



## Clinical trial results:

### A PHASE IV, OPEN-LABEL, MULTICENTER STUDY OF DASATINIB IN CHRONIC-PHASE CHRONIC MYELOID LEUKEMIA (CP-CML) PATIENTS WITH CHRONIC LOW-GRADE NONHEMATOLOGIC TOXICITY TO IMATINIB

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2011-006180-21  |
| Trial protocol           | IT DE           |
| Global end of trial date | 01 October 2015 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 14 October 2016 |
| First version publication date | 14 October 2016 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | CA180-400 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01660906 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Bristol-Myers Squibb   |
| Sponsor organisation address | Chausée de la Hulpe 185, Brussels, Belgium, 1170   |
| Public contact               | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com |
| Scientific contact           | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb International Corporation, 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                       | 01 October 2015 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 01 October 2015 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the frequency of reduction in grade (Grade 2 to 1) or resolution of imatinib-related chronic Grade 1 or Grade 2 non-hematologic adverse events (AEs) within 3 months after switch to dasatinib in subjects with Chronic-Phase Chronic Myeloid Leukemia (CP-CML).

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:

Adults subjects diagnosed with CP-CML that had achieved an optimal response to imatinib ( $\leq 400$  mg/day treatment) who had Grade 1 or 2 non-hematologic AEs persisting for at least 2 months, or recurring at least 3 times in the preceding 12 months, despite best supportive care.

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 31 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 | France: 4              |
| Country: Number of subjects enrolled | Germany: 1             |
| Country: Number of subjects enrolled | Italy: 9               |
| Country: Number of subjects enrolled | Korea, Republic of: 22 |
| Country: Number of subjects enrolled | United States: 3       |
| Worldwide total number of subjects   | 39                     |
| EEA total number of subjects         | 14                     |

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)      | 27 |
| From 65 to 84 years       | 12 |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 22 sites in France, Germany, Italy, Republic of Korea, and the United States.

### Pre-assignment

Screening details:

A total of 39 subjects were enrolled and treated.

### Period 1

|                              |                                     |
|------------------------------|-------------------------------------|
| Period 1 title               | Dasatinib (100 mg) (overall period) |
| Is this the baseline period? | Yes                                 |
| Allocation method            | Not applicable                      |
| Blinding used                | Not blinded                         |

### Arms

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Dasatinib (100 mg) |
|------------------|--------------------|

Arm description:

Subjects that were previously on an imatinib therapy were treated with a 100 mg tablet of dasatinib taken orally once a day for up to 12 months while on study.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Dasatinib    |
| Investigational medicinal product code | BMS-354825   |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Subjects were administered with dasatinib 100 mg tablet orally once daily for up to 12 months while on study.

|   |                    |
|---|--------------------|
| <b>Number of subjects in period 1</b>   | Dasatinib (100 mg) |
| Started                                 | 39                 |
| Completed                               | 36                 |
| Not completed                           | 3                  |
| Discontinued due to study drug toxicity | 3                  |

## Baseline characteristics

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Dasatinib (100 mg) |
|-----------------------|--------------------|

Reporting group description:

Subjects that were previously on an imatinib therapy were treated with a 100 mg tablet of dasatinib taken orally once a day for up to 12 months while on study.

| Reporting group values   | Dasatinib (100 mg) | Total |  |
|--|--------------------|-------|--|
| Number of subjects   | 39                 | 39    |  |
| Age categorical  |                    |       |  |
| Units: Subjects  |                    |       |  |
| Adults (18-64 years)   | 27                 | 27    |  |
| From 65-84 years   | 12                 | 12    |  |
| Age continuous   |                    |       |  |
| Units: years   |                    |       |  |
| arithmetic mean  | 55.1               |       |  |
| standard deviation   | ± 15.13            | -     |  |
| Gender categorical   |                    |       |  |
| Units: Subjects  |                    |       |  |
| Female   | 18                 | 18    |  |
| Male   | 21                 | 21    |  |
| Race/Ethnicity   |                    |       |  |
| Units: Subjects  |                    |       |  |
| White  | 12                 | 12    |  |
| Black or African American  | 1                  | 1     |  |
| American Indian or Alaska Native   | 0                  | 0     |  |
| Asian  | 22                 | 22    |  |
| Native Hawaiian or Other Pacific Islander  | 0                  | 0     |  |
| Other  | 4                  | 4     |  |
| Imatinib dose at baseline  |                    |       |  |
| Units: Subjects  |                    |       |  |
| < 400 milligrams   | 19                 | 19    |  |
| 400 milligrams   | 20                 | 20    |  |
| Best baseline response   |                    |       |  |
| MR4.5, 4.5- log reduction in gene breakpoint cluster region -abelson murine leukemia viral oncogene (BCR-ABL) transcript from the standardized baseline (0.0032% IS); Major Molecular Response (MMR). Complete cytogenetic response (CCyR). Partial cytogenetic response (PCyR). |                    |       |  |
| Units: Subjects  |                    |       |  |
| MR4.5  | 10                 | 10    |  |
| MMR  | 20                 | 20    |  |
| CCyR   | 4                  | 4     |  |
| PCyR   | 2                  | 2     |  |
| Cytogenetic Test Not Performed   | 3                  | 3     |  |
| Median time since CML-CP diagnosis   |                    |       |  |
| CML-CP   |                    |       |  |
| Units: months  |                    |       |  |
| median   | 51.3               |       |  |
| full range (min-max)   | 3.9 to 214.6       | -     |  |

|                             |              |   |  |
|-----------------------------|--------------|---|--|
| Median duration of imatinib |              |   |  |
| Units: months               |              |   |  |
| median                      | 51.2         |   |  |
| full range (min-max)        | 3.1 to 160.4 | - |  |

## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | Dasatinib (100 mg) |
| Reporting group description:  |                    |
| Subjects that were previously on an imatinib therapy were treated with a 100 mg tablet of dasatinib taken orally once a day for up to 12 months while on study. |                    |

### Primary: Number of Imatinib-related Adverse Events (AEs) That Were Resolved, Improved, Remained Unchanged, or Worsened After 3 Months of Dasatinib Treatment

|                 |  |
|-----------------|--|
| End point title | Number of Imatinib-related Adverse Events (AEs) That Were Resolved, Improved, Remained Unchanged, or Worsened After 3 Months of Dasatinib Treatment <sup>[1]</sup> |
|-----------------|--|

#### End point description:

Prior to dasatinib treatment, subjects were on imatinib therapy and reported 121 imatinib-related Grade 1 or 2 (Grade 1/2) AEs. Dasatinib treatment was administered and its impact on the imatinib-related Grade 1/2 AEs was assessed. Imatinib-related chronic AEs were defined as Grade 1 or 2 non-hematologic AEs persisting for at least 2 months or recurring at least 3 times in the preceding 12 months, despite best supportive care. The severity of an adverse event is ranked based on grades that range from 1 to 4 according to National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03. Grade 1=Mild, Grade 2=Moderate, Grade 3=Severe, Grade 4= Potentially Life-threatening or disabling. Resolved, AE no longer present or resolution of imatinib-related chronic Grade 1 or Grade 2 non-hematologic AEs. Improved, AE grade reduced from Grade 2 to Grade 1. Unchanged, AE did not improve or worsen or no change in grade. Worsened, grade increased. All treated subjects.

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

#### End point timeframe:

From screening up to 3 months after switch to dasatinib

#### 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: Only descriptive statistics was planned for this safety end-point.

| End point values            | Dasatinib (100 mg) |  |  |  |
|-----------------------------|--------------------|--|--|--|
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 39                 |  |  |  |
| Units: Number of events     |                    |  |  |  |
| Resolved                    | 91                 |  |  |  |
| Improved                    | 2                  |  |  |  |
| Unchanged                   | 27                 |  |  |  |
| Worsened                    | 1                  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Subject Reported CML Symptom Severity and Interference by MD Anderson Symptom Inventory (MDASI) CML Score After Switching to Dasatinib

|   |  |
|---|--|
| End point title   | Change From Baseline in Subject Reported CML Symptom Severity and Interference by MD Anderson Symptom Inventory (MDASI) CML Score After Switching to Dasatinib |
| End point description:  |  |
| The MDASI-CML is a validated questionnaire completed by study subjects to assess symptom severity and symptom interference on daily function. These categories are divided into 5 domain summary scores: Core Symptom Severity Score, Interference Score, Symptom Severity Score, CML-Specific Symptom Severity Score, and 5 Most Severe Symptom Score. Scores were evaluated at baseline and after switching to dasatinib on a range from 1 to 10; 1=not present/did not interfere, 10=as bad as you can imagine/interfered completely. All treated subjects. Small "n" refers to the total number of subjects that responded to the survey at the specified interval. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Baseline, Month 3, 6, and 12  |  |

| End point values                                    | Dasatinib (100 mg) |  |  |  |
|---|--------------------|--|--|--|
| Subject group type                                  | Reporting group    |  |  |  |
| Number of subjects analysed                         | 39                 |  |  |  |
| Units: Score on a scale                             |                    |  |  |  |
| arithmetic mean (standard deviation)                |                    |  |  |  |
| Core Symptom Severity Score, Month 3; n=37          | -1.35 (± 1.78)     |  |  |  |
| Core Symptom Severity Score, Month 6; n=36          | -1.44 (± 1.84)     |  |  |  |
| Core Symptom Severity Score, Month 12; n=37         | -1.06 (± 1.87)     |  |  |  |
| Interference Score, Month 3; n=37                   | -1.24 (± 2.36)     |  |  |  |
| Interference Score, Month 6; n=35                   | -1.28 (± 2.45)     |  |  |  |
| Interference Score, Month 12; n=36                  | -1.3 (± 2.56)      |  |  |  |
| Symptom Severity Score, Month 3; n=37               | -1.73 (± 1.8)      |  |  |  |
| Symptom Severity Score, Month 6; n=36               | -1.8 (± 1.85)      |  |  |  |
| Symptom Severity Score, Month 12; n=37              | -1.46 (± 1.75)     |  |  |  |
| CML-specific Symptom Severity Score, Month 3; n=37  | -2.52 (± 2.35)     |  |  |  |
| CML-specific Symptom Severity Score, Month 6; n=36  | -2.6 (± 2.15)      |  |  |  |
| CML-specific Symptom Severity Score, Month 12; n=36 | -2.24 (± 1.87)     |  |  |  |
| 5 Most Severe Symptom Score, Month 3; n=37          | -1.61 (± 1.76)     |  |  |  |
| 5 Most Severe Symptom Score, Month 6; n=36          | -1.69 (± 1.84)     |  |  |  |
| 5 Most Severe Symptom Score, Month 12; n=37         | -1.43 (± 1.72)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point



**Secondary: Change From Baseline in Subject Reported Quality of Life Measurements by The European Organization for Research and Treatment of Cancer - Quality of Life (QoL) Questionnaire (EORTC QLQ) Score After Switching to Dasatinib at Month 6 and 12**

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Subject Reported Quality of Life Measurements by The European Organization for Research and Treatment of Cancer - Quality of Life (QoL) Questionnaire (EORTC QLQ) Score After Switching to Dasatinib at Month 6 and 12 |
|-----------------|--|

**End point description:**

The EORTC QLQ-C30 questionnaire was completed by study subjects to assess quality of life through nine multi-item scales: five functional scales (physical, role, cognitive, emotional and social functioning); three symptom scales (fatigue, pain and nausea/vomiting); and a global health status/QoL scale. Six single-item scales were included (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). All scales and single-item measures were evaluated at baseline and after switching to Dasatinib as an average raw score that was standardized by transformation, so that final scores were on a range in score from 0 to 100. A high score for a functional scale represented a healthy level of functioning, a high score for the global health status/QoL represented a high QoL, but a high score for a symptom scale represented a high level of problematic symptomatology. All treated subjects. Small "n" refers to total number of subjects that responded to the questionnaire.

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

**End point timeframe:**

Baseline, Month 6 , Month 12

| <b>End point values</b>                   | Dasatinib (100 mg) |  |  |  |
|---|--------------------|--|--|--|
| Subject group type                        | Reporting group    |  |  |  |
| Number of subjects analysed               | 39                 |  |  |  |
| Units: Score on a scale                   |                    |  |  |  |
| arithmetic mean (standard deviation)      |                    |  |  |  |
| Global Health Status/QOL, Month 6 (n=36)  | 0.46 (± 23.733)    |  |  |  |
| Global Health Status/QOL, Month 12 (n=35) | 2.86 (± 27.782)    |  |  |  |
| Cognitive Functioning, Month 6 (n=35)     | 1.9 (± 20.119)     |  |  |  |
| Cognitive Functioning, Month 12 (n=35)    | 1.43 (± 18.245)    |  |  |  |
| Emotional Functioning, Month 6 (n=35)     | 11.19 (± 23.216)   |  |  |  |
| Emotional Functioning, Month 12 (n=35)    | 12.62 (± 25.595)   |  |  |  |
| Physical Functioning, Month 6 (n=36)      | -1.67 (± 10.923)   |  |  |  |
| Physical Functioning, Month 12 (n=36)     | 0.74 (± 19.241)    |  |  |  |
| Role Functioning, Month 6 (n=36)          | -4.17 (± 27.422)   |  |  |  |
| Role Functioning, Month 12 (n=36)         | 2.78 (± 23.401)    |  |  |  |
| Social Functioning, Month 6 (n=35)        | 13.81 (± 26.036)   |  |  |  |
| Social Functioning, Month 12 (n=35)       | 14.76 (± 24.512)   |  |  |  |
| Fatigue, Month 6 (n=36)                   | -6.79 (± 20.102)   |  |  |  |
| Fatigue, Month 12 (n=36)                  | -8.33 (± 21.639)   |  |  |  |

|   |                   |  |  |  |
|---|-------------------|--|--|--|
| Nausea and Vomiting, Month 6 (n=36)     | -9.72 (± 31.966)  |  |  |  |
| Nausea and Vomiting, Month 12 (n=36)    | -4.63 (± 30.76)   |  |  |  |
| Pain, Month 6 (n=36)                    | -2.78 (± 38.318)  |  |  |  |
| Pain, Month 12 (n=36)                   | -8.8 (± 25.35)    |  |  |  |
| Appetite Loss, Month 6 (n=35)           | 1.9 (± 29.085)    |  |  |  |
| Appetite Loss, Month 12 (n=36)          | 1.85 (± 29.755)   |  |  |  |
| Constipation, Month 6 (n=36)            | -0.93 (± 28.156)  |  |  |  |
| Constipation, Month 12 (n=35)           | 8.57 (± 23.351)   |  |  |  |
| Diarrhoea, Month 6 (n=36)               | 0 (± 36.515)      |  |  |  |
| Diarrhoea, Month 12 (n=35)              | -2.86 (± 40.722)  |  |  |  |
| Dyspnoea, Month 6 (n=36)                | 5.56 (± 36.947)   |  |  |  |
| Dyspnoea, Month 12 (n=36)               | 9.26 (± 39.53)    |  |  |  |
| Financial Difficulties, Month 6 (n=35)  | -10.48 (± 21.038) |  |  |  |
| Financial Difficulties, Month 12 (n=35) | -13.33 (± 18.436) |  |  |  |
| Insomnia, Month 6 (n=36)                | 0.93 (± 42.528)   |  |  |  |
| Insomnia, Month 12 (n=36)               | -1.85 (± 38.991)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With at least One AE, Discontinuations Due to AE, Treatment-related AE, Serious Adverse Event (SAE), Treatment-related SAE, or Death as an Outcome

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With at least One AE, Discontinuations Due to AE, Treatment-related AE, Serious Adverse Event (SAE), Treatment-related SAE, or Death as an Outcome |
|-----------------|---|

End point description:

SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. Treatment-related=having certain, probable, possible, or missing relationship to study drug, dasatinib. All treated subjects.

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

End point timeframe:

SAEs: From screening period and within 30 days of discontinuation of dosing.

AEs: From first-treatment dose to 12 months

|                             |                    |  |  |  |
|-----------------------------|--------------------|--|--|--|
| <b>End point values</b>     | Dasatinib (100 mg) |  |  |  |
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 39                 |  |  |  |
| Units: Subjects             |                    |  |  |  |
| At least 1 AE               | 37                 |  |  |  |
| Discontinuations due to AE  | 3                  |  |  |  |
| Treatment-related AEs       | 34                 |  |  |  |
| SAEs                        | 11                 |  |  |  |
| Treatment-related SAEs      | 3                  |  |  |  |
| Death                       | 0                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With at Least 1 Imatinib-related Grade 1 or Grade 2 Chronic Adverse Events (AEs) That Improved Without Worsening Within 3 Months of Switching to Dasatinib

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With at Least 1 Imatinib-related Grade 1 or Grade 2 Chronic Adverse Events (AEs) That Improved Without Worsening Within 3 Months of Switching to Dasatinib |
|-----------------|---|

End point description:

The percentage of subjects is based on the number that had pre-existing Imatinib-related AEs. Subjects with reduction or improvement of at least 1 Imatinib-related Grade 1 or Grade 2 chronic AE, without a worsening of any Imatinib-related, chronic adverse events after dasatinib treatment were assessed. The severity of an adverse event is ranked based on grades that range from 1 to 4. Grade 1=Mild, Grade 2=Moderate, Grade 3=Severe, Grade 4= Potentially Life-threatening or disabling. Improved, AE grade reduced from Grade 2 to Grade 1. Worsened, Grade Increased. Confidence interval from Clopper-Pearson method. All treated subjects.

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

End point timeframe:

3 months

|                                   |                     |  |  |  |
|-----------------------------------|---------------------|--|--|--|
| <b>End point values</b>           | Dasatinib (100 mg)  |  |  |  |
| Subject group type                | Reporting group     |  |  |  |
| Number of subjects analysed       | 39 <sup>[2]</sup>   |  |  |  |
| Units: Percentage of participants |                     |  |  |  |
| number (confidence interval 95%)  | 87.1 (72.5 to 95.7) |  |  |  |

Notes:

[2] - All treated subjects.

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of Subjects With a Major Molecular Response (MMR) and MR 4.5 After Switching to Dasatinib

|   |  |
|---|--|
| End point title   | Number of Subjects With a Major Molecular Response (MMR) and MR 4.5 After Switching to Dasatinib |
| End point description:<br>Molecular responses were assessed at 6 and 12 months after switching to dasatinib to determine if these baseline responses could be maintained. All treated subjects. |  |
| End point type  | Other pre-specified  |
| End point timeframe:<br>Month 6, Month 12   |  |

|                             |                    |  |  |  |
|-----------------------------|--------------------|--|--|--|
| <b>End point values</b>     | Dasatinib (100 mg) |  |  |  |
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 39                 |  |  |  |
| Units: Subjects             |                    |  |  |  |
| MR4.5, Month 6              | 18                 |  |  |  |
| MR4.5, Month 12             | 22                 |  |  |  |
| MMR, Month 6                | 13                 |  |  |  |
| MMR, Month 12               | 13                 |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Date of first dose of study drug to 30 days post discontinuation of the last dose, up to October 2015

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Dasatinib (100 mg) |
|-----------------------|--------------------|

Reporting group description:

Subjects that were previously on an imatinib therapy were treated with a 100 mg tablet of dasatinib taken orally once a day for up to 12 months while on study

| Serious adverse events                               | Dasatinib (100 mg) |  |  |
|--|--------------------|--|--|
| Total subjects affected by serious adverse events    |                    |  |  |
| subjects affected / exposed                          | 11 / 39 (28.21%)   |  |  |
| number of deaths (all causes)                        | 0                  |  |  |
| number of deaths resulting from adverse events       |                    |  |  |
| Injury, poisoning and procedural complications       |                    |  |  |
| Rib fracture   |                    |  |  |
| subjects affected / exposed                          | 1 / 39 (2.56%)     |  |  |
| occurrences causally related to treatment / all      | 0 / 1              |  |  |
| deaths causally related to treatment / all           | 0 / 0              |  |  |
| General disorders and administration site conditions |                    |  |  |
| Pyrexia  |                    |  |  |
| subjects affected / exposed                          | 1 / 39 (2.56%)     |  |  |
| occurrences causally related to treatment / all      | 2 / 2              |  |  |
| deaths causally related to treatment / all           | 0 / 0              |  |  |
| Gastrointestinal disorders                           |                    |  |  |
| Anal fissure   |                    |  |  |
| subjects affected / exposed                          | 1 / 39 (2.56%)     |  |  |
| occurrences causally related to treatment / all      | 0 / 1              |  |  |
| deaths causally related to treatment / all           | 0 / 0              |  |  |
| Haemorrhoids   |                    |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 2 / 39 (5.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Pleural effusion                                |                |  |  |
| subjects affected / exposed                     | 2 / 39 (5.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumothorax                                    |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary arterial hypertension                 |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary oedema                                |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Intervertebral disc protrusion                  |                |  |  |
| subjects affected / exposed                     | 2 / 39 (5.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Appendicitis                                    |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia                                       |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 2 / 39 (5.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Upper respiratory tract infection               |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                     | Dasatinib (100 mg) |  |  |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events |                    |  |  |
| subjects affected / exposed                           | 36 / 39 (92.31%)   |  |  |
| Investigations  |                    |  |  |
| Alanine aminotransferase increased                    |                    |  |  |
| subjects affected / exposed                           | 2 / 39 (5.13%)     |  |  |
| occurrences (all)                                     | 2                  |  |  |
| Blood creatinine increased                            |                    |  |  |
| subjects affected / exposed                           | 3 / 39 (7.69%)     |  |  |
| occurrences (all)                                     | 6                  |  |  |
| Blood urea increased                                  |                    |  |  |
| subjects affected / exposed                           | 2 / 39 (5.13%)     |  |  |
| occurrences (all)                                     | 2                  |  |  |
| Cardiac disorders                                     |                    |  |  |
| Left ventricular hypertrophy                          |                    |  |  |
| subjects affected / exposed                           | 2 / 39 (5.13%)     |  |  |
| occurrences (all)                                     | 2                  |  |  |
| Pericardial effusion                                  |                    |  |  |
| subjects affected / exposed                           | 3 / 39 (7.69%)     |  |  |
| occurrences (all)                                     | 3                  |  |  |
| Nervous system disorders                              |                    |  |  |
| Dizziness   |                    |  |  |
| subjects affected / exposed                           | 4 / 39 (10.26%)    |  |  |
| occurrences (all)                                     | 5                  |  |  |
| Headache  |                    |  |  |

|   |  |  |  |
|---|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Paraesthesia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>15 / 39 (38.46%)</p> <p>19</p> <p>3 / 39 (7.69%)</p> <p>4</p>   |  |  |
| <p>Blood and lymphatic system disorders</p> <p>Anaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>5 / 39 (12.82%)</p> <p>13</p>   |  |  |
| <p>General disorders and administration site conditions</p> <p>Asthenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Face oedema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>General physical health deterioration</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 39 (5.13%)</p> <p>2</p> <p>2 / 39 (5.13%)</p> <p>2</p> <p>10 / 39 (25.64%)</p> <p>15</p> <p>2 / 39 (5.13%)</p> <p>3</p> <p>6 / 39 (15.38%)</p> <p>6</p> |  |  |
| <p>Gastrointestinal disorders</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gastrooesophageal reflux disease</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p>  | <p>4 / 39 (10.26%)</p> <p>4</p> <p>11 / 39 (28.21%)</p> <p>16</p> <p>2 / 39 (5.13%)</p> <p>2</p>   |  |  |



|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 8 / 39 (20.51%)  |  |  |
| occurrences (all)                               | 8                |  |  |
| Vomiting  |                  |  |  |
| subjects affected / exposed                     | 3 / 39 (7.69%)   |  |  |
| occurrences (all)                               | 3                |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Cough   |                  |  |  |
| subjects affected / exposed                     | 6 / 39 (15.38%)  |  |  |
| occurrences (all)                               | 7                |  |  |
| Dysphonia                                       |                  |  |  |
| subjects affected / exposed                     | 2 / 39 (5.13%)   |  |  |
| occurrences (all)                               | 2                |  |  |
| Dyspnoea  |                  |  |  |
| subjects affected / exposed                     | 10 / 39 (25.64%) |  |  |
| occurrences (all)                               | 13               |  |  |
| Pleural effusion                                |                  |  |  |
| subjects affected / exposed                     | 10 / 39 (25.64%) |  |  |
| occurrences (all)                               | 17               |  |  |
| Pulmonary hypertension                          |                  |  |  |
| subjects affected / exposed                     | 2 / 39 (5.13%)   |  |  |
| occurrences (all)                               | 2                |  |  |
| Rhinitis allergic                               |                  |  |  |
| subjects affected / exposed                     | 2 / 39 (5.13%)   |  |  |
| occurrences (all)                               | 2                |  |  |
| Skin and subcutaneous tissue disorders          |                  |  |  |
| Pruritus  |                  |  |  |
| subjects affected / exposed                     | 4 / 39 (10.26%)  |  |  |
| occurrences (all)                               | 5                |  |  |
| Rash  |                  |  |  |
| subjects affected / exposed                     | 10 / 39 (25.64%) |  |  |
| occurrences (all)                               | 13               |  |  |
| Psychiatric disorders                           |                  |  |  |
| Depression                                      |                  |  |  |
| subjects affected / exposed                     | 3 / 39 (7.69%)   |  |  |
| occurrences (all)                               | 3                |  |  |
| Musculoskeletal and connective tissue disorders |                  |  |  |

|                                    |                 |  |  |
|------------------------------------|-----------------|--|--|
| Arthralgia                         |                 |  |  |
| subjects affected / exposed        | 6 / 39 (15.38%) |  |  |
| occurrences (all)                  | 9               |  |  |
| Musculoskeletal pain               |                 |  |  |
| subjects affected / exposed        | 3 / 39 (7.69%)  |  |  |
| occurrences (all)                  | 5               |  |  |
| Myalgia                            |                 |  |  |
| subjects affected / exposed        | 2 / 39 (5.13%)  |  |  |
| occurrences (all)                  | 3               |  |  |
| Pain in extremity                  |                 |  |  |
| subjects affected / exposed        | 3 / 39 (7.69%)  |  |  |
| occurrences (all)                  | 8               |  |  |
| Tendonitis                         |                 |  |  |
| subjects affected / exposed        | 2 / 39 (5.13%)  |  |  |
| occurrences (all)                  | 2               |  |  |
| Infections and infestations        |                 |  |  |
| Bronchitis                         |                 |  |  |
| subjects affected / exposed        | 3 / 39 (7.69%)  |  |  |
| occurrences (all)                  | 4               |  |  |
| Metabolism and nutrition disorders |                 |  |  |
| Hyperuricaemia                     |                 |  |  |
| subjects affected / exposed        | 3 / 39 (7.69%)  |  |  |
| occurrences (all)                  | 5               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 31 August 2012   | This protocol required subject to have the ability to complete patient reported outcome measure; the changes to this protocol in the Informed Consent and Inclusion/Exclusion Criteria sections reflected this requirement. Parameters regarding fluorescence in situ hybridization (FISH) testing were clarified and added to ensure accurate and feasible testing procedures for this study. The differences between disease progression and treatment failure were differentiated.   |
| 21 November 2012 | The Purpose of this amendment was to:<br><br>Chest x-rays are not considered to be standard of care in Germany. Therefore, this Amendment is designed to remove the requirement of pre-specified chest x-rays and allow the testing to be completed as clinically indicated. The exclusion criterion of pleural effusion is also changed to known pleural effusion as a result of this change. These changes will immediately affect all patients in the study sites located in Germany. Also, added the address in Belgium on the cover page.  |
| 09 October 2013  | Based on an analysis of the BMS Dasatinib safety database (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 subjects of childbearing potential to monthly pregnancy testing.<br>Additional changes related to this initiative were: <ul style="list-style-type: none"><li>• updated language related to WOCBP to harmonize with the new BMS directive including requiring 2 highly effective forms of birth control</li><li>• defined highly effective forms of birth control</li><li>• adjusted 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).</li></ul> Finally, an appendix was added to specify criteria for response required for study enrollment and clarifications were added to the time and events schedule. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported