



Clinical trial results:

AN OPEN LABEL, RANDOMIZED (2:1) PHASE 2B STUDY OF DASATINIB VS IMATINIB IN PATIENTS WITH CHRONIC PHASE CHRONIC MYELOID LEUKEMIA WHO HAVE NOT ACHIEVED AN OPTIMAL RESPONSE TO 3 MONTHS OF THERAPY WITH 400 MG IMATINIB

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2011-006181-41 |
| Trial protocol | ES CZ BE IT AT PL HU |
| Global end of trial date | 12 April 2022 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 28 April 2023 |
| First version publication date | 28 April 2023 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | CA180-399 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01593254 |
| 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 | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, 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) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 24 April 2022 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 April 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Compare the rate of MMR at 12 months after Day 1 initiation of first-line treatment with imatinib, in patients randomized at month 3 to treatment with dasatinib 100mg QD or imatinib at any dose, after less than optimal response to first-line imatinib (BCR-ABL > 10% IS).

Protection of trial subjects:

The study was 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 | 29 October 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Argentina: 6 |
| Country: Number of subjects enrolled | Austria: 5 |
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | Brazil: 21 |
| Country: Number of subjects enrolled | Canada: 2 |
| Country: Number of subjects enrolled | China: 175 |
| Country: Number of subjects enrolled | Czechia: 1 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Italy: 7 |
| Country: Number of subjects enrolled | Poland: 12 |
| Country: Number of subjects enrolled | Korea, Republic of: 5 |
| Country: Number of subjects enrolled | Spain: 2 |
| Country: Number of subjects enrolled | Thailand: 8 |
| Country: Number of subjects enrolled | United States: 13 |
| Worldwide total number of subjects | 260 |
| EEA total number of subjects | 30 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 248 |
| From 65 to 84 years | 12 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

260 participants treated

Period 1

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

Arms

| | |
|------------------------------|----------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Arm 1: Imatinib (≥ 400 mg) |

Arm description:

Imatinib ≥ 400 mg tablets by mouth once daily (QD) or twice daily (BID) up to 60 months. Participants randomized to Imatinib that crossover to Dasatinib (n= 42); Participants randomized to Imatinib, no crossover (n = 44)

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Imatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

100mg, 400mg

| | |
|------------------|---------------------------|
| Arm title | Arm 2: Dasatinib (100 mg) |
|------------------|---------------------------|

Arm description:

Dasatinib 100 mg tablet by mouth QD up to 60 months

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Dasatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

20 mg, 50 mg, 80 mg,
100 mg and 140 mg

| Number of subjects in period 1 | Arm 1: Imatinib (≥ 400 mg) | Arm 2: Dasatinib (100 mg) |
|---------------------------------------|-------------------------------------|------------------------------|
| Started | 86 | 174 |
| Crossed Over to Dasatinib | 46 | 0 |
| Completed | 0 | 0 |
| Not completed | 86 | 174 |

| | | |
|--|----|-----|
| Adverse event, serious fatal | 3 | 3 |
| Disease progression | 2 | 7 |
| Admin reason by sponsor | 7 | 3 |
| participant withdrew consent | - | 9 |
| Poor/non compliance | 1 | 1 |
| participant request to discontinue study treatment | 1 | 3 |
| Study drug toxicity | 6 | 20 |
| Other Reasons | 61 | 115 |
| participant no longer meets study criteria | 1 | 1 |
| Imatinib treatment failure | 2 | - |
| lost to follow up | 1 | 6 |
| AE unrelated to study drug | - | 1 |
| Pregnancy | - | 3 |
| maximum clinical benefit | 1 | 2 |

Baseline characteristics

Reporting groups

| | |
|---|---------------------------|
| Reporting group title | Arm 1: Imatinib (≥400 mg) |
| Reporting group description: Imatinib ≥400 mg tablets by mouth once daily (QD) or twice daily (BID) up to 60 months. Participants randomized to Imatinib that crossover to Dasatinib (n= 42); Participants randomized to Imatinib, no crossover (n = 44) | |
| Reporting group title | Arm 2: Dasatinib (100 mg) |
| Reporting group description: Dasatinib 100 mg tablet by mouth QD up to 60 months | |

| Reporting group values | Arm 1: Imatinib (≥400 mg) | Arm 2: Dasatinib (100 mg) | Total |
|---|---------------------------|---------------------------|-------|
| Number of subjects | 86 | 174 | 260 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 82 | 166 | 248 |
| From 65-84 years | 4 | 8 | 12 |
| Age Continuous | | | |
| Units: years | | | |
| median | 39.5 | 35.0 | |
| full range (min-max) | 18 to 73 | 18 to 82 | - |
| Sex: Female, Male | | | |
| Units: | | | |
| Female | 16 | 41 | 57 |
| Male | 70 | 133 | 203 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 63 | 127 | 190 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 3 | 4 | 7 |
| White | 15 | 36 | 51 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 5 | 7 | 12 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 0 | 0 | 0 |
| Unknown or Not Reported | 86 | 174 | 260 |

End points

End points reporting groups

| | |
|---|----------------------------------|
| Reporting group title | Arm 1: Imatinib (≥ 400 mg) |
| Reporting group description: Imatinib ≥ 400 mg tablets by mouth once daily (QD) or twice daily (BID) up to 60 months. Participants randomized to Imatinib that crossover to Dasatinib (n= 42); Participants randomized to Imatinib, no crossover (n = 44) | |
| Reporting group title | Arm 2: Dasatinib (100 mg) |
| Reporting group description: Dasatinib 100 mg tablet by mouth QD up to 60 months | |

Primary: Percentage of patients achieving Major Molecular Response (MMR) after 12 months of CML treatment

| | |
|---|--|
| End point title | Percentage of patients achieving Major Molecular Response (MMR) after 12 months of CML treatment |
| End point description: Major Molecular Response, is defined as a 3-log reduction in BCR-ABL transcripts from the standardized baseline, which represents 100% on the international scale, so a 3-log reduction is fixed at 0.1% for MMR; N/A = not applicable. 95% CI is Clopper-Pearson(Exact) two-sided 95% confidence intervals. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by Sokal score(high, intermediate, low, and unknown) and time between 3 month molecular analysis and randomization (≤ 4 weeks vs > 4 weeks). Month 12 is calculated from | |
| End point type | Primary |
| End point timeframe: At 12 months after Day 1 initiation of 1st line treatment with imatinib or imatinib at any dose, after less than optimal response to first-line imatinib. | |

| End point values | Arm 1: Imatinib (≥ 400 mg) | Arm 2: Dasatinib (100 mg) | | |
|----------------------------------|-------------------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 86 | 174 | | |
| Units: Percentage of Patients | | | | |
| number (confidence interval 95%) | 12.8 (6.6 to 21.7) | 28.7 (22.1 to 36.1) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Statistical Analysis |
| Comparison groups | Arm 1: Imatinib (≥ 400 mg) v Arm 2: Dasatinib (100 mg) |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 260 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.005 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Median Time to Major Molecular Response (MMR)

| | |
|---|---|
| End point title | Median Time to Major Molecular Response (MMR) |
| End point description: | |
| Median time to major molecular response is the time between randomization date and first date that MMR (or MR4.5) criteria are satisfied. Participants who do not achieve MMR (or MR4.5) will be censored. | |
| Major Molecular Response, is defined as a 3-log reduction in BCR-ABL transcripts from the standardized baseline, which represents 100% on the international scale, so a 3-log reduction is fixed at 0.1% for MMR. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization to study completion. Approximately 115 months | |

| End point values | Arm 1: Imatinib (≥400 mg) | Arm 2: Dasatinib (100 mg) | | |
|----------------------------------|------------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 86 | 174 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 19.7 (14.2 to 26.4) | 13.9 (11.6 to 17.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

| | |
|---|---------------------------------|
| End point title | Progression Free Survival (PFS) |
| End point description: | |
| PFS is the time from randomization date to progression date or death date, whichever occurs first. Participants who neither progress nor die will be censored. | |
| Progression is defined as the following, meeting the criteria for accelerated or blast crisis CML are met at any time or death from any cause during treatment. | |
| Accelerated phase of CML: | |
| -The presence of ≥15%, but < 30% blasts in the blood or bone marrow | |
| -At least 30% blasts plus promyelocytes in the blood or bone marrow | |
| -At least 20% peripheral basophils | |
| -Thrombocytopenia (fewer than 100,000 platelets/mm ³) unrelated to treatment. | |
| Blast phase of CML | |
| -At least 30% blasts in the blood or bone marrow | |
| -Extramedullary involvement (e.g., chloromas), but not hepatosplenomegaly | |

Here "99999" means NA

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

End point timeframe:

From randomization to study completion. Approximately 115 months

| End point values | Arm 1: Imatinib (≥400 mg) | Arm 2: Dasatinib (100 mg) | | |
|----------------------------------|------------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 15 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99999 (89.3 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS is the time from randomization date to death date. Participants who have not died will be censored on the last date they are known to be alive.

Here "99999" means NA

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

End point timeframe:

From randomization to study completion. Approximately 115 months

| End point values | Arm 1: Imatinib (≥400 mg) | Arm 2: Dasatinib (100 mg) | | |
|----------------------------------|------------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 11 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99999 (89.3 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Molecular Response (MR)^4.5

| | |
|---|-------------------------------------|
| End point title | Time to Molecular Response (MR)^4.5 |
| End point description: | |
| Time to molecular response (MR)^4.5 is the time between randomization date and first date that MMR (or MR4.5) criteria are satisfied. Participants who do not achieve MMR (or MR4.5) will be censored. | |
| MR4.5 is defined as a 4.5-log reduction in BCR-ABL transcript from the standardized baseline (0.0032% IS, either detectable disease <= 0.0032% BCR-ABL (IS) or undetectable disease in cDNA (in same volume used for BCR-ABL) with >= 32,000 ABL transcripts. | |
| Here "99999" means NA | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization to study completion. Approximately 115 months | |

| End point values | Arm 1: Imatinib (≥400 mg) | Arm 2: Dasatinib (100 mg) | | |
|----------------------------------|------------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 86 | 174 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 67.7 (55.9 to 99999) | 74.5 (67.1 to 91.8) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose date up to 30 days after last dose of study therapy. Assessed from Sept. 2012 to Nov. 2017 (approximately 62 months)

Adverse event reporting additional description:

3 patients allocated to dasatinib decided to withdraw their consent prior to start taking the study drug and were never exposed. This is why the safety population is 171 in dasatinib arm even though 174 were randomized to Dasatinib

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

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|-----------------------|-----------|
| Reporting group title | Dasatinib |
|-----------------------|-----------|

Reporting group description:

Imatinib ≥400 mg tablets by mouth once daily (QD) or twice daily (BID) up to 60 months.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Dasatinib after Crossover Imatinib |
|-----------------------|------------------------------------|

Reporting group description:

Dasatinib 100 mg tablet by mouth QD

| | |
|-----------------------|----------|
| Reporting group title | Imatinib |
|-----------------------|----------|

Reporting group description:

Imatinib ≥400 mg tablets by mouth once daily (QD) or twice daily (BID) up to 60 months.

| Serious adverse events | Dasatinib | Dasatinib after Crossover Imatinib | Imatinib |
|---|-------------------|------------------------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 48 / 171 (28.07%) | 8 / 46 (17.39%) | 11 / 86 (12.79%) |
| number of deaths (all causes) | 11 | 4 | 1 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Central nervous system leukaemia | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Chronic myeloid leukaemia transformation | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Chronic myeloid leukaemia | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Benign breast neoplasm | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Thyroid cancer | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Surgical and medical procedures | | | |
| Hysterectomy | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Sudden death | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------|----------------|----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 11 / 171 (6.43%) | 3 / 46 (6.52%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 11 / 11 | 4 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 1 / 46 (2.17%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 2 / 171 (1.17%) | 0 / 46 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 2 / 171 (1.17%) | 1 / 46 (2.17%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Platelet count decreased | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 171 (0.00%) | 1 / 46 (2.17%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Limb injury | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Craniocerebral injury | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Paternal exposure timing unspecified | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Cardiac disorders | | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |

| | | | |
|---|-----------------|----------------|----------------|
| Pericardial effusion | | | |
| subjects affected / exposed | 2 / 171 (1.17%) | 1 / 46 (2.17%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 1 / 46 (2.17%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 1 / 46 (2.17%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Lymphadenitis | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 171 (1.17%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Visual impairment | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 171 (0.00%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vitreous haemorrhage | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Diabetic retinopathy | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periorbital oedema | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 1 / 46 (2.17%) | 0 / 86 (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 disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gingival cyst | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Haemorrhoids | | | |
| subjects affected / exposed | 2 / 171 (1.17%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Salivary gland cyst | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Duodenal ulcer | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 171 (0.00%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis haemorrhagic | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Large intestine polyp | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 2 / 171 (1.17%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic foot | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |

| | | | |
|---|-----------------|----------------|----------------|
| Glomerulonephritis chronic | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 1 / 46 (2.17%) | 0 / 86 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 1 / 46 (2.17%) | 0 / 86 (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 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 2 / 171 (1.17%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Anal abscess | | | |
| subjects affected / exposed | 2 / 171 (1.17%) | 1 / 46 (2.17%) | 0 / 86 (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 |
| Dengue fever | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |

| | | | |
|---|-----------------|-----------------|----------------|
| Tracheobronchitis | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| 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 sepsis | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 1 / 46 (2.17%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 5 / 171 (2.92%) | 6 / 46 (13.04%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 5 / 8 | 2 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| Lymphangitis | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Folliculitis | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 1 / 46 (2.17%) | 0 / 86 (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 |
| Erysipelas | | | |
| subjects affected / exposed | 2 / 171 (1.17%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 3 / 171 (1.75%) | 0 / 46 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Post procedural sepsis | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |
| Tuberculosis of central nervous system | | | |
| subjects affected / exposed | 0 / 171 (0.00%) | 0 / 46 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Complicated appendicitis | | | |
| subjects affected / exposed | 1 / 171 (0.58%) | 0 / 46 (0.00%) | 0 / 86 (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 |

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

| Non-serious adverse events | Dasatinib | Dasatinib after Crossover Imatinib | Imatinib |
|---|--------------------|------------------------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 159 / 171 (92.98%) | 42 / 46 (91.30%) | 68 / 86 (79.07%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 11 / 171 (6.43%) | 3 / 46 (6.52%) | 5 / 86 (5.81%) |
| occurrences (all) | 11 | 3 | 5 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 21 / 171 (12.28%) | 10 / 46 (21.74%) | 3 / 86 (3.49%) |
| occurrences (all) | 25 | 11 | 4 |
| Fatigue | | | |
| subjects affected / exposed | 9 / 171 (5.26%) | 0 / 46 (0.00%) | 7 / 86 (8.14%) |
| occurrences (all) | 11 | 0 | 8 |
| Asthenia | | | |
| subjects affected / exposed | 11 / 171 (6.43%) | 2 / 46 (4.35%) | 2 / 86 (2.33%) |
| occurrences (all) | 17 | 2 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 24 / 171 (14.04%) | 9 / 46 (19.57%) | 0 / 86 (0.00%) |
| occurrences (all) | 39 | 11 | 0 |
| Cough | | | |
| subjects affected / exposed | 18 / 171 (10.53%) | 3 / 46 (6.52%) | 3 / 86 (3.49%) |
| occurrences (all) | 23 | 3 | 3 |
| Dyspnoea | | | |
| subjects affected / exposed | 11 / 171 (6.43%) | 6 / 46 (13.04%) | 4 / 86 (4.65%) |
| occurrences (all) | 14 | 6 | 5 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 4 / 171 (2.34%) | 1 / 46 (2.17%) | 7 / 86 (8.14%) |
| occurrences (all) | 6 | 1 | 7 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 14 / 171 (8.19%) | 3 / 46 (6.52%) | 8 / 86 (9.30%) |
| occurrences (all) | 20 | 5 | 13 |
| Aspartate aminotransferase increased | | | |

| | | | |
|--|-------------------|------------------|------------------|
| subjects affected / exposed | 15 / 171 (8.77%) | 4 / 46 (8.70%) | 6 / 86 (6.98%) |
| occurrences (all) | 18 | 6 | 9 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 14 / 171 (8.19%) | 2 / 46 (4.35%) | 4 / 86 (4.65%) |
| occurrences (all) | 23 | 2 | 4 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 12 / 171 (7.02%) | 1 / 46 (2.17%) | 1 / 86 (1.16%) |
| occurrences (all) | 27 | 2 | 1 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 19 / 171 (11.11%) | 4 / 46 (8.70%) | 11 / 86 (12.79%) |
| occurrences (all) | 27 | 6 | 19 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 14 / 171 (8.19%) | 2 / 46 (4.35%) | 2 / 86 (2.33%) |
| occurrences (all) | 15 | 4 | 2 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 11 / 171 (6.43%) | 5 / 46 (10.87%) | 3 / 86 (3.49%) |
| occurrences (all) | 18 | 5 | 3 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 11 / 171 (6.43%) | 1 / 46 (2.17%) | 3 / 86 (3.49%) |
| occurrences (all) | 19 | 1 | 3 |
| High density lipoprotein decreased | | | |
| subjects affected / exposed | 10 / 171 (5.85%) | 1 / 46 (2.17%) | 2 / 86 (2.33%) |
| occurrences (all) | 16 | 1 | 3 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 26 / 171 (15.20%) | 10 / 46 (21.74%) | 15 / 86 (17.44%) |
| occurrences (all) | 64 | 27 | 23 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 26 / 171 (15.20%) | 13 / 46 (28.26%) | 13 / 86 (15.12%) |
| occurrences (all) | 53 | 28 | 16 |
| Platelet count decreased | | | |
| subjects affected / exposed | 36 / 171 (21.05%) | 12 / 46 (26.09%) | 19 / 86 (22.09%) |
| occurrences (all) | 78 | 27 | 25 |
| Low density lipoprotein increased | | | |

| | | | |
|---|--------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 9 / 171 (5.26%) 13 | 0 / 46 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Weight increased subjects affected / exposed occurrences (all) | 5 / 171 (2.92%) 5 | 3 / 46 (6.52%) 3 | 2 / 86 (2.33%) 2 |
| Cardiac disorders Pericardial effusion subjects affected / exposed occurrences (all) | 9 / 171 (5.26%) 10 | 4 / 46 (8.70%) 4 | 0 / 86 (0.00%) 0 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 11 / 171 (6.43%) 17 | 1 / 46 (2.17%) 1 | 6 / 86 (6.98%) 6 |
| Headache subjects affected / exposed occurrences (all) | 40 / 171 (23.39%) 53 | 6 / 46 (13.04%) 7 | 3 / 86 (3.49%) 3 |
| Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) | 42 / 171 (24.56%) 152 | 20 / 46 (43.48%) 84 | 20 / 86 (23.26%) 45 |
| Anaemia subjects affected / exposed occurrences (all) | 53 / 171 (30.99%) 102 | 15 / 46 (32.61%) 37 | 20 / 86 (23.26%) 38 |
| Leukopenia subjects affected / exposed occurrences (all) | 17 / 171 (9.94%) 45 | 8 / 46 (17.39%) 16 | 8 / 86 (9.30%) 20 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 40 / 171 (23.39%) 75 | 10 / 46 (21.74%) 36 | 12 / 86 (13.95%) 26 |
| Eye disorders Eyelid oedema subjects affected / exposed occurrences (all) | 4 / 171 (2.34%) 5 | 1 / 46 (2.17%) 1 | 8 / 86 (9.30%) 10 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 12 / 171 (7.02%) 13 | 0 / 46 (0.00%) 0 | 3 / 86 (3.49%) 5 |

| | | | |
|--|-------------------------|----------------------|------------------------|
| Vomiting subjects affected / exposed occurrences (all) | 9 / 171 (5.26%) 11 | 0 / 46 (0.00%) 0 | 5 / 86 (5.81%) 7 |
| Nausea subjects affected / exposed occurrences (all) | 17 / 171 (9.94%) 25 | 0 / 46 (0.00%) 0 | 9 / 86 (10.47%) 16 |
| Diarrhoea subjects affected / exposed occurrences (all) | 33 / 171 (19.30%) 52 | 8 / 46 (17.39%) 9 | 11 / 86 (12.79%) 23 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 14 / 171 (8.19%) 14 | 4 / 46 (8.70%) 5 | 4 / 86 (4.65%) 4 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 21 / 171 (12.28%) 29 | 3 / 46 (6.52%) 5 | 8 / 86 (9.30%) 8 |
| Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) | 10 / 171 (5.85%) 10 | 1 / 46 (2.17%) 1 | 7 / 86 (8.14%) 8 |
| Myalgia subjects affected / exposed occurrences (all) | 11 / 171 (6.43%) 11 | 2 / 46 (4.35%) 2 | 3 / 86 (3.49%) 3 |
| Muscle spasms subjects affected / exposed occurrences (all) | 3 / 171 (1.75%) 4 | 1 / 46 (2.17%) 1 | 11 / 86 (12.79%) 15 |
| Back pain subjects affected / exposed occurrences (all) | 8 / 171 (4.68%) 8 | 0 / 46 (0.00%) 0 | 5 / 86 (5.81%) 5 |
| Arthralgia subjects affected / exposed occurrences (all) | 8 / 171 (4.68%) 9 | 4 / 46 (8.70%) 4 | 6 / 86 (6.98%) 6 |
| Infections and infestations Influenza subjects affected / exposed occurrences (all) | 10 / 171 (5.85%) 12 | 0 / 46 (0.00%) 0 | 1 / 86 (1.16%) 1 |

| | | | |
|---|-------------------------|------------------------|------------------------|
| Nasopharyngitis subjects affected / exposed occurrences (all) | 16 / 171 (9.36%) 26 | 4 / 46 (8.70%) 5 | 6 / 86 (6.98%) 6 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 29 / 171 (16.96%) 56 | 12 / 46 (26.09%) 19 | 13 / 86 (15.12%) 21 |
| Bronchitis subjects affected / exposed occurrences (all) | 7 / 171 (4.09%) 10 | 1 / 46 (2.17%) 1 | 5 / 86 (5.81%) 5 |
| Metabolism and nutrition disorders | | | |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 27 / 171 (15.79%) 53 | 6 / 46 (13.04%) 12 | 18 / 86 (20.93%) 32 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 10 / 171 (5.85%) 13 | 2 / 46 (4.35%) 2 | 10 / 86 (11.63%) 13 |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 14 / 171 (8.19%) 23 | 0 / 46 (0.00%) 0 | 6 / 86 (6.98%) 9 |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 12 / 171 (7.02%) 31 | 1 / 46 (2.17%) 1 | 3 / 86 (3.49%) 4 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 9 / 171 (5.26%) 15 | 1 / 46 (2.17%) 1 | 5 / 86 (5.81%) 10 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 10 August 2012 | Imatinib changed to investigational agent; clarification of endpoints and procedures; modification of definition of progression-free survival; FISH (peripheral blood) added as alternative to conventional cytogenetic assessments; visit windows slightly lengthened; annual follow-up visit specified; timing of some assessments refined with extra detail such as ECG timing and addition of Morisky Medication Adherence Scale at visit 1; details of some procedures added (eg pill count specified for adherence); minor editorial changes . |
| 20 February 2013 | <p>This amendment includes changes to the protocol made in compliance with requests from the French Health Authority and the Korean Health Authority related to the monitoring of the safety of patients enrolled in the study and to the specifications of those subjects who are eligible for the study.</p> <p>In addition, the role of the internal data monitoring committee has been specified with respect to the frequency and scope of review, and language to specify that patients will be followed for overall survival post study follow-up has been added.</p> <p>Editorial changes for clarification made throughout the protocol.</p> |
| 10 April 2013 | <p>Country specific amendment for Austria Changes to the definition of post-menopausal woman.</p> <p>For women of childbearing potential (WOCBP) duration of contraceptive use after discontinuation of study drug must be a minimum of five half-lives of the investigational product.</p> <p>Duration of contraceptive use after discontinuation of study drug must be a minimum of five half-lives of the investigational product plus the addition of one sperm cycle of 60-90 days for sexually active men whose partners are WOCBP.</p> |
| 09 October 2013 | <p>(CARES) and a revision to an internal BMS directive related to "Women of Childbearing Potential (WOCBP) in clinical trials", this protocol was amended to adjust the frequency of pregnancy testing for sexually active female patients of childbearing potential to monthly pregnancy testing, Additional changes related to this initiative are:</p> <ul style="list-style-type: none">updated language related to WOCBP to harmonize with the new BMS directive including requiring 2 highly effective forms of birth controldefine highly effective forms of birth controladjust language related to sexually active fertile men with WOCBP partners and adapt the length of birth control to be used after the last dose of investigational product (90 days) <p>In addition, clarifications were added to the exclusion criteria for uncontrolled or significant cardiovascular disease and to the bone marrow assessment. Analyses conducted for safety and efficacy are now categorized under other analysis rather than interim analysis</p> |

| | |
|---------------|---|
| 07 May 2015 | <p>Increase in sample size</p> <p>Secondary and Tertiary objectives and endpoints modified</p> <p>Inclusion criteria for imatinib dose interruption prior to randomization and tolerance to imatinib further specified</p> <p>Patients with no evidence of clonal evolution, including those patients without cytogenetic testing at 3 months clarified as eligible for the study</p> <p>Interim Analyses added</p> <p>Change in assessment schedule for chest x-ray, echocardiogram, and complete blood count (CBC).</p> <p>The last on study visit has been clarified to "At study close: 60 months after LPFV" due to a change in the anticipated time for enrollment. Headings in the Table 5.1C have been adjusted accordingly.</p> <p>Update per BMS template for Destruction of Study Drug.</p> <p>Pill counts (drug adherence) deleted study assessment.</p> <p>Patient Reported Outcome and MDASI CML Symptom Burden deleted study assessment.</p> <p>Toxicity rates for CTC grades changed from "Grade 3" to "Grade 3 or above" (synopsis, statistical safety section)</p> <p>Exclusion from study due to pleural or pericardial effusion is clarified to at randomization rather than at "study entry";</p> <p>FISH (peripheral blood) allowed as a substitute for conventional cytogenetics at all time points except screening</p> <p>For cytogenetic response, the suggested number of metaphases (20) to be examined is no longer specified.</p> <p>Section 6.6, Potential Drug Induced Liver Injury (DILI) has been updated to reflect standard definitions for no known liver toxicities at baseline.</p> <p>Appendix 3: Medical Conditions and Drugs Which May Cause QTC Prolongation and Torsade De Pointes (Not All Inclusive):</p> <p>Update to Category Titles.</p> <p>Appendix 8: ELN 2013 replaces ELN 2009</p> <p>Updated references</p> <p>Editorial changes.</p> |
| 22 April 2016 | <p>Hepatitis B serology status of all randomized subjects now required and recommendations for subjects with positive serology included.</p> <p>Pregnancy Log (Appendix 9) has been revised to include method of contraception guidelines.</p> <p>Methods of contraception have been aligned with the most recent international guidance and are presented in Appendix 10.</p> <p>Protocol requirements for contraception while on treatment with dasatinib and for protocol-specified periods after the withdrawal or termination of treatment will now be reviewed with subjects as part of study assessments.</p> <p>The number of enrolled subjects has been increased to approximately 1100 due to enrollment/screen failure rate.</p> |
| 09 March 2018 | <p>Added clarifications for study assessments and assessment schedule for patients who crossover to treatment with dasatinib after ELN defined failure after treatment with imatinib and for all patients who remain on treatment after 60 months.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported