



Clinical trial results:

Post-marketing clinical study of Glivec® in patients with chronic phase chronic myeloid leukemia without a history of alpha interferon therapy

Summary

EudraCT number	2017-001804-31
Trial protocol	Outside EU/EEA
Global end of trial date	20 June 2007

Results information

Result version number	v1 (current)
This version publication date	26 July 2018
First version publication date	26 July 2018

Trial information

Trial identification

Sponsor protocol code	CSTI571AJP02
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00237120
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	20 June 2007
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 June 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy, safety, and long-term prognosis of monotherapy of Glivec and combination therapy with IFN- α in patients with an inadequate cytogenetic response. Specifically, overall survival and chronic phase maintenance period were evaluated as the efficacy study endpoints.

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	11 November 2002
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	Japan: 107
Worldwide total number of subjects	107
EEA total number of subjects	0

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)	1
Adults (18-64 years)	92
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was a multi-center, open, non-comparable study in patients diagnosed with Ph chromosome positive chronic phase CML without a history of alpha interferon therapy, based on the central registration method.

Period 1

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

Arms

Arm title	All subjects
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Arm description:

Glivec® Capsule or Tablets 100 mg 4 was orally administered after a meal. The dose was increased to 600 mg depending on efficacy and safety evaluation. Depending on cytogenetic response evaluation after 9 months, co-administration with IFN-α was initiated.

Arm type	Experimental
Investigational medicinal product name	Glivec®
Investigational medicinal product code	
Other name	Imatinib
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Commercially available Glivec® Capsule 100 mg or Glivec® Tablet 100 mg was orally administered 400 mg once daily; up to 600 mg after the meal.

Number of subjects in period 1	All subjects
Started	107
Completed	83
Not completed	24
Adverse event, serious fatal	1
Consent withdrawn by subject	5
Found as ineligible after study initiation	1
Adverse event, non-fatal	7
Other issues related to study administration	1
Switch to hematopoietic stem cell transplantation	4
Lost to follow-up	1
Lack of efficacy	4

Baseline characteristics

Reporting groups

Reporting group title	Overall Period
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Reporting group description: -

Reporting group values	Overall Period	Total	
Number of subjects	107	107	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	92	92	
From 65-84 years	14	14	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	47.1		
standard deviation	± 14.7	-	
Gender categorical			
Units: Subjects			
Female	36	36	
Male	71	71	

End points

End points reporting groups

Reporting group title	All subjects
Reporting group description:	
Glivec® Capsule or Tablets 100 mg 4 was orally administered after a meal. The dose was increased to 600 mg depending on efficacy and safety evaluation. Depending on cytogenetic response evaluation after 9 months, co-administration with IFN-α was initiated.	

Primary: Overall survival

End point title	Overall survival ^[1]
End point description:	
Overall survival is defined as time from initiation to death of any cause.	
End point type	Primary
End point timeframe:	
up to 3 years	

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	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	107 ^[2]			
Units: survival rate				
number (confidence interval 95%)				
1-year survival rate	97.2 (94.0 to 100.0)			
2-year survival rate	95.2 (91.1 to 99.3)			
3-year survival rate	93.2 (88.3 to 98.1)			

Notes:

[2] - Full Analysis Set (FAS)

Statistical analyses

No statistical analyses for this end point

Primary: Chronic phase maintenance rate

End point title	Chronic phase maintenance rate ^[3]
End point description:	
. Shift to accelerated or blast phase was defined as an event and the duration from the treatment initiation to the day of event occurrence was defined as chronic phase maintenance period.	
End point type	Primary
End point timeframe:	
up to 3 years	

Notes:

[3] - 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	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	107 ^[4]			
Units: maintenance rate				
number (confidence interval 95%)				
1-year chronic phase maintenance rate	95.3 (91.3 to 99.3)			
2-year chronic phase maintenance rate	93.4 (88.6 to 98.1)			
3-year chronic phase maintenance rate	91.4 (86.1 to 96.8)			

Notes:

[4] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Hematologic response: Complete response rate

End point title	Hematologic response: Complete response rate
End point description: Best response of each patient.	
End point type	Secondary
End point timeframe: up to 3 months	

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	106 ^[5]			
Units: response rate				
number (confidence interval 95%)				
Complete response	99.1 (94.9 to 100.0)			

Notes:

[5] - FAS excluding 1 patient with no response.

Statistical analyses

No statistical analyses for this end point

Secondary: Complete cytogenetic response (CR) rate

End point title	Complete cytogenetic response (CR) rate
End point description: Best response of each patient.	

End point type	Secondary
End point timeframe: up to 3 years	

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	107 ^[6]			
Units: response rate				
number (not applicable)				
Complete CR	86.0			
Major partial CR	3.7			
Minor partial CR	0.9			
Minimal partial CR	8.4			
No Response	0.9			

Notes:

[6] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Cytogenetic response rate: Major partial CR or better

End point title	Cytogenetic response rate: Major partial CR or better
End point description:	

End point type	Secondary
End point timeframe: up to 3 years	

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	107 ^[7]			
Units: response rate				
number (confidence interval 95%)	89.7 (82.3 to 94.8)			

Notes:

[7] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to complete response induction by molecular genetic response and complete response maintenance period

End point title	Time to complete response induction by molecular genetic
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End point description:

Patients who achieved complete response by molecular genetic response.

End point type

Secondary

End point timeframe:

up to 3 years

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	39 ^[8]			
Units: days				
arithmetic mean (standard deviation)				
Response induction	611.1 (± 348.9)			
Response maintenance	333.3 (± 310.4)			

Notes:

[8] - Patients whose cytogenetic response was Complete CR.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	5.1
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Reporting groups

Reporting group title	All subjects
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Reporting group description:

Glivec® Capsule or Tablets 100 mg 4 was orally administered after a meal. The dose was increased to 600 mg depending on efficacy and safety evaluation. Depending on cytogenetic response evaluation after 9 months, co-administration with IFN-α was initiated.

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 107 (28.97%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	4 / 107 (3.74%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
White blood cell count decreased			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and			

unspecified (incl cysts and polyps)			
Blast crisis in myelogenous leukemia			
subjects affected / exposed	3 / 107 (2.80%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Bladder cancer			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic myeloid leukemia			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thermal burn			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Iron deficiency anemia			

subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Cyst			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastric antral vascular ectasia			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Crohn's disease			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric hemorrhage			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal hemorrhage			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastric mucosal lesion			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperventilation			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			

subjects affected / exposed	2 / 107 (1.87%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Subcutaneous abscess				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary infection				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal abscess				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis bacterial				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis viral				

subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 107 (100.00%)		
General disorders and administration site conditions			
Face edema			
subjects affected / exposed	29 / 107 (27.10%)		
occurrences (all)	29		
Pyrexia			
subjects affected / exposed	26 / 107 (24.30%)		
occurrences (all)	26		
Edema			
subjects affected / exposed	24 / 107 (22.43%)		
occurrences (all)	24		
Edema peripheral			
subjects affected / exposed	23 / 107 (21.50%)		
occurrences (all)	23		
Malaise			
subjects affected / exposed	22 / 107 (20.56%)		
occurrences (all)	22		
Chest pain			
subjects affected / exposed	11 / 107 (10.28%)		
occurrences (all)	11		
Immune system disorders			

Seasonal allergy subjects affected / exposed occurrences (all)	12 / 107 (11.21%) 12		
Respiratory, thoracic and mediastinal disorders Upper respiratory tract inflammation subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Pharyngolaryngeal pain subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	27 / 107 (25.23%) 27 13 / 107 (12.15%) 13 11 / 107 (10.28%) 11 6 / 107 (5.61%) 6		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	10 / 107 (9.35%) 10		
Investigations Neutrophil count decreased subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all) Lymphocyte count decreased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	55 / 107 (51.40%) 55 51 / 107 (47.66%) 51 47 / 107 (43.93%) 47 43 / 107 (40.19%) 43 17 / 107 (15.89%) 17		

Weight increased subjects affected / exposed occurrences (all)	15 / 107 (14.02%) 15		
Eosinophil count increased subjects affected / exposed occurrences (all)	14 / 107 (13.08%) 14		
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	9 / 107 (8.41%) 9		
Hemoglobin decreased subjects affected / exposed occurrences (all)	9 / 107 (8.41%) 9		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	8 / 107 (7.48%) 8		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	7 / 107 (6.54%) 7		
Blood bilirubin increased subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 6		
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	23 / 107 (21.50%) 23		
Muscle spasticity subjects affected / exposed occurrences (all)	17 / 107 (15.89%) 17		
Dizziness subjects affected / exposed occurrences (all)	14 / 107 (13.08%) 14		
Hypoesthesia subjects affected / exposed occurrences (all)	8 / 107 (7.48%) 8		
Blood and lymphatic system disorders			

Anemia subjects affected / exposed occurrences (all)	30 / 107 (28.04%) 30		
Eye disorders			
Eyelid edema subjects affected / exposed occurrences (all)	30 / 107 (28.04%) 30		
Conjunctival hemorrhage subjects affected / exposed occurrences (all)	16 / 107 (14.95%) 16		
Conjunctivitis subjects affected / exposed occurrences (all)	7 / 107 (6.54%) 7		
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	43 / 107 (40.19%) 43		
Nausea subjects affected / exposed occurrences (all)	35 / 107 (32.71%) 35		
Vomiting subjects affected / exposed occurrences (all)	16 / 107 (14.95%) 16		
Stomatitis subjects affected / exposed occurrences (all)	14 / 107 (13.08%) 14		
Stomach discomfort subjects affected / exposed occurrences (all)	13 / 107 (12.15%) 13		
Gastritis subjects affected / exposed occurrences (all)	11 / 107 (10.28%) 11		
Dental caries subjects affected / exposed occurrences (all)	10 / 107 (9.35%) 10		
Abdominal pain upper			

subjects affected / exposed	9 / 107 (8.41%)		
occurrences (all)	9		
Constipation			
subjects affected / exposed	9 / 107 (8.41%)		
occurrences (all)	9		
Abdominal pain			
subjects affected / exposed	8 / 107 (7.48%)		
occurrences (all)	8		
Periodontitis			
subjects affected / exposed	8 / 107 (7.48%)		
occurrences (all)	8		
Enterocolitis			
subjects affected / exposed	7 / 107 (6.54%)		
occurrences (all)	7		
Abdominal discomfort			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Hemorrhoids			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	9 / 107 (8.41%)		
occurrences (all)	9		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	50 / 107 (46.73%)		
occurrences (all)	50		
Eczema			
subjects affected / exposed	13 / 107 (12.15%)		
occurrences (all)	13		
Pruritus			
subjects affected / exposed	9 / 107 (8.41%)		
occurrences (all)	9		
Purpura			

subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 6		
Renal and urinary disorders Calculus ureteric subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 6		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	27 / 107 (25.23%) 27		
Muscle spasms subjects affected / exposed occurrences (all)	25 / 107 (23.36%) 25		
Back pain subjects affected / exposed occurrences (all)	21 / 107 (19.63%) 21		
Arthralgia subjects affected / exposed occurrences (all)	14 / 107 (13.08%) 14		
Pain in extremity subjects affected / exposed occurrences (all)	11 / 107 (10.28%) 11		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	70 / 107 (65.42%) 70		
Gastroenteritis subjects affected / exposed occurrences (all)	10 / 107 (9.35%) 10		
Pharyngitis subjects affected / exposed occurrences (all)	9 / 107 (8.41%) 9		
Influenza subjects affected / exposed occurrences (all)	8 / 107 (7.48%) 8		
Herpes zoster			

subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Subcutaneous abscess			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	9 / 107 (8.41%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2003	Inclusion criteria updated. Since the test method for definitive diagnosis was not clearly described, it was stated that diagnosis is possible by a method other than bone marrow test at Visit 0. Countermeasures in case of the onset of non-minor adverse reactions in which causal relationship with Glivec cannot be ruled out. (except serious adverse events). Due to Ministerial Ordinance to partially revise for Enforcement of Pharmaceutical Affairs Act (March 17, 2005), the reporting criteria for post-marketing safety measures was changed. Accordingly, the procedure was modified as well.
05 April 2005	Administration of the study drug. Due to approval and launch of Glivec® Tablet, additional descriptions were made to the study drug.
28 November 2005	Pregnancy. Operating Procedure for the collection of pregnancy information in clinical studies was issued. As a result, this procedure was added.

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.

The coding data of the reason for death, which is needed to produce non-SAE table by programming, does not exist. Non-SAE table in this document is the data for all AEs. For full, disclosure, all data available has been reported for both SAE and AEs.

Notes: