



Clinical trial results:

An extension to a phase II study to determine the efficacy and the safety of STI571 in patients with chronic myeloid leukemia who are refractory to or intolerant of interferon-alpha

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2005-001382-33 |
| Trial protocol | IT |
| Global end of trial date | 29 November 2013 |

Results information

| | |
|--------------------------------|-------------|
| Result version number | v1 |
| This version publication date | 11 May 2017 |
| First version publication date | 11 May 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | CSTI571A0110E2 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00171223 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, +41 613241111 , |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, +41 613241111 , |

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 | 29 November 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 November 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The objective of the core study was to determine the rate of complete and major cytogenetic response to STI571 as demonstrated by a decrease in the percentage of Philadelphia chromosome positive (Ph+) cells in the bone marrow, for patients with chronic myeloid leukemia who were hematologically or cytogenetically refractory to, or intolerant of, interferon-alpha.

The objective of the extension phase was to decrease the frequency of bone marrow evaluations to once a year from once every 6 months for all patients who have achieved a complete cytogenetic response, to enable patients to continue to have access to study treatment, and to decrease data collection after month 48 of the extension phase to include only overall survival and serious adverse events.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 22 November 1999 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | France: 41 |
| Country: Number of subjects enrolled | Switzerland: 8 |
| Country: Number of subjects enrolled | United Kingdom: 28 |
| Country: Number of subjects enrolled | Germany: 68 |
| Country: Number of subjects enrolled | United States: 342 |
| Country: Number of subjects enrolled | Italy: 45 |
| Worldwide total number of subjects | 532 |
| EEA total number of subjects | 182 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|-----|
| wk | |
| 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) | 409 |
| From 65 to 84 years | 122 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were screened for eligibility over a period of one week.

Period 1

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | No |
| Arm title | All Patients With Chronic Myeloid Leukemia |

Arm description:

During the Core Phase of the study, subjects received STI571 daily for up to 12 months. Subjects completing 12 months of therapy were eligible to continue treatment in the Extension Phase of the study, and they continued STI571 for as long as the therapy was beneficial or until death, intolerable toxicity or the decision to discontinue by the investigator, whichever came first.

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | STI571 |
| Investigational medicinal product code | |
| Other name | imatinib mesylate, Gleevec/Glivec |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered 100 mg capsules for a total dose of 400 mg or 600 mg once daily or 800 mg twice daily (2 x 400 mg). Study drug was taken with 250 ml of water after breakfast and the evening meal (for the 800 mg/day dose). Subjects who demonstrated a complete hematologic response at 3 months, or who achieved a complete hematologic response but relapsed within 3 months of achieving the response (documented by two samples taken 2 weeks apart), or who did not demonstrate a complete or major cytogenetic response at 12 months, or who achieved only a partial cytogenetic response at 12 months, may have had the dose increased to a total of 800 mg daily. As per Amendment 1 to extension protocol #2, STI571 was re-supplied as tablets instead of capsules. Subjects continued to use capsules until the supply was finished and were then supplied with 100 and 400 mg tablets.

| | |
|------------------|---------------------|
| Arm title | Hematologic Failure |
|------------------|---------------------|

Arm description:

Subjects failed to achieve a complete hematologic response, defined as lasting for at least 1 month despite 6 or more months of an interferon-alpha containing regimen, or had a rising WBC count (to a level $20 \times 10^9/L$) confirmed by two samples taken at least two weeks apart after achieving a complete hematological response while receiving an interferon- alpha containing regimen of at least 25 million international units (MIU) per week. During the Core Phase of the study, subjects received STI571 daily for up to 12 months. Subjects completing 12 months of therapy were eligible to continue treatment in the Extension Phase of the study, and they continued STI571 for as long as the therapy was beneficial or until death, intolerable toxicity or the decision to discontinue by the investigator, whichever came first.

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | STI571 |
| Investigational medicinal product code | |
| Other name | imatinib mesylate, Gleevec/Glivec |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered 100 mg capsules for a total dose of 400 mg or 600 mg once daily or 800 mg twice daily (2 x 400 mg). Study drug was taken with 250 ml of water after breakfast and the evening meal (for the 800 mg/day dose). Subjects who demonstrated a complete hematologic response at 3 months, or who achieved a complete hematologic response but relapsed within 3 months of achieving the response (documented by two samples taken 2 weeks apart), or who did not demonstrate a complete or major cytogenetic response at 12 months, or who achieved only a partial cytogenetic response at 12 months, may have had the dose increased to a total of 800 mg daily. As per Amendment 1 to extension protocol #2, STI571 was re-supplied as tablets instead of capsules. Subjects continued to use capsules until the supply was finished and were then supplied with 100 and 400 mg tablets.

| | |
|------------------|---------------------|
| Arm title | Cytogenetic Failure |
|------------------|---------------------|

Arm description:

Subjects' bone marrow (BM) cytogenetics showed $\geq 65\%$ Philadelphia chromosome positivity after one year of an interferon-alpha containing regimen or an increase in the Philadelphia chromosome positive BM cells by at least 30 percentage points (e.g., from 20% to 50%, or from 30% to 60%) confirmed by two samples at least 1 month apart, or an increase to $\geq 65\%$. During the Core Phase of the study, subjects received STI571 daily for up to 12 months. Subjects completing 12 months of therapy were eligible to continue treatment in the Extension Phase of the study, and they continued STI571 for as long as the therapy was beneficial or until death, intolerable toxicity or the decision to discontinue by the investigator, whichever came first.

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | STI571 |
| Investigational medicinal product code | |
| Other name | imatinib mesylate, Gleevec/Glivec |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered 100 mg capsules for a total dose of 400 mg or 600 mg once daily or 800 mg twice daily (2 x 400 mg). Study drug was taken with 250 ml of water after breakfast and the evening meal (for the 800 mg/day dose). Subjects who demonstrated a complete hematologic response at 3 months, or who achieved a complete hematologic response but relapsed within 3 months of achieving the response (documented by two samples taken 2 weeks apart), or who did not demonstrate a complete or major cytogenetic response at 12 months, or who achieved only a partial cytogenetic response at 12 months, may have had the dose increased to a total of 800 mg daily. As per Amendment 1 to extension protocol #2, STI571 was re-supplied as tablets instead of capsules. Subjects continued to use capsules until the supply was finished and were then supplied with 100 and 400 mg tablets.

| | |
|------------------|------------------------------|
| Arm title | Interferon-alpha Intolerance |
|------------------|------------------------------|

Arm description:

Subjects demonstrated intolerance to interferon-alpha therapy defined as a documented $>$ Grade 3 non-hematologic toxicity persisting for more than 1 month after receiving an interferon-alpha containing regimen of at least 25 million international units (MIU)/week. Subjects must have been more than 6 months from time of diagnosis. During the Core Phase of the study, subjects received STI571 daily for up to 12 months. Subjects completing 12 months of therapy were eligible to continue treatment in the Extension Phase of the study, and they continued STI571 for as long as the therapy was beneficial or until death, intolerable toxicity or the decision to discontinue by the investigator, whichever came first.

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | STI571 |
| Investigational medicinal product code | |
| Other name | imatinib mesylate, Gleevec/Glivec |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered a combination 100 mg capsules for a total dose of 400 mg or 600 mg once daily or 800 mg twice daily (2 x 400 mg). Study drug was taken with 250 ml of water after breakfast and the evening meal (for the 800 mg/day dose). Subjects who demonstrated a complete hematologic response at 3 months, or who achieved a complete hematologic response but relapsed within 3 months of achieving the response (documented by two samples taken 2 weeks apart), or who did not demonstrate a complete or major cytogenetic response at 12 months, or who achieved only a partial cytogenetic response at 12 months, may have had the dose increased to a total of 800 mg daily. As per Amendment 1 to extension protocol #2, STI571 was re-supplied as tablets instead of capsules. Subjects continued to use capsules until the supply was finished and were then supplied with 100 and 400 mg

tablets.

| Number of subjects in period 1 | All Patients With Chronic Myeloid Leukemia | Hematologic Failure | Cytogenetic Failure |
|--|--|---------------------|---------------------|
| | | | |
| Started | 532 | 152 | 188 |
| Completed core treatment phase | 395 | 111 | 151 |
| Completed extension phase I | 307 | 74 | 123 |
| Completed | 81 | 12 | 47 |
| Not completed | 451 | 140 | 141 |
| Adverse event, serious fatal | 23 | 6 | 8 |
| Subject withdrew consent | 48 | 12 | 21 |
| Adverse event, non-fatal | 30 | 6 | 5 |
| Protocol violation | 7 | 2 | 2 |
| Unsatisfactory therapeutic effect | 152 | 57 | 43 |
| Administrative problems | 17 | 4 | 7 |
| No longer requires study drug (BMT) | 8 | 2 | 4 |
| Abnormal laboratory values | 9 | 4 | 2 |
| Lost to follow-up | 10 | 5 | 2 |
| Abnormal procedure | 1 | 1 | - |
| Not specified; no data collected after cut-off | 146 | 41 | 47 |

| Number of subjects in period 1 | Interferon-alpha Intolerance |
|-------------------------------------|------------------------------|
| Started | 192 |
| Completed core treatment phase | 133 |
| Completed extension phase I | 110 |
| Completed | 22 |
| Not completed | 170 |
| Adverse event, serious fatal | 9 |
| Subject withdrew consent | 15 |
| Adverse event, non-fatal | 19 |
| Protocol violation | 3 |
| Unsatisfactory therapeutic effect | 52 |
| Administrative problems | 6 |
| No longer requires study drug (BMT) | 2 |

| | |
|--|----|
| Abnormal laboratory values | 3 |
| Lost to follow-up | 3 |
| Abnormal procedure | - |
| Not specified; no data collected after cut-off | 58 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | All Patients With Chronic Myeloid Leukemia |
|-----------------------|--|

Reporting group description:

During the Core Phase of the study, subjects received STI571 daily for up to 12 months. Subjects completing 12 months of therapy were eligible to continue treatment in the Extension Phase of the study, and they continued STI571 for as long as the therapy was beneficial or until death, intolerable toxicity or the decision to discontinue by the investigator, whichever came first.

| | |
|-----------------------|---------------------|
| Reporting group title | Hematologic Failure |
|-----------------------|---------------------|

Reporting group description:

Subjects failed to achieve a complete hematologic response, defined as lasting for at least 1 month despite 6 or more months of an interferon-alpha containing regimen, or had a rising WBC count (to a level $20 \times 10^9/L$) confirmed by two samples taken at least two weeks apart after achieving a complete hematological response while receiving an interferon- alpha containing regimen of at least 25 million international units (MIU) per week. During the Core Phase of the study, subjects received STI571 daily for up to 12 months. Subjects completing 12 months of therapy were eligible to continue treatment in the Extension Phase of the study, and they continued STI571 for as long as the therapy was beneficial or until death, intolerable toxicity or the decision to discontinue by the investigator, whichever came first.

| | |
|-----------------------|---------------------|
| Reporting group title | Cytogenetic Failure |
|-----------------------|---------------------|

Reporting group description:

Subjects' bone marrow (BM) cytogenetics showed $\geq 65\%$ Philadelphia chromosome positivity after one year of an interferon-alpha containing regimen or an increase in the Philadelphia chromosome positive BM cells by at least 30 percentage points (e.g., from 20% to 50%, or from 30% to 60%) confirmed by two samples at least 1 month apart, or an increase to $\geq 65\%$. During the Core Phase of the study, subjects received STI571 daily for up to 12 months. Subjects completing 12 months of therapy were eligible to continue treatment in the Extension Phase of the study, and they continued STI571 for as long as the therapy was beneficial or until death, intolerable toxicity or the decision to discontinue by the investigator, whichever came first.

| | |
|-----------------------|------------------------------|
| Reporting group title | Interferon-alpha Intolerance |
|-----------------------|------------------------------|

Reporting group description:

Subjects demonstrated intolerance to interferon-alpha therapy defined as a documented $>$ Grade 3 non-hematologic toxicity persisting for more than 1 month after receiving an interferon-alpha containing regimen of at least 25 million international units (MIU)/week. Subjects must have been more than 6 months from time of diagnosis. During the Core Phase of the study, subjects received STI571 daily for up to 12 months. Subjects completing 12 months of therapy were eligible to continue treatment in the Extension Phase of the study, and they continued STI571 for as long as the therapy was beneficial or until death, intolerable toxicity or the decision to discontinue by the investigator, whichever came first.

| Reporting group values | All Patients With Chronic Myeloid Leukemia | Hematologic Failure | Cytogenetic Failure |
|------------------------------------|--|---------------------|---------------------|
| Number of subjects | 532 | 152 | 188 |
| Age categorical Units: Subjects | | | |
| < 50 years | 168 | 57 | 64 |
| ≥ 50 to ≤ 60 years | 153 | 38 | 65 |
| ≥ 60 to ≤ 70 years | 159 | 47 | 44 |
| ≥ 70 years | 52 | 10 | 15 |
| Age continuous Units: years | | | |
| median | 57 | 55.5 | 53 |
| full range (min-max) | 18 to 90 | 18 to 79 | 23 to 77 |

| | | | |
|---------------------------------------|-----|-----|-----|
| Gender categorical Units: Subjects | | | |
| Female | 221 | 50 | 77 |
| Male | 311 | 102 | 111 |

| | | | |
|---------------------------------------|---------------------------------|-------|--|
| Reporting group values | Interferon-alpha Intolerance | Total | |
| Number of subjects | 192 | 532 | |
| Age categorical Units: Subjects | | | |
| < 50 years | 47 | 168 | |
| >= 50 to <= 60 years | 50 | 153 | |
| >= 60 to <= 70 years | 68 | 159 | |
| >= 70 years | 27 | 52 | |
| Age continuous Units: years | | | |
| median | 59 | | |
| full range (min-max) | 20 to 90 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 94 | 221 | |
| Male | 98 | 311 | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | All Patients With Chronic Myeloid Leukemia |
| Reporting group description: | |
| During the Core Phase of the study, subjects received STI571 daily for up to 12 months. Subjects completing 12 months of therapy were eligible to continue treatment in the Extension Phase of the study, and they continued STI571 for as long as the therapy was beneficial or until death, intolerable toxicity or the decision to discontinue by the investigator, whichever came first. | |
| Reporting group title | Hematologic Failure |
| Reporting group description: | |
| Subjects failed to achieve a complete hematologic response, defined as lasting for at least 1 month despite 6 or more months of an interferon-alpha containing regimen, or had a rising WBC count (to a level $20 \times 10^9/L$) confirmed by two samples taken at least two weeks apart after achieving a complete hematological response while receiving an interferon- alpha containing regimen of at least 25 million international units (MIU) per week. During the Core Phase of the study, subjects received STI571 daily for up to 12 months. Subjects completing 12 months of therapy were eligible to continue treatment in the Extension Phase of the study, and they continued STI571 for as long as the therapy was beneficial or until death, intolerable toxicity or the decision to discontinue by the investigator, whichever came first. | |
| Reporting group title | Cytogenetic Failure |
| Reporting group description: | |
| Subjects' bone marrow (BM) cytogenetics showed $\geq 65\%$ Philadelphia chromosome positivity after one year of an interferon-alpha containing regimen or an increase in the Philadelphia chromosome positive BM cells by at least 30 percentage points (e.g., from 20% to 50%, or from 30% to 60%) confirmed by two samples at least 1 month apart, or an increase to $\geq 65\%$. During the Core Phase of the study, subjects received STI571 daily for up to 12 months. Subjects completing 12 months of therapy were eligible to continue treatment in the Extension Phase of the study, and they continued STI571 for as long as the therapy was beneficial or until death, intolerable toxicity or the decision to discontinue by the investigator, whichever came first. | |
| Reporting group title | Interferon-alpha Intolerance |
| Reporting group description: | |
| Subjects demonstrated intolerance to interferon-alpha therapy defined as a documented $>$ Grade 3 non-hematologic toxicity persisting for more than 1 month after receiving an interferon-alpha containing regimen of at least 25 million international units (MIU)/week. Subjects must have been more than 6 months from time of diagnosis. During the Core Phase of the study, subjects received STI571 daily for up to 12 months. Subjects completing 12 months of therapy were eligible to continue treatment in the Extension Phase of the study, and they continued STI571 for as long as the therapy was beneficial or until death, intolerable toxicity or the decision to discontinue by the investigator, whichever came first. | |

Primary: Percent of Subjects With Cytogenetic Response to STI571

| | |
|--|--|
| End point title | Percent of Subjects With Cytogenetic Response to STI571 ^[1] |
| End point description: | |
| Response was evaluated from bone marrow aspirates and biopsy samples. Bone marrow (BM) cytogenetic studies were performed every 3 months during the core phase of the study, then twice yearly, then annually. Based on the percentage of Philadelphia chromosome positive (Ph+) cells = (positive cells/ examined cells) $\times 100$, at each BM assessment the cytogenetic response was classified as: Complete, 0% Ph+ cells; Partial, $>0 - 35\%$ Ph+ cells; Minor, $>35 - 65\%$ Ph+ cells; and Minimal, $>65 - 95\%$ Ph+ cells. Major cytogenetic response was defined as confirmed complete or partial response. This endpoint analyzed the Intent-to-Treat (ITT) population, defined as all subjects enrolled in the study. | |
| End point type | Primary |
| End point timeframe: | |
| Up to 6 years after the start of treatment | |

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: No statistical analysis was planned for this primary outcome measure.

| End point values | All Patients With Chronic Myeloid Leukemia | Hematologic Failure | Cytogenetic Failure | Interferon-alpha Intolerance |
|----------------------------------|--|---------------------|---------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 532 | 152 | 188 | 192 |
| Units: percent of subjects | | | | |
| number (confidence interval 95%) | | | | |
| Complete Response | 50.4 (46 to 54.7) | 38.8 (31 to 47) | 52.7 (45.3 to 60) | 57.3 (50 to 64.4) |
| Major Response | 62.4 (58.1 to 66.5) | 48.7 (40.5 to 56.9) | 68.6 (61.5 to 75.2) | 67.2 (60.1 to 73.8) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With Duration of Complete Cytogenetic Response to STI571

| | |
|-----------------|---|
| End point title | Percent of Subjects With Duration of Complete Cytogenetic Response to STI571 ^[2] |
|-----------------|---|

End point description:

Duration of complete cytogenetic response was calculated from the day the major (1-35% Philadelphia chromosome positive cells) response was documented until the day of relapse (defined as an increase in the Ph+ chromosome bone marrow cells by at least 30 percentage points, or an increase to $\geq 65\%$), discontinuation due to unsatisfactory therapeutic effect or death.

This endpoint analyzed the ITT population, defined as all subjects enrolled in the study.

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

End point timeframe:

Up to 6 years after the start of treatment

Notes:

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

Justification: This outcome was analyzed for all subjects as a group.

| End point values | All Patients With Chronic Myeloid Leukemia | | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 532 | | | |
| Units: months | | | | |
| number (confidence interval 95%) | | | | |
| 12 months | 90.1 (87 to 93.2) | | | |
| 24 months | 85.7 (82 to 89.3) | | | |
| 36 months | 81.5 (77.3 to 85.6) | | | |

| | | | | |
|-----------|---------------------|--|--|--|
| 48 months | 78.3 (73.9 to 82.8) | | | |
| 60 months | 74.8 (70 to 79.6) | | | |
| 72 months | 70.1 (64.4 to 75.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects Who Achieved Major Cytogenetic Response to STI571 at Intermediate Time Points

| | |
|-----------------|--|
| End point title | Percent of Subjects Who Achieved Major Cytogenetic Response to STI571 at Intermediate Time Points ^[3] |
|-----------------|--|

End point description:

Based on the percentage of Philadelphia chromosome positive (Ph+) cells = (positive cells/ examined cells)x100, at each BM assessment the cytogenetic response was classified as: Complete, 0% Ph+ cells; Partial, >0 – 35% Ph+ cells; Minor, >35 – 65% Ph+ cells; and Minimal, >65 – 95% Ph+ cells. Major cytogenetic response was defined as confirmed complete or partial response.

This endpoint analyzed the ITT population, defined as all subjects enrolled in the study.

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

End point timeframe:

Up to 5 years after the start of treatment

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This outcome was analyzed for all subjects as a group.

| | | | | |
|-----------------------------|--|--|--|--|
| End point values | All Patients With Chronic Myeloid Leukemia | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 532 | | | |
| Units: months | | | | |
| number (not applicable) | | | | |
| 12 months | 56 | | | |
| 24 months | 63 | | | |
| 48 months | 66 | | | |
| 60 months | 67 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With Complete Hematologic Response to STI571

| | |
|-----------------|--|
| End point title | Percent of Subjects With Complete Hematologic Response to STI571 |
|-----------------|--|

End point description:

Hematologic response was evaluated from hematology measurements in the peripheral blood. Complete

hematological response was defined as normalization of peripheral blood counts (WBC and platelet count < ULN at the laboratory where the analysis was performed), with a normal WBC differential, and no immature granulocytes present, lasting for 4 weeks.

This endpoint analyzed the ITT population, defined as all subjects enrolled in the study.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 12 months after the start of treatment | |

| End point values | All Patients With Chronic Myeloid Leukemia | Hematologic Failure | Cytogenetic Failure | Interferon-alpha Intolerance |
|----------------------------------|--|---------------------|---------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 503 | 143 | 184 | 176 |
| Units: percent of subjects | | | | |
| number (confidence interval 95%) | 94.5 (92.3 to 96.3) | 94.1 (89.1 to 97.3) | 97.9 (94.6 to 99.4) | 91.7 (86.8 to 95.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Complete Hematologic Response to STI571

| | |
|-----------------|--|
| End point title | Duration of Complete Hematologic Response to STI571 ^[4] |
|-----------------|--|

End point description:

Duration of hematologic response was defined as the time from the first documentation of the complete hematologic response (as defined above) to the date the loss of complete hematologic response is documented. Loss of complete hematological response was defined as a rising WBC count (increased to a level above the upper limit of normal (ULN) at the laboratory where the analysis was performed confirmed by two samples obtained one month apart). The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

This endpoint analyzed the ITT population, defined as all subjects enrolled in the study.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 12 months after the start of treatment | |

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This outcome was not analyzed for all subjects as a group.

| End point values | Hematologic Failure | Cytogenetic Failure | Interferon-alpha Intolerance | |
|----------------------------------|---------------------|---------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 143 | 184 | 176 | |
| Units: months | | | | |
| arithmetic mean (standard error) | 19.3672 (± 0.6383) | 23.9389 (± 0.506) | 24.6818 (± 0.6507) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Hematologic Response to STI571

| | |
|-----------------|---|
| End point title | Time to Complete Hematologic Response to STI571 |
|-----------------|---|

End point description:

Complete hematological response was defined as normalization of peripheral blood counts (WBC and platelet count < ULN at the laboratory where the analysis was performed), with a normal WBC differential, and no immature granulocytes present, lasting for 4 weeks.
This endpoint analyzed the ITT population, defined as all subjects enrolled in the study.

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

End point timeframe:

12 months after the start of treatment

| End point values | All Patients With Chronic Myeloid Leukemia | Hematologic Failure | Cytogenetic Failure | Interferon-alpha Intolerance |
|---------------------------------------|--|---------------------|---------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 503 | 143 | 184 | 176 |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 0.76 (0.3 to 2.8) | 1.64 (0.6 to 2.8) | 0.72 (0.3 to 2.8) | 0.72 (0.3 to 2.8) |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Common Toxicity Criteria Grade 3 or 4 Cancer-related Symptoms

| | |
|-----------------|---|
| End point title | Number of Subjects With Common Toxicity Criteria Grade 3 or 4 Cancer-related Symptoms |
|-----------------|---|

End point description:

National Cancer Institute (NCI)/ National Institute of Health (NIH) provides a grading (severity) scale for each AE term, the Common Toxicity Criteria (CTC). Grade 3 refers to severe AE and Grade 4 refers to life-threatening or disabling AE. Values reported are the sum of 3, 6, and 9 months.
This endpoint analyzed the ITT population, defined as all subjects enrolled in the study.

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

End point timeframe:

3, 6, and 9 months after the start of treatment

| End point values | All Patients With Chronic Myeloid Leukemia | Hematologic Failure | Cytogenetic Failure | Interferon- alpha Intolerance |
|------------------------------|---|------------------------|------------------------|-------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 532 | 152 | 188 | 192 |
| Units: subjects | | | | |
| Abdominal discomfort Grade 3 | 0 | 0 | 0 | 0 |
| Abdominal discomfort Grade 4 | 0 | 0 | 0 | 0 |
| Anorexia Grade 3 | 0 | 0 | 0 | 0 |
| Anorexia Grade 4 | 0 | 0 | 0 | 0 |
| Arthralgia Grade 3 | 1 | 0 | 0 | 1 |
| Arthralgia Grade 4 | 0 | 0 | 0 | 0 |
| Bone pain Grade 3 | 1 | 0 | 1 | 0 |
| Bone pain Grade 4 | 0 | 0 | 0 | 0 |
| Fatigue Grade 3 | 1 | 1 | 0 | 0 |
| Fatigue Grade 4 | 0 | 0 | 0 | 0 |
| Fever Grade 3 | 0 | 0 | 0 | 0 |
| Fever Grade 4 | 0 | 0 | 0 | 0 |
| Night sweats Grade 3 | 0 | 0 | 0 | 0 |
| Night sweats Grade 4 | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Grade 3 or 4 Eastern Cooperative Oncology Group Performance Status

| | |
|-----------------|--|
| End point title | Number of Subjects With Grade 3 or 4 Eastern Cooperative Oncology Group Performance Status |
|-----------------|--|

End point description:

The Eastern Cooperative Oncology Group (ECOG) performance status was recorded at baseline and every 3 months during the core study. The ECOG Performance Scale has 5 grades. 0 = Fully active, able to carry out all pre-disease activities; 1 = Restricted in strenuous activity but ambulatory and able to carry out work of light or sedentary nature; 2 = Ambulatory and capable of all self-care but unable to carry out work activities. Active about 50% of waking hours; 3 = Capable of limited self-care, confined to bed/chair more than 50% of waking hours; 4 = Completely disabled; cannot carry on self-care. Totally confined to bed/chair. Values reported are the sum of 3, 6, and 9 months. This endpoint analyzed the ITT population, defined as all subjects enrolled in the study.

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

End point timeframe:

3, 6, and 9 months after the start of treatment

| End point values | All Patients With Chronic Myeloid Leukemia | Hematologic Failure | Cytogenetic Failure | Interferon-alpha Intolerance |
|-----------------------------|--|---------------------|---------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 532 | 152 | 188 | 192 |
| Units: subjects | | | | |
| Grade 3 | 1 | 1 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With Accelerated Phase Disease or Blast Crisis at 72 Months

| | |
|-----------------|--|
| End point title | Percent of Subjects With Accelerated Phase Disease or Blast Crisis at 72 Months ^[5] |
|-----------------|--|

End point description:

The time to accelerated or blast crisis is defined as the time from the first dose of STI571 to the first documentation of accelerated phase, or blast crisis. Accelerated phase is defined as the percentage of blasts in blood or bone marrow > 15% but < 30%, or percentage of blasts plus promyelocytes in the peripheral blood or bone marrow 30%, or peripheral basophils > 20%, or thrombocytopenia < 100 x 10⁹/L unrelated to therapy. Blast crisis is defined as > 30% blasts in peripheral blood or bone marrow. This endpoint analyzed the ITT population, defined as all subjects enrolled in the study.

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

End point timeframe:

6 years after the start of treatment

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This outcome was not analyzed for all subjects as a group.

| End point values | Hematologic Failure | Cytogenetic Failure | Interferon-alpha Intolerance | |
|----------------------------------|---------------------|---------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 152 | 188 | 192 | |
| Units: percent of subjects | | | | |
| number (confidence interval 95%) | 49.8 (40.8 to 58.7) | 68.4 (61.2 to 75.6) | 62.1 (54.5 to 69.7) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates of Overall Survival

| | |
|-----------------|--|
| End point title | Kaplan-Meier Estimates of Overall Survival |
|-----------------|--|

End point description:

Overall survival was defined as the time from the first dose of STI571 to the death of the subject. To

evaluate overall survival, all subjects were followed after the last dose of study drug every three to six months until death or for a period of up to a total of five years, inclusive from the date the patient commenced the extension protocol. If a patient is not known to have died, survival will be censored at the time of last contact.

This endpoint analyzed the ITT population, defined as all subjects enrolled in the study.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to 13 years after the start of treatment | |

| End point values | All Patients With Chronic Myeloid Leukemia | Hematologic Failure | Cytogenetic Failure | Interferon-alpha Intolerance |
|----------------------------------|--|---------------------|---------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 532 | 152 | 188 | 192 |
| Units: percent of subjects | | | | |
| number (confidence interval 95%) | | | | |
| 12 months | 97.2 (95.4 to 98.3) | 94.7 (89.8 to 97.3) | 98.9 (95.8 to 99.7) | 97.4 (93.9 to 98.9) |
| 24 months | 90.6 (87.8 to 92.8) | 88.1 (81.8 to 92.3) | 93.6 (89 to 96.3) | 89.5 (84.3 to 93.1) |
| 36 months | 86.6 (83.4 to 89.2) | 84 (77.1 to 89) | 91.5 (86.5 to 94.7) | 83.8 (77.7 to 88.3) |
| 48 months | 80.8 (77.1 to 83.9) | 78.4 (70.9 to 84.2) | 87.1 (81.4 to 91.2) | 76.3 (69.6 to 81.7) |
| 60 months | 77.1 (73.3 to 80.5) | 73.3 (65.2 to 79.7) | 83.8 (77.6 to 88.4) | 73.6 (66.7 to 79.3) |
| 72 months | 74 (70 to 77.6) | 70.1 (61.9 to 76.9) | 79.7 (73.1 to 84.9) | 71.4 (64.3 to 77.3) |
| 84 months | 72 (67.8 to 75.7) | 68.5 (60 to 75.5) | 79.7 (73.1 to 84.9) | 67.2 (59.9 to 73.5) |
| 96 months | 70.8 (66.6 to 74.6) | 66.5 (57.9 to 73.8) | 79.1 (72.3 to 84.3) | 65.9 (58.6 to 72.3) |
| 108 months | 69.5 (65.2 to 73.4) | 63.3 (54.3 to 71) | 78.4 (71.6 to 83.7) | 65.3 (57.9 to 71.7) |
| 120 months | 67.9 (63.5 to 71.9) | 61 (51.8 to 69) | 77 (70 to 82.5) | 63.8 (56.3 to 70.4) |
| 132 months | 66.4 (61.9 to 70.5) | 59.7 (50.4 to 67.9) | 75.4 (68.2 to 81.2) | 62.3 (54.6 to 69) |
| 144 months | 64.6 (60 to 68.8) | 57 (47.2 to 65.5) | 73.8 (66.4 to 79.8) | 60.8 (53 to 67.6) |
| 156 months | 62.7 (58 to 67.1) | 55.5 (45.6 to 64.3) | 70.1 (62.1 to 76.7) | 60.8 (53 to 67.6) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Safety information provided in the final CSR is based on SAEs reported in the safety (ARGUS) database. All AEs reported in the clinical database had been included in the CSR based on 31-Jul-2002 data cut-off.

August 1, 2002 to November 29, 2013

Adverse event reporting additional description:

Information about all serious adverse events was collected on the SAE form and recorded in the safety database only. To ensure patient safety each serious adverse event also had to be reported to Novartis within 24 hours of learning its occurrence.

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | STI571 all doses |
|-----------------------|------------------|

Reporting group description:

As dosage administration was not captured after the 31-Jul-06 data cut-off, no analyses could be performed for this final CSR.

Notes:

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

Justification: All AEs which had been reported in the clinical database had been included in the CSR based on 31-Jul-2002 data cut-off. AE data was not collected in extension 2

| Serious adverse events | STI571 all doses | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 13 / 532 (2.44%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | 1 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Sarcoma | | | |
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostate Adenocarcinoma | | | |
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| fall | | | |
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Head injury | | | |
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Generalised oedema | | | |
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Anal fistula | | | |
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inflammatory bowel disease | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal pain | | | |
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Mental disorder | | | |
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 532 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

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

| | | | |
|---|------------------|--|--|
| Non-serious adverse events | STI571 all doses | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 532 (0.00%) | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 16 December 1999 | <p>In addition to minor clarifications to the protocol, the purpose of this amendment was:</p> <ul style="list-style-type: none">- To clarify the definition of the interferon refractory patient population.- To include patients with a documented hematologic resistance to an interferonalpha containing regimen.- To revise the statistical analysis for the inclusion of patients with a documented hematologic resistance to an interferon-alpha containing regimen.- To add two additional timepoints to the full pharmacokinetic profile to sampling to more accurately evaluate the profile of STI571.- To expand the time for the screening bone marrow from within one week of study start to within one month. |
| 12 September 2000 | <p>The purpose of this amendment was:</p> <ul style="list-style-type: none">- To clarify dose interruptions/reductions for Grade 3-4 hematologic toxicity (as outlined in letter to investigators dated 24 April 2000).- To revise the guidelines for oral administration of STI571 relative to breakfast. Preliminary study of the effect of food on the bioavailability of STI571 indicate that when administered with food STI571 had a minimal impact on the bioavailability, which did not achieve statistical significance (refer to the Investigator's Brochure, dated June 2000). STI571 may be administered before, during or after meals.- To clarify Visit Schedule (Extension Phase) specifically for bone marrow exams. In the Extension Phase bone marrows are due every 12 weeks, therefore, the first bone marrow should be done on Week 61, not Week 55.- To update patient informed consent to include changes to administration of STI571 and evolving STI571 safety profile (refer to the Investigator's Brochure, dated June 2000). |
| 13 March 2008 | <p>Changes to the protocol are listed below:</p> <ul style="list-style-type: none">- Follow up study visits will be decreased from every six months to every year (± 3 months) at which time a yearly supply of study drug will be dispensed.- For discontinued patients, survival information data collection will be decreased from every six months to every year (± 3 months) until death, or for a period of up to a total of five years, inclusive from the date the patient commenced the extension protocol, whichever is longer.- The addition of a new section to include protocol deviation language that states that under no circumstances are protocol deviations allowed.- Patients will be discontinued if they do not adhere to the study requirements.- Study drug will only be shipped directly to the investigational sites only.- Study drug STI571 tablets will be used instead of capsules.- Bone marrow evaluations are no longer required. |

| | |
|----------------|---|
| 17 August 2012 | <p>Changes to the protocol, and the sections affected, are detailed below:</p> <p>Section 1, Introduction</p> <ul style="list-style-type: none"> - Addition of statement to reflect that the study will be closed following the final visit of patients. Patients that are currently benefiting from the study medication can enroll in the roll-over protocol (CSTI571A2406) and receive the same dose of imatinib. <p>Section 3.3.1, Dispensing of Drug</p> <ul style="list-style-type: none"> - Addition of statement to reflect that study treatment will not be dispensed to the patients at their final visit. On-going patients that are currently benefiting from the treatment with imatinib as determined by the investigator, will continue to have access to imatinib in the roll-over protocol (CSTI571A2406). <p>Section 3.4.1, Visit Schedule</p> <ul style="list-style-type: none"> - The evaluation schedule is updated to reflect that once the roll-over protocol is approved at the study site patients will have their final visit. No study treatment will be dispensed to the patient at this final visit. Patients will need to sign an informed consent (amendment 2) as part of their final visit on the parent study informing them about these changes. <p>Section 3.4.2.2, Overall Survival</p> <ul style="list-style-type: none"> - Addition of statement for patients that have discontinued the study treatment no further follow-up visits are to be conducted. <p>Section 5, Data Management</p> <ul style="list-style-type: none"> - Addition of statement to reflect that the investigator must enter the information for patients who have discontinued the study drug as well as for those patients who will enroll in the roll-over protocol. For those patients given the opportunity to enroll in the roll-over protocol the Comments CRF is to document "Patient to enroll in Study CSTI571A2406" or similar wording |
|----------------|---|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported