Clinical trial results:
A Phase 1 Study of BMS-354825 (Dasatinib) in Children with Recurrent/Refractory Solid Tumors or Imatinib Resistant Ph+ Leukemia. ADVL0516

Summary

EudraCT number	2010-022945-52
Trial protocol	Outside EU/EEA
Global end of trial date	07 February 2009

Results information

Result version number	v1 (current)
This version publication date	04 November 2017
First version publication date	04 November 2017

Trial information

Trial identification

Sponsor protocol code	CA180-038

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00316953
WHO universal trial number (UTN)	-
Other trial identifiers	Bristol Myers Squibb: CA180-038

Notes:

Sponsors

Sponsor organisation name	Children's Oncology Group
Sponsor organisation address	3615 Civic Center Blvd., Philadelphia, United States, 19104
Public contact	Richard Aplenc, Study Chair, The Children's Hospital of Philadelphia, 1 267426 7252, raplenc@mail.med.upenn.edu
Scientific contact	Richard Aplenc, Study Chair, The Children's Hospital of Philadelphia, 1 267426 7252, raplenc@mail.med.upenn.edu

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000567-PIP01-09
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 February 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 February 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the trial were: - Describe and define the toxicities, estimate the MTD, and recommend a Phase 2 dose of dasatinib administered as an oral agent given twice daily in children with refractory solid tumors. - Describe and define the toxicities of dasatinib administered as an oral agent given twice daily in children with imatinib resistant Ph+ leukemia. - Characterize the PK of dasatinib in children with refractory solid tumors and imatinib resistant Ph+ leukemia.

Protection of trial subjects:

The study was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 March 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	40
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)	23
Adolescents (12-17 years)	15
Adults (18-64 years)	2
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 19 sites in the United States.

Pre-assignment

Screening details:

A total of 40 subjects were enrolled and treated in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Solid Tumor, pediatric

Arm description:

Dasatinib was administered orally twice daily for 28 days (1 course of therapy). A course could be repeated every 28 days if the subject had stable disease and met pre-specified laboratory criteria. A course could be repeated 24 times, for a total of 24 courses. All subjects were started on 50 mg/m2/dose twice daily (BID). Doses were adjusted based on body surface area (BSA) determined at the beginning of each course. Dose level 1 had a dose of 50 mg/m2/dose BID, Dose level 2 had a dose of 65 mg/m2/dose BID, Dose level 3 had a dose of 85 mg/m2/dose BID, and Dose level 4 had a dose of 110 mg/m2/dose BID

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Dasatinib tablets orally at a starting dose of 50 mg/m2 twice daily (BID). Doses were adjusted based on body surface area determined at the beginning of each course. Dose escalation occurred in the solid tumors stratum and the maximum tolerated dose (MTD) for each dose level is as follows: dose level 1 was 50 mg/m2 BID, dose level 2 was 65 mg/m2 BID, dose level 3 was 85 mg/m2 BID, and dose level 4 was 110 mg/m2 BID. If MTD was exceeded at the first dose level, then the subsequent cohort of subjects were treated with 40 mg/m2 BID. Dasatinib was supplied as white to off-white round or biconvex round or oval film-coated tablets in doses of 5 mg, 20 mg, 50 mg, and 70 mg. mg=milligram

Arm title	Leukemia, pediactric

Arm description:

Dasatinib was administered orally twice daily for 28 days (1 course of therapy). A course could be repeated every 28 days if the subject had stable disease and met pre-specified laboratory criteria. A course could be repeated 24 times, for a total of 24 courses. All subjects were started on 50 mg/m2/dose twice daily (BID). Doses were adjusted based on body surface area (BSA) determined at the beginning of each course. Dose level 1 had a dose of 50 mg/m2/dose BID, Dose level 2 had a dose of 65 mg/m2/dose BID, Dose level 3 had a dose of 85 mg/m2/dose BID, and Dose level 4 had a dose of 110 mg/m2/dose BID

Arm type	Experimental

Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Dasatinib tablets orally at a starting dose of 50 mg/m2 twice daily (BID). Subjects in this stratum dose-escalated one dose below the one under study in solid tumors subjects. If the 50 mg/m2 BID dose was not tolerated in a full cohort of refractory Ph+ leukemia subjects, then the dose was de-escalated to 40 mg/m2 BID in this stratum. Dasatinib was supplied as white to off-white round or biconvex round or oval film-coated tablets in doses of 5 mg, 20 mg, 50 mg, and 70 mg. mg=milligram

Arm title	Solid tumor, adult

Arm description:

Dasatinib was administered orally twice daily for 28 days (1 course of therapy). A course could be repeated every 28 days if the subject had stable disease and met pre-specified laboratory criteria. A course could be repeated 24 times, for a total of 24 courses. All subjects were started on 50 mg/m2/dose twice daily (BID). Doses were adjusted based on body surface area (BSA) determined at the beginning of each course. Dose level 1 had a dose of 50 mg/m2/dose BID, Dose level 2 had a dose of 65 mg/m2/dose BID, Dose level 3 had a dose of 85 mg/m2/dose BID, and Dose level 4 had a dose of 110 mg/m2/dose BID

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Dasatinib tablets orally at a starting dose of 50 mg/m2 twice daily (BID). Doses were adjusted based on body surface area determined at the beginning of each course. Dose escalation occurred in the solid tumors stratum and the maximum tolerated dose (MTD) for each dose level is as follows: dose level 1 was 50 mg/m2 BID, dose level 2 was 65 mg/m2 BID, dose level 3 was 85 mg/m2 BID, and dose level 4 was 110 mg/m2 BID. If MTD was exceeded at the first dose level, then the subsequent cohort of subjects were treated with 40 mg/m2 BID. Dasatinib was supplied as white to off-white round or biconvex round or oval film-coated tablets in doses of 5 mg, 20 mg, 50 mg, and 70 mg. mg=milligram

Number of subjects in period 1	Solid Tumor, pediatric	Leukemia, pediactric	Solid tumor, adult
Started	27	11	2
Completed	0	0	0
Not completed	27	11	2
Completion of protocol planned therapy	-	2	-
Adverse events requiring removal from theraphy	5	-	-
Adverse events requiring removal from therapy	-	2	-
Death on treatment	-	-	1
Clinical or radiographic disease progression	15	1	-
Phycisian determined non-compliance	-	1	-
Refusal of further protocol therapy	5	3	1

Physician determined not in patient’ s interest	-	2	-
Physician determined not in the patient’s interest	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Solid Tumor, pediatric
Reporting group description:	
Dasatinib was administered orally twice daily for 28 days (1 course of therapy). A course could be repeated every 28 days if the subject had stable disease and met pre-specified laboratory criteria. A course could be repeated 24 times, for a total of 24 courses. All subjects were started on 50 mg/m2/dose twice daily (BID). Doses were adjusted based on body surface area (BSA) determined at the beginning of each course. Dose level 1 had a dose of 50 mg/m2/dose BID, Dose level 2 had a dose of 65 mg/m2/dose BID, Dose level 3 had a dose of 85 mg/m2/dose BID, and Dose level 4 had a dose of 110 mg/m2/dose BID	
Reporting group title	Leukemia, pediactric
Reporting group description:	
Dasatinib was administered orally twice daily for 28 days (1 course of therapy). A course could be repeated every 28 days if the subject had stable disease and met pre-specified laboratory criteria. A course could be repeated 24 times, for a total of 24 courses. All subjects were started on 50 mg/m2/dose twice daily (BID). Doses were adjusted based on body surface area (BSA) determined at the beginning of each course. Dose level 1 had a dose of 50 mg/m2/dose BID, Dose level 2 had a dose of 65 mg/m2/dose BID, Dose level 3 had a dose of 85 mg/m2/dose BID, and Dose level 4 had a dose of 110 mg/m2/dose BID	
Reporting group title	Solid tumor, adult
Reporting group description:	
Dasatinib was administered orally twice daily for 28 days (1 course of therapy). A course could be repeated every 28 days if the subject had stable disease and met pre-specified laboratory criteria. A course could be repeated 24 times, for a total of 24 courses. All subjects were started on 50 mg/m2/dose twice daily (BID). Doses were adjusted based on body surface area (BSA) determined at the beginning of each course. Dose level 1 had a dose of 50 mg/m2/dose BID, Dose level 2 had a dose of 65 mg/m2/dose BID, Dose level 3 had a dose of 85 mg/m2/dose BID, and Dose level 4 had a dose of 110 mg/m2/dose BID	

Reporting group values	Solid Tumor, pediatric	Leukemia, pediactric	Solid tumor, adult
Number of subjects	27	11	2
Age categorical Units: Subjects			
2 - <11 years	13	6	0
11 - <18 years	14	5	0
>=18 years	0	0	2
Age continuous Units: years			
arithmetic mean	10.25	10.45	19
full range (min-max)	2 to 17	2 to 17	18 to 20
Gender categorical Units: Subjects			
Female	14	4	1
Male	13	7	1
Race Units: Subjects			
White	19	7	2
Black or African American	5	1	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Asian Indian/Pakistani/Filipino	2	0	0

Other	1	1	0
Unknown	0	2	0

Reporting group values	Total		
Number of subjects	40		
Age categorical Units: Subjects			
2 - <11 years	19		
11 - <18 years	19		
>=18 years	2		
Age continuous Units: years			
arithmetic mean			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	19		
Male	21		
Race Units: Subjects			
White	28		
Black or African American	6		
American Indian or Alaska Native	0		
Native Hawaiian or Other Pacific Islander	0		
Asian Indian/Pakistani/Filipino	2		
Other	2		
Unknown	2		

End points

End points reporting groups

Reporting group title	Solid Tumor, pediatric

Reporting group description:

Dasatinib was administered orally twice daily for 28 days (1 course of therapy). A course could be repeated every 28 days if the subject had stable disease and met pre-specified laboratory criteria. A course could be repeated 24 times, for a total of 24 courses. All subjects were started on 50 mg/m2/dose twice daily (BID). Doses were adjusted based on body surface area (BSA) determined at the beginning of each course. Dose level 1 had a dose of 50 mg/m2/dose BID, Dose level 2 had a dose of 65 mg/m2/dose BID, Dose level 3 had a dose of 85 mg/m2/dose BID, and Dose level 4 had a dose of 110 mg/m2/dose BID

Reporting group title	Leukemia, pediactric

Reporting group description:

Dasatinib was administered orally twice daily for 28 days (1 course of therapy). A course could be repeated every 28 days if the subject had stable disease and met pre-specified laboratory criteria. A course could be repeated 24 times, for a total of 24 courses. All subjects were started on 50 mg/m2/dose twice daily (BID). Doses were adjusted based on body surface area (BSA) determined at the beginning of each course. Dose level 1 had a dose of 50 mg/m2/dose BID, Dose level 2 had a dose of 65 mg/m2/dose BID, Dose level 3 had a dose of 85 mg/m2/dose BID, and Dose level 4 had a dose of 110 mg/m2/dose BID

Reporting group title	Solid tumor, adult

Reporting group description:

Dasatinib was administered orally twice daily for 28 days (1 course of therapy). A course could be repeated every 28 days if the subject had stable disease and met pre-specified laboratory criteria. A course could be repeated 24 times, for a total of 24 courses. All subjects were started on 50 mg/m2/dose twice daily (BID). Doses were adjusted based on body surface area (BSA) determined at the beginning of each course. Dose level 1 had a dose of 50 mg/m2/dose BID, Dose level 2 had a dose of 65 mg/m2/dose BID, Dose level 3 had a dose of 85 mg/m2/dose BID, and Dose level 4 had a dose of 110 mg/m2/dose BID

Primary: Number of Subjects With Death, Serious Adverse Events (SAEs), SAE Leading to Discontinuation, and Drug-Related Adverse Event (AE)

End point title	Number of Subjects With Death, Serious Adverse Events (SAEs), SAE Leading to Discontinuation, and Drug-Related Adverse Event (AE)[1]

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Treatment-related=having certain, probable, possible, or missing relationship to study drug. Grade (Gr) 1=Mild, Gr 2=Moderate, Gr 3=Severe, Gr 4= Potentially Life-threatening or disabling.

End point type	Primary

End point timeframe:

From the date of first dose of study medication to within 30 days post the last dose (approx. 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: Only summary statistics were planned for this endpoint

End point values	Solid Tumor, pediatric	Leukemia, pediactric	Solid tumor, adult	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	11	2	
Units: subjects				
SAE	9	4	2	
SAE Leading to Discontinuation	4	2	1	
Drug-Related AE	24	11	1	
Deaths	16	1	1	
Deaths Within 30 Days of End of Study	3	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with At Least One Dose-Limiting Toxicity (DLT)

End point title	Number of Subjects with At Least One Dose-Limiting Toxicity (DLT)[2]

End point description:

Dose-limiting toxicity was defined as specific AEs that were considered by the investigator to be possibly, probably, or definitely attributable to dasatinib treatment. Population includes DLT Evaluable Subjects: all subjects who received dasatinib and either experienced a DLT at any time during treatment or received at least 85% of the prescribed dose per the protocol.

End point type	Primary

End point timeframe:

From the date of first dose of study medication to within 30 days post the last dose (approx. 3 years)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary statistics were planned for this endpoint

End point values	Solid Tumor, pediatric	Leukemia, pediactric	Solid tumor, adult	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	11	1	
Units: subjects	2	3	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the first dose of study drug until the last dose of study drug plus 30 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Solid Tumors (pediatric)
Reporting group description: Solid Tumors	
Reporting group title	Leukemia
Reporting group description: Leukemia	
Reporting group title	Solid Tumors (adult)
Reporting group description: Dasatinib was administered orally twice daily for 28 days (1 course of therapy). A course could be repeated every 28 days if the subject had stable disease and met pre-specified laboratory criteria. A course could be repeated 24 times, for a total of 24 courses. All subjects were started on 50 mg/m2/dose twice daily (BID). Doses were adjusted based on body surface area (BSA) determined at the beginning of each course. Dose level 1 had a dose of 50 mg/m2/dose BID, Dose level 2 had a dose of 65 mg/m2/dose BID, Dose level 3 had a dose of 85 mg/m2/dose BID, and Dose level 4 had a dose of 110 mg/m2/dose BID	

Serious adverse events	Solid Tumors (pediatric)	Leukemia	Solid Tumors (adult)
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 27 (33.33%)	4 / 11 (36.36%)	2 / 2 (100.00%)
number of deaths (all causes)	3	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 11 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 27 (3.70%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	4 / 27 (14.81%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	3 / 27 (11.11%)	0 / 11 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 1
Disease progression			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Apnoea			
subjects affected / exposed	1 / 27 (3.70%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 27 (3.70%)	0 / 11 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Photophobia			

subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granulocyte count decreased			
subjects affected / exposed	2 / 27 (7.41%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	2 / 27 (7.41%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	2 / 27 (7.41%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	3 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	1 / 27 (3.70%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 27 (3.70%)	2 / 11 (18.18%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	1 / 1	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	2 / 27 (7.41%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 27 (3.70%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 27 (3.70%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 27 (3.70%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exfoliative rash			
subjects affected / exposed	1 / 27 (3.70%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 27 (3.70%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 27 (3.70%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 27 (7.41%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	1 / 27 (3.70%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	2 / 27 (7.41%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Solid Tumors (pediatric)	Leukemia	Solid Tumors (adult)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 27 (96.30%)	11 / 11 (100.00%)	2 / 2 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Flushing			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Hypotension			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 27 (7.41%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	3	1	0
Chills			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Disease progression			
subjects affected / exposed	1 / 27 (3.70%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	11 / 27 (40.74%)	4 / 11 (36.36%)	0 / 2 (0.00%)
occurrences (all)	12	8	0
Gait disturbance			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0

Pyrexia			
subjects affected / exposed	7 / 27 (25.93%)	4 / 11 (36.36%)	0 / 2 (0.00%)
occurrences (all)	8	5	0
Oedema			
subjects affected / exposed	4 / 27 (14.81%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	5	2	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 27 (22.22%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	7	2	0
Bronchospasm			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Dyspnoea			
subjects affected / exposed	4 / 27 (14.81%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	4	0	0
Epistaxis			
subjects affected / exposed	3 / 27 (11.11%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	3	0	0
Hypoxia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 27 (3.70%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
Pleural effusion			
subjects affected / exposed	3 / 27 (11.11%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	4	1	0

Respiratory alkalosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	1 / 27 (3.70%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Wheezing			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Tachypnoea			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 27 (3.70%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	2 / 27 (7.41%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Alanine aminotransferase increased			
subjects affected / exposed	8 / 27 (29.63%)	6 / 11 (54.55%)	0 / 2 (0.00%)
occurrences (all)	10	9	0
Amylase increased			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	15 / 27 (55.56%)	6 / 11 (54.55%)	0 / 2 (0.00%)
occurrences (all)	18	13	0
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 27 (11.11%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	3	2	0
Blood bicarbonate decreased			
subjects affected / exposed	2 / 27 (7.41%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	3	3	0
Blood bilirubin increased			

subjects affected / exposed	1 / 27 (3.70%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Blood cholesterol increased			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Blood creatinine increased			
subjects affected / exposed	1 / 27 (3.70%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Gamma-Glutamyltransferase increased			
subjects affected / exposed	4 / 27 (14.81%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	4	1	0
Granulocyte count decreased			
subjects affected / exposed	9 / 27 (33.33%)	5 / 11 (45.45%)	0 / 2 (0.00%)
occurrences (all)	10	5	0
Haemoglobin decreased			
subjects affected / exposed	11 / 27 (40.74%)	8 / 11 (72.73%)	0 / 2 (0.00%)
occurrences (all)	19	32	0
Liver palpable			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
International normalised ratio increased			
subjects affected / exposed	4 / 27 (14.81%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	4	1	0
Neutrophil count decreased			
subjects affected / exposed	9 / 27 (33.33%)	5 / 11 (45.45%)	0 / 2 (0.00%)
occurrences (all)	11	7	0
Platelet count decreased			
subjects affected / exposed	9 / 27 (33.33%)	5 / 11 (45.45%)	1 / 2 (50.00%)
occurrences (all)	12	8	1
Weight decreased			

subjects affected / exposed	2 / 27 (7.41%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Weight increased			
subjects affected / exposed	0 / 27 (0.00%)	3 / 11 (27.27%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
White blood cell count decreased			
subjects affected / exposed	9 / 27 (33.33%)	7 / 11 (63.64%)	0 / 2 (0.00%)
occurrences (all)	13	11	0
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Sinus tachycardia			
subjects affected / exposed	4 / 27 (14.81%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	4	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 27 (25.93%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	8	4	0
Neuropathy peripheral			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Tremor			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Bone marrow failure			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Lymphopenia			
subjects affected / exposed	7 / 27 (25.93%)	3 / 11 (27.27%)	0 / 2 (0.00%)
occurrences (all)	12	10	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Eye disorders			

Dry eye			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 27 (7.41%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Abdominal pain			
subjects affected / exposed	8 / 27 (29.63%)	4 / 11 (36.36%)	0 / 2 (0.00%)
occurrences (all)	10	7	0
Abdominal pain upper			
subjects affected / exposed	1 / 27 (3.70%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Colitis			
subjects affected / exposed	1 / 27 (3.70%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Constipation			
subjects affected / exposed	2 / 27 (7.41%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Diarrhoea			
subjects affected / exposed	11 / 27 (40.74%)	4 / 11 (36.36%)	1 / 2 (50.00%)
occurrences (all)	15	7	1
Haematochezia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	10 / 27 (37.04%)	5 / 11 (45.45%)	0 / 2 (0.00%)
occurrences (all)	12	7	0
Stomatitis			
subjects affected / exposed	3 / 27 (11.11%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	3	1	0
Vomiting			

subjects affected / exposed	9 / 27 (33.33%)	2 / 11 (18.18%)	1 / 2 (50.00%)
occurrences (all)	14	4	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 27 (7.41%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	2	2	0
Dry skin			
subjects affected / exposed	1 / 27 (3.70%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	1	3	0
Exfoliative rash			
subjects affected / exposed	7 / 27 (25.93%)	5 / 11 (45.45%)	1 / 2 (50.00%)
occurrences (all)	11	8	1
Hair colour changes			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Petechiae			
subjects affected / exposed	1 / 27 (3.70%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Photosensitivity reaction			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	4 / 27 (14.81%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	5	0	0
Urinary bladder haemorrhage			
subjects affected / exposed	3 / 27 (11.11%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	3	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 27 (14.81%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	7	1	0
Back pain			
subjects affected / exposed	4 / 27 (14.81%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	4	1	0
Musculoskeletal stiffness			

subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Neck pain			
subjects affected / exposed	3 / 27 (11.11%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	3	0	0
Pain in extremity			
subjects affected / exposed	8 / 27 (29.63%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	10	1	0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Candidiasis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Catheter related infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gingivitis			
subjects affected / exposed	1 / 27 (3.70%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Influenza			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0

Lice infestation			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Otitis media			
subjects affected / exposed	3 / 27 (11.11%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	3	1	0
Pneumonia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Rhinitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Sepsis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	2 / 27 (7.41%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 27 (3.70%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 27 (11.11%)	3 / 11 (27.27%)	0 / 2 (0.00%)
occurrences (all)	3	4	0
Dehydration			
subjects affected / exposed	3 / 27 (11.11%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	3	2	0
Hyperglycaemia			
subjects affected / exposed	8 / 27 (29.63%)	5 / 11 (45.45%)	1 / 2 (50.00%)
occurrences (all)	14	11	1
Hyperkalaemia			

subjects affected / exposed	2 / 27 (7.41%)	1 / 11 (9.09%)	1 / 2 (50.00%)
occurrences (all)	3	4	1
Hypermagnesaemia			
subjects affected / exposed	5 / 27 (18.52%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	7	1	0
Hypertriglyceridaemia			
subjects affected / exposed	1 / 27 (3.70%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Hypoalbuminaemia			
subjects affected / exposed	9 / 27 (33.33%)	4 / 11 (36.36%)	1 / 2 (50.00%)
occurrences (all)	10	9	1
Hypocalcaemia			
subjects affected / exposed	11 / 27 (40.74%)	5 / 11 (45.45%)	1 / 2 (50.00%)
occurrences (all)	16	6	1
Hypoglycaemia			
subjects affected / exposed	1 / 27 (3.70%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Hypokalaemia			
subjects affected / exposed	8 / 27 (29.63%)	5 / 11 (45.45%)	0 / 2 (0.00%)
occurrences (all)	8	6	0
Hypomagnesaemia			
subjects affected / exposed	3 / 27 (11.11%)	3 / 11 (27.27%)	0 / 2 (0.00%)
occurrences (all)	6	3	0
Hyponatraemia			
subjects affected / exposed	11 / 27 (40.74%)	1 / 11 (9.09%)	1 / 2 (50.00%)
occurrences (all)	14	4	1
Hypophosphataemia			
subjects affected / exposed	9 / 27 (33.33%)	3 / 11 (27.27%)	0 / 2 (0.00%)
occurrences (all)	9	7	0
Metabolic alkalosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2006	The purpose of this amendment was to update Section 11.4, "Dose escalation and determination of MTD in Ph+ leukemia subjects," which was incorrectly revised during protocol development, and to include the most recent Comprehensive Adverse Event and Potential Risks (CAEPR) list (Version 2.0, dated 29-Mar-2006) for dasatinib.
22 October 2006	This amendment included various clarifications and administrative changes. The significant revisions were: • As solid tumor acquisition will not be pursued in this study, this secondary study aim was removed. • Timing guidelines for blood transfusions were added. • The renal function criteria were updated to use those developed by COG's Developmental Therapeutics Committee. • The liver function eligibility criterion for ALT was changed from < 5xULN to < 110 U/L, and the ULN was established as 45 U/L. • Included PK sampling timepoints for subjects weighing < 10 kg. • The pharmacy section was updated to include the most recently COG Pharmacy Committee-approved monograph for Intrathecal Triple.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported