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	v3 (current)
This version publication date	17 October 2021
First version publication date	11 May 2017
Version creation reason	• New data added to full data set • Changes to summary attachments full results attached

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 STTI571 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	06 December 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	Switzerland: 8
Country: Number of subjects enrolled	United Kingdom: 28
Country: Number of subjects enrolled	United States: 342
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 68
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	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 x 109/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 >/= 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 >/= 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
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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	Hematologic Failure	Cytogenetic Failure	Interferon-alpha Intolerance
Started	152	188	192
Completed	12	47	22
Not completed	140	141	170
Adverse event, serious fatal	6	8	9
Subject withdrew consent	12	21	15
Adverse event, non-fatal	6	5	19
Protocol violation	2	2	3
Unsatisfactory therapeutic effect	57	43	52
Administrative problems	4	7	6

Abnormal laboratory values	4	2	3
No longer requires study drug (BMT)	2	4	2
Lost to follow-up	5	2	3
Abnormal procedure	1	-	-
Not specified; no data collected after cut-off	41	47	58

Baseline characteristics

Reporting groups	
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 x 109/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 >/= 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 >/= 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	Hematologic Failure	Cytogenetic Failure	Interferon-alpha Intolerance
Number of subjects	152	188	192
Age categorical Units: Subjects			
< 50 years	57	64	47
>/= 50 to </= 60 years	38	65	50
>/= 60 to </= 70 years	47	44	68
>/= 70 years	10	15	27
Age continuous Units: years			
median	55.5	53	59
full range (min-max)	18 to 79	23 to 77	20 to 90
Gender categorical Units: Subjects			
Female	50	77	94
Male	102	111	98

Reporting group values	Total		
Number of subjects	532		

Age categorical Units: Subjects			
< 50 years	168		
>/= 50 to </= 60 years	153		
>/= 60 to </= 70 years	159		
>/= 70 years	52		
Age continuous Units: years median full range (min-max)	 -		
Gender categorical Units: Subjects			
Female	221		
Male	311		

End points

End points reporting groups

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 x 109/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 >/= 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 >/= 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)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 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 analyses have been reported for this primary end point

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%)				
Complete Response	38.8 (31 to 47)	52.7 (45.3 to 60)	57.3 (50 to 64.4)	
Major Response	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 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	Hematologic Failure	Cytogenetic Failure	Interferon-alpha Intolerance	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	143	184	176	
Units: percent of subjects				
number (confidence interval 95%)	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

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

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	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				
median (inter-quartile range (Q1-Q3))	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 Sypmptoms

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

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	Hematologic Failure	Cytogenetic Failure	Interferon-alpha Intolerance	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	188	192	
Units: subjects				
Abdominal discomfort Grade 3	0	0	0	
Abdominal discomfort Grade 4	0	0	0	
Anorexia Grade 3	0	0	0	
Anorexia Grade 4	0	0	0	
Arthralgia Grade 3	0	0	1	
Arthralgia Grade 4	0	0	0	
Bone pain Grade 3	0	1	0	
Bone pain Grade 4	0	0	0	
Fatigue Grade 3	1	0	0	
Fatigue Grade 4	0	0	0	
Fever Grade 3	0	0	0	
Fever Grade 4	0	0	0	
Night sweats Grade 3	0	0	0	
Night sweats Grade 4	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	Hematologic Failure	Cytogenetic Failure	Interferon-alpha Intolerance	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	188	192	
Units: subjects				
Grade 3	1	0	0	
Grade 4	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

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

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 sixs 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	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%)				
12 months	94.7 (89.8 to 97.3)	98.9 (95.8 to 99.7)	97.4 (93.9 to 98.9)	
24 months	88.1 (81.8 to 92.3)	93.6 (89 to 96.3)	89.5 (84.3 to 93.1)	
36 months	84 (77.1 to 89)	91.5 (86.5 to 94.7)	83.8 (77.7 to 88.3)	
48 months	78.4 (70.9 to 84.2)	87.1 (81.4 to 91.2)	76.3 (69.6 to 81.7)	
60 months	73.3 (65.2 to 79.7)	83.8 (77.6 to 88.4)	73.6 (66.7 to 79.3)	
72 months	70.1 (61.9 to 76.9)	79.7 (73.1 to 84.9)	71.4 (64.3 to 77.3)	
84 months	68.5 (60 to 75.5)	79.7 (73.1 to 84.9)	67.2 (59.9 to 73.5)	
96 months	66.5 (57.9 to 73.8)	79.1 (72.3 to 84.3)	65.9 (58.6 to 72.3)	
108 months	63.3 (54.3 to 71)	78.4 (71.6 to 83.7)	65.3 (57.9 to 71.7)	
120 months	61 (51.8 to 69)	77 (70 to 82.5)	63.8 (56.3 to 70.4)	
132 months	59.7 (50.4 to 67.9)	75.4 (68.2 to 81.2)	62.3 (54.6 to 69)	
144 months	57 (47.2 to 65.5)	73.8 (66.4 to 79.8)	60.8 (53 to 67.6)	

156 months	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: Other non-serious adverse events were not collected during the extension phase within the clinical database.

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	In addition to minor clarifications to the protocol, the purpose of this amendment was: - 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 evalute 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	The purpose of this amendment was: - 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	Changes to the protocol are listed below: - 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	Changes to the protocol, and the sections affected, are detailed below: Section 1, Introduction - 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. Section 3.3.1, Dispensing of Drug - 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). Section 3.4.1, Visit Schedule - 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. Section 3.4.2.2, Overall Survival - Addition of statement for patients that have discontinued the study treatment no further follow-up visits are to be conducted. Section 5, Data Management - 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