Clinical trial results:
A Phase II Study of Dasatinib Therapy in Children and Adolescents with Ph+ Leukemia with Resistance or Intolerance to Imatinib.

Summary

EudraCT number	2008-002260-33
Trial protocol	IT ES FR NL GB DE Outside EU/EEA
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	30 December 2017
First version publication date	30 December 2017

Trial information

Trial identification

Sponsor protocol code	CA180-226

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00777036
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

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	Interim
Date of interim/final analysis	01 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine whether dasatinib is safe and effective in children and adolescents with newly diagnosed chronic myeloid leukemia (CML), or in children with Ph+ acute lymphoblastic leukemia (ALL), accelerated or blast phases CML who relapse after imatinib or who are resistant or intolerant to imatinib. The side effects of this oral investigational drug in children and adolescents will be evaluated

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 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Brazil: 15
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	India: 19
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	South Africa: 5
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Korea, Republic of: 15

Worldwide total number of subjects	145
EEA total number of subjects	33

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)	3
Children (2-11 years)	63
Adolescents (12-17 years)	77
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 80 sites (Argentina, Australia, Brazil, Canada, France, Germany, Great Britain, India, Italy, Korea, Mexico, Netherlands, Romania, Russia, Singapore, South Africa, Spain, and USA).

Pre-assignment

Screening details:

A total of 145 Subjects were enrolled and 130 Subjects were treated in the study. Reasons for non-treatment include 2 withdrew consent, 1 died, 11 failed to meet study criteria, and 1 other non-specified.

Period 1

Period 1 title	On Treatment
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Children and adolescents with CP-CML who were resistant or intolerant to imatinib received dasatinib tablets at 60 mg/m2 QD on a continuous oral regimen.

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

Dosage and administration details:

Dasatinib tablets at 60 mg/m2 QD, with a maximum dose of 100 mg QD for subjects with high BSA

Arm title	Cohort 2

Arm description:

Children and adolescents with Ph+ ALL, AP-CML or BP-CML who were resistant or intolerant to, or relapsed after imatinib therapy received dasatinib tablets at a dose schedule of 80 mg/m2 QD on a continuous oral regimen.

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

Dosage and administration details:

Dasatinib tablets at dose schedule of 80 mg/m2 QD, with a maximum dose of 140 mg QD for subjects with high BSA

Arm title	Cohort 3

Arm description:

Children and adolescents with CP-CML who were treatment-naive received dasatinib tablets at 60 mg/m2 QD or powder for oral suspension (PFOS) at 72 mg/m2 QD on a continuous oral regimen.

Arm type	Experimental

Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Dasatinib powder for oral suspension (PFOS) at 72 mg/m2 QD on a continuous oral regimen.

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

Dosage and administration details:

Dasatinib tablets at 60 mg/m2 QD, with a maximum dose of 100 mg QD for subjects with high BSA

Number of subjects in period 1[1]	Cohort 1	Cohort 2	Cohort 3
Started	29	17	84
Completed	14	1	61
Not completed	15	16	23
Adverse event, serious fatal	-	2	-
Non-compliance with Study Drug	1	-	-
Consent withdrawn by subject	3	2	3
Reason Not Specified	4	7	12
Progressive Disease	5	4	6
Maximum Clinical Benefit	2	-	1
Failure to Meet Study Criteria	-	1	-
Study Drug Toxicity	-	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 145 subjects were enrolled and 130 subjects were treated in the study and included in the baseline period. Reasons for non-treatment include 2 withdrew consent, 1 died, 11 failed to meet study criteria, and 1 other non-specified.

Period 2

Period 2 title	Follow-Up
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	Cohort 1

Arm description:

Children and adolescents with CP-CML who were resistant or intolerant to imatinib received dasatinib tablets at 60 mg/m2 QD on a continuous oral regimen.

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

Dosage and administration details:

Dasatinib tablets at 60 mg/m2 QD, with a maximum dose of 100 mg QD for subjects with high BSA

Arm title	Cohort 2

Arm description:

Children and adolescents with Ph+ ALL, AP-CML or BP-CML who were resistant or intolerant to, or relapsed after imatinib therapy received dasatinib tablets at a dose schedule of 80 mg/m2 QD on a continuous oral regimen.

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

Dosage and administration details:

Dasatinib tablets at dose schedule of 80 mg/m2 QD, with a maximum dose of 140 mg QD for subjects with high BSA

Arm title	Cohort 3

Arm description:

Children and adolescents with CP-CML who were treatment-naive received dasatinib tablets at 60 mg/m2 QD or powder for oral suspension (PFOS) at 72 mg/m2 QD on a continuous oral regimen.

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

Dosage and administration details:

Dasatinib tablets at 60 mg/m2 QD, with a maximum dose of 100 mg QD for subjects with high BSA

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

Dosage and administration details:

Dasatinib tablets at 60 mg/m2 QD, with a maximum dose of 100 mg QD for subjects with high BSA

Number of subjects in period 2[2]	Cohort 1	Cohort 2	Cohort 3
Started	14	13	23
Completed	9	5	19
Not completed	5	8	4
Adverse event, serious fatal	1	8	-
Consent withdrawn by subject	1	-	4
Reason Not Specified	2	-	-
Lost to follow-up	1	-	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all participants who discontinued treatment entered the follow-up period

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
Children and adolescents with CP-CML who were resistant or intolerant to imatinib received dasatinib tablets at 60 mg/m2 QD on a continuous oral regimen.	
Reporting group title	Cohort 2
Reporting group description:	
Children and adolescents with Ph+ ALL, AP-CML or BP-CML who were resistant or intolerant to, or relapsed after imatinib therapy received dasatinib tablets at a dose schedule of 80 mg/m2 QD on a continuous oral regimen.	
Reporting group title	Cohort 3
Reporting group description:	
Children and adolescents with CP-CML who were treatment-naive received dasatinib tablets at 60 mg/m2 QD or powder for oral suspension (PFOS) at 72 mg/m2 QD on a continuous oral regimen.	

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	29	17	84
Age Categorical Units: Subjects			
< 2 years	1	0	2
>= 2 to < 7 years	3	2	10
>= 7 to < 12 years	6	6	28
>= 12 to < 18 years	17	9	44
>= 18 years	2	0	0
Age Continuous Units: years			
arithmetic mean	12.60	12.10	11.95
standard deviation	± 4.774	± 3.680	± 4.418
Gender, Male/Female Units: Subjects			
Female	16	9	39
Male	13	8	45
Race/Ethnicity, Customized Units: Subjects			
White	20	13	56
Black or African American	2	0	4
Asian	6	3	23
American Indian or Alaska Native	0	0	1
Other	1	1	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	0	5
Not Hispanic or Latino	4	0	20
Unknown or Not Reported	23	17	59

Reporting group values	Total		
Number of subjects	130		

Age Categorical Units: Subjects			
< 2 years	3		
>= 2 to < 7 years	15		
>= 7 to < 12 years	40		
>= 12 to < 18 years	70		
>= 18 years	2		
Age Continuous Units: years arithmetic mean standard deviation	 -		
Gender, Male/Female Units: Subjects			
Female	64		
Male	66		
Race/Ethnicity, Customized Units: Subjects			
White	89		
Black or African American	6		
Asian	32		
American Indian or Alaska Native	1		
Other	2		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7		
Not Hispanic or Latino	24		
Unknown or Not Reported	99		

Subject analysis sets

Subject analysis set title	Cohort 3a
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Children and adolescents with CP-CML who were treatment-naive received dasatinib tablets at 60 mg/m2 QD on a continuous oral regimen.

Subject analysis set title	Cohort 3b
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Children and adolescents with CP-CML who were treatment-naive received dasatinib powder for oral suspension (PFOS) at 72 mg/m2 QD on a continuous oral regimen.

Reporting group values	Cohort 3a	Cohort 3b	
Number of subjects	51	33	
Age Categorical Units: Subjects			
< 2 years	1	1	
>= 2 to < 7 years	5	5	
>= 7 to < 12 years	16	12	
>= 12 to < 18 years	29	15	
>= 18 years	0	0	

Age Continuous Units: years			
arithmetic mean	12.28	11.44	
standard deviation	± 4.084	± 4.912	
Gender, Male/Female Units: Subjects			
Female	25	14	
Male	26	19	
Race/Ethnicity, Customized Units: Subjects			
White	31	25	
Black or African American	3	1	
Asian	16	7	
American Indian or Alaska Native	1	0	
Other	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	4	
Not Hispanic or Latino	13	7	
Unknown or Not Reported	37	22	

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description:	
Children and adolescents with CP-CML who were resistant or intolerant to imatinib received dasatinib tablets at 60 mg/m2 QD on a continuous oral regimen.	
Reporting group title	Cohort 2
Reporting group description:	
Children and adolescents with Ph+ ALL, AP-CML or BP-CML who were resistant or intolerant to, or relapsed after imatinib therapy received dasatinib tablets at a dose schedule of 80 mg/m2 QD on a continuous oral regimen.	
Reporting group title	Cohort 3
Reporting group description:	
Children and adolescents with CP-CML who were treatment-naive received dasatinib tablets at 60 mg/m2 QD or powder for oral suspension (PFOS) at 72 mg/m2 QD on a continuous oral regimen.	
Reporting group title	Cohort 1
Reporting group description:	
Children and adolescents with CP-CML who were resistant or intolerant to imatinib received dasatinib tablets at 60 mg/m2 QD on a continuous oral regimen.	
Reporting group title	Cohort 2
Reporting group description:	
Children and adolescents with Ph+ ALL, AP-CML or BP-CML who were resistant or intolerant to, or relapsed after imatinib therapy received dasatinib tablets at a dose schedule of 80 mg/m2 QD on a continuous oral regimen.	
Reporting group title	Cohort 3
Reporting group description:	
Children and adolescents with CP-CML who were treatment-naive received dasatinib tablets at 60 mg/m2 QD or powder for oral suspension (PFOS) at 72 mg/m2 QD on a continuous oral regimen.	
Subject analysis set title	Cohort 3a
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Children and adolescents with CP-CML who were treatment-naive received dasatinib tablets at 60 mg/m2 QD on a continuous oral regimen.	
Subject analysis set title	Cohort 3b
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Children and adolescents with CP-CML who were treatment-naive received dasatinib powder for oral suspension (PFOS) at 72 mg/m2 QD on a continuous oral regimen.	

Primary: Major Cytogenetic Response (MCyR) Rate

End point title	Major Cytogenetic Response (MCyR) Rate[1][2]
End point description:	
Major Cytogenetic Response (MCyR) rate is defined as the proportion of all treated subjects who achieved a complete (0%) or partial (1%-35% Ph+ metaphases in at least 20 metaphases in bone marrow) cytogenetic response, expressed as percentage. The denominator of the MCyR response rate consists of all treated subjects in Cohort 1, and the numerator is all subjects in Cohort 1 achieving MCyR. 95% confidence interval was calculated by Clopper-Pearson exact method.	
End point type	Primary
End point timeframe:	
From first dose of study therapy until 30 days after last dose (Assessed up to September 2016, approximately 90 months)	

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: This endpoint was only planned to analyze select arms

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was only planned to analyze select arms

End point values	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: percentage of subjects				
number (confidence interval 95%)	89.7 (72.6 to 97.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Complete Hematologic Response (CHR) Rate

End point title	Complete Hematologic Response (CHR) Rate[3][4]

End point description:

Complete Hematologic Response (CHR) rate is defined as the proportion of all treated subjects who achieve a confirmed CHR while on-study, expressed as percentage. CHR is defined as including no more than 5% blasts in bone marrow and normal white blood cell count without blasts in peripheral blood, expressed as percentage. The denominator of the CHR response rate consists of all treated subjects in Cohort 2, and the numerator is all subjects in Cohort 2 achieving CHR. 95% confidence interval was calculated by Clopper-Pearson exact method.

End point type	Primary

End point timeframe:

From first dose of study therapy until 30 days after last dose (Assessed up to September 2016, approximately 90 months)

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: Only summary statistics were planned for this endpoint

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was only planned to analyze select arms

End point values	Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: percentage of subjects				
number (confidence interval 95%)	29.4 (10.3 to 56.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Complete Cytogenetic Response (CCyR) Rate

End point title	Complete Cytogenetic Response (CCyR) Rate[5][6]

End point description:

Complete Cytogenetic Response (CCyR) rate is defined as the proportion of all treated subjects who achieve a CCyR while on-study, expressed as a percentage. CCyR rate is defined as 0% Ph+ metaphases in at least 20 metaphases in bone marrow. The denominator of the CCyR response rate consists of all treated subjects in Cohort 3, and the numerator is all subjects in Cohort 3 achieving CCyR. 95% confidence interval was calculated by Clopper-Pearson exact method.

End point type	Primary

End point timeframe:

From first dose of study therapy until 30 days after last dose (Assessed up to September 2016, approximately 90 months)

Notes:

[5] - 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

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was only planned to analyze select arms

End point values	Cohort 3			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: percentage of subjects				
number (confidence interval 95%)	94.0 (86.7 to 98.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Major Cytogenetic Response (MCyR) Rate in Cohort 2

End point title	Major Cytogenetic Response (MCyR) Rate in Cohort 2[7]

End point description:

Major Cytogenetic Response (MCyR) rate was defined as the proportion of all treated subjects who achieved a complete (0%) or partial (1%-35% Ph+ metaphases in at least 20 metaphases in bone marrow) cytogenetic response. The percentage of treated subjects in each arm with MCyR is reported.

End point type	Secondary

End point timeframe:

From first dose of study therapy until 30 days after last dose (Assessed up to September 2016, approximately 90 months)

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: This endpoint was only planned to analyze select arms

End point values	Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: percent of subjects				
number (confidence interval 95%)	58.8 (32.9 to 81.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Hematologic Response (CHR) Rate in Cohorts 1 and 3

End point title	Complete Hematologic Response (CHR) Rate in Cohorts 1 and

End point description:

Complete Hematologic Response (CHR) rate defined as the proportion of all treated subjects who achieve a confirmed CHR while on-study. CHR is defined as including no more than 5% blasts in bone marrow and normal white blood cell count without blasts in peripheral blood. The percentage of treated subjects in each arm with CHR is reported.

End point type	Secondary

End point timeframe:

From first dose of study therapy until 30 days after last dose (Assessed up to September 2016, approximately 90 months)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was only planned to analyze select arms

End point values	Cohort 1	Cohort 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	84		
Units: percentage of subjects				
number (confidence interval 95%)	93.1 (77.2 to 99.2)	96.4 (89.9 to 99.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Best Cytogenetic Response

End point title	Rate of Best Cytogenetic Response

End point description:

The number of subjects achieving their best on-study cytogenetic response was reported as a percentage of all treated subjects in that arm.

End point type	Secondary

End point timeframe:

From first dose of study therapy until 30 days after last dose (Assessed up to September 2016, approximately 90 months)

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	17	84	51
Units: percentage of subjects				
number (not applicable)				
Complete (0%)	82.8	29.4	94.0	96.1
Partial (>0% - 35%)	6.9	23.5	2.4	2.0
Minor (>35% - 65%)	3.4	0	0	0
Minimal (>65% - 95%)	3.4	0	1.2	2.0
No Response (>95% - 100%)	0	5.9	0	0
Unable to Determine	3.4	41.2	2.4	0

End point values	Cohort 3b			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: percentage of subjects				
number (not applicable)				
Complete (0%)	90.9			
Partial (>0% - 35%)	3.0			
Minor (>35% - 65%)	0			
Minimal (>65% - 95%)	0			
No Response (>95% - 100%)	0			
Unable to Determine	6.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Major Cytogenetic Response (MCyR)

End point title	Time to Major Cytogenetic Response (MCyR)

End point description:

Time to MCyR is defined as the time from first dose of dasatinib until the first day MCyR criteria are met, computed only for subjects whose best response is MCyR.

End point type	Secondary

End point timeframe:

From first dose until MCyR criteria are met (assessed up to September 2016, approximately 90 months)

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	26	9	81	50
Units: months				
median (confidence interval 95%)	3.1 (2.8 to 4.1)	1.6 (0.5 to 5.7)	3.0 (2.9 to 4.3)	3.3 (2.9 to 5.6)

End point values	Cohort 3b			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: months				
median (confidence interval 95%)	3.0 (2.8 to 5.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Major Cytogenetic Response (MCyR)

End point title	Duration of Major Cytogenetic Response (MCyR)

End point description:

Duration of MCyR will be computed from the first day criteria are met for MCyR until the date PD is reported (or treatment is discontinued for PD) or death. Subjects who neither discontinue due to PD nor die will be censored on the date of their last hematologic or cytogenetic assessment, whichever comes last. Only subjects with MCyR were analyzed.

End point type	Secondary

End point timeframe:

From first day criteria are met for MCyR until the date PD is reported or death (assessed up to September 2016, approximately 90 months)

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	26	9	81	50
Units: months				
median (confidence interval 95%)	99999 (54.9 to 99999)	11.2 (0.3 to 99999)	99999 (52.7 to 99999)	99999 (52.7 to 99999)

End point values	Cohort 3b			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Cytogenetic Response (CCyR)

End point title	Time to Complete Cytogenetic Response (CCyR)

End point description:

Time to CCyR is defined as the time from first dose of dasatinib until the first day CCyR criteria are met, computed only for subjects whose best response is CCyR.

End point type	Secondary

End point timeframe:

From first dose until CCyR criteria are met, assessed up to September 2016 (approximately 90 months)

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	24	7	79	49
Units: months				
median (confidence interval 95%)	3.9 (2.8 to 5.6)	1.6 (0.5 to 5.7)	5.6 (5.0 to 6.0)	5.7 (3.7 to 6.2)

End point values	Cohort 3b			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: months				
median (confidence interval 95%)	5.6 (3.1 to 6.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Complete Cytogenetic Response (CCyR)

End point title	Duration of Complete Cytogenetic Response (CCyR)

End point description:

Duration of CCyR will be computed from the first day criteria are met for CCyR until the date PD is reported (or treatment is discontinued for PD) or death. Subjects who neither discontinue due to PD nor die will be censored on the date of their last hematologic or cytogenetic assessment, whichever comes last.

End point type	Secondary

End point timeframe:

From first day criteria are met for CCyR until the date of progressive disease or death (assessed up to September 2016, approximately 90 months)

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	24	5	79	49
Units: months				
median (confidence interval 95%)	99999 (54.9 to 99999)	99999 (1.0 to 99999)	99999 (49.9 to 99999)	99999 (49.9 to 99999)

End point values	Cohort 3b			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Rate at 2 years

End point title	Progression-Free Survival (PFS) Rate at 2 years

End point description:

PFS is defined as time from the first dosing date until the time PD is first documented by the investigator or death. Subjects who die without a reported date of progression will be considered to have progressed on the date of death. Subjects who neither progress nor die will be censored on the date of their last cytogenetic or hematologic assessment. The percentages of progression-free subjects at 2 years are based on Kaplan-Meier estimation.

End point type	Secondary

End point timeframe:

2 years

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	17	84	51
Units: percentage				
median (confidence interval 95%)	81.7 (61.4 to 92.0)	20.5 (3.7 to 46.4)	95.1 (87.4 to 98.1)	94.0 (82.6 to 98.0)

End point values	Cohort 3b			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: percentage				
median (confidence interval 95%)	96.8 (79.2 to 99.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Hematologic Response (CHR)

End point title	Time to Complete Hematologic Response (CHR)

End point description:

Time to CHR is defined as the time from first dose of dasatinib until the first day CHR criteria are met, provided they are confirmed 4 weeks later, computed only for subjects whose best response is CHR.

End point type	Secondary

End point timeframe:

From first dose until CHR criteria are met, assessed up to September 2016 (approximately 90 months)

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	5	81	51
Units: months				
median (confidence interval 95%)	0.7 (0.5 to 1.8)	2.5 (0.5 to 2.8)	1.2 (0.9 to 1.4)	1.2 (0.9 to 1.4)

End point values	Cohort 3b			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: months				
median (confidence interval 95%)	1.0 (0.7 to 1.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Complete Hemotologic Response (CHR)

End point title	Duration of Complete Hemotologic Response (CHR)

End point description:

Duration of CHR will be computed from the first day all criteria are met for CHR, provided they are confirmed 4 weeks later, until the date progressive disease (PD) is reported (or treatment is discontinued for PD) or death. Subjects who neither discontinue due to PD nor die will be censored on the date of their last hematologic assessment. Only subjects with CHR were analyzed.

End point type	Secondary

End point timeframe:

From first day criteria are met for CHR until date of disease progression or death (assessed up to September 2016, approximately 90 months)

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	5	81	51
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (1.9 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)

End point values	Cohort 3b			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival Rate at 2 years

End point title	Disease-Free Survival Rate at 2 years

End point description:

Disease free survival is defined as time from CCyR for Subjects with newly diagnosed chronic phase CML and for Subjects with chronic phase CML who are resistant or intolerant to imatinib (cohort 3 and cohort 1), and as time from CHR for Subjects with advanced phase CML and PH + ALL (cohort 2) until the time progression is first documented by the investigator or death from any cause. The percentages of disease-free subjects at 2 years are based on Kaplan-Meier estimation.

End point type	Secondary

End point timeframe:

2 years

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	24	5	79	49
Units: percentage				
median (confidence interval 95%)	86.9 (64.6 to 95.6)	60.0 (12.6 to 88.2)	98.7 (91.2 to 99.8)	97.9 (86.1 to 99.7)

End point values	Cohort 3b			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: percentage				
median (confidence interval 95%)	100 (100 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Rate at 2 years

End point title	Overall Survival (OS) Rate at 2 years

End point description:

OS is defined as time from the first dosing date until the time of death. All subjects will be followed yearly for survival for up to 5 years after treatment discontinuation. Subjects who have not died or who are lost to follow-up will be censored on the last date the subject is known to be alive. The percentages of surviving participants at 2 years are based on Kaplan-Meier estimation.

End point type	Secondary

End point timeframe:

2 years

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	17	84	51
Units: percentage				
median (confidence interval 95%)	96.4 (77.2 to 99.5)	32.2 (10.6 to 56.4)	100 (100 to 100)	100 (100 to 100)

End point values	Cohort 3b			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: percentage				
median (confidence interval 95%)	100 (100 to			

100)

Statistical analyses

No statistical analyses for this end point

Secondary: Major Molecular Response (MMR) Rate

End point title	Major Molecular Response (MMR) Rate

End point description:

Molecular response was assessed using BCR-ABL transcript levels measurement by real-time quantitative polymerase chain
reaction (qPCR). MMR for subjects with the p210 BCR-ABL transcript variant was defined as a ratio BCR-ABL/ABL <= 10-3
or 0.1% on the international scale. In this study, ABL was used as the control-gene. For a subject with the p190 BCR-ABL
transcript variant (occurring in Cohort 2 only), on-study assessments were compared to the participant's individual baseline BCR-ABL/ABL ratio and a reduction to < 0.1% or a 3-log reduction from baseline was considered an MMR.

End point type	Secondary

End point timeframe:

From date of first treatment to date of MMR (assessed up to September 2016, approximately 90 months)

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	17	84	51
Units: percentage of subjects				
number (confidence interval 95%)	62.1 (42.3 to 79.3)	29.4 (10.3 to 56.0)	79.8 (69.6 to 87.7)	88.2 (76.1 to 95.6)

End point values	Cohort 3b			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: percentage of subjects				
number (confidence interval 95%)	66.7 (48.2 to 82.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Molecular Response (CMR) Rate

End point title	Complete Molecular Response (CMR) Rate

End point description:

Molecular response was assessed using BCR-ABL transcript levels measurement by real-time quantitative polymerase chain reaction (qPCR). CMR is defined as absence of BCR-ABL rearrangements by real-time qPCR analysis. The percentage of treated subjects with CMR is reported by arm.

End point type	Secondary

End point timeframe:

From date of first treatment to date of CMR (assessed up to September 2016, approximately 90 months)

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	17	84	51
Units: percentage				
number (confidence interval 95%)	24.1 (10.3 to 43.5)	17.6 (3.8 to 43.4)	29.8 (20.3 to 40.7)	43.1 (29.3 to 57.8)

End point values	Cohort 3b			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: percentage				
number (confidence interval 95%)	9.1 (1.9 to 24.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Major Cytogenetic Response (MCyR) Rate up to 2 years

End point title	Major Cytogenetic Response (MCyR) Rate up to 2 years

End point description:

Major Cytogenetic Response (MCyR) rate is defined as the proportion of all treated subjects who achieved a complete (0%) or partial (1%-35% Ph+ metaphases in at least 20 metaphases in bone marrow) cytogenetic response. The percentage of treated subjects with MCyR is reported by arm.

End point type	Secondary

End point timeframe:

24 months

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	17	84	51
Units: percentage of subjects				
number (confidence interval 95%)				
12 months	89.7 (72.6 to 97.8)	58.8 (32.9 to 81.6)	96.4 (89.9 to 99.3)	98.0 (89.6 to 100.0)
24 months	89.7 (72.6 to 97.8)	58.8 (32.9 to 81.6)	96.4 (89.9 to 99.3)	98.0 (89.6 to 100.0)

End point values	Cohort 3b			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: percentage of subjects				
number (confidence interval 95%)				
12 months	93.9 (79.8 to 99.3)			
24 months	93.9 (79.8 to 99.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Cytogenetic Response (CCyR) Rate up to 2 years

End point title	Complete Cytogenetic Response (CCyR) Rate up to 2 years

End point description:

Complete Cytogenetic Response (CCyR) rate is defined as the proportion of all treated subjects who achieve a CCyR while on-study. CCyR rate is defined as 0% Ph+ metaphases in at least 20 metaphases in bone marrow. The percentage of treated subjects with CCyR is reported by arm.

End point type	Secondary

End point timeframe:

24 months

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	17	84	51
Units: percentage of subjects				
number (confidence interval 95%)				
12 months	75.9 (56.5 to 89.7)	41.2 (18.4 to 67.1)	92.9 (85.1 to 97.3)	96.1 (86.5 to 99.5)
24 months	82.8 (64.2 to 94.2)	41.2 (18.4 to 67.1)	94.0 (86.7 to 98.0)	96.1 (86.5 to 99.5)

End point values	Cohort 3b			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: percentage of subjects				
number (confidence interval 95%)				
12 months	87.9 (71.8 to 96.6)			
24 months	90.9 (75.7 to 98.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Major Molecular Response (MMR) Rate up to 2 years

End point title	Major Molecular Response (MMR) Rate up to 2 years

End point description:

Molecular response was assessed using BCR-ABL transcript levels measurement by real-time qPCR. MMR for Subjects with the p210 BCR-ABL transcript variant is defined according to the recommendations of Hughes et al. as a ratio BCR-ABL/ABL <= 10-3 or 0.1% on the international scale proposed by the authors. The standardized baseline, as established in the IRIS trial, is taken to represent 100% on the international scale and a 3-log reduction in ratio (BCR-ABL transcripts/ABL or BCR) from the standardized baseline (MMR) is fixed at 0.1%. In this study, ABL or other housekeeping gene, will be used as the control-gene. For a Subject with the p190 BCR-ABL transcript variant, on-study assessments will be compared to the Subject's individual baseline BCR-ABL/ABL ratio and a reduction to < 0.1% or a 3-log reduction from baseline will be considered an MMR. The percentage of treated subjects with MMR is reported by arm.

End point type	Secondary

End point timeframe:

24 months

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	17	84	51
Units: percentage of subjects				
number (confidence interval 95%)				
12 months	41.4 (23.5 to 61.1)	23.5 (6.8 to 49.9)	52.4 (41.2 to 63.4)	56.9 (42.2 to 70.7)
24 months	55.2 (35.7 to 73.6)	29.4 (10.3 to 56.0)	70.2 (59.3 to 79.7)	74.5 (60.4 to 85.7)

End point values	Cohort 3b			

Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: percentage of subjects				
number (confidence interval 95%)				
12 months	45.5 (28.1 to 63.6)			
24 months	63.6 (45.1 to 79.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Molecular Response (CMR) Rate up to 2 years

End point title	Complete Molecular Response (CMR) Rate up to 2 years

End point description:

Molecular response was assessed using BCR-ABL transcript levels measurement by real-time quantitative polymerase chain reaction (qPCR). (CMR) is defined as absence of BCR-ABL rearrangements by real-time qPCR analysis. The percentage of treated subjects with CMR is reported by arm.

End point type	Secondary

End point timeframe:

24 months

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 3a
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	17	84	51
Units: percentage				
number (confidence interval 95%)				
12 months	6.9 (0.8 to 22.8)	11.8 (1.5 to 36.4)	8.3 (3.4 to 16.4)	9.8 (3.3 to 21.4)
24 months	17.2 (5.8 to 35.8)	11.8 (1.5 to 36.4)	21.4 (13.2 to 31.7)	29.4 (17.5 to 43.8)

End point values	Cohort 3b			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: percentage				
number (confidence interval 95%)				
12 months	6.1 (0.7 to 20.2)			
24 months	9.1 (1.9 to 24.3)			

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	Cohort 3a
Reporting group description:	
Children and adolescents with CP-CML who were treatment-naive received dasatinib tablets at 60 mg/m2 QD on a continuous oral regimen.	
Reporting group title	Cohort 3b
Reporting group description:	
Children and adolescents with CP-CML who were treatment-naive received dasatinib powder for oral suspension (PFOS) at 72 mg/m2 QD on a continuous oral regimen.	
Reporting group title	Cohort 1
Reporting group description:	
Children and adolescents with CP-CML who were resistant or intolerant to imatinib received dasatinib tablets at 60 mg/m2 QD on a continuous oral regimen.	
Reporting group title	Cohort 2 BP-CML
Reporting group description:	
Children and adolescents with BP-CML who were resistant or intolerant to, or relapsed after imatinib therapy received dasatinib tablets at a dose schedule of 80 mg/m2 QD on a continuous oral regimen.	
Reporting group title	Cohort 2 Ph+ ALL
Reporting group description:	
Children and adolescents with Ph+ ALL who were resistant or intolerant to, or relapsed after imatinib therapy received dasatinib tablets at a dose schedule of 80 mg/m2 QD on a continuous oral regimen.	

Serious adverse events	Cohort 3a	Cohort 3b	Cohort 1
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 51 (37.25%)	9 / 33 (27.27%)	13 / 29 (44.83%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia recurrent			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blast cell proliferation			

subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blast crisis in myelogenous leukaemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	0 / 29 (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
Leukaemia recurrent			
subjects affected / exposed	0 / 51 (0.00%)	2 / 33 (6.06%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Bone marrow transplant			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Disease progression			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Oedema peripheral			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Pain			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 51 (3.92%)	3 / 33 (9.09%)	2 / 29 (6.90%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Genital haemorrhage			

subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Personality change			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Suicidal ideation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	2 / 51 (3.92%)	0 / 33 (0.00%)	0 / 29 (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
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Gun shot wound			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Hand fracture			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Overdose			
subjects affected / exposed	1 / 51 (1.96%)	1 / 33 (3.03%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	1 / 1	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Left ventricular dysfunction			

subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Arachnoiditis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial nerve disorder			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Peripheral motor neuropathy			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 51 (5.88%)	1 / 33 (3.03%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	6 / 7	0 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	2 / 51 (3.92%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Neutropenia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	2 / 29 (6.90%)
occurrences causally related to treatment / all	0 / 0	0 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 51 (3.92%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal ulcer			

subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 51 (0.00%)	3 / 33 (9.09%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	0 / 29 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Pancreatitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			

subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 51 (0.00%)	3 / 33 (9.09%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 51 (1.96%)	1 / 33 (3.03%)	0 / 29 (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
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Pain in extremity			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	2 / 29 (6.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Myringitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Oral herpes			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis externa			

subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Periorbital cellulitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Sepsis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper aerodigestive tract infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	0 / 29 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	2 / 51 (3.92%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 2 BP-CML	Cohort 2 Ph+ ALL	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	6 / 9 (66.67%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia recurrent			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blast cell proliferation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blast crisis in myelogenous leukaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia recurrent			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	2 / 8 (25.00%)	2 / 9 (22.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Vascular disorders			
Jugular vein thrombosis			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Bone marrow transplant			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Genital haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality change			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gun shot wound			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Overdose			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Arachnoiditis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial nerve disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Seizure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 8 (25.00%)	3 / 9 (33.33%)	
occurrences causally related to treatment / all	3 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Leukopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal ulcer			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial sepsis			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myringitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			

subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper aerodigestive tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 3a	Cohort 3b	Cohort 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 51 (98.04%)	33 / 33 (100.00%)	27 / 29 (93.10%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	3 / 51 (5.88%)	3 / 33 (9.09%)	1 / 29 (3.45%)
occurrences (all)	3	4	1
Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 51 (3.92%)	3 / 33 (9.09%)	1 / 29 (3.45%)
occurrences (all)	2	5	1
Hot flush			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	5 / 51 (9.80%)	4 / 33 (12.12%)	1 / 29 (3.45%)
occurrences (all)	6	5	1
Thrombophlebitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Phlebitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	2 / 51 (3.92%)	0 / 33 (0.00%)	3 / 29 (10.34%)
occurrences (all)	3	0	4
Chills			
subjects affected / exposed	0 / 51 (0.00%)	3 / 33 (9.09%)	1 / 29 (3.45%)
occurrences (all)	0	3	1
Fatigue			

subjects affected / exposed	10 / 51 (19.61%)	7 / 33 (21.21%)	8 / 29 (27.59%)
occurrences (all)	22	18	14
Influenza like illness			
subjects affected / exposed	0 / 51 (0.00%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	0	2	0
Malaise			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Mass			
subjects affected / exposed	1 / 51 (1.96%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	1	3	0
Mucosal inflammation			
subjects affected / exposed	0 / 51 (0.00%)	2 / 33 (6.06%)	1 / 29 (3.45%)
occurrences (all)	0	2	1
Non-Cardiac chest pain			
subjects affected / exposed	3 / 51 (5.88%)	3 / 33 (9.09%)	0 / 29 (0.00%)
occurrences (all)	3	3	0
Oedema peripheral			
subjects affected / exposed	2 / 51 (3.92%)	1 / 33 (3.03%)	3 / 29 (10.34%)
occurrences (all)	2	1	3
Pain			
subjects affected / exposed	6 / 51 (11.76%)	5 / 33 (15.15%)	3 / 29 (10.34%)
occurrences (all)	9	7	3
Peripheral swelling			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	2 / 29 (6.90%)
occurrences (all)	0	0	2
Pyrexia			
subjects affected / exposed	23 / 51 (45.10%)	10 / 33 (30.30%)	14 / 29 (48.28%)
occurrences (all)	77	22	46
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 51 (0.00%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	0	2	0
Hypersensitivity			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	2 / 29 (6.90%)
occurrences (all)	0	0	5

Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences (all)	1	0	1
Dysmenorrhoea			
subjects affected / exposed	4 / 51 (7.84%)	1 / 33 (3.03%)	1 / 29 (3.45%)
occurrences (all)	14	1	3
Menstruation irregular			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	2 / 29 (6.90%)
occurrences (all)	0	0	2
Vaginal discharge			
subjects affected / exposed	3 / 51 (5.88%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	5	0	0
Vaginal haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 51 (31.37%)	9 / 33 (27.27%)	13 / 29 (44.83%)
occurrences (all)	38	20	25
Dyspnoea			
subjects affected / exposed	4 / 51 (7.84%)	2 / 33 (6.06%)	3 / 29 (10.34%)
occurrences (all)	6	2	7
Epistaxis			
subjects affected / exposed	5 / 51 (9.80%)	4 / 33 (12.12%)	3 / 29 (10.34%)
occurrences (all)	5	4	4
Nasal congestion			
subjects affected / exposed	3 / 51 (5.88%)	2 / 33 (6.06%)	3 / 29 (10.34%)
occurrences (all)	4	4	5
Oropharyngeal pain			
subjects affected / exposed	10 / 51 (19.61%)	11 / 33 (33.33%)	6 / 29 (20.69%)
occurrences (all)	16	18	10
Pharyngeal erythema			
subjects affected / exposed	3 / 51 (5.88%)	5 / 33 (15.15%)	0 / 29 (0.00%)
occurrences (all)	5	8	0
Productive cough			

subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Respiratory failure			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Respiratory tract congestion			
subjects affected / exposed	0 / 51 (0.00%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	0	3	0
Rhinalgia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	3 / 51 (5.88%)	3 / 33 (9.09%)	2 / 29 (6.90%)
occurrences (all)	3	3	2
Rhinorrhoea			
subjects affected / exposed	11 / 51 (21.57%)	4 / 33 (12.12%)	3 / 29 (10.34%)
occurrences (all)	15	6	4
Wheezing			
subjects affected / exposed	3 / 51 (5.88%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	3	2	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 51 (3.92%)	3 / 33 (9.09%)	2 / 29 (6.90%)
occurrences (all)	2	3	3
Depression			
subjects affected / exposed	4 / 51 (7.84%)	1 / 33 (3.03%)	1 / 29 (3.45%)
occurrences (all)	4	1	1
Insomnia			
subjects affected / exposed	3 / 51 (5.88%)	2 / 33 (6.06%)	1 / 29 (3.45%)
occurrences (all)	3	2	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 51 (5.88%)	4 / 33 (12.12%)	4 / 29 (13.79%)
occurrences (all)	5	6	5
Aspartate aminotransferase increased			

subjects affected / exposed	3 / 51 (5.88%)	3 / 33 (9.09%)	3 / 29 (10.34%)
occurrences (all)	3	4	3
Blood creatinine increased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 51 (3.92%)	4 / 33 (12.12%)	0 / 29 (0.00%)
occurrences (all)	4	5	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Gamma-Glutamyltransferase increased			
subjects affected / exposed	0 / 51 (0.00%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	0	2	0
Haemoglobin decreased			
subjects affected / exposed	0 / 51 (0.00%)	5 / 33 (15.15%)	1 / 29 (3.45%)
occurrences (all)	0	8	1
Neutrophil count decreased			
subjects affected / exposed	1 / 51 (1.96%)	5 / 33 (15.15%)	0 / 29 (0.00%)
occurrences (all)	1	6	0
Platelet count decreased			
subjects affected / exposed	2 / 51 (3.92%)	11 / 33 (33.33%)	1 / 29 (3.45%)
occurrences (all)	3	19	1
Weight decreased			
subjects affected / exposed	3 / 51 (5.88%)	1 / 33 (3.03%)	1 / 29 (3.45%)
occurrences (all)	3	1	1
Weight increased			
subjects affected / exposed	3 / 51 (5.88%)	3 / 33 (9.09%)	2 / 29 (6.90%)
occurrences (all)	3	5	2
Injury, poisoning and procedural complications			

Arthropod bite			
subjects affected / exposed	0 / 51 (0.00%)	2 / 33 (6.06%)	1 / 29 (3.45%)
occurrences (all)	0	2	2
Contusion			
subjects affected / exposed	3 / 51 (5.88%)	4 / 33 (12.12%)	2 / 29 (6.90%)
occurrences (all)	6	8	3
Foot fracture			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	2 / 51 (3.92%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	2	5	0
Sunburn			
subjects affected / exposed	1 / 51 (1.96%)	1 / 33 (3.03%)	2 / 29 (6.90%)
occurrences (all)	1	1	2
Nervous system disorders			
Arachnoiditis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Brain oedema			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	12 / 51 (23.53%)	3 / 33 (9.09%)	2 / 29 (6.90%)
occurrences (all)	19	4	3
Dysgeusia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Facial paralysis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	24 / 51 (47.06%)	15 / 33 (45.45%)	17 / 29 (58.62%)
occurrences (all)	82	25	52
Neuropathy peripheral			

subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	5 / 29 (17.24%)
occurrences (all)	0	1	5
Somnolence			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	2 / 29 (6.90%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 51 (19.61%)	5 / 33 (15.15%)	2 / 29 (6.90%)
occurrences (all)	16	16	6
Febrile neutropenia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Haemoglobinaemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	3 / 51 (5.88%)	2 / 33 (6.06%)	2 / 29 (6.90%)
occurrences (all)	6	13	2
Lymphadenopathy			
subjects affected / exposed	1 / 51 (1.96%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	1	2	0
Lymphopenia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences (all)	1	2	0
Neutropenia			
subjects affected / exposed	17 / 51 (33.33%)	8 / 33 (24.24%)	6 / 29 (20.69%)
occurrences (all)	35	21	14
Pancytopenia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	13 / 51 (25.49%)	7 / 33 (21.21%)	5 / 29 (17.24%)
occurrences (all)	22	17	7

Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	7 / 51 (13.73%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	8	3	0
Hypoacusis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 51 (1.96%)	2 / 33 (6.06%)	1 / 29 (3.45%)
occurrences (all)	3	2	1
Eye oedema			
subjects affected / exposed	1 / 51 (1.96%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	1	4	0
Eye pain			
subjects affected / exposed	3 / 51 (5.88%)	1 / 33 (3.03%)	3 / 29 (10.34%)
occurrences (all)	4	1	3
Periorbital oedema			
subjects affected / exposed	0 / 51 (0.00%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	0	2	0
Vision blurred			
subjects affected / exposed	3 / 51 (5.88%)	1 / 33 (3.03%)	1 / 29 (3.45%)
occurrences (all)	3	1	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	18 / 51 (35.29%)	7 / 33 (21.21%)	10 / 29 (34.48%)
occurrences (all)	42	12	37
Abdominal pain upper			
subjects affected / exposed	12 / 51 (23.53%)	4 / 33 (12.12%)	8 / 29 (27.59%)
occurrences (all)	32	9	16
Anal fissure			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Anal ulcer			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Colitis			

subjects affected / exposed	3 / 51 (5.88%)	1 / 33 (3.03%)	1 / 29 (3.45%)
occurrences (all)	7	2	1
Constipation			
subjects affected / exposed	9 / 51 (17.65%)	5 / 33 (15.15%)	4 / 29 (13.79%)
occurrences (all)	11	6	4
Diarrhoea			
subjects affected / exposed	27 / 51 (52.94%)	12 / 33 (36.36%)	17 / 29 (58.62%)
occurrences (all)	87	21	72
Dyspepsia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	2 / 29 (6.90%)
occurrences (all)	0	1	2
Flatulence			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	2 / 29 (6.90%)
occurrences (all)	0	1	2
Gastritis			
subjects affected / exposed	6 / 51 (11.76%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences (all)	9	1	0
Gingival bleeding			
subjects affected / exposed	2 / 51 (3.92%)	0 / 33 (0.00%)	2 / 29 (6.90%)
occurrences (all)	2	0	2
Mouth ulceration			
subjects affected / exposed	0 / 51 (0.00%)	2 / 33 (6.06%)	1 / 29 (3.45%)
occurrences (all)	0	3	1
Nausea			
subjects affected / exposed	20 / 51 (39.22%)	10 / 33 (30.30%)	11 / 29 (37.93%)
occurrences (all)	38	24	28
Oral pain			
subjects affected / exposed	2 / 51 (3.92%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	3	2	0
Stomatitis			
subjects affected / exposed	2 / 51 (3.92%)	4 / 33 (12.12%)	0 / 29 (0.00%)
occurrences (all)	2	17	0
Tongue ulceration			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences (all)	0	3	0
Toothache			

subjects affected / exposed	4 / 51 (7.84%)	1 / 33 (3.03%)	3 / 29 (10.34%)
occurrences (all)	4	1	5
Vomiting			
subjects affected / exposed	22 / 51 (43.14%)	11 / 33 (33.33%)	15 / 29 (51.72%)
occurrences (all)	55	30	45
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 51 (1.96%)	7 / 33 (21.21%)	3 / 29 (10.34%)
occurrences (all)	1	7	5
Alopecia			
subjects affected / exposed	5 / 51 (9.80%)	1 / 33 (3.03%)	2 / 29 (6.90%)
occurrences (all)	6	1	2
Dermatitis acneiform			
subjects affected / exposed	2 / 51 (3.92%)	2 / 33 (6.06%)	2 / 29 (6.90%)
occurrences (all)	3	2	2
Dry skin			
subjects affected / exposed	2 / 51 (3.92%)	0 / 33 (0.00%)	4 / 29 (13.79%)
occurrences (all)	2	0	6
Eczema			
subjects affected / exposed	1 / 51 (1.96%)	1 / 33 (3.03%)	2 / 29 (6.90%)
occurrences (all)	1	1	2
Erythema			
subjects affected / exposed	4 / 51 (7.84%)	2 / 33 (6.06%)	2 / 29 (6.90%)
occurrences (all)	4	4	2
Papule			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Petechiae			
subjects affected / exposed	1 / 51 (1.96%)	1 / 33 (3.03%)	1 / 29 (3.45%)
occurrences (all)	4	3	1
Pruritus			
subjects affected / exposed	7 / 51 (13.73%)	4 / 33 (12.12%)	5 / 29 (17.24%)
occurrences (all)	8	4	5
Rash			
subjects affected / exposed	14 / 51 (27.45%)	11 / 33 (33.33%)	8 / 29 (27.59%)
occurrences (all)	19	25	11

Rash erythematous			
subjects affected / exposed	3 / 51 (5.88%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	4	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 51 (0.00%)	3 / 33 (9.09%)	1 / 29 (3.45%)
occurrences (all)	0	3	1
Rash papular			
subjects affected / exposed	3 / 51 (5.88%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences (all)	3	1	0
Skin exfoliation			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Skin hypopigmentation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	2 / 29 (6.90%)
occurrences (all)	1	0	2
Skin induration			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	3 / 51 (5.88%)	3 / 33 (9.09%)	2 / 29 (6.90%)
occurrences (all)	4	6	2
Xeroderma			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	2 / 29 (6.90%)
occurrences (all)	0	0	2
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	4 / 51 (7.84%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences (all)	5	1	0
Urinary incontinence			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 51 (21.57%)	6 / 33 (18.18%)	6 / 29 (20.69%)
occurrences (all)	22	7	15
Back pain			

subjects affected / exposed	7 / 51 (13.73%)	6 / 33 (18.18%)	4 / 29 (13.79%)
occurrences (all)	14	6	6
Bone pain			
subjects affected / exposed	5 / 51 (9.80%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences (all)	5	0	1
Coccydynia			
subjects affected / exposed	0 / 51 (0.00%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	0	2	0
Groin pain			
subjects affected / exposed	3 / 51 (5.88%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	3	0	0
Muscle spasms			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	1 / 51 (1.96%)	4 / 33 (12.12%)	1 / 29 (3.45%)
occurrences (all)	1	4	1
Musculoskeletal pain			
subjects affected / exposed	5 / 51 (9.80%)	7 / 33 (21.21%)	2 / 29 (6.90%)
occurrences (all)	9	7	4
Musculoskeletal stiffness			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	3 / 51 (5.88%)	6 / 33 (18.18%)	2 / 29 (6.90%)
occurrences (all)	3	9	10
Neck pain			
subjects affected / exposed	2 / 51 (3.92%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	2	3	0
Pain in extremity			
subjects affected / exposed	11 / 51 (21.57%)	14 / 33 (42.42%)	15 / 29 (51.72%)
occurrences (all)	24	26	23
Pain in jaw			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	3 / 29 (10.34%)
occurrences (all)	0	1	3
Tendonitis			

subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	2 / 29 (6.90%)
occurrences (all)	0	0	2
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	3 / 29 (10.34%)
occurrences (all)	0	1	3
Cellulitis			
subjects affected / exposed	3 / 51 (5.88%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences (all)	3	0	1
Conjunctivitis			
subjects affected / exposed	2 / 51 (3.92%)	2 / 33 (6.06%)	3 / 29 (10.34%)
occurrences (all)	3	2	3
Ear infection			
subjects affected / exposed	5 / 51 (9.80%)	3 / 33 (9.09%)	1 / 29 (3.45%)
occurrences (all)	10	5	2
Febrile infection			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	2 / 51 (3.92%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	2	2	0
Gastroenteritis			
subjects affected / exposed	7 / 51 (13.73%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	12	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	2 / 29 (6.90%)
occurrences (all)	0	1	3
Gingivitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences (all)	1	0	1
Herpes virus infection			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0

Hordeolum			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	2 / 29 (6.90%)
occurrences (all)	0	1	3
Influenza			
subjects affected / exposed	6 / 51 (11.76%)	1 / 33 (3.03%)	3 / 29 (10.34%)
occurrences (all)	14	1	3
Localised infection			
subjects affected / exposed	1 / 51 (1.96%)	2 / 33 (6.06%)	1 / 29 (3.45%)
occurrences (all)	1	2	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 51 (0.00%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	10 / 51 (19.61%)	4 / 33 (12.12%)	7 / 29 (24.14%)
occurrences (all)	16	8	9
Oral herpes			
subjects affected / exposed	4 / 51 (7.84%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences (all)	4	1	0
Otitis media			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	6 / 51 (11.76%)	1 / 33 (3.03%)	2 / 29 (6.90%)
occurrences (all)	8	1	2
Rhinitis			
subjects affected / exposed	7 / 51 (13.73%)	4 / 33 (12.12%)	3 / 29 (10.34%)
occurrences (all)	10	6	3
Sinusitis			
subjects affected / exposed	3 / 51 (5.88%)	2 / 33 (6.06%)	4 / 29 (13.79%)
occurrences (all)	8	2	4
Tonsillitis			
subjects affected / exposed	3 / 51 (5.88%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences (all)	3	1	0
Tooth infection			
subjects affected / exposed	3 / 51 (5.88%)	0 / 33 (0.00%)	1 / 29 (3.45%)
occurrences (all)	3	0	1

Upper respiratory tract infection			
subjects affected / exposed	16 / 51 (31.37%)	11 / 33 (33.33%)	9 / 29 (31.03%)
occurrences (all)	30	25	23
Viral infection			
subjects affected / exposed	3 / 51 (5.88%)	0 / 33 (0.00%)	3 / 29 (10.34%)
occurrences (all)	3	0	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 51 (7.84%)	1 / 33 (3.03%)	2 / 29 (6.90%)
occurrences (all)	8	1	2
Fluid retention			
subjects affected / exposed	0 / 51 (0.00%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	0	3	0
Hypercalcaemia			
subjects affected / exposed	0 / 51 (0.00%)	2 / 33 (6.06%)	0 / 29 (0.00%)
occurrences (all)	0	2	0
Hyperkalaemia			
subjects affected / exposed	0 / 51 (0.00%)	3 / 33 (9.09%)	0 / 29 (0.00%)
occurrences (all)	0	7	0
Hypermagnesaemia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences (all)	2	2	0
Hypernatraemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 51 (0.00%)	4 / 33 (12.12%)	0 / 29 (0.00%)
occurrences (all)	0	4	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Hypocalcaemia			

subjects affected / exposed	2 / 51 (3.92%)	3 / 33 (9.09%)	2 / 29 (6.90%)
occurrences (all)	2	3	2
Hypokalaemia			
subjects affected / exposed	2 / 51 (3.92%)	1 / 33 (3.03%)	0 / 29 (0.00%)
occurrences (all)	2	1	0
Hypomagnesaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 33 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 2 BP-CML	Cohort 2 Ph+ ALL	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	9 / 9 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hot flush			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Thrombophlebitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Phlebitis			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Chills			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Influenza like illness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Malaise			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	4	
Mass			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Mucosal inflammation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	5	0	
Non-Cardiac chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Oedema peripheral			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pain			

subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	2	
Peripheral swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	5 / 9 (55.56%)	
occurrences (all)	1	12	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dysmenorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Menstruation irregular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vaginal discharge			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 8 (12.50%)	4 / 9 (44.44%)	
occurrences (all)	6	5	
Dyspnoea			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pharyngeal erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Productive cough			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Respiratory tract congestion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rhinalgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Wheezing			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	2	
Depression			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Insomnia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 8 (37.50%)	1 / 9 (11.11%)	
occurrences (all)	6	1	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Blood creatinine increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	6	0	
Blood phosphorus decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Blood urea increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Gamma-Glutamyltransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Haemoglobin decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Neutrophil count decreased			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Platelet count decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Weight decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Weight increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Contusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Foot fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Sunburn			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Arachnoiditis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Brain oedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dizziness			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Dysgeusia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Facial paralysis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	3 / 8 (37.50%)	5 / 9 (55.56%)	
occurrences (all)	16	9	
Neuropathy peripheral			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Somnolence			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 8 (25.00%)	2 / 9 (22.22%)	
occurrences (all)	5	3	
Febrile neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Haemoglobinaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Leukopenia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Lymphadenopathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	

Lymphopenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Neutropenia			
subjects affected / exposed	4 / 8 (50.00%)	3 / 9 (33.33%)	
occurrences (all)	9	8	
Pancytopenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	4 / 8 (50.00%)	4 / 9 (44.44%)	
occurrences (all)	12	5	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypoacusis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Eye oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Eye pain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Periorbital oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vision blurred			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	
occurrences (all)	1	4	
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Anal fissure			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Anal ulcer			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Colitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	
occurrences (all)	5	0	
Diarrhoea			
subjects affected / exposed	3 / 8 (37.50%)	3 / 9 (33.33%)	
occurrences (all)	3	6	
Dyspepsia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Flatulence			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Gastritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Gingival bleeding			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Mouth ulceration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	

Nausea			
subjects affected / exposed	3 / 8 (37.50%)	2 / 9 (22.22%)	
occurrences (all)	3	3	
Oral pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Stomatitis			
subjects affected / exposed	2 / 8 (25.00%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Tongue ulceration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	3 / 8 (37.50%)	3 / 9 (33.33%)	
occurrences (all)	14	5	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Alopecia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Dermatitis acneiform			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Dry skin			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Erythema			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Papule			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Petechiae			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rash			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Rash erythematous			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rash maculo-papular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rash papular			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Skin exfoliation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Skin hypopigmentation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Skin induration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Xeroderma			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Back pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Bone pain			
subjects affected / exposed	1 / 8 (12.50%)	3 / 9 (33.33%)	
occurrences (all)	1	3	
Coccydynia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Groin pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal stiffness			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Neck pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Pain in jaw			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Tendonitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	2	
Bronchitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Cellulitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Conjunctivitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Ear infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Febrile infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Folliculitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Gastroenteritis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Gastroenteritis viral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Gingivitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Herpes virus infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hordeolum			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Localised infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Oral herpes			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Otitis media			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Pharyngitis			
subjects affected / exposed	2 / 8 (25.00%)	2 / 9 (22.22%)	
occurrences (all)	3	3	
Rhinitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	
occurrences (all)	1	2	
Viral infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Fluid retention			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypercalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hyperkalaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypermagnesaemia			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Hypernatraemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hyperphosphataemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Hyperuricaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	6	0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Hypocalcaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Hypokalaemia			
subjects affected / exposed	2 / 8 (25.00%)	1 / 9 (11.11%)	
occurrences (all)	5	1	
Hypomagnesaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Hyponatraemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hypophosphataemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2009	The primary purpose of this amendment is to include a new cohort of pediatric subjects with newly diagnosed treatment-naive chronic phase chronic myelogenous leukemia (CP-CML) in this trial (Cohort #3) and to align the protocol with the Pediatric Investigational Plan (PIP). The changes include the following: - Expand the primary objective to include Cohort #3 - Clarify the study duration and drug dispensation. - Established a data monitoring committee (DMC). - In order to improve safety, subjects who have a dose escalation will also be required to have another ECG performed if one was not previously done at that dose. - In order to improve safety, Cohort #3 subjects are required to have ECGs and echocardiograms performed yearly. - Expand the dose selection rationale. - Expand and update safety and efficacy summaries. - Clarify inclusion criteria for all cohorts. - Clarify the resistance criteria for Ph+ ALL. - Clarify the dose escalation criteria for Cohort #2. - Clarify the exclusion criteria for subjects with extramedullary disease to include subjects with isolated CNS involvement. - Add the T315I mutation to the exclusion criteria. - Add hypersensitivity to the active substance or to any of the excipients to the exclusion criteria. - Add patients with hereditary problems of galactose intolerance or Lapp lactase deficiency or glucose-galactose malabsorption to the exclusion criteria. - Clarify statistical definitions, including the definitions for progression-free survival (PFS) and disease-free survival (DFS). - Clarification as to the mode of drug administration. - Synchronized visit and assessment schedules (Table 6.1-1). - Change the molecular analysis schedule to coincide with scheduled visits. - Add the long-term follow-up plan for patients on protocol therapy. - Indicate the modalities of body surface area calculation in children. - Change in the medical monitor of the trial. - Correction of typographical errors.
04 October 2010	The primary purpose of this amendment is to provide updated information regarding the use of dasatinib for first line treatment in adults with chronic phase CML as further justification to study the same patient population in children and adolescents (cohort #3). The changes include the following: - Expand Rationale in Section 1.3.1 - Revised estimated number of sites - Separated diagnosis criteria for cohort #3 for clarity - Clarified diagnosis criteria for cohort #2 - Revised resistance criteria to cap previous imatinib dose at 400 mg/day for subjects with high BSAs - Corrected multiple typographical errors - Clarified footnotes in flow chart
12 June 2012	The primary purpose of this amendment is to clarify the objective of estimating the complete cytogenetic response (CCyR) rate to dasatinib therapy in children and adolescents with newly diagnosed CP-CML who are treatment-naive. Additional changes to the protocol include: - Modify Definition of Complete and Major Molecular Response - Define disease free survival for each cohort - Addition of exploratory objective and endpoints for growth and development and bone mineral content - Primary and Secondary Endpoint Clarification - Clarification of Efficacy Analyses - Administrative Changes

13 December 2012	The purpose of this amendment is to expand cohort 3 to include a sub-cohort of 30 pediatric subjects < 18 years of age with treatment naive chronic phase CML who will receive dasatinib powder for oral suspension (PFOS). This increase in subject number will change our current plan to treat at least 50 newly diagnosed CP- CML pediatric subjects to 80 subjects in cohort 3. Subjects will be required to take the PFOS for a minimum of 12 months, during which data will be collected. We will assess the PK of dasatinib following oral administration of the PFOS in this sub-cohort. Hematologic, cytogenetic, and molecular responses by 12 months will be reported for the sub-cohort taking standard tablets, the sub-cohort using PFOS, and in Cohort 3 as a whole. Similarly, safety analysis will also be reported for both sub-cohorts (taking the standard tablets and PFOS) and in the cohort as a whole. We will also assess the taste properties of the PFOS formulation. This data collected and analyzed on this expanded cohort will be used support registration of the dasatinib PFOS in pediatric subjects. The dose of dasatinib when administered in PFOS formulation will be increased by 20% from the tablet dose, i.e, a dose of 72mg/m2 in this expanded cohort. The purpose of such dose adjustment is to match the exposure of the PFOS formulation to the reference tablet in order to maintain a desired efficacy. It was based on the findings from a bioequivalent study, which showed that AUC(INF) of the PFOS formulation was 19.2% lower compared to the reference tablet.
18 July 2013	The purpose of this amendment is to permanently close Cohort 2 to further enrollment and update the WOCBP guidelines.
24 October 2013	The purpose of this amendment is to correct the criteria for women of child bearing potential (WOCBP) and remove information on post menopausal women.
13 April 2016	This amendment: 1) adds testing for Hepatitis B virus (HBV) and 2) updates recommendations for methods of contraception and reemphasizes the need for contraception.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported