Clinical trial results:
An extension to a phase II study to determine the safety and the anti-leukemic effects of STI571 in adults patients with Philadelphia chromosome positive leukemia including acute lymphoblastic leukemia, acute myeloid leukemia and accelerated phase chronic myeloid leukemia.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2005-001381-14
Trial protocol	IT
Global end of trial date	23 September 2013
Results information	
Result version number	v1
This version publication date	05 July 2018
First version publication date	05 July 2018
Summary attachment (see zip file)	CSTI5710109E2 (CSTI5710109E2.pdf)

Trial information

Trial identification	
Sponsor protocol code	CSTI5710109E2
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00171249
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Novartis Pharmaceuticals, Novartis Pharmaceuticals, +41 61-324-1111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma, +41 61-324-1111,

Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	23 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of Part 1 of the study were:
-To determine the rate of hematologic response (HR) lasting >/= 4 weeks in subjects iwth Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in the accelerated phase (AP).
-To evaluate duration of HR, overall survival, cytogenetic response (CyR), time to blast crisis in CML patients in the AP, improvement of symptomatic parameters, tolerability and safety of STI571 treatment.
The objective of the extenstion (Part 2) was:
-To enable patients to have access to study drug and continue study treatment and to decrease data collection 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	09 August 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	Italy: 28
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 52
Country: Number of subjects enrolled	United Kingdom: 34
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	United States: 152
Worldwide total number of subjects	293
EEA total number of subjects	134

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)	228
From 65 to 84 years	64
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This multicenter study was carried out in the following countries (number of centers): France (2), Germany (4), Italy (2), UK (1), Switzerland (1) and USA (4).

Pre-assignment

Screening details:

For Part 1 of the study, patients were screened over a 1- week period. Patients completing extension visit 5 (i.e., visit E5) or remaining on study treatment up to and including 31-Jul-2004, and fulfilling all requirements outlined for the End of Study Visit on STI 109 extension protocol #1 were eligible to participate in extension protocol #2.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Accelerated phase chronic myeloid/myelogenous leukemia 400 mg

Arm description:

Patients with accelerated phase chronic myeloid/myelogenous leukemia received STI571 400 mg until death, the development of intolerable toxicity, or the investigator felt it was no longer in the patient's best interest to continue therapy, whichever came first.

Arm type	Experimental
Investigational medicinal product name	STI571 400 mg
Investigational medicinal product code	
Other name	Glivec, Gleevec
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg, 50 mg, and 100 mg capsules, once daily (QD) with 250 ml of water after breakfast, in a combination to achieve a 400 mg daily dose. As per Extension protocol, STI571 was supplied as tablets instead of capsules. Patients continued to use capsules until the supply of capsules was finished and were supplied with tablets. The capsules and tablets are bioequivalent.
Subjects who were resistant or relapsed while receiving treatment with STI571 at 400 mg may have had the dose increased to 600 mg. The decision to dose-escalate was made by the investigator and the sponsor on a case by case basis.

Arm title	Lymphoid blast crisis 400 mg

Arm description:

Patients with lymphoid blast crisis received STI571 400 mg until death, the development of intolerable toxicity, or the investigator felt it was no longer in the patient's best interest to continue therapy, whichever came first.

Arm type	Experimental
Investigational medicinal product name	STI571 400 mg
Investigational medicinal product code	
Other name	Glivec, Gleevec
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg, 50 mg, and 100 mg capsules, once daily (QD) with 250 ml of water after breakfast, in a combination to achieve a 400 mg daily dose. As per Extension protocol, STI571 was supplied as tablets instead of capsules. Patients continued to use capsules until the supply of capsules was finished and

were supplied with tablets. The capsules and tablets are bioequivalent.
Subjects who were resistant or relapsed while receiving treatment with STI571 at 400 mg may have had the dose increased to 600 mg. The decision to dose-escalate was made by the investigator and the sponsor on a case by case basis.

Arm title	Acute lymphoblastic leukemia 400 mg

Arm description:

Patients with acute lymphoblastic leukemia received STI571 400 mg until death, the development of intolerable toxicity, or the investigator felt it was no longer in the patient's best interest to continue therapy, whichever came first.

Arm type	Experimental
Investigational medicinal product name	STI571 400 mg
Investigational medicinal product code	
Other name	Glivec, Gleevec
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg, 50 mg, and 100 mg capsules, once daily (QD) with 250 ml of water after breakfast, in a combination to achieve a 400 mg daily dose. As per Extension protocol, STI571 was supplied as tablets instead of capsules. Patients continued to use capsules until the supply of capsules was finished and were supplied with tablets. The capsules and tablets are bioequivalent.
Subjects who were resistant or relapsed while receiving treatment with STI571 at 400 mg may have had the dose increased to 600 mg. The decision to dose-escalate was made by the investigator and the sponsor on a case by case basis.

Arm title	Accelerated phase chronic myeloid/myelogenous leukemia 600 mg

Arm description:

Patients with accelerated phase chronic myeloid/myelogenous leukemia received STI571 600 mg until death, the development of intolerable toxicity, or the investigator felt it was no longer in the patient's best interest to continue therapy, whichever came first.

Arm type	Experimental
Investigational medicinal product name	STI571 600 mg
Investigational medicinal product code	
Other name	Glivec, Gleevec
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg, 50 mg, and 100 mg capsules, once daily (QD) with 250 ml of water after breakfast, in a combination to achieve a 600 mg daily dose. As per Extension protocol, STI571 was supplied as tablets instead of capsules. Patients continued to use capsules until the supply of capsules was finished and were supplied with tablets. The capsules and tablets are bioequivalent.
Subjects who were resistant or relapsed while receiving treatment with STI571 at 600 mg may have had the dose increased to 800 mg (administered as 400 mg b.i.d.). The decision to dose-escalate was made by the investigator and the sponsor on a case by case basis.

Arm title	Lymphoid blast crisis 600 mg

Arm description:

Patients with lymphoid blast crisis received STI571 600 mg until death, the development of intolerable toxicity, or the investigator felt it was no longer in the patient's best interest to continue therapy, whichever came first.

Arm type	Experimental
Investigational medicinal product name	STI571 600 mg
Investigational medicinal product code	
Other name	Glivec, Gleevec
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg, 50 mg, and 100 mg capsules, once daily (QD) with 250 ml of water after breakfast, in a combination to achieve a 600 mg daily dose. As per Extension protocol, STI571 was supplied as tablets instead of capsules. Patients continued to use capsules until the supply of capsules was finished and were supplied with tablets. The capsules and tablets are bioequivalent.
Subjects who were resistant or relapsed while receiving treatment with STI571 at 600 mg may have had the dose increased to 800 mg (administered as 400 mg b.i.d.). The decision to dose-escalate was made by the investigator and the sponsor on a case by case basis.

Arm title	Acute lymphoblastic leukemia 600 mg

Arm description:

Patients with acute lymphoblastic leukemia received STI571 600 mg until death, the development of intolerable toxicity, or the investigator felt it was no longer in the patient's best interest to continue therapy, whichever came first.

Arm type	Experimental
Investigational medicinal product name	STI571 600 mg
Investigational medicinal product code	
Other name	Glivec, Gleevec
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg, 50 mg, and 100 mg capsules, once daily (QD) with 250 ml of water after breakfast, in a combination to achieve a 600 mg daily dose. As per Extension protocol, STI571 was supplied as tablets instead of capsules. Patients continued to use capsules until the supply of capsules was finished and were supplied with tablets. The capsules and tablets are bioequivalent.
Subjects who were resistant or relapsed while receiving treatment with STI571 at 600 mg may have had the dose increased to 800 mg (administered as 400 mg b.i.d.). The decision to dose-escalate was made by the investigator and the sponsor on a case by case basis.

Arm title	Acute myeloid/myelogenous leukemia 600 mg

Arm description:

Patients with acute myeloid/myelogenous leukemia received STI571 600 mg until death, the development of intolerable toxicity, or the investigator felt it was no longer in the patient's best interest to continue therapy, whichever came first.

Arm type	Experimental
Investigational medicinal product name	STI571 600 mg
Investigational medicinal product code	
Other name	Glivec, Gleevec
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg, 50 mg, and 100 mg capsules, once daily (QD) with 250 ml of water after breakfast, in a combination to achieve a 600 mg daily dose. As per Extension protocol, STI571 was supplied as tablets instead of capsules. Patients continued to use capsules until the supply of capsules was finished and were supplied with tablets. The capsules and tablets are bioequivalent.
Subjects who were resistant or relapsed while receiving treatment with STI571 at 600 mg may have had the dose increased to 800 mg (administered as 400 mg b.i.d.). The decision to dose-escalate was made by the investigator and the sponsor on a case by case basis.

Number of subjects in period 1	Accelerated phase chronic myeloid/myelogenous leukemia 400 mg	Lymphoid blast crisis 400 mg	Acute lymphoblastic leukemia 400 mg
Started	77	5	5
Completed Part 1	50	0	1
Completed	1	0	0
Not completed	76	5	5

Adverse event, serious fatal	7	1	-
Subject withdrew consent	2	-	-
Adverse event, non-fatal	3	1	-
Unsatisfactory therapeutic effect	44	3	5
Not specified	10	-	-
Administrative problems	1	-	-
No longer requires study drug	4	-	-
Lost to follow-up	5	-	-

Number of subjects in period 1	Accelerated phase chronic myeloid/myelogenous leukemia 600 mg	Lymphoid blast crisis 600 mg	Acute lymphoblastic leukemia 600 mg
Started	158	3	43
Completed Part 1	125	2	6
Completed	6	0	0
Not completed	152	3	43
Adverse event, serious fatal	4	-	3
Subject withdrew consent	6	-	-
Adverse event, non-fatal	15	-	2
Unsatisfactory therapeutic effect	70	3	31
Not specified	43	-	2
Administrative problems	2	-	-
No longer requires study drug	3	-	5
Lost to follow-up	9	-	-

Number of subjects in period 1	Acute myeloid/myelogenous leukemia 600 mg
Started	2
Completed Part 1	0
Completed	0
Not completed	2
Adverse event, serious fatal	1
Subject withdrew consent	-
Adverse event, non-fatal	-
Unsatisfactory therapeutic effect	1
Not specified	-
Administrative problems	-
No longer requires study drug	-
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
All patients, all doses	

Reporting group values	Overall Study	Total	
Number of subjects	293	293	
Age categorical Units: Subjects			
< 50 years	88	88	
>/= 50 to < 60 years	99	99	
>/= 60 to < 70 years	75	75	
>/= 70 years	31	31	
Age continuous Units: years			
arithmetic mean	54.3		
standard deviation	± 12.84	-	
Gender categorical Units: Subjects			
Female	146	146	
Male	147	147	

End points

End points reporting groups

Reporting group title	Accelerated phase chronic myeloid/myelogenous leukemia 400 mg
Reporting group description:	
Patients with accelerated phase chronic myeloid/myelogenous leukemia received STI571 400 mg until death, the development of intolerable toxicity, or the investigator felt it was no longer in the patient's best interest to continue therapy, whichever came first.	
Reporting group title	Lymphoid blast crisis 400 mg
Reporting group description:	
Patients with lymphoid blast crisis received STI571 400 mg until death, the development of intolerable toxicity, or the investigator felt it was no longer in the patient's best interest to continue therapy, whichever came first.	
Reporting group title	Acute lymphoblastic leukemia 400 mg
Reporting group description:	
Patients with acute lymphoblastic leukemia received STI571 400 mg until death, the development of intolerable toxicity, or the investigator felt it was no longer in the patient's best interest to continue therapy, whichever came first.	
Reporting group title	Accelerated phase chronic myeloid/myelogenous leukemia 600 mg
Reporting group description:	
Patients with accelerated phase chronic myeloid/myelogenous leukemia received STI571 600 mg until death, the development of intolerable toxicity, or the investigator felt it was no longer in the patient's best interest to continue therapy, whichever came first.	
Reporting group title	Lymphoid blast crisis 600 mg
Reporting group description:	
Patients with lymphoid blast crisis received STI571 600 mg until death, the development of intolerable toxicity, or the investigator felt it was no longer in the patient's best interest to continue therapy, whichever came first.	
Reporting group title	Acute lymphoblastic leukemia 600 mg
Reporting group description:	
Patients with acute lymphoblastic leukemia received STI571 600 mg until death, the development of intolerable toxicity, or the investigator felt it was no longer in the patient's best interest to continue therapy, whichever came first.	
Reporting group title	Acute myeloid/myelogenous leukemia 600 mg
Reporting group description:	
Patients with acute myeloid/myelogenous leukemia received STI571 600 mg until death, the development of intolerable toxicity, or the investigator felt it was no longer in the patient's best interest to continue therapy, whichever came first.	
Subject analysis set title	Accelerated phase chronic myeloid/myelogenous leukemia
Subject analysis set type	Full analysis
Subject analysis set description:	
This set includes patients who received either dose of STI571.	
Subject analysis set title	Lymphoid blast crisis
Subject analysis set type	Full analysis
Subject analysis set description:	
This set includes patients who received either dose of STI571.	
Subject analysis set title	Acute lymphoid leukemia
Subject analysis set type	Full analysis
Subject analysis set description:	
This set includes patients who received either dose of STI571.	

Primary: Percent of Subjects With Hematologic Response

End point title	Percent of Subjects With Hematologic Response[1][2]

End point description:

Hematologic response was evaluated from hematology measurements in the peripheral blood (PB) and bone marrow (BM) and assessments of extramedullary leukemic involvement (EMD) at physical examination. Response was defined as complete hematologic remission (CHR), no evidence of leukemia (NEL), or return to chronic phase (RTC).

End point type	Primary

End point timeframe:

25 weeks after 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.

[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: The main focus of the analysis was the disease group of chronic myeloid/myelogenous leukemia in accelerated phase; the other three acute leukemia disease groups are exploratory only.

End point values	Accelerated phase chronic myeloid/myelogenous leukemia 400 mg	Accelerated phase chronic myeloid/myelogenous leukemia 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	158		
Units: percent of subjects				
number (confidence interval 95%)	64.9 (53.2 to 75.5)	74.7 (67.2 to 81.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With Cytogenetic Response

End point title	Percent of Subjects With Cytogenetic Response[3]

End point description:

Bone marrow (BM) cytogenetic analysis was required at baseline, after 12 weeks (visit 22) and after 24 weeks (visit 28) to evaluate Ph chromosome positivity. In several patients, this was also done after 4 and 8 weeks. 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; Minimal, >65 – 95% Ph+ cells; None, >95% Ph+ cells; Not done: <20 metaphases were examined and/or response could not be assigned. Cytogenetic response was defined as confirmed complete or partial response. A BM sample was considered as assessable for cytogenetic response only if it contained ≥20 metaphases. However, an assessment of partial response was retained in a sample with <20 metaphases when it was immediately preceded or followed by a complete or partial response in another sample with ≥20 metaphases.

End point type	Secondary

End point timeframe:

25 weeks after 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: The main focus of the analysis was the disease group of chronic myeloid/myelogenous

leukemia in accelerated phase; the other three acute leukemia disease groups are exploratory only.

End point values	Accelerated phase chronic myeloid/myelogenous leukemia 400 mg	Accelerated phase chronic myeloid/myelogenous leukemia 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	158		
Units: percent of subjects				
number (confidence interval 95%)	14.3 (7.4 to 24.1)	24.7 (18.2 to 32.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response[4]

End point description:

Time to response was defined for all subjects as the time until first documented response (which was confirmed >/= 4 weeks later).

End point type	Secondary

End point timeframe:

25 weeks after 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: The main focus of the analysis was the disease group of chronic myeloid/myelogenous leukemia in accelerated phase; the other three acute leukemia disease groups are exploratory only.

End point values	Accelerated phase chronic myeloid/myelogenous leukemia 400 mg	Accelerated phase chronic myeloid/myelogenous leukemia 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77[5]	158[6]		
Units: months				
median (confidence interval 95%)				
Hematologic response	0.95 (0.95 to 1.1)	0.99 (0.99 to 1)		
Cytogenetic response	2.83 (1.9 to 5.6)	2.96 (2.8 to 5.5)		

Notes:

[5] - N for hematologic response = 50; N for cytogenetic response = 15

[6] - N for hematologic response = 118; N for cytogenetic response = 49

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response[7]

End point description:

Duration of response was defined as the time between first documented response (which was confirmed >/= 4 weeks later) and the earliest date of the following: loss of response (when any of the criteria for response were no longer fulfilled); progression to blast crisis (>/= 30% blasts in peripheral blood or bone marrow, extramedullary involvement other than liver/spleen enlargement); discontinuation due to adverse event, laboratory abnormality, unsatisfactory therapeutic effect or death.

End point type	Secondary

End point timeframe:

25 weeks after start of treatment

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The main focus of the analysis was the disease group of chronic myeloid/myelogenous leukemia in accelerated phase; the other three acute leukemia disease groups are exploratory only.

End point values	Accelerated phase chronic myeloid/myelogenous leukemia 400 mg	Accelerated phase chronic myeloid/myelogenous leukemia 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77[8]	158[9]		
Units: months				
median (confidence interval 95%)				
Hematologic response	16.46 (10.4 to 27.4)	28.81 (25.7 to 999999)		
Cytogenetic response	26.28 (6.6 to 999999)	27.63 (15.9 to 999999)		

Notes:

[8] - N for hematologic response = 50; N for cytogenetic response = 15

[9] - N for hematologic response = 118; N for cytogenetic response = 49

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression to Blast Crisis

End point title	Time to Progression to Blast Crisis[10]

End point description:

Progression to blast crisis was defined as >/= 30% blasts in peripheral blood or bone marrow or as extramedullary involvement other than liver or spleen enlargement.

End point type	Secondary

End point timeframe:

25 weeks after start of treatment

Notes:

[10] - 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: The main focus of the analysis was the disease group of chronic myeloid/myelogenous leukemia in accelerated phase; the other three acute leukemia disease groups are exploratory only.

End point values	Accelerated phase chronic myeloid/myelogenous leukemia 400 mg	Accelerated phase chronic myeloid/myelogenous leukemia 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	158		
Units: months				
median (confidence interval 95%)	9.95 (6.6 to 14.4)	25.13 (18.1 to 29.8)		

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:

To evaluate overall survival, all patients were to be followed after the last dose of study drug every month for the first three months and thereafter every three months until death. Overall survival was calculated for all patients as the time between start of treatment and death due to any reason. The time was censored at the date of last contact for patients who discontinued treatment and were in survival follow-up. For patients without survival follow-up information, the time was censored at last available visit / treatment date.

End point type	Secondary

End point timeframe:

12, 24, 36, 48, 60, 72, 84, 96, 108, 120, and 132, 144, and 156 months after start of treatment

End point values	Accelerated phase chronic myeloid/myelogenous leukemia	Lymphoid blast crisis	Acute lymphoid leukemia	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	235	8	48	
Units: percent of subjects				
number (confidence interval 95%)				
12 months	74.4 (68.3 to 79.5)	12.5 (0.7 to 42.3)	10.4 (3.8 to 20.9)	
24 months	58.8 (52.2 to 64.8)	0 (0 to 0)	8.3 (2.7 to 18.2)	
36 months	48 (41.4 to 54.2)	0 (0 to 0)	8.3 (2.7 to 18.2)	
48 months	39.9 (33.5 to 46.2)	0 (0 to 0)	8.3 (2.7 to 18.2)	
60 months	32.2 (26.1 to 38.4)	0 (0 to 0)	8.3 (2.7 to 18.2)	
72 months	26.3 (20.6 to 32.3)	0 (0 to 0)	8.3 (2.7 to 18.2)	
84 months	24.1 (18.6 to 30.1)	0 (0 to 0)	8.3 (2.7 to 18.2)	

96 months	21.9 (16.5 to 27.8)	0 (0 to 0)	5.6 (1.2 to 15.2)	
108 months	20.6 (15.3 to 26.4)	0 (0 to 0)	5.6 (1.2 to 15.2)	
120 months	20.6 (15.3 to 26.4)	0 (0 to 0)	5.6 (1.2 to 15.2)	
132 months	18.9 (13.6 to 24.8)	0 (0 to 0)	5.6 (1.2 to 15.2)	
144 months	18.9 (13.6 to 24.8)	0 (0 to 0)	5.6 (1.2 to 15.2)	
156 months	18.9 (13.6 to 24.8)	0 (0 to 0)	5.6 (1.2 to 15.2)	

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 data cut-off of core document.

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:

The only data available during this part of the trial are data from spontaneous reporting furnished to Novartis externally.

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: Only serious adverse events were available through safety reporting. No adverse events were captured during the extension phase within the clinical database.

Serious adverse events	STI571 all doses		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 293 (6.83%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	2 / 293 (0.68%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Breast cancer recurrent			
subjects affected / exposed	1 / 293 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal neoplasm			

subjects affected / exposed	1 / 293 (0.34%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant neoplasm progression				
subjects affected / exposed	1 / 293 (0.34%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Injury, poisoning and procedural complications				
Subdural haematoma				
subjects affected / exposed	1 / 293 (0.34%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Transfusion reaction				
subjects affected / exposed	1 / 293 (0.34%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Haemorrhage intracranial				
subjects affected / exposed	1 / 293 (0.34%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dementia Alzheimer's type				
subjects affected / exposed	1 / 293 (0.34%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Death	Additional description: Sudden death			
subjects affected / exposed	2 / 293 (0.68%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Respiratory, thoracic and mediastinal disorders				
Pulmonary haemorrhage				

subjects affected / exposed	1 / 293 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion	Additional description: Pleural effusion (grade 3)		
subjects affected / exposed	1 / 293 (0.34%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 293 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 293 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 293 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoporosis			
subjects affected / exposed	1 / 293 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 293 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atypical mycobacterial infection			
subjects affected / exposed	1 / 293 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pneumonia			
subjects affected / exposed	1 / 293 (0.34%)		
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 / 293 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 1999	The main changes are summarized as follows: - Recruitment to the three exploratory disease groups: Ph+ CML in LBC, Ph+ ALL, Ph+AML, was put on hold. - Patients with total serum bilirubin </= 3x the ULN were allowed to enter the study. - It was decided to limit the number of patients treated at 400 mg o.d. in this study, and to add a cohort at 600 mg o.d. - Dose escalation from 400 to 600 mg daily for patients who became resistant or relapsed while receiving STI571 treatment was allowed. - Trough plasma concentrations of STI571 on days 8 and 28 were to be determined in patients from US centers only. - Patients were allowed to be followed at the referral center after a minimum period of two months of follow-up at the study center. - Fluorescence in situ hybridisation (FISH) analysis was to be performed on bone marrow samples with less than 20 identified metaphases for cytogenetics.
21 December 1999	The main changes are summarized as follows: - Additional patients with CML in AP were to be recruited onto the study at the 600 mg o.d. dose level, after significant initial response rates had been observed in this population. - Patients with CML in AP were to be included only if they had never been in the blastic phase of the disease. - The adult Ph+ ALL and AML groups were to be re-opened for accrual, after analysis of data from the Phase 1 study showed significant response rates in these groups. - Accrual into the CML LBC disease group was discontinued. - Patients receiving therapy with drugs known to significantly affect gastric pH were allowed to enter the study. - Patients with disease progression while on STI571 treatment at a dose of 600 mg o.d. could have the dose increased to 800 mg, administered as 400 mg b.i.d., since no drug-related SAEs had been recorded in the cohort of patients receiving this dose in the Phase I study. - The dose reduction steps for non-hematological toxicity were simplified. - Procedures for management of grade 4 neutropenia were modified. - The evaluation of PK of STI571 was extended, by implementing a population PK study which included patients in CML in AP only. - The statistical section of the protocol was revised.
30 August 2000	The main changes are summarized as follows: - Patients were allowed to take STI571 immediately before and during meals, following results from a study, which showed that the effect of food on the bioavailability of STI571 was minimal. - During Part 2 of the study only, the monthly requirement for evaluation of the patient at the study center was changed to 3-monthly during the first 6 months and 4-monthly thereafter. The visits could be conducted at the referral site. - The supply of STI571 to patients was changed to monthly during study Part 1, 3-monthly during the first 6 months of Part 2 and 4-monthly thereafter.

13 March 2008	The main changes are summarized as follows: - 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 (±3months) 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. - Study drug STI571 tablets will be used instead of capsules.
17 August 2012	This amendment introduced the following changes: 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. - 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 3.4.2.1, 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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: