



Clinical trial results:

A phase IB/II study to evaluate the safety and efficacy of vismodegib in relapsed/refractory acute myelogenous leukemia (AML) and relapsed/refractory high-risk myelodysplastic syndrome (MDS).

Summary

EudraCT number	2013-001570-14
Trial protocol	DE
Global end of trial date	03 November 2014

Results information

Result version number	v1 (current)
This version publication date	17 February 2016
First version publication date	17 February 2016

Trial information

Trial identification

Sponsor protocol code	GO28852
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01880437
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F.Hoffmann-LaRocheAG
Sponsor organisation address	Grenzacherstrasse124, Basel, CH-4070, Switzerland,
Public contact	RocheTrialInformationHotline, F.Hoffmann-LaRocheAG, +41 616878333, global.trial_information@roche.com
Scientific contact	RocheTrialInformationHotline, F.Hoffmann-LaRocheAG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 January 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	03 November 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study was a single-arm, open-label study to assess the overall response rate and safety of single-agent vismodegib in participants with relapsed/refractory acute myeloid leukemia (AML) or relapsed/refractory high-risk myelodysplastic syndrome (MDS). There were two planned stages in this study: (1) efficacy and safety assessment of single-agent vismodegib (Cohort 1), and (2) efficacy and safety assessment of vismodegib in combination with cytarabine (Cohort 2). Cohort 2 was only to occur if efficacy was observed in Cohort 1.

Protection of trial subjects:

This study was conducted in full conformance with the International Conference on Harmonisation (ICH) E6 guideline for Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever afforded the greater protection to the individual. Study conducted in the United States (US) or under a U.S. Investigational New Drug (IND) application complied with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. The study complied with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting) and also with the European Union (EU) Clinical Trial Directive (2001/20/EC).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 September 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 19
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Germany: 13
Worldwide total number of subjects	38
EEA total number of subjects	13

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	18
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 47 participants were screened; of which, 7 participants failed screening and 2 participants were erroneously entered but did not receive study drug. A total of 38 participants were enrolled and treated in Cohort 1. Cohort 2 was planned but no participants were enrolled.

Pre-assignment

Screening details:

Based on lower-than-expected efficacy observed in interim data review, study was terminated prior to initiation of Cohort 2. Results are reported as per subgroups of Cohort 1: "Poor Risk Cytogenetics", "FLT-3 Mutation Positive", "Neither Poor Risk Cytogenetics Nor FLT-3", unless otherwise specified.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Poor Risk Cytogenetics

Arm description:

Participants with relapsed/refractory AML or relapsed/refractory high-risk MDS falling under 'poor risk cytogenetics' subgroup received oral 150 milligrams (mg) dose of vismodegib capsule once daily until disease progression, intolerable toxicity most probably attributable to vismodegib, or participant withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Vismodegib
Investigational medicinal product code	RO5450815
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants received vismodegib at a dose of 150 mg once daily with at least 4 ounces of water.

Arm title	FLT-3 Mutation Positive
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Arm description:

Participants with relapsed/refractory AML or relapsed/refractory high-risk MDS falling under 'FLT-3 mutation positive' subgroup received oral 150 mg dose of vismodegib capsule once daily until disease progression, intolerable toxicity most probably attributable to vismodegib, or participant withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Vismodegib
Investigational medicinal product code	RO5450815
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants received vismodegib at a dose of 150 mg once daily with at least 4 ounces of water.

Arm title	Neither Poor Risk Cytogenetics Nor FLT-3
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Arm description:

Participants with relapsed/refractory AML or relapsed/refractory high-risk MDS falling neither under 'poor risk cytogenetics' nor 'FLT-3 mutation positive' subgroup were included in this group and received oral 150 mg dose of vismodegib capsule once daily until disease progression, intolerable toxicity most

probably attributable to vismodegib, or participant withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Vismodegib
Investigational medicinal product code	RO5450815
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants received vismodegib at a dose of 150 mg once daily with at least 4 ounces of water.

Number of subjects in period 1	Poor Risk Cytogenetics	FLT-3 Mutation Positive	Neither Poor Risk Cytogenetics Nor FLT-3
Started	15	4	19
Completed	0	0	0
Not completed	15	4	19
Study terminated by Sponsor	3	-	2
Death	12	4	17

Baseline characteristics

Reporting groups

Reporting group title	Poor Risk Cytogenetics
Reporting group description: Participants with relapsed/refractory AML or relapsed/refractory high-risk MDS falling under 'poor risk cytogenetics' subgroup received oral 150 milligrams (mg) dose of vismodegib capsule once daily until disease progression, intolerable toxicity most probably attributable to vismodegib, or participant withdrawal of consent.	
Reporting group title	FLT-3 Mutation Positive
Reporting group description: Participants with relapsed/refractory AML or relapsed/refractory high-risk MDS falling under 'FLT-3 mutation positive' subgroup received oral 150 mg dose of vismodegib capsule once daily until disease progression, intolerable toxicity most probably attributable to vismodegib, or participant withdrawal of consent.	
Reporting group title	Neither Poor Risk Cytogenetics Nor FLT-3
Reporting group description: Participants with relapsed/refractory AML or relapsed/refractory high-risk MDS falling neither under 'poor risk cytogenetics' nor 'FLT-3 mutation positive' subgroup were included in this group and received oral 150 mg dose of vismodegib capsule once daily until disease progression, intolerable toxicity most probably attributable to vismodegib, or participant withdrawal of consent.	

Reporting group values	Poor Risk Cytogenetics	FLT-3 Mutation Positive	Neither Poor Risk Cytogenetics Nor FLT-3
Number of subjects	15	4	19
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	61.5 ± 20.7	54.5 ± 5.9	66.2 ± 14.7
Gender categorical Units: Subjects			
Female	6	2	9
Male	9	2	10

Reporting group values	Total		
Number of subjects	38		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	17		
Male	21		

End points

End points reporting groups

Reporting group title	Poor Risk Cytogenetics
Reporting group description: Participants with relapsed/refractory AML or relapsed/refractory high-risk MDS falling under 'poor risk cytogenetics' subgroup received oral 150 milligrams (mg) dose of vismodegib capsule once daily until disease progression, intolerable toxicity most probably attributable to vismodegib, or participant withdrawal of consent.	
Reporting group title	FLT-3 Mutation Positive
Reporting group description: Participants with relapsed/refractory AML or relapsed/refractory high-risk MDS falling under 'FLT-3 mutation positive' subgroup received oral 150 mg dose of vismodegib capsule once daily until disease progression, intolerable toxicity most probably attributable to vismodegib, or participant withdrawal of consent.	
Reporting group title	Neither Poor Risk Cytogenetics Nor FLT-3
Reporting group description: Participants with relapsed/refractory AML or relapsed/refractory high-risk MDS falling neither under 'poor risk cytogenetics' nor 'FLT-3 mutation positive' subgroup were included in this group and received oral 150 mg dose of vismodegib capsule once daily until disease progression, intolerable toxicity most probably attributable to vismodegib, or participant withdrawal of consent.	

Primary: Percentage of Participants With a Complete Response (CR) or CR With Incomplete Blood Count Recovery (CRi) or Morphologic Leukemia Free State (MLFS) or Partial Response (PR) at Week 8

End point title	Percentage of Participants With a Complete Response (CR) or CR With Incomplete Blood Count Recovery (CRi) or Morphologic Leukemia Free State (MLFS) or Partial Response (PR) at Week 8 ^[1]
End point description: CR: defined as achieved if the neutrophils count was greater than (>) 1000 cells per microliter (µL), platelets count >100000/µL, bone marrow blasts (BMB) percent (%) less than (<) 5, no Auer rods (clumps of azurophilic granular material that form elongated needles seen in the cytoplasm of leukemic blasts), no transfusion requirements and no signs of extra medullary disease (EMD). CRi: defined if either of the cell (neutrophil or platelet) lineage was not recovered (neutrophils >1000 cells/µL or Not applicable [NA] or platelets count >100000/µL or NA), BMB <5% with no Auer rods and confirmed by flow cytometry with no signs of EMD. MLFS (neutrophil and platelet criteria were NA): defined as BMB <5% with no Auer rods and confirmed by flow cytometry with no signs of EMD. PR: defined as neutrophils count >1000 cells/µL, platelets count >100000/µL, and >50% decrease from baseline to a range of 5-25% of BMB or BMB <5% with Auer rods.	
End point type	Primary
End point timeframe: Week 8	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analysis was planned for this end point.	

End point values	Poor Risk Cytogenetics	FLT-3 Mutation Positive	Neither Poor Risk Cytogenetics Nor FLT-3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[2]	0 ^[3]	0 ^[4]	
Units: percentage of participants				
number (not applicable)				

Notes:

[2] - No participants analyzed as the study was terminated before Week 8 based on interim analysis.

[3] - No participants analyzed as the study was terminated before Week 8 based on interim analysis.

[4] - No participants analyzed as the study was terminated before Week 8 based on interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With CR, CRi, MLFS or PR at Anytime During Study Treatment

End point title	Percentage of Participants With CR, CRi, MLFS or PR at Anytime During Study Treatment
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End point description:

CR: defined as achieved if the neutrophils count >1000 cells/ μ L, platelets count >100000/ μ L, BMB <5%, no Auer rods (clumps of azurophilic granular material that form elongated needles seen in the cytoplasm of leukemic blasts), no transfusion requirements and no signs of EMD. CRi: defined if either of the cell (neutrophil or platelet) lineage was not recovered (neutrophils > 1000 cells/ μ L or NA or platelets count >100000/ μ L or NA, BMB <5% with no Auer rods and confirmed by flow cytometry with no signs of EMD. MLFS (neutrophil and platelet criteria were NA): defined as BMB <5% with no Auer rods and confirmed by flow cytometry with no signs of EMD. PR: defined as neutrophils count >1000 cells/ μ L, platelets count >100000/ μ L, and >50% decrease from baseline to a range of 5-25% of BMB or BMB <5% with Auer rods. Efficacy analysis population included all enrolled participants. "Number of subjects analyzed" = participants who were evaluable for tumor response at anytime during the study.

End point type	Secondary
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End point timeframe:

Up to 30 days of last dose of study drug (maximum treatment duration = 225 days)

End point values	Poor Risk Cytogenetics	FLT-3 Mutation Positive	Neither Poor Risk Cytogenetics Nor FLT-3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	4	16	
Units: percentage of participants				
number (confidence interval 95%)				
CR	0 (0 to 22.51)	0 (0 to 52.71)	0 (0 to 19.75)	
CRi	0 (0 to 22.51)	0 (0 to 52.71)	6.3 (0.32 to 29.88)	
MLFS	0 (0 to 22.51)	0 (0 to 52.71)	0 (0 to 19.75)	
PR	0 (0 to 22.51)	0 (0 to 52.71)	6.3 (0.32 to 29.88)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Overall Response (DOR)

End point title	Duration of Overall Response (DOR)
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End point description:

DOR is defined as the time from the first occurrence of a documented overall response to the time of relapse, as determined by the investigator using International Working Group (IWG) criteria (Participants not falling under any of the response criteria [CR or CRi or MLFS or PR] described under outcome measure 1 were considered as non-responders) or death from any cause during the study (defined as death within 30 days after the last dose of study drug). Efficacy population included participants who were considered as responders. The 95% confidence interval was not estimable as only 1 participant was evaluable and reported as -99999 to 99999.

End point type	Secondary
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End point timeframe:

Up to 30 days of last dose of study drug (maximum treatment duration = 225 days)

End point values	Poor Risk Cytogenetics	FLT-3 Mutation Positive	Neither Poor Risk Cytogenetics Nor FLT-3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[5]	0 ^[6]	2	
Units: weeks				
number (confidence interval 95%)				
DOR of participants with CRi (n=0,0,1)	(to)	(to)	13 (-99999 to 99999)	
DOR of participants with PR (n=0,0,1)	(to)	(to)	6.1 (-99999 to 99999)	

Notes:

[5] - No Responders were present in this group.

[6] - No Responders were present in this group.

Statistical analyses

No statistical analyses for this end point

Secondary: Median Overall Survival (OS) Time

End point title	Median Overall Survival (OS) Time
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End point description:

OS was defined as the time from start of study drug to death from any cause. OS was estimated using Kaplan-Meier analysis. Participants alive at the last date known to be alive were censored for the analysis. Efficacy analysis population was considered for analysis of this end point.

End point type	Secondary
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End point timeframe:

Up to death or 30 days of last dose of study drug (maximum treatment duration = 225 days)

End point values	Poor Risk Cytogenetics	FLT-3 Mutation Positive	Neither Poor Risk Cytogenetics Nor FLT-3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	4	19	
Units: months				
median (confidence interval 95%)	3.38 (2.37 to 4.83)	1.43 (0.33 to 3.94)	3.65 (1.94 to 5.36)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With an Event of Death During the Study

End point title	Percentage of Participants With an Event of Death During the Study
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End point description:

Efficacy analysis population was considered for analysis of this end point.

End point type	Secondary
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End point timeframe:

Up to death or 30 days of last dose of study drug (maximum treatment duration = 225 days)

End point values	Poor Risk Cytogenetics	FLT-3 Mutation Positive	Neither Poor Risk Cytogenetics Nor FLT-3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	4	19	
Units: percentage of participants				
number (not applicable)	80	100	89.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Steady-state Plasma Concentration of Vismodegib

End point title	Pharmacokinetics (PK): Steady-state Plasma Concentration of Vismodegib
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End point description:

PK data was planned to be reported only if the results of Cohort 2 are available. As the study was terminated prior to Cohort 2 enrollment, PK analysis could not be performed, as planned.

End point type	Secondary
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End point timeframe:

Predose (0 hour) on Days 8, 29 and 57 or unplanned early termination visit for participants who terminate early

End point values	Poor Risk Cytogenetics	FLT-3 Mutation Positive	Neither Poor Risk Cytogenetics Nor FLT-3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[7]	0 ^[8]	0 ^[9]	
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[7] - No participants were analyzed.

[8] - No participants were analyzed.

[9] - No participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening until study completion or early termination visit (Up to 14 months)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Poor Risk Cytogenetics
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Reporting group description:

Participants with relapsed/refractory AML or relapsed/refractory high-risk MDS falling under 'poor risk cytogenetics' subgroup received oral 150 mg dose of vismodegib once daily until disease progression, intolerable toxicity most probably attributable to vismodegib, or participant withdrawal of consent.

Reporting group title	FLT-3 Mutation Positive
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Reporting group description:

Participants with relapsed/refractory AML or relapsed/refractory high-risk MDS falling under 'FLT-3 mutation positive' subgroup received oral 150 mg dose of vismodegib once daily until disease progression, intolerable toxicity most probably attributable to vismodegib, or participant withdrawal of consent.

Reporting group title	Neither Poor Risk Cytogenetics nor FLT-3
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Reporting group description:

Participants with relapsed/refractory AML or relapsed/refractory high-risk MDS falling neither under 'poor risk cytogenetics' nor 'FLT-3 mutation positive' subgroup were included in this group and received oral 150 mg dose of vismodegib once daily until disease progression, intolerable toxicity most probably attributable to vismodegib, or participant withdrawal of consent.

Serious adverse events	Poor Risk Cytogenetics	FLT-3 Mutation Positive	Neither Poor Risk Cytogenetics nor FLT-3
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 15 (66.67%)	3 / 4 (75.00%)	13 / 19 (68.42%)
number of deaths (all causes)	12	4	17
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (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
Subdural haematoma			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Wrist fracture			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (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
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (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
Surgical and medical procedures			
Central venous catheterisation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (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
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 4 (25.00%)	4 / 19 (21.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (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
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 4 (25.00%)	6 / 19 (31.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 4 (0.00%)	0 / 19 (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
Haemorrhoids			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (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

Lower gastrointestinal haemorrhage subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (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
Nausea subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (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
Oesophageal pain subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (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
Renal failure acute subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (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
Urinary retention subjects affected / exposed	2 / 15 (13.33%)	0 / 4 (0.00%)	0 / 19 (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
Urinary tract pain subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 15 (6.67%) 0 / 1 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	0 / 19 (0.00%) 0 / 0 0 / 0
Atypical pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 15 (0.00%) 0 / 0 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	1 / 19 (5.26%) 0 / 1 0 / 0
Bacteraemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 15 (0.00%) 0 / 0 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	1 / 19 (5.26%) 0 / 1 0 / 1
Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 15 (6.67%) 0 / 1 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	0 / 19 (0.00%) 0 / 0 0 / 0
Hepatic infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 15 (0.00%) 0 / 0 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	1 / 19 (5.26%) 0 / 1 0 / 0
Infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 15 (6.67%) 0 / 1 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	0 / 19 (0.00%) 0 / 0 0 / 0
Lung infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 15 (20.00%) 0 / 4 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	1 / 19 (5.26%) 0 / 2 0 / 0
Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 15 (6.67%) 0 / 1 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	3 / 19 (15.79%) 0 / 4 0 / 0
Sepsis			

subjects affected / exposed	0 / 15 (0.00%)	1 / 4 (25.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal abscess			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Poor Risk Cytogenetics	FLT-3 Mutation Positive	Neither Poor Risk Cytogenetics nor FLT-3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 15 (86.67%)	4 / 4 (100.00%)	19 / 19 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Chloroma			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Renal cell carcinoma			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Haematoma			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	3 / 19 (15.79%)
occurrences (all)	0	0	3

Hypertension subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	2 / 19 (10.53%) 3
Hypotension subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	4 / 19 (21.05%) 4
Subclavian vein thrombosis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	0 / 19 (0.00%) 0
Vasculitis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	0 / 19 (0.00%) 0
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	0 / 19 (0.00%) 0
Catheter site pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	0 / 19 (0.00%) 0
Chest discomfort subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Chest pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Chills subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	1 / 4 (25.00%) 1	2 / 19 (10.53%) 2
Early satiety subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Fatigue subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	2 / 4 (50.00%) 2	5 / 19 (26.32%) 8
Feeling cold			

subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Localised oedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Mucosal dryness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Mucosal inflammation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Multi-organ failure			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Oedema			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	4 / 15 (26.67%)	0 / 4 (0.00%)	4 / 19 (21.05%)
occurrences (all)	4	0	4
Pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	3 / 19 (15.79%)
occurrences (all)	1	0	3
Peripheral swelling			
subjects affected / exposed	2 / 15 (13.33%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	3	0	1
Pyrexia			
subjects affected / exposed	3 / 15 (20.00%)	3 / 4 (75.00%)	5 / 19 (26.32%)
occurrences (all)	6	3	5
Reproductive system and breast			

disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Vulval ulceration			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	3 / 19 (15.79%)
occurrences (all)	1	0	3
Dysphonia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	3 / 15 (20.00%)	0 / 4 (0.00%)	3 / 19 (15.79%)
occurrences (all)	4	0	3
Dyspnoea exertional			
subjects affected / exposed	0 / 15 (0.00%)	1 / 4 (25.00%)	2 / 19 (10.53%)
occurrences (all)	0	1	2
Epistaxis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	8 / 19 (42.11%)
occurrences (all)	2	0	9
Hypoxia			
subjects affected / exposed	3 / 15 (20.00%)	1 / 4 (25.00%)	1 / 19 (5.26%)
occurrences (all)	3	1	1
Nasal congestion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 4 (25.00%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 4 (25.00%)	3 / 19 (15.79%)
occurrences (all)	0	1	3
Pleural effusion			

subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Productive cough			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Pulmonary oedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Respiratory failure			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 15 (6.67%)	1 / 4 (25.00%)	2 / 19 (10.53%)
occurrences (all)	1	1	2
Sleep apnoea syndrome			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Snoring			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Disorientation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	4
Mental status changes			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0

Restlessness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Sleep disorder			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Blood bilirubin increased			
subjects affected / exposed	2 / 15 (13.33%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Blood creatine increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Cardiac murmur			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Liver function test abnormal			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Neutrophil count decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	3
Platelet count decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Weight decreased			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Fall			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Laceration			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Ligament sprain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Scratch			
subjects affected / exposed	0 / 15 (0.00%)	1 / 4 (25.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Skin abrasion			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pericardial effusion			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Sinus tachycardia			

subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 15 (13.33%)	0 / 4 (0.00%)	6 / 19 (31.58%)
occurrences (all)	2	0	6
Dysgeusia			
subjects affected / exposed	4 / 15 (26.67%)	1 / 4 (25.00%)	7 / 19 (36.84%)
occurrences (all)	5	1	9
Headache			
subjects affected / exposed	2 / 15 (13.33%)	1 / 4 (25.00%)	1 / 19 (5.26%)
occurrences (all)	2	2	1
Hyperaesthesia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Neuropathy peripheral			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Orthostatic intolerance			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Radicular pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Restless legs syndrome			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Sinus headache			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 4 (25.00%)	4 / 19 (21.05%)
occurrences (all)	2	1	12
Febrile neutropenia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 4 (25.00%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Haemoglobinaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Leukocytosis			
subjects affected / exposed	0 / 15 (0.00%)	2 / 4 (50.00%)	2 / 19 (10.53%)
occurrences (all)	0	2	2
Leukopenia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	3 / 19 (15.79%)
occurrences (all)	0	0	5
Neutropenia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Thrombocytopenia			
subjects affected / exposed	2 / 15 (13.33%)	0 / 4 (0.00%)	3 / 19 (15.79%)
occurrences (all)	2	0	3
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hearing impaired			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hypoacusis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Eye pruritus			

subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Scleral discolouration			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 15 (26.67%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	4	0	2
Abdominal pain upper			
subjects affected / exposed	0 / 15 (0.00%)	1 / 4 (25.00%)	2 / 19 (10.53%)
occurrences (all)	0	1	2
Anal fissure			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Aphthous stomatitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Breath odour			
subjects affected / exposed	0 / 15 (0.00%)	1 / 4 (25.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Cheilitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	4 / 15 (26.67%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	4	0	2
Dental caries			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	6 / 19 (31.58%)
occurrences (all)	1	0	6

Dry mouth			
subjects affected / exposed	0 / 15 (0.00%)	1 / 4 (25.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 4 (25.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Faecal incontinence			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gingival bleeding			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Haematochezia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 4 (25.00%)	1 / 19 (5.26%)
occurrences (all)	0	1	2
Haemorrhoids			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Melaena			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	4 / 15 (26.67%)	0 / 4 (0.00%)	10 / 19 (52.63%)
occurrences (all)	4	0	13
Oesophageal pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Oesophagitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Oral pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Rectal haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0

Salivary hypersecretion subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Stomatitis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	2 / 19 (10.53%) 2
Toothache subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	0 / 19 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	1 / 4 (25.00%) 1	4 / 19 (21.05%) 6
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	2 / 19 (10.53%) 2
Decubitus ulcer subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Dermatitis acneiform subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	0 / 19 (0.00%) 0
Drug eruption subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Dry skin subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	1 / 4 (25.00%) 1	1 / 19 (5.26%) 1
Ecchymosis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	0 / 19 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 4 (25.00%) 1	1 / 19 (5.26%) 1
Night sweats			

subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Petechiae			
subjects affected / exposed	1 / 15 (6.67%)	1 / 4 (25.00%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Pruritus			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Rash			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Urinary incontinence			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 15 (13.33%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	2	0	2
Back pain			
subjects affected / exposed	2 / 15 (13.33%)	1 / 4 (25.00%)	1 / 19 (5.26%)
occurrences (all)	2	1	1
Bone pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	2
Flank pain			

subjects affected / exposed	0 / 15 (0.00%)	1 / 4 (25.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Groin pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	2 / 15 (13.33%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Muscle spasms			
subjects affected / exposed	3 / 15 (20.00%)	1 / 4 (25.00%)	5 / 19 (26.32%)
occurrences (all)	4	1	6
Muscular weakness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	2
Neck pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	2 / 15 (13.33%)	0 / 4 (0.00%)	3 / 19 (15.79%)
occurrences (all)	2	0	3
Infections and infestations			
Candida			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Catheter site infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Cellulitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2

Clostridium difficile infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	0 / 19 (0.00%) 0
Enterococcal infection subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	2 / 19 (10.53%) 2
Erysipelas subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	0 / 19 (0.00%) 0
Escherichia bacteraemia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Herpes simplex subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	0 / 19 (0.00%) 0
Influenza subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	2 / 19 (10.53%) 2
Liver abscess subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Localised infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	0 / 19 (0.00%) 0
Mucosal infection subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Oral candidiasis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	0 / 19 (0.00%) 0
Oral fungal infection subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Oral herpes subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	2 / 19 (10.53%) 2

Post procedural infection subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Rhinitis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Staphylococcal infection subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 4 (25.00%) 1	1 / 19 (5.26%) 2
Tooth infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	4 / 15 (26.67%) 4	1 / 4 (25.00%) 1	4 / 19 (21.05%) 4
Dehydration subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3	0 / 4 (0.00%) 0	2 / 19 (10.53%) 2
Electrolyte imbalance subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 4 (0.00%) 0	1 / 19 (5.26%) 1
Failure to thrive subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 4 (0.00%) 0	0 / 19 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	1 / 4 (25.00%) 1	1 / 19 (5.26%) 1
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	1 / 4 (25.00%) 1	1 / 19 (5.26%) 1
Hyperalbuminaemia			

subjects affected / exposed	2 / 15 (13.33%)	0 / 4 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Hypokalaemia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 4 (25.00%)	6 / 19 (31.58%)
occurrences (all)	1	1	7
Hypomagnesaemia			
subjects affected / exposed	3 / 15 (20.00%)	0 / 4 (0.00%)	3 / 19 (15.79%)
occurrences (all)	3	0	3
Hyponatraemia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 4 (25.00%)	2 / 19 (10.53%)
occurrences (all)	3	1	2
Hypophosphataemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Vitamin B12 deficiency			
subjects affected / exposed	0 / 15 (0.00%)	0 / 4 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2013	Clarified the number of participants with poor-risk cytogenetics and FLT3-positive disease to be enrolled, added interim safety review 8 weeks after the first 12 participants were enrolled, added early stopping rules for lack of efficacy (futility). Changed sperm donation period following the last dose of vismodegib to 2 months for consistency with other vismodegib protocols and clarified that if bone marrow aspirate and biopsy, whole blood samples, and plasma samples were required at early termination, they were to be performed within 5 days of stopping study drug.
24 June 2014	Removed cytarabine PK sampling and added additional bone marrow aspirations and biopsies at Weeks 24 and 48 for participants who remained on treatment after Week 8.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 November 2014	This study was prematurely terminated because of lower-than-expected efficacy observed in interim data analyses.	-

Notes:

Limitations and caveats

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

Study was prematurely terminated due to lower-than-expected efficacy observed in interim data analyses. The end point related to Cohort 2, "Area Under the Concentration-time Curve of Cytarabine" was not reported as Cohort 2 was not initiated.

Notes: