm description: Children and adolescents with CP-CML who were resistant or intolerant to imatinib received dasatinib tablets at 60 mg/m ² QD on a continuous oral regimen. | |
| Arm type | Experimental |
| Investigational medicinal product name | Dasatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Dasatinib tablets at 60 mg/m ² QD, with a maximum dose of 100 mg QD for subjects with high BSA | |
| Arm title | Cohort 2 |
| Arm description: Children and adolescents with Ph+ ALL, AP-CML or BP-CML who were resistant or intolerant to, or relapsed after imatinib therapy received dasatinib tablets at a dose schedule of 80 mg/m ² QD on a continuous oral regimen. | |
| Arm type | Experimental |
| Investigational medicinal product name | Dasatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Dasatinib tablets at dose schedule of 80 mg/m ² QD, with a maximum dose of 140 mg QD for subjects with high BSA | |
| Arm title | Cohort 3 |
| Arm description: Children and adolescents with CP-CML who were treatment-naïve received dasatinib tablets at 60 mg/m ² QD or powder for oral suspension (PFOS) at 72 mg/m ² QD on a continuous oral regimen. | |
| Arm type | Experimental |
| Investigational medicinal product name | Dasatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Dasatinib tablets at 60 mg/m ² QD, with a maximum dose of 100 mg QD for subjects with high BSA | |
| Investigational medicinal product name | Dasatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Dasatinib tablets at 60 mg/m ² QD, with a maximum dose of 100 mg QD for subjects with high BSA | |

| Number of subjects in period 2^[2] | Cohort 1 | Cohort 2 | Cohort 3 |
|---|----------|----------|----------|
| Started | 14 | 13 | 23 |
| Completed | 9 | 5 | 19 |
| Not completed | 5 | 8 | 4 |
| Adverse event, serious fatal | 1 | 8 | - |
| Consent withdrawn by subject | 1 | - | 4 |
| Reason Not Specified | 2 | - | - |
| Lost to follow-up | 1 | - | - |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all participants who discontinued treatment entered the follow-up period

Baseline characteristics

Reporting groups

| | |
|--|----------|
| Reporting group title | Cohort 1 |
| Reporting group description: Children and adolescents with CP-CML who were resistant or intolerant to imatinib received dasatinib tablets at 60 mg/m ² QD on a continuous oral regimen. | |
| Reporting group title | Cohort 2 |
| Reporting group description: Children and adolescents with Ph+ ALL, AP-CML or BP-CML who were resistant or intolerant to, or relapsed after imatinib therapy received dasatinib tablets at a dose schedule of 80 mg/m ² QD on a continuous oral regimen. | |
| Reporting group title | Cohort 3 |
| Reporting group description: Children and adolescents with CP-CML who were treatment-naïve received dasatinib tablets at 60 mg/m ² QD or powder for oral suspension (PFOS) at 72 mg/m ² QD on a continuous oral regimen. | |

| Reporting group values | Cohort 1 | Cohort 2 | Cohort 3 |
|----------------------------------|----------|----------|----------|
| Number of subjects | 29 | 17 | 84 |
| Age Categorical | | | |
| Units: Subjects | | | |
| < 2 years | 1 | 0 | 2 |
| >= 2 to < 7 years | 3 | 2 | 10 |
| >= 7 to < 12 years | 6 | 6 | 28 |
| >= 12 to < 18 years | 17 | 9 | 44 |
| >= 18 years | 2 | 0 | 0 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 12.60 | 12.10 | 11.95 |
| standard deviation | ± 4.774 | ± 3.680 | ± 4.418 |
| Gender, Male/Female | | | |
| Units: Subjects | | | |
| Female | 16 | 9 | 39 |
| Male | 13 | 8 | 45 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| White | 20 | 13 | 56 |
| Black or African American | 2 | 0 | 4 |
| Asian | 6 | 3 | 23 |
| American Indian or Alaska Native | 0 | 0 | 1 |
| Other | 1 | 1 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 2 | 0 | 5 |
| Not Hispanic or Latino | 4 | 0 | 20 |
| Unknown or Not Reported | 23 | 17 | 59 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 130 | | |

| | | | |
|---|----|--|--|
| Age Categorical Units: Subjects | | | |
| < 2 years | 3 | | |
| >= 2 to < 7 years | 15 | | |
| >= 7 to < 12 years | 40 | | |
| >= 12 to < 18 years | 70 | | |
| >= 18 years | 2 | | |
| Age Continuous Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender, Male/Female Units: Subjects | | | |
| Female | 64 | | |
| Male | 66 | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | 89 | | |
| Black or African American | 6 | | |
| Asian | 32 | | |
| American Indian or Alaska Native | 1 | | |
| Other | 2 | | |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 7 | | |
| Not Hispanic or Latino | 24 | | |
| Unknown or Not Reported | 99 | | |

Subject analysis sets

| | |
|--|--------------------|
| Subject analysis set title | Cohort 3a |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Children and adolescents with CP-CML who were treatment-naïve received dasatinib tablets at 60 mg/m ² QD on a continuous oral regimen. | |
| Subject analysis set title | Cohort 3b |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Children and adolescents with CP-CML who were treatment-naïve received dasatinib powder for oral suspension (PFOS) at 72 mg/m ² QD on a continuous oral regimen. | |

| Reporting group values | Cohort 3a | Cohort 3b | |
|------------------------------------|-----------|-----------|--|
| Number of subjects | 51 | 33 | |
| Age Categorical Units: Subjects | | | |
| < 2 years | 1 | 1 | |
| >= 2 to < 7 years | 5 | 5 | |
| >= 7 to < 12 years | 16 | 12 | |
| >= 12 to < 18 years | 29 | 15 | |
| >= 18 years | 0 | 0 | |

| | | | |
|---|------------------|------------------|--|
| Age Continuous Units: years arithmetic mean standard deviation | 12.28 ± 4.084 | 11.44 ± 4.912 | |
| Gender, Male/Female Units: Subjects | | | |
| Female | 25 | 14 | |
| Male | 26 | 19 | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | 31 | 25 | |
| Black or African American | 3 | 1 | |
| Asian | 16 | 7 | |
| American Indian or Alaska Native | 1 | 0 | |
| Other | 0 | 0 | |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 1 | 4 | |
| Not Hispanic or Latino | 13 | 7 | |
| Unknown or Not Reported | 37 | 22 | |

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | Cohort 1 |
| Reporting group description: Children and adolescents with CP-CML who were resistant or intolerant to imatinib received dasatinib tablets at 60 mg/m ² QD on a continuous oral regimen. | |
| Reporting group title | Cohort 2 |
| Reporting group description: Children and adolescents with Ph+ ALL, AP-CML or BP-CML who were resistant or intolerant to, or relapsed after imatinib therapy received dasatinib tablets at a dose schedule of 80 mg/m ² QD on a continuous oral regimen. | |
| Reporting group title | Cohort 3 |
| Reporting group description: Children and adolescents with CP-CML who were treatment-naïve received dasatinib tablets at 60 mg/m ² QD or powder for oral suspension (PFOS) at 72 mg/m ² QD on a continuous oral regimen. | |
| Reporting group title | Cohort 1 |
| Reporting group description: Children and adolescents with CP-CML who were resistant or intolerant to imatinib received dasatinib tablets at 60 mg/m ² QD on a continuous oral regimen. | |
| Reporting group title | Cohort 2 |
| Reporting group description: Children and adolescents with Ph+ ALL, AP-CML or BP-CML who were resistant or intolerant to, or relapsed after imatinib therapy received dasatinib tablets at a dose schedule of 80 mg/m ² QD on a continuous oral regimen. | |
| Reporting group title | Cohort 3 |
| Reporting group description: Children and adolescents with CP-CML who were treatment-naïve received dasatinib tablets at 60 mg/m ² QD or powder for oral suspension (PFOS) at 72 mg/m ² QD on a continuous oral regimen. | |
| Subject analysis set title | Cohort 3a |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Children and adolescents with CP-CML who were treatment-naïve received dasatinib tablets at 60 mg/m ² QD on a continuous oral regimen. | |
| Subject analysis set title | Cohort 3b |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Children and adolescents with CP-CML who were treatment-naïve received dasatinib powder for oral suspension (PFOS) at 72 mg/m ² QD on a continuous oral regimen. | |

Primary: Major Cytogenetic Response (MCyR) Rate

| | |
|---|--|
| End point title | Major Cytogenetic Response (MCyR) Rate ^{[1][2]} |
| End point description: Major Cytogenetic Response (MCyR) rate is defined as the proportion of all treated subjects who achieved a complete (0%) or partial (1%-35% Ph+ metaphases in at least 20 metaphases in bone marrow) cytogenetic response, expressed as percentage. The denominator of the MCyR response rate consists of all treated subjects in Cohort 1, and the numerator is all subjects in Cohort 1 achieving MCyR. 95% confidence interval was calculated by Clopper-Pearson exact method. | |
| End point type | Primary |
| End point timeframe: From first dose of study therapy until 30 days after last dose (Assessed up to September 2016, approximately 90 months) | |

Notes:

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

Justification: This endpoint was only planned to analyze select arms

[2] - 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: This endpoint was only planned to analyze select arms

| End point values | Cohort 1 | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 29 | | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 89.7 (72.6 to 97.8) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Complete Hematologic Response (CHR) Rate

| | |
|-----------------|--|
| End point title | Complete Hematologic Response (CHR) Rate ^{[3][4]} |
|-----------------|--|

End point description:

Complete Hematologic Response (CHR) rate is defined as the proportion of all treated subjects who achieve a confirmed CHR while on-study, expressed as percentage. CHR is defined as including no more than 5% blasts in bone marrow and normal white blood cell count without blasts in peripheral blood, expressed as percentage. The denominator of the CHR response rate consists of all treated subjects in Cohort 2, and the numerator is all subjects in Cohort 2 achieving CHR. 95% confidence interval was calculated by Clopper-Pearson exact method.

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

End point timeframe:

From first dose of study therapy until 30 days after last dose (Assessed up to September 2016, approximately 90 months)

Notes:

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

Justification: Only summary statistics were planned for this endpoint

[4] - 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: This endpoint was only planned to analyze select arms

| End point values | Cohort 2 | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 17 | | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 29.4 (10.3 to 56.0) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Complete Cytogenetic Response (CCyR) Rate

| | |
|--|---|
| End point title | Complete Cytogenetic Response (CCyR) Rate ^{[5][6]} |
| End point description: Complete Cytogenetic Response (CCyR) rate is defined as the proportion of all treated subjects who achieve a CCyR while on-study, expressed as a percentage. CCyR rate is defined as 0% Ph+ metaphases in at least 20 metaphases in bone marrow. The denominator of the CCyR response rate consists of all treated subjects in Cohort 3, and the numerator is all subjects in Cohort 3 achieving CCyR. 95% confidence interval was calculated by Clopper-Pearson exact method. | |
| End point type | Primary |
| End point timeframe: From first dose of study therapy until 30 days after last dose (Assessed up to September 2016, approximately 90 months) | |

Notes:

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

Justification: Only summary statistics were planned for this endpoint

[6] - 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: This endpoint was only planned to analyze select arms

| | | | | |
|----------------------------------|---------------------|--|--|--|
| End point values | Cohort 3 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 84 | | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 94.0 (86.7 to 98.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Major Cytogenetic Response (MCyR) Rate in Cohort 2

| | |
|---|---|
| End point title | Major Cytogenetic Response (MCyR) Rate in Cohort 2 ^[7] |
| End point description: Major Cytogenetic Response (MCyR) rate was defined as the proportion of all treated subjects who achieved a complete (0%) or partial (1%-35% Ph+ metaphases in at least 20 metaphases in bone marrow) cytogenetic response. The percentage of treated subjects in each arm with MCyR is reported. | |
| End point type | Secondary |
| End point timeframe: From first dose of study therapy until 30 days after last dose (Assessed up to September 2016, approximately 90 months) | |

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: This endpoint was only planned to analyze select arms

| End point values | Cohort 2 | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 17 | | | |
| Units: percent of subjects | | | | |
| number (confidence interval 95%) | 58.8 (32.9 to 81.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Hematologic Response (CHR) Rate in Cohorts 1 and 3

| | |
|-----------------|---|
| End point title | Complete Hematologic Response (CHR) Rate in Cohorts 1 and |
|-----------------|---|

End point description:

Complete Hematologic Response (CHR) rate defined as the proportion of all treated subjects who achieve a confirmed CHR while on-study. CHR is defined as including no more than 5% blasts in bone marrow and normal white blood cell count without blasts in peripheral blood. The percentage of treated subjects in each arm with CHR is reported.

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

End point timeframe:

From first dose of study therapy until 30 days after last dose (Assessed up to September 2016, approximately 90 months)

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: This endpoint was only planned to analyze select arms

| End point values | Cohort 1 | Cohort 3 | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 84 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 93.1 (77.2 to 99.2) | 96.4 (89.9 to 99.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Best Cytogenetic Response

| | |
|-----------------|-----------------------------------|
| End point title | Rate of Best Cytogenetic Response |
|-----------------|-----------------------------------|

End point description:

The number of subjects achieving their best on-study cytogenetic response was reported as a percentage of all treated subjects in that arm.

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

End point timeframe:

From first dose of study therapy until 30 days after last dose (Assessed up to September 2016, approximately 90 months)

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|-------------------------------|-----------------|-----------------|-----------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 29 | 17 | 84 | 51 |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Complete (0%) | 82.8 | 29.4 | 94.0 | 96.1 |
| Partial (>0% - 35%) | 6.9 | 23.5 | 2.4 | 2.0 |
| Minor (>35% - 65%) | 3.4 | 0 | 0 | 0 |
| Minimal (>65% - 95%) | 3.4 | 0 | 1.2 | 2.0 |
| No Response (>95% - 100%) | 0 | 5.9 | 0 | 0 |
| Unable to Determine | 3.4 | 41.2 | 2.4 | 0 |

| End point values | Cohort 3b | | | |
|-------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 33 | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Complete (0%) | 90.9 | | | |
| Partial (>0% - 35%) | 3.0 | | | |
| Minor (>35% - 65%) | 0 | | | |
| Minimal (>65% - 95%) | 0 | | | |
| No Response (>95% - 100%) | 0 | | | |
| Unable to Determine | 6.1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Major Cytogenetic Response (MCyR)

| | |
|---|---|
| End point title | Time to Major Cytogenetic Response (MCyR) |
| End point description: | |
| Time to MCyR is defined as the time from first dose of dasatinib until the first day MCyR criteria are met, computed only for subjects whose best response is MCyR. | |
| End point type | Secondary |
| End point timeframe: | |
| From first dose until MCyR criteria are met (assessed up to September 2016, approximately 90 months) | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|----------------------------------|------------------|------------------|------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 26 | 9 | 81 | 50 |
| Units: months | | | | |
| median (confidence interval 95%) | 3.1 (2.8 to 4.1) | 1.6 (0.5 to 5.7) | 3.0 (2.9 to 4.3) | 3.3 (2.9 to 5.6) |

| End point values | Cohort 3b | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 31 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 3.0 (2.8 to 5.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Major Cytogenetic Response (MCyR)

| | |
|--|---|
| End point title | Duration of Major Cytogenetic Response (MCyR) |
| End point description: | |
| Duration of MCyR will be computed from the first day criteria are met for MCyR until the date PD is reported (or treatment is discontinued for PD) or death. Subjects who neither discontinue due to PD nor die will be censored on the date of their last hematologic or cytogenetic assessment, whichever comes last. Only subjects with MCyR were analyzed. | |
| End point type | Secondary |
| End point timeframe: | |
| From first day criteria are met for MCyR until the date PD is reported or death (assessed up to September 2016, approximately 90 months) | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|----------------------------------|-----------------------|---------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 26 | 9 | 81 | 50 |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (54.9 to 99999) | 11.2 (0.3 to 99999) | 99999 (52.7 to 99999) | 99999 (52.7 to 99999) |

| End point values | Cohort 3b | | | |
|----------------------------------|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 31 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Cytogenetic Response (CCyR)

| | |
|-----------------|--|
| End point title | Time to Complete Cytogenetic Response (CCyR) |
|-----------------|--|

End point description:

Time to CCyR is defined as the time from first dose of dasatinib until the first day CCyR criteria are met, computed only for subjects whose best response is CCyR.

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

End point timeframe:

From first dose until CCyR criteria are met, assessed up to September 2016 (approximately 90 months)

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|----------------------------------|------------------|------------------|------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 24 | 7 | 79 | 49 |
| Units: months | | | | |
| median (confidence interval 95%) | 3.9 (2.8 to 5.6) | 1.6 (0.5 to 5.7) | 5.6 (5.0 to 6.0) | 5.7 (3.7 to 6.2) |

| End point values | Cohort 3b | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 30 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.6 (3.1 to 6.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Complete Cytogenetic Response (CCyR)

| | |
|-----------------|--|
| End point title | Duration of Complete Cytogenetic Response (CCyR) |
|-----------------|--|

End point description:

Duration of CCyR will be computed from the first day criteria are met for CCyR until the date PD is reported (or treatment is discontinued for PD) or death. Subjects who neither discontinue due to PD nor die will be censored on the date of their last hematologic or cytogenetic assessment, whichever comes last.

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

End point timeframe:

From first day criteria are met for CCyR until the date of progressive disease or death (assessed up to September 2016, approximately 90 months)

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|----------------------------------|-----------------------|----------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 24 | 5 | 79 | 49 |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (54.9 to 99999) | 99999 (1.0 to 99999) | 99999 (49.9 to 99999) | 99999 (49.9 to 99999) |

| End point values | Cohort 3b | | | |
|----------------------------------|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 30 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Rate at 2 years

| | |
|-----------------|---|
| End point title | Progression-Free Survival (PFS) Rate at 2 years |
|-----------------|---|

End point description:

PFS is defined as time from the first dosing date until the time PD is first documented by the investigator or death. Subjects who die without a reported date of progression will be considered to have progressed on the date of death. Subjects who neither progress nor die will be censored on the date of their last cytogenetic or hematologic assessment. The percentages of progression-free subjects at 2 years are based on Kaplan-Meier estimation.

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

End point timeframe:

2 years

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|----------------------------------|---------------------|--------------------|---------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 29 | 17 | 84 | 51 |
| Units: percentage | | | | |
| median (confidence interval 95%) | 81.7 (61.4 to 92.0) | 20.5 (3.7 to 46.4) | 95.1 (87.4 to 98.1) | 94.0 (82.6 to 98.0) |

| End point values | Cohort 3b | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 33 | | | |
| Units: percentage | | | | |
| median (confidence interval 95%) | 96.8 (79.2 to 99.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Hematologic Response (CHR)

| | |
|---|---|
| End point title | Time to Complete Hematologic Response (CHR) |
| End point description: | |
| Time to CHR is defined as the time from first dose of dasatinib until the first day CHR criteria are met, provided they are confirmed 4 weeks later, computed only for subjects whose best response is CHR. | |
| End point type | Secondary |
| End point timeframe: | |
| From first dose until CHR criteria are met, assessed up to September 2016 (approximately 90 months) | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|----------------------------------|------------------|------------------|------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 27 | 5 | 81 | 51 |
| Units: months | | | | |
| median (confidence interval 95%) | 0.7 (0.5 to 1.8) | 2.5 (0.5 to 2.8) | 1.2 (0.9 to 1.4) | 1.2 (0.9 to 1.4) |

| End point values | Cohort 3b | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 30 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.0 (0.7 to 1.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Complete Hematologic Response (CHR)

| | |
|--|---|
| End point title | Duration of Complete Hemotologic Response (CHR) |
| End point description: | |
| Duration of CHR will be computed from the first day all criteria are met for CHR, provided they are confirmed 4 weeks later, until the date progressive disease (PD) is reported (or treatment is discontinued for PD) or death. Subjects who neither discontinue due to PD nor die will be censored on the date of their last hematologic assessment. Only subjects with CHR were analyzed. | |
| End point type | Secondary |
| End point timeframe: | |
| From first day criteria are met for CHR until date of disease progression or death (assessed up to September 2016, approximately 90 months) | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|----------------------------------|------------------------|----------------------|------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 27 | 5 | 81 | 51 |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (1.9 to 99999) | 99999 (99999 to 99999) | 99999 (99999 to 99999) |

| End point values | Cohort 3b | | | |
|----------------------------------|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 30 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival Rate at 2 years

| | |
|---|---------------------------------------|
| End point title | Disease-Free Survival Rate at 2 years |
| End point description: | |
| Disease free survival is defined as time from CCyR for Subjects with newly diagnosed chronic phase CML and for Subjects with chronic phase CML who are resistant or intolerant to imatinib (cohort 3 and cohort 1), and as time from CHR for Subjects with advanced phase CML and PH + ALL (cohort 2) until the time progression is first documented by the investigator or death from any cause. The percentages of disease-free subjects at 2 years are based on Kaplan-Meier estimation. | |
| End point type | Secondary |
| End point timeframe: | |
| 2 years | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|----------------------------------|---------------------|---------------------|---------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 24 | 5 | 79 | 49 |
| Units: percentage | | | | |
| median (confidence interval 95%) | 86.9 (64.6 to 95.6) | 60.0 (12.6 to 88.2) | 98.7 (91.2 to 99.8) | 97.9 (86.1 to 99.7) |

| End point values | Cohort 3b | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 30 | | | |
| Units: percentage | | | | |
| median (confidence interval 95%) | 100 (100 to 100) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Rate at 2 years

| | |
|-----------------|---------------------------------------|
| End point title | Overall Survival (OS) Rate at 2 years |
|-----------------|---------------------------------------|

End point description:

OS is defined as time from the first dosing date until the time of death. All subjects will be followed yearly for survival for up to 5 years after treatment discontinuation. Subjects who have not died or who are lost to follow-up will be censored on the last date the subject is known to be alive. The percentages of surviving participants at 2 years are based on Kaplan-Meier estimation.

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

End point timeframe:

2 years

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|----------------------------------|---------------------|---------------------|------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 29 | 17 | 84 | 51 |
| Units: percentage | | | | |
| median (confidence interval 95%) | 96.4 (77.2 to 99.5) | 32.2 (10.6 to 56.4) | 100 (100 to 100) | 100 (100 to 100) |

| End point values | Cohort 3b | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 33 | | | |
| Units: percentage | | | | |
| median (confidence interval 95%) | 100 (100 to | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Major Molecular Response (MMR) Rate

| | |
|-----------------|-------------------------------------|
| End point title | Major Molecular Response (MMR) Rate |
|-----------------|-------------------------------------|

End point description:

Molecular response was assessed using BCR-ABL transcript levels measurement by real-time quantitative polymerase chain reaction (qPCR). MMR for subjects with the p210 BCR-ABL transcript variant was defined as a ratio BCR-ABL/ABL $\leq 10^{-3}$ or 0.1% on the international scale. In this study, ABL was used as the control-gene. For a subject with the p190 BCR-ABL transcript variant (occurring in Cohort 2 only), on-study assessments were compared to the participant's individual baseline BCR-ABL/ABL ratio and a reduction to $< 0.1\%$ or a 3-log reduction from baseline was considered an MMR.

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

End point timeframe:

From date of first treatment to date of MMR (assessed up to September 2016, approximately 90 months)

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|----------------------------------|---------------------|---------------------|---------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 29 | 17 | 84 | 51 |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 62.1 (42.3 to 79.3) | 29.4 (10.3 to 56.0) | 79.8 (69.6 to 87.7) | 88.2 (76.1 to 95.6) |

| End point values | Cohort 3b | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 33 | | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 66.7 (48.2 to 82.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Molecular Response (CMR) Rate

| | |
|---|--|
| End point title | Complete Molecular Response (CMR) Rate |
| End point description: | |
| Molecular response was assessed using BCR-ABL transcript levels measurement by real-time quantitative polymerase chain reaction (qPCR). CMR is defined as absence of BCR-ABL rearrangements by real-time qPCR analysis. The percentage of treated subjects with CMR is reported by arm. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of first treatment to date of CMR (assessed up to September 2016, approximately 90 months) | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|----------------------------------|---------------------|--------------------|---------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 29 | 17 | 84 | 51 |
| Units: percentage | | | | |
| number (confidence interval 95%) | 24.1 (10.3 to 43.5) | 17.6 (3.8 to 43.4) | 29.8 (20.3 to 40.7) | 43.1 (29.3 to 57.8) |

| End point values | Cohort 3b | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 33 | | | |
| Units: percentage | | | | |
| number (confidence interval 95%) | 9.1 (1.9 to 24.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Major Cytogenetic Response (MCyR) Rate up to 2 years

| | |
|---|--|
| End point title | Major Cytogenetic Response (MCyR) Rate up to 2 years |
| End point description: | |
| Major Cytogenetic Response (MCyR) rate is defined as the proportion of all treated subjects who achieved a complete (0%) or partial (1%-35% Ph+ metaphases in at least 20 metaphases in bone marrow) cytogenetic response. The percentage of treated subjects with MCyR is reported by arm. | |
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|----------------------------------|---------------------|---------------------|---------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 29 | 17 | 84 | 51 |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| 12 months | 89.7 (72.6 to 97.8) | 58.8 (32.9 to 81.6) | 96.4 (89.9 to 99.3) | 98.0 (89.6 to 100.0) |
| 24 months | 89.7 (72.6 to 97.8) | 58.8 (32.9 to 81.6) | 96.4 (89.9 to 99.3) | 98.0 (89.6 to 100.0) |

| End point values | Cohort 3b | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 33 | | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| 12 months | 93.9 (79.8 to 99.3) | | | |
| 24 months | 93.9 (79.8 to 99.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Cytogenetic Response (CCyR) Rate up to 2 years

| | |
|--|---|
| End point title | Complete Cytogenetic Response (CCyR) Rate up to 2 years |
| End point description: | |
| Complete Cytogenetic Response (CCyR) rate is defined as the proportion of all treated subjects who achieve a CCyR while on-study. CCyR rate is defined as 0% Ph+ metaphases in at least 20 metaphases in bone marrow. The percentage of treated subjects with CCyR is reported by arm. | |
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|----------------------------------|---------------------|---------------------|---------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 29 | 17 | 84 | 51 |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| 12 months | 75.9 (56.5 to 89.7) | 41.2 (18.4 to 67.1) | 92.9 (85.1 to 97.3) | 96.1 (86.5 to 99.5) |
| 24 months | 82.8 (64.2 to 94.2) | 41.2 (18.4 to 67.1) | 94.0 (86.7 to 98.0) | 96.1 (86.5 to 99.5) |

| End point values | Cohort 3b | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 33 | | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| 12 months | 87.9 (71.8 to 96.6) | | | |
| 24 months | 90.9 (75.7 to 98.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Major Molecular Response (MMR) Rate up to 2 years

| | |
|--|---|
| End point title | Major Molecular Response (MMR) Rate up to 2 years |
| End point description: | |
| Molecular response was assessed using BCR-ABL transcript levels measurement by real-time qPCR. MMR for Subjects with the p210 BCR-ABL transcript variant is defined according to the recommendations of Hughes et al. as a ratio BCR-ABL/ABL $\leq 10^{-3}$ or 0.1% on the international scale proposed by the authors. The standardized baseline, as established in the IRIS trial, is taken to represent 100% on the international scale and a 3-log reduction in ratio (BCR-ABL transcripts/ABL or BCR) from the standardized baseline (MMR) is fixed at 0.1%. In this study, ABL or other housekeeping gene, will be used as the control-gene. For a Subject with the p190 BCR-ABL transcript variant, on-study assessments will be compared to the Subject's individual baseline BCR-ABL/ABL ratio and a reduction to $< 0.1\%$ or a 3-log reduction from baseline will be considered an MMR. The percentage of treated subjects with MMR is reported by arm. | |
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|----------------------------------|---------------------|---------------------|---------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 29 | 17 | 84 | 51 |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| 12 months | 41.4 (23.5 to 61.1) | 23.5 (6.8 to 49.9) | 52.4 (41.2 to 63.4) | 56.9 (42.2 to 70.7) |
| 24 months | 55.2 (35.7 to 73.6) | 29.4 (10.3 to 56.0) | 70.2 (59.3 to 79.7) | 74.5 (60.4 to 85.7) |

| End point values | Cohort 3b | | | |
|------------------|-----------|--|--|--|
|------------------|-----------|--|--|--|

| | | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 33 | | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| 12 months | 45.5 (28.1 to 63.6) | | | |
| 24 months | 63.6 (45.1 to 79.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Molecular Response (CMR) Rate up to 2 years

| | |
|---|--|
| End point title | Complete Molecular Response (CMR) Rate up to 2 years |
| End point description: | |
| Molecular response was assessed using BCR-ABL transcript levels measurement by real-time quantitative polymerase chain reaction (qPCR). (CMR) is defined as absence of BCR-ABL rearrangements by real-time qPCR analysis. The percentage of treated subjects with CMR is reported by arm. | |
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 3a |
|----------------------------------|--------------------|--------------------|---------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 29 | 17 | 84 | 51 |
| Units: percentage | | | | |
| number (confidence interval 95%) | | | | |
| 12 months | 6.9 (0.8 to 22.8) | 11.8 (1.5 to 36.4) | 8.3 (3.4 to 16.4) | 9.8 (3.3 to 21.4) |
| 24 months | 17.2 (5.8 to 35.8) | 11.8 (1.5 to 36.4) | 21.4 (13.2 to 31.7) | 29.4 (17.5 to 43.8) |

| End point values | Cohort 3b | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 33 | | | |
| Units: percentage | | | | |
| number (confidence interval 95%) | | | | |
| 12 months | 6.1 (0.7 to 20.2) | | | |
| 24 months | 9.1 (1.9 to 24.3) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug until the last dose of study drug plus 30 days

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Cohort 3a |
|-----------------------|-----------|

Reporting group description:

Children and adolescents with CP-CML who were treatment-naïve received dasatinib tablets at 60 mg/m² QD on a continuous oral regimen.

| | |
|-----------------------|-----------|
| Reporting group title | Cohort 3b |
|-----------------------|-----------|

Reporting group description:

Children and adolescents with CP-CML who were treatment-naïve received dasatinib powder for oral suspension (PFOS) at 72 mg/m² QD on a continuous oral regimen.

| | |
|-----------------------|----------|
| Reporting group title | Cohort 1 |
|-----------------------|----------|

Reporting group description:

Children and adolescents with CP-CML who were resistant or intolerant to imatinib received dasatinib tablets at 60 mg/m² QD on a continuous oral regimen.

| | |
|-----------------------|-----------------|
| Reporting group title | Cohort 2 BP-CML |
|-----------------------|-----------------|

Reporting group description:

Children and adolescents with BP-CML who were resistant or intolerant to, or relapsed after imatinib therapy received dasatinib tablets at a dose schedule of 80 mg/m² QD on a continuous oral regimen.

| | |
|-----------------------|------------------|
| Reporting group title | Cohort 2 Ph+ ALL |
|-----------------------|------------------|

Reporting group description:

Children and adolescents with Ph+ ALL who were resistant or intolerant to, or relapsed after imatinib therapy received dasatinib tablets at a dose schedule of 80 mg/m² QD on a continuous oral regimen.

| Serious adverse events | Cohort 3a | Cohort 3b | Cohort 1 |
|---|------------------|-----------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 19 / 51 (37.25%) | 9 / 33 (27.27%) | 13 / 29 (44.83%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute lymphocytic leukaemia recurrent | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blast cell proliferation | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blast crisis in myelogenous leukaemia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic myeloid leukaemia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukaemia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukaemia recurrent | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 33 (6.06%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Bone marrow transplant | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|----------------|----------------|----------------|
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disease progression | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 3 / 33 (9.09%) | 2 / 29 (6.90%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Genital haemorrhage | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Personality change | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Facial bones fracture | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gun shot wound | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 33 (3.03%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Left ventricular dysfunction | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Arachnoiditis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial nerve disorder | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 1 / 33 (3.03%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 6 / 7 | 0 / 1 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 2 / 29 (6.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal ulcer | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 3 / 33 (9.09%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 3 / 33 (9.09%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 2 / 29 (6.90%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis aseptic | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myringitis | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis externa | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periorbital cellulitis | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper aerodigestive tract infection | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Cohort 2 BP-CML | Cohort 2 Ph+ ALL | |
|---|-----------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 8 (87.50%) | 6 / 9 (66.67%) | |
| number of deaths (all causes) | 1 | 3 | |
| number of deaths resulting from adverse events | | | |

| | | | |
|---|----------------|----------------|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute lymphocytic leukaemia recurrent | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Blast cell proliferation | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blast crisis in myelogenous leukaemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukaemia recurrent | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 9 (22.22%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Vascular disorders | | | |
| Jugular vein thrombosis | | | |

| | | | |
|--|----------------|---------------|--|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Bone marrow transplant | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disease progression | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Genital haemorrhage | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Personality change | | | |

| | | | |
|---|----------------|---------------|--|
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Facial bones fracture | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gun shot wound | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Overdose | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Arachnoiditis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial nerve disorder | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Seizure | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 3 / 9 (33.33%) | |
| occurrences causally related to treatment / all | 3 / 5 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 9 (11.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal ulcer | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bacterial sepsis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis aseptic | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myringitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral herpes | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis externa | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periorbital cellulitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Upper aerodigestive tract infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Cohort 3a | Cohort 3b | Cohort 1 |
|---|------------------|-------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 50 / 51 (98.04%) | 33 / 33 (100.00%) | 27 / 29 (93.10%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 3 / 33 (9.09%) | 1 / 29 (3.45%) |
| occurrences (all) | 3 | 4 | 1 |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 3 / 33 (9.09%) | 1 / 29 (3.45%) |
| occurrences (all) | 2 | 5 | 1 |
| Hot flush | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 5 / 51 (9.80%) | 4 / 33 (12.12%) | 1 / 29 (3.45%) |
| occurrences (all) | 6 | 5 | 1 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 0 / 33 (0.00%) | 3 / 29 (10.34%) |
| occurrences (all) | 3 | 0 | 4 |
| Chills | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 3 / 33 (9.09%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 3 | 1 |
| Fatigue | | | |

| | | | |
|-----------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 10 / 51 (19.61%) | 7 / 33 (21.21%) | 8 / 29 (27.59%) |
| occurrences (all) | 22 | 18 | 14 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Mass | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 33 (6.06%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 2 | 1 |
| Non-Cardiac chest pain | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 3 / 33 (9.09%) | 0 / 29 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 1 / 33 (3.03%) | 3 / 29 (10.34%) |
| occurrences (all) | 2 | 1 | 3 |
| Pain | | | |
| subjects affected / exposed | 6 / 51 (11.76%) | 5 / 33 (15.15%) | 3 / 29 (10.34%) |
| occurrences (all) | 9 | 7 | 3 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 2 |
| Pyrexia | | | |
| subjects affected / exposed | 23 / 51 (45.10%) | 10 / 33 (30.30%) | 14 / 29 (48.28%) |
| occurrences (all) | 77 | 22 | 46 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 5 |

| | | | |
|---|------------------|------------------|------------------|
| Reproductive system and breast disorders | | | |
| Breast mass | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 1 | 0 | 1 |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 1 / 33 (3.03%) | 1 / 29 (3.45%) |
| occurrences (all) | 14 | 1 | 3 |
| Menstruation irregular | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 2 |
| Vaginal discharge | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 16 / 51 (31.37%) | 9 / 33 (27.27%) | 13 / 29 (44.83%) |
| occurrences (all) | 38 | 20 | 25 |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 2 / 33 (6.06%) | 3 / 29 (10.34%) |
| occurrences (all) | 6 | 2 | 7 |
| Epistaxis | | | |
| subjects affected / exposed | 5 / 51 (9.80%) | 4 / 33 (12.12%) | 3 / 29 (10.34%) |
| occurrences (all) | 5 | 4 | 4 |
| Nasal congestion | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 2 / 33 (6.06%) | 3 / 29 (10.34%) |
| occurrences (all) | 4 | 4 | 5 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 10 / 51 (19.61%) | 11 / 33 (33.33%) | 6 / 29 (20.69%) |
| occurrences (all) | 16 | 18 | 10 |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 5 / 33 (15.15%) | 0 / 29 (0.00%) |
| occurrences (all) | 5 | 8 | 0 |
| Productive cough | | | |

| | | | |
|--------------------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract congestion | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Rhinalgia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 3 / 33 (9.09%) | 2 / 29 (6.90%) |
| occurrences (all) | 3 | 3 | 2 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 11 / 51 (21.57%) | 4 / 33 (12.12%) | 3 / 29 (10.34%) |
| occurrences (all) | 15 | 6 | 4 |
| Wheezing | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 3 / 33 (9.09%) | 2 / 29 (6.90%) |
| occurrences (all) | 2 | 3 | 3 |
| Depression | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 1 / 33 (3.03%) | 1 / 29 (3.45%) |
| occurrences (all) | 4 | 1 | 1 |
| Insomnia | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 2 / 33 (6.06%) | 1 / 29 (3.45%) |
| occurrences (all) | 3 | 2 | 2 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 4 / 33 (12.12%) | 4 / 29 (13.79%) |
| occurrences (all) | 5 | 6 | 5 |
| Aspartate aminotransferase increased | | | |

| | | | |
|--|----------------|------------------|-----------------|
| subjects affected / exposed | 3 / 51 (5.88%) | 3 / 33 (9.09%) | 3 / 29 (10.34%) |
| occurrences (all) | 3 | 4 | 3 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 4 / 33 (12.12%) | 0 / 29 (0.00%) |
| occurrences (all) | 4 | 5 | 0 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gamma-Glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 5 / 33 (15.15%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 8 | 1 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 5 / 33 (15.15%) | 0 / 29 (0.00%) |
| occurrences (all) | 1 | 6 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 11 / 33 (33.33%) | 1 / 29 (3.45%) |
| occurrences (all) | 3 | 19 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 1 / 33 (3.03%) | 1 / 29 (3.45%) |
| occurrences (all) | 3 | 1 | 1 |
| Weight increased | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 3 / 33 (9.09%) | 2 / 29 (6.90%) |
| occurrences (all) | 3 | 5 | 2 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|-----------------------------|------------------|------------------|------------------|
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 33 (6.06%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 2 | 2 |
| Contusion | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 4 / 33 (12.12%) | 2 / 29 (6.90%) |
| occurrences (all) | 6 | 8 | 3 |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Procedural pain | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 5 | 0 |
| Sunburn | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 33 (3.03%) | 2 / 29 (6.90%) |
| occurrences (all) | 1 | 1 | 2 |
| Nervous system disorders | | | |
| Arachnoiditis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 12 / 51 (23.53%) | 3 / 33 (9.09%) | 2 / 29 (6.90%) |
| occurrences (all) | 19 | 4 | 3 |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Facial paralysis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 24 / 51 (47.06%) | 15 / 33 (45.45%) | 17 / 29 (58.62%) |
| occurrences (all) | 82 | 25 | 52 |
| Neuropathy peripheral | | | |

| | | | |
|--------------------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 5 / 29 (17.24%) |
| occurrences (all) | 0 | 1 | 5 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 10 / 51 (19.61%) | 5 / 33 (15.15%) | 2 / 29 (6.90%) |
| occurrences (all) | 16 | 16 | 6 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haemoglobinaemia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 2 / 33 (6.06%) | 2 / 29 (6.90%) |
| occurrences (all) | 6 | 13 | 2 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 17 / 51 (33.33%) | 8 / 33 (24.24%) | 6 / 29 (20.69%) |
| occurrences (all) | 35 | 21 | 14 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 13 / 51 (25.49%) | 7 / 33 (21.21%) | 5 / 29 (17.24%) |
| occurrences (all) | 22 | 17 | 7 |

| | | | |
|-----------------------------|------------------|-----------------|------------------|
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 7 / 51 (13.73%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 8 | 3 | 0 |
| Hypoacusis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 2 / 33 (6.06%) | 1 / 29 (3.45%) |
| occurrences (all) | 3 | 2 | 1 |
| Eye oedema | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Eye pain | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 1 / 33 (3.03%) | 3 / 29 (10.34%) |
| occurrences (all) | 4 | 1 | 3 |
| Periorbital oedema | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 1 / 33 (3.03%) | 1 / 29 (3.45%) |
| occurrences (all) | 3 | 1 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 18 / 51 (35.29%) | 7 / 33 (21.21%) | 10 / 29 (34.48%) |
| occurrences (all) | 42 | 12 | 37 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 12 / 51 (23.53%) | 4 / 33 (12.12%) | 8 / 29 (27.59%) |
| occurrences (all) | 32 | 9 | 16 |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Anal ulcer | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Colitis | | | |

| | | | |
|-----------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 3 / 51 (5.88%) | 1 / 33 (3.03%) | 1 / 29 (3.45%) |
| occurrences (all) | 7 | 2 | 1 |
| Constipation | | | |
| subjects affected / exposed | 9 / 51 (17.65%) | 5 / 33 (15.15%) | 4 / 29 (13.79%) |
| occurrences (all) | 11 | 6 | 4 |
| Diarrhoea | | | |
| subjects affected / exposed | 27 / 51 (52.94%) | 12 / 33 (36.36%) | 17 / 29 (58.62%) |
| occurrences (all) | 87 | 21 | 72 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 1 | 2 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 1 | 2 |
| Gastritis | | | |
| subjects affected / exposed | 6 / 51 (11.76%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences (all) | 9 | 1 | 0 |
| Gingival bleeding | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 0 / 33 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 2 | 0 | 2 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 33 (6.06%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 3 | 1 |
| Nausea | | | |
| subjects affected / exposed | 20 / 51 (39.22%) | 10 / 33 (30.30%) | 11 / 29 (37.93%) |
| occurrences (all) | 38 | 24 | 28 |
| Oral pain | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 4 / 33 (12.12%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 17 | 0 |
| Tongue ulceration | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Toothache | | | |

| | | | |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 4 / 51 (7.84%) 4 | 1 / 33 (3.03%) 1 | 3 / 29 (10.34%) 5 |
| Vomiting subjects affected / exposed occurrences (all) | 22 / 51 (43.14%) 55 | 11 / 33 (33.33%) 30 | 15 / 29 (51.72%) 45 |
| Skin and subcutaneous tissue disorders | | | |
| Acne subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 7 / 33 (21.21%) 7 | 3 / 29 (10.34%) 5 |
| Alopecia subjects affected / exposed occurrences (all) | 5 / 51 (9.80%) 6 | 1 / 33 (3.03%) 1 | 2 / 29 (6.90%) 2 |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 3 | 2 / 33 (6.06%) 2 | 2 / 29 (6.90%) 2 |
| Dry skin subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 2 | 0 / 33 (0.00%) 0 | 4 / 29 (13.79%) 6 |
| Eczema subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 1 / 33 (3.03%) 1 | 2 / 29 (6.90%) 2 |
| Erythema subjects affected / exposed occurrences (all) | 4 / 51 (7.84%) 4 | 2 / 33 (6.06%) 4 | 2 / 29 (6.90%) 2 |
| Papule subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 33 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Petechiae subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 4 | 1 / 33 (3.03%) 3 | 1 / 29 (3.45%) 1 |
| Pruritus subjects affected / exposed occurrences (all) | 7 / 51 (13.73%) 8 | 4 / 33 (12.12%) 4 | 5 / 29 (17.24%) 5 |
| Rash subjects affected / exposed occurrences (all) | 14 / 51 (27.45%) 19 | 11 / 33 (33.33%) 25 | 8 / 29 (27.59%) 11 |

| | | | |
|---|------------------------|----------------------|-----------------------|
| Rash erythematous subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 4 | 0 / 33 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 3 / 33 (9.09%) 3 | 1 / 29 (3.45%) 1 |
| Rash papular subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 3 | 1 / 33 (3.03%) 1 | 0 / 29 (0.00%) 0 |
| Skin exfoliation subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 33 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Skin hypopigmentation subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 33 (0.00%) 0 | 2 / 29 (6.90%) 2 |
| Skin induration subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Urticaria subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 4 | 3 / 33 (9.09%) 6 | 2 / 29 (6.90%) 2 |
| Xeroderma subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 33 (0.00%) 0 | 2 / 29 (6.90%) 2 |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 4 / 51 (7.84%) 5 | 1 / 33 (3.03%) 1 | 0 / 29 (0.00%) 0 |
| Urinary incontinence subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 11 / 51 (21.57%) 22 | 6 / 33 (18.18%) 7 | 6 / 29 (20.69%) 15 |
| Back pain | | | |

| | | | |
|-----------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 7 / 51 (13.73%) | 6 / 33 (18.18%) | 4 / 29 (13.79%) |
| occurrences (all) | 14 | 6 | 6 |
| Bone pain | | | |
| subjects affected / exposed | 5 / 51 (9.80%) | 0 / 33 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 5 | 0 | 1 |
| Coccydynia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Groin pain | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 4 / 33 (12.12%) | 1 / 29 (3.45%) |
| occurrences (all) | 1 | 4 | 1 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 5 / 51 (9.80%) | 7 / 33 (21.21%) | 2 / 29 (6.90%) |
| occurrences (all) | 9 | 7 | 4 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 6 / 33 (18.18%) | 2 / 29 (6.90%) |
| occurrences (all) | 3 | 9 | 10 |
| Neck pain | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 11 / 51 (21.57%) | 14 / 33 (42.42%) | 15 / 29 (51.72%) |
| occurrences (all) | 24 | 26 | 23 |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 3 / 29 (10.34%) |
| occurrences (all) | 0 | 1 | 3 |
| Tendonitis | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 33 (0.00%) 0 | 2 / 29 (6.90%) 2 |
| Infections and infestations | | | |
| Abscess | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 3 / 29 (10.34%) |
| occurrences (all) | 0 | 1 | 3 |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 0 / 33 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 3 | 0 | 1 |
| Conjunctivitis | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 2 / 33 (6.06%) | 3 / 29 (10.34%) |
| occurrences (all) | 3 | 2 | 3 |
| Ear infection | | | |
| subjects affected / exposed | 5 / 51 (9.80%) | 3 / 33 (9.09%) | 1 / 29 (3.45%) |
| occurrences (all) | 10 | 5 | 2 |
| Febrile infection | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Folliculitis | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 7 / 51 (13.73%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 12 | 0 | 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 1 | 3 |
| Gingivitis | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 1 | 0 | 1 |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------------|------------------|-----------------|-----------------|
| Hordeolum | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 33 (3.03%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 1 | 3 |
| Influenza | | | |
| subjects affected / exposed | 6 / 51 (11.76%) | 1 / 33 (3.03%) | 3 / 29 (10.34%) |
| occurrences (all) | 14 | 1 | 3 |
| Localised infection | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 2 / 33 (6.06%) | 1 / 29 (3.45%) |
| occurrences (all) | 1 | 2 | 1 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 33 (6.06%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 10 / 51 (19.61%) | 4 / 33 (12.12%) | 7 / 29 (24.14%) |
| occurrences (all) | 16 | 8 | 9 |
| Oral herpes | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Pharyngitis | | | |
| subjects affected / exposed | 6 / 51 (11.76%) | 1 / 33 (3.03%) | 2 / 29 (6.90%) |
| occurrences (all) | 8 | 1 | 2 |
| Rhinitis | | | |
| subjects affected / exposed | 7 / 51 (13.73%) | 4 / 33 (12.12%) | 3 / 29 (10.34%) |
| occurrences (all) | 10 | 6 | 3 |
| Sinusitis | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 2 / 33 (6.06%) | 4 / 29 (13.79%) |
| occurrences (all) | 8 | 2 | 4 |
| Tonsillitis | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 0 / 33 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 3 | 0 | 1 |

| | | | |
|---|------------------------|------------------------|-----------------------|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 16 / 51 (31.37%) 30 | 11 / 33 (33.33%) 25 | 9 / 29 (31.03%) 23 |
| Viral infection subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 3 | 0 / 33 (0.00%) 0 | 3 / 29 (10.34%) 3 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 4 / 51 (7.84%) 8 | 1 / 33 (3.03%) 1 | 2 / 29 (6.90%) 2 |
| Fluid retention subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 2 / 33 (6.06%) 3 | 0 / 29 (0.00%) 0 |
| Hypercalcaemia subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 2 / 33 (6.06%) 2 | 0 / 29 (0.00%) 0 |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 3 / 33 (9.09%) 7 | 0 / 29 (0.00%) 0 |
| Hypermagnesaemia subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 2 | 1 / 33 (3.03%) 2 | 0 / 29 (0.00%) 0 |
| Hypernatraemia subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Hyperphosphataemia subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 33 (3.03%) 1 | 0 / 29 (0.00%) 0 |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 4 / 33 (12.12%) 4 | 0 / 29 (0.00%) 0 |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 33 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Hypocalcaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 51 (3.92%) | 3 / 33 (9.09%) | 2 / 29 (6.90%) |
| occurrences (all) | 2 | 3 | 2 |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 1 / 33 (3.03%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 33 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Cohort 2 BP-CML | Cohort 2 Ph+ ALL | |
|---|-----------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 8 (87.50%) | 9 / 9 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Phlebitis | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Chills | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 9 (22.22%) | |
| occurrences (all) | 1 | 2 | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 4 | |
| Mass | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Non-Cardiac chest pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain | | | |

| | | | |
|--|---------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 9 (11.11%) 2 | |
| Peripheral swelling subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 5 / 9 (55.56%) 12 | |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Reproductive system and breast disorders Breast mass subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 9 (0.00%) 0 | |
| Dysmenorrhoea subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Menstruation irregular subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Vaginal discharge subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Vaginal haemorrhage subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 9 (11.11%) 1 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 6 | 4 / 9 (44.44%) 5 | |
| Dyspnoea | | | |

| | | | |
|------------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Productive cough | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory tract congestion | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rhinalgia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 9 (11.11%) | |
| occurrences (all) | 1 | 1 | |
| Wheezing | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |

| | | | |
|---------------------------------------|----------------|----------------|--|
| Anxiety | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 9 (11.11%) | |
| occurrences (all) | 1 | 2 | |
| Depression | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 1 / 9 (11.11%) | |
| occurrences (all) | 6 | 1 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Gamma-Glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Neutrophil count decreased | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Weight decreased subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Weight increased subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 9 (0.00%) 0 | |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Contusion subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Foot fracture subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 9 (11.11%) 1 | |
| Procedural pain subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Sunburn subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Nervous system disorders | | | |
| Arachnoiditis subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 9 (0.00%) 0 | |
| Brain oedema subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 9 (0.00%) 0 | |
| Dizziness | | | |

| | | | |
|--------------------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Facial paralysis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Headache | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 5 / 9 (55.56%) | |
| occurrences (all) | 16 | 9 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 9 (22.22%) | |
| occurrences (all) | 5 | 3 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Haemoglobinaemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |

| | | | |
|---|----------------------|---------------------|--|
| Lymphopenia subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 3 | 0 / 9 (0.00%) 0 | |
| Neutropenia subjects affected / exposed occurrences (all) | 4 / 8 (50.00%) 9 | 3 / 9 (33.33%) 8 | |
| Pancytopenia subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 9 (11.11%) 1 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 4 / 8 (50.00%) 12 | 4 / 9 (44.44%) 5 | |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Hypoacusis subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 9 (0.00%) 0 | |
| Eye disorders Dry eye subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 9 (0.00%) 0 | |
| Eye oedema subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Eye pain subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 2 / 9 (22.22%) 2 | |
| Periorbital oedema subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Vision blurred subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 9 (0.00%) 0 | |
| Gastrointestinal disorders | | | |

| | | |
|-----------------------------|----------------|----------------|
| Abdominal pain | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 9 (22.22%) |
| occurrences (all) | 1 | 4 |
| Abdominal pain upper | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Anal fissure | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 |
| Anal ulcer | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 |
| Colitis | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 1 |
| Constipation | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 5 | 0 |
| Diarrhoea | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 3 / 9 (33.33%) |
| occurrences (all) | 3 | 6 |
| Dyspepsia | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Flatulence | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Gastritis | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Gingival bleeding | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Mouth ulceration | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |

| | | | |
|--|----------------|----------------|--|
| Nausea | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 2 / 9 (22.22%) | |
| occurrences (all) | 3 | 3 | |
| Oral pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 2 | 1 | |
| Tongue ulceration | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Toothache | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 3 / 9 (33.33%) | |
| occurrences (all) | 14 | 5 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Eczema | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Erythema | | | |

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|-----------------------------|----------------|----------------|
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Papule | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 |
| Petechiae | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 |
| Pruritus | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Rash | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 1 |
| Rash erythematous | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Rash maculo-papular | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Rash papular | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 |
| Skin exfoliation | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 |
| Skin hypopigmentation | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 |
| Skin induration | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 |
| Urticaria | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Xeroderma | | |

| | | | |
|--|--------------------|--------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 9 (0.00%) 0 | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urinary incontinence | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 9 (11.11%) | |
| occurrences (all) | 1 | 1 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 3 / 9 (33.33%) | |
| occurrences (all) | 1 | 3 | |
| Coccydynia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Groin pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal stiffness | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tendonitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Infections and infestations | | | |
| Abscess | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 9 (11.11%) | |
| occurrences (all) | 1 | 2 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Ear infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Febrile infection | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | |
|-----------------------------------|----------------|----------------|
| Folliculitis | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Gastroenteritis | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 1 |
| Gastroenteritis viral | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Gingivitis | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 |
| Herpes virus infection | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hordeolum | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 |
| Influenza | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Localised infection | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Lower respiratory tract infection | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Nasopharyngitis | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 |
| Oral herpes | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 3 | 0 |
| Otitis media | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 |

| | | | |
|------------------------------------|----------------|----------------|--|
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 9 (22.22%) | |
| occurrences (all) | 3 | 3 | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 9 (11.11%) | |
| occurrences (all) | 1 | 2 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypermagnesaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 5 | 1 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 17 December 2009 | <p>The primary purpose of this amendment is to include a new cohort of pediatric subjects with newly diagnosed treatment-naïve chronic phase chronic myelogenous leukemia (CP-CML) in this trial (Cohort #3) and to align the protocol with the Pediatric Investigational Plan (PIP). The changes include the following:</p> <ul style="list-style-type: none">- Expand the primary objective to include Cohort #3- Clarify the study duration and drug dispensation.- Established a data monitoring committee (DMC).- In order to improve safety, subjects who have a dose escalation will also be required to have another ECG performed if one was not previously done at that dose.- In order to improve safety, Cohort #3 subjects are required to have ECGs and echocardiograms performed yearly.- Expand the dose selection rationale.- Expand and update safety and efficacy summaries.- Clarify inclusion criteria for all cohorts.- Clarify the resistance criteria for Ph+ ALL.- Clarify the dose escalation criteria for Cohort #2.- Clarify the exclusion criteria for subjects with extramedullary disease to include subjects with isolated CNS involvement.- Add the T315I mutation to the exclusion criteria.- Add hypersensitivity to the active substance or to any of the excipients to the exclusion criteria.- Add patients with hereditary problems of galactose intolerance or Lapp lactase deficiency or glucose-galactose malabsorption to the exclusion criteria.- Clarify statistical definitions, including the definitions for progression-free survival (PFS) and disease-free survival (DFS).- Clarification as to the mode of drug administration.- Synchronized visit and assessment schedules (Table 6.1-1).- Change the molecular analysis schedule to coincide with scheduled visits.- Add the long-term follow-up plan for patients on protocol therapy.- Indicate the modalities of body surface area calculation in children.- Change in the medical monitor of the trial.- Correction of typographical errors. |
| 04 October 2010 | <p>The primary purpose of this amendment is to provide updated information regarding the use of dasatinib for first line treatment in adults with chronic phase CML as further justification to study the same patient population in children and adolescents (cohort #3). The changes include the following:</p> <ul style="list-style-type: none">- Expand Rationale in Section 1.3.1- Revised estimated number of sites- Separated diagnosis criteria for cohort #3 for clarity- Clarified diagnosis criteria for cohort #2- Revised resistance criteria to cap previous imatinib dose at 400 mg/day for subjects with high BSAs- Corrected multiple typographical errors- Clarified footnotes in flow chart |
| 12 June 2012 | <p>The primary purpose of this amendment is to clarify the objective of estimating the complete cytogenetic response (CCyR) rate to dasatinib therapy in children and adolescents with newly diagnosed CP-CML who are treatment-naïve. Additional changes to the protocol include:</p> <ul style="list-style-type: none">- Modify Definition of Complete and Major Molecular Response- Define disease free survival for each cohort- Addition of exploratory objective and endpoints for growth and development and bone mineral content- Primary and Secondary Endpoint Clarification- Clarification of Efficacy Analyses- Administrative Changes |

| | |
|------------------|--|
| 13 December 2012 | The purpose of this amendment is to expand cohort 3 to include a sub-cohort of 30 pediatric subjects < 18 years of age with treatment naive chronic phase CML who will receive dasatinib powder for oral suspension (PFOS). This increase in subject number will change our current plan to treat at least 50 newly diagnosed CP- CML pediatric subjects to 80 subjects in cohort 3. Subjects will be required to take the PFOS for a minimum of 12 months, during which data will be collected. We will assess the PK of dasatinib following oral administration of the PFOS in this sub-cohort. Hematologic, cytogenetic, and molecular responses by 12 months will be reported for the sub-cohort taking standard tablets, the sub-cohort using PFOS, and in Cohort 3 as a whole. Similarly, safety analysis will also be reported for both sub-cohorts (taking the standard tablets and PFOS) and in the cohort as a whole. We will also assess the taste properties of the PFOS formulation. This data collected and analyzed on this expanded cohort will be used support registration of the dasatinib PFOS in pediatric subjects. The dose of dasatinib when administered in PFOS formulation will be increased by 20% from the tablet dose, i.e, a dose of 72mg/m2 in this expanded cohort. The purpose of such dose adjustment is to match the exposure of the PFOS formulation to the reference tablet in order to maintain a desired efficacy. It was based on the findings from a bioequivalent study, which showed that AUC(INF) of the PFOS formulation was 19.2% lower compared to the reference tablet. |
| 18 July 2013 | The purpose of this amendment is to permanently close Cohort 2 to further enrollment and update the WOCBP guidelines. |
| 24 October 2013 | The purpose of this amendment is to correct the criteria for women of child bearing potential (WOCBP) and remove information on post menopausal women. |
| 13 April 2016 | This amendment: 1) adds testing for Hepatitis B virus (HBV) and 2) updates recommendations for methods of contraception and reemphasizes the need for contraception. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported