



Clinical trial results:

Open-Label, Multicenter Phase II Study For the Evaluation of Dasatinib (Sprycel™) Following Induction and Consolidation Therapy as well as in Maintenance Therapy in Patients With Newly Diagnosed Core-Binding Factor (CBF) Acute Myeloid Leukemia (AML)

Summary

EudraCT number	2008-008238-35
Trial protocol	DE AT
Global end of trial date	30 November 2015

Results information

Result version number	v1 (current)
This version publication date	16 December 2016
First version publication date	16 December 2016
Summary attachment (see zip file)	AMLSG 11-08 Final report (AMLSG11-08_finalreport_231116.pdf)

Trial information

Trial identification

Sponsor protocol code	AMLSG11-08
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00850382
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Ulm
Sponsor organisation address	Albert-Einstein-Allee 29, Ulm, Germany, 89081
Public contact	AMLSG Studienzentrale, Universitätsklinikum Ulm, +49 731500 56072,
Scientific contact	Prof. Dr. Hartmut Döhner, Universitätsklinikum Ulm, +49 731500 45901, hartmut.doehner@uniklinik-ulm.de

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	23 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2015
Global end of trial reached?	Yes
Global end of trial date	30 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective:

To assess the feasibility of dasatinib 100 mg QD given after intensive induction (daunorubicin and cytarabine) and consolidation chemotherapy (high-dose cytarabine) and as single agent in maintenance therapy.

The primary endpoint was a combined endpoint integrating the rates of early/hypoplastic death (Rate(ED/HD)), rate of pleural or pericardial effusion grade 3/4 (Rate(effuse)), rate of liver toxicity grade 3 or 4 that does not improve to grade 2 or less within 14 days after discontinuing responsible medication (Rate(liver)), and rate of refractory disease (Rate(RD)). Feasibility/tolerability for an individual patient was defined as a pleural or cardiac effusion level that does not exceed grade 2, as well as a liver toxicity equal to or less than grade 2 and the achievement of a complete remission after

Protection of trial subjects:

In this study, safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, chest X-ray, echo scan, physical examination findings, monitoring of concomitant therapy. For each safety parameter, all findings (whether normal or abnormal) were recorded in the CRF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Germany: 83
Worldwide total number of subjects	91
EEA total number of subjects	91

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	75
From 65 to 84 years	15
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

First patient in: 03.09.2009

Last patient last visit: 30.11.2015 (completion date)

After the enrollment of initially planned 25 patients on 22.06.2010, recruitment was interrupted until approval of the amended protocol Version 3.1 (01.09.2010). Re-cruitment was restarted on 01.12.2010.

Overall, n=91 patients were enrolled

Pre-assignment

Screening details:

Molecular genetic analysis (central AMLSG reference lab) of blood and bone marrow for CBF-associated gene fusions was performed at baseline within 48 hours to make an enrollment possible.

Period 1

Period 1 title	Enrollment
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment
-----------	-----------

Arm description:

All patients received induction chemotherapy (cytarabine and daunorubicin) in combination with dasatinib followed by consolidation therapy with either high-dose cytarabine in combination with dasatinib. After consolidation therapy a one-year maintenance therapy with dasatinib (continuously over 365 days) was intended in all patients.

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	Sprycel
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dasatinib was administered oral, in a daily dose of 100 mg (one a day, two tablets à 50 mg) Patients should have taken their daily dose at approximately the same time in the morning. Each daily dose should have been given with food and a glass of water (~240 mL). Patients should have been instructed to swallow capsules whole and not chew capsules.

Induction therapy:

100 mg/day, days 8-21

Consolidation therapy:

100 mg/day, days 6-28

Maintenance therapy:

100 mg/day over 365 days

Number of subjects in period 1	Treatment
Started	91
Completed	89
Not completed	2
violation of inclusion/exclusion criteria	2

Period 2

Period 2 title	Overall trial
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment
------------------	-----------

Arm description:

All patients received induction chemotherapy (cytarabine and daunorubicin) in combination with dasatinib followed by consolidation therapy with either high-dose cytarabine in combination with dasatinib. After consolidation therapy a one-year maintenance therapy with dasatinib (continuously over 365 days) was intended in all patients.

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	Sprycel
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dasatinib was administered oral, in a daily dose of 100 mg (one a day, two tablets à 50 mg). Patients should have taken their daily dose at approximately the same time in the morning. Each daily dose should have been given with food and a glass of water (~240 mL). Patients should have been instructed to swallow capsules whole and not chew capsules.

Induction therapy:

100 mg/day, days 8-21

Consolidation therapy:

100 mg/day, days 6-28

Maintenance therapy:

100 mg/day over 365 days

Number of subjects in period 2	Treatment
Started	89
Induction cycle I	89
Induction cycle II (optional)	7 ^[1]
Consolidation cycle I	69
Consolidation cycle II	64
Consolidation cycle III	61
Consolidation cycle IV	55
Maintenance therapy	53
Completed	22
Not completed	67
Adverse event, serious fatal	4
Consent withdrawn by subject	5

Adverse event, non-fatal	33
Other reasons	2
Lack of efficacy	23

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Induction cycle II was administered only in patients not achieving a CR/CRi after Induction cycle I. Therefore, only 7 patients started this Milestone. 69 patients started consolidation cycle I, either directly after induction cycle I or after induction cycle II.

Baseline characteristics

Reporting groups

Reporting group title	Enrollment
Reporting group description: -	

Reporting group values	Enrollment	Total	
Number of subjects	91	91	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
median	49.6		
full range (min-max)	19 to 85	-	
Gender categorical			
Units: Subjects			
Female	43	43	
Male	48	48	
ECOG Performance status			
Units: Subjects			
Score 0	38	38	
Score 1	40	40	
Score 2	9	9	
Not recorded	4	4	
Type of AML			
Units: Subjects			
De Novo	78	78	
sAML	2	2	
tAML	10	10	
not recorded	1	1	
NPM1 mutation status			
Units: Subjects			
Mutated	0	0	
Wildtype	88	88	
Not recorded	3	3	
FLT3 TKD status			
Units: Subjects			
negative	82	82	

positive	8	8	
not recorded	1	1	
FLT3 ITD status			
Units: Subjects			
positive	4	4	
negative	86	86	
not recorded	1	1	
KIT mutation status			
Units: Subjects			
Mutation	19	19	
Wildtype	66	66	
not recorded	6	6	
NRAS mutation status			
Units: Subjects			
Mutation	27	27	
Wildtype	61	61	
not recorded	3	3	
Type CBF			
Units: Subjects			
t(8;21)	37	37	
inv(16)	53	53	
not recorded	1	1	
Hemoglobin			
Units: g/dl			
median	9.2		
full range (min-max)	4.6 to 14.8	-	
Platelets			
Units: G/l			
median	37		
full range (min-max)	2 to 279	-	
White blood count			
Units: G/l			
median	19.4		
full range (min-max)	1.2 to 192.2	-	
Bone marrow blasts			
Units: per cent			
median	70		
full range (min-max)	11 to 95	-	
Peripheral blood blasts			
Units: per cent			
median	38		
full range (min-max)	0 to 94	-	

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

All patients scheduled for study Treatment and started with induction cycle I were included into the full Analysis set which is used for efficacy and safety Analysis.

Reporting group values	Full analysis set		
Number of subjects	89		
Age categorical			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Units: years			
median	49.5		
full range (min-max)	19 to 73		
Gender categorical			
Units: Subjects			
Female	42		
Male	47		
ECOG Performance status			
Units: Subjects			
Score 0	38		
Score 1	39		
Score 2	9		
Not recorded	3		
Type of AML			
Units: Subjects			
De Novo	77		
sAML	2		
tAML	10		
not recorded	0		
NPM1 mutation status			
Units: Subjects			
Mutated	0		
Wildtype	86		
Not recorded	3		
FLT3 TKD status			
Units: Subjects			
negative	81		
positive	7		
not recorded	1		
FLT3 ITD status			
Units: Subjects			
positive	4		
negative	84		
not recorded	1		
KIT mutation status			
Units: Subjects			

Mutation	19		
Wildtype	65		
not recorded	5		
NRAS mutation status			
Units: Subjects			
Mutation	27		
Wildtype	60		
not recorded	2		
Type CBF			
Units: Subjects			
t(8;21)	37		
inv(16)	52		
not recorded	0		
Hemoglobin			
Units: g/dl			
median	9.2		
full range (min-max)	4.6 to 14.8		
Platelets			
Units: G/l			
median	37		
full range (min-max)	2 to 279		
White blood count			
Units: G/l			
median	19.4		
full range (min-max)	1.2 to 192.2		
Bone marrow blasts			
Units: per cent			
median	70		
full range (min-max)	11 to 95		
Peripheral blood blasts			
Units: per cent			
median	40		
full range (min-max)	0 to 94		

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description: All patients received induction chemotherapy (cytarabine and daunorubicin) in combination with dasatinib followed by consolidation therapy with either high-dose cytarabine in combination with dasatinib. After consolidation therapy a one-year maintenance therapy with dasatinib (continuously over 365 days) was intended in all patients.	
Reporting group title	Treatment
Reporting group description: All patients received induction chemotherapy (cytarabine and daunorubicin) in combination with dasatinib followed by consolidation therapy with either high-dose cytarabine in combination with dasatinib. After consolidation therapy a one-year maintenance therapy with dasatinib (continuously over 365 days) was intended in all patients.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: All patients scheduled for study Treatment and started with induction cycle I were included into the full Analysis set which is used for efficacy and safety Analysis.	

Primary: Feasibility

End point title	Feasibility ^[1]
End point description: The primary endpoint was a combined endpoint integrating the rates of early/hypoplastic death (Rate(ED/HD)), rate of pleural or pericardial effusion grade 3/4 (Rate(effuse)), rate of liver toxicity grade 3 or 4 that does not improve to grade 2 or less within 14 days after discontinuing responsible medication (Rate(liver)), and rate of refractory disease (Rate(RD)). Feasibility/tolerability for an individual patient was defined as a pleural or cardiac effusion level that does not exceed grade 2, as well as a liver toxicity equal to or less than grade 2 and the achievement of a complete remission after	
End point type	Primary
End point timeframe: Whole Treatment period of patients (maximally 19 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: No statistical analysis was done for Primary endpoint. Everytime an event of one of the four single endpoints occurred, the cumulative number of Events of the specific endpoint was compared to the predefined critical number of Events at this enrollment stage (current number of enrolled patients). At every sequential testing time point during the study and for all single primary endpoints, the cum. number of events was below the critical value. Thus, primary endpoint was met, feasibility was shown.

End point values	Treatment	Full analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	89	89		
Units: subject				
Refractory Disease	2	2		
Early Death/Hypoplastic Death	4	4		
Pleural/pericardial effusion	6	6		
Liver toxicities	6	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival
-----------------	------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

4 years after inclusion into the study

End point values	Treatment	Full analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	89	89		
Units: per cent				
number (confidence interval 95%)	74.7 (66.1 to 84.5)	74.7 (66.1 to 84.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of relapse

End point title	Cumulative incidence of relapse
-----------------	---------------------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

4 years after inclusion into the trial

End point values	Treatment	Full analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	73	73		
Units: per cent				
number (not applicable)	35.2	35.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of death

End point title	Cumulative incidence of death
-----------------	-------------------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

after 4 years after inclusion into the trial

End point values	Treatment	Full analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	73	73		
Units: per cent				
number (not applicable)	4.2	4.2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse event reporting period for this trial began upon signing of informed consent and ended 28 days after the last treatment administration or until all drug-related toxicities were resolved, whichever was later or until the Investigators assessed

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Safety data set
-----------------------	-----------------

Reporting group description:

The safety analysis set included 89 patients scheduled for study Treatment.

Serious adverse events	Safety data set		
Total subjects affected by serious adverse events			
subjects affected / exposed	56 / 89 (62.92%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Secondary malignancy (possibly related to cancer treatment)			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombosis/embolism			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Other vascular disorder			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			

subjects affected / exposed	3 / 89 (3.37%)		
occurrences causally related to treatment / all	4 / 7		
deaths causally related to treatment / all	0 / 0		
Rigor/chills			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death not associated with CTCAE term			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Other haemorrhage			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Other disorders			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Other pulmonary disorder			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Airway obstruction			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Dyspnea			

subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
CRP increase			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Supraventricular arrhythmia			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Other cardiac disorders			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac ischemia/infarction			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
cTnT			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Left ventricular systolic dysfunction			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
CNS hemorrhage			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuropathy sensory			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychosis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Blood - Other disorders			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hemoglobin			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukocytes			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Neutrophils			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Platelets			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Splenic function			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Blurred vision			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Colitis				
subjects affected / exposed	3 / 89 (3.37%)			
occurrences causally related to treatment / all	6 / 7			
deaths causally related to treatment / all	1 / 1			
Constipation				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhea				
subjects affected / exposed	2 / 89 (2.25%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Other gastrointestinal disorders				
subjects affected / exposed	2 / 89 (2.25%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hemorrhage gastrointestinal				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pain abdomen				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				

Cholecystitis			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Other hepatobiliary disorders			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Petechiae			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Other renal disorder			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Trismus			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Colitis, infectious			

subjects affected / exposed	5 / 89 (5.62%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	10 / 89 (11.24%)			
occurrences causally related to treatment / all	6 / 13			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	18 / 89 (20.22%)			
occurrences causally related to treatment / all	11 / 20			
deaths causally related to treatment / all	1 / 2			
Other infection				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection abdomen				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Infection anal/perianal				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection colon				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Infection peritoneal cavity				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lung (pneumonia)				

subjects affected / exposed	17 / 89 (19.10%)		
occurrences causally related to treatment / all	9 / 18		
deaths causally related to treatment / all	0 / 0		
Infection pleura (empyema)			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection upper airway			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infection urinary tract			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety data set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	89 / 89 (100.00%)		
Vascular disorders			
Phlebitis			
subjects affected / exposed	8 / 89 (8.99%)		
occurrences (all)	10		
Thrombosis/Embolism			
subjects affected / exposed	6 / 89 (6.74%)		
occurrences (all)	6		
General disorders and administration site conditions			
Other constitutional symptom			
subjects affected / exposed	7 / 89 (7.87%)		
occurrences (all)	11		
Fatigue			

subjects affected / exposed	34 / 89 (38.20%)		
occurrences (all)	108		
Fever			
subjects affected / exposed	58 / 89 (65.17%)		
occurrences (all)	183		
Insomnia			
subjects affected / exposed	35 / 89 (39.33%)		
occurrences (all)	83		
rigor/chills			
subjects affected / exposed	12 / 89 (13.48%)		
occurrences (all)	19		
sweating			
subjects affected / exposed	7 / 89 (7.87%)		
occurrences (all)	9		
Weight gain			
subjects affected / exposed	16 / 89 (17.98%)		
occurrences (all)	24		
Hemorrhage - other			
subjects affected / exposed	10 / 89 (11.24%)		
occurrences (all)	14		
Pain - other			
subjects affected / exposed	20 / 89 (22.47%)		
occurrences (all)	46		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	25 / 89 (28.09%)		
occurrences (all)	34		
Reproductive system and breast disorders			
Hemorrhage genitourinary			
subjects affected / exposed	8 / 89 (8.99%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			
Hemorrhage pulmonary			
subjects affected / exposed	18 / 89 (20.22%)		
occurrences (all)	26		
Pain - Chest/thorax			

subjects affected / exposed	11 / 89 (12.36%)		
occurrences (all)	17		
Pain - Throat/pharynx/larynx			
subjects affected / exposed	10 / 89 (11.24%)		
occurrences (all)	11		
Cough			
subjects affected / exposed	25 / 89 (28.09%)		
occurrences (all)	39		
Dyspnea			
subjects affected / exposed	19 / 89 (21.35%)		
occurrences (all)	32		
Pleural effusion			
subjects affected / exposed	16 / 89 (17.98%)		
occurrences (all)	46		
Pneumonitis			
subjects affected / exposed	10 / 89 (11.24%)		
occurrences (all)	13		
Investigations			
Alanine aminotransferase			
subjects affected / exposed	17 / 89 (19.10%)		
occurrences (all)	44		
Aspartate aminotransferase			
subjects affected / exposed	15 / 89 (16.85%)		
occurrences (all)	33		
Bilirubin			
subjects affected / exposed	7 / 89 (7.87%)		
occurrences (all)	12		
Gamma-glutamyltransferase			
subjects affected / exposed	10 / 89 (11.24%)		
occurrences (all)	17		
Hyperuricemia			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	6		
Hypoalbuminemia			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	6		

Hypocalcemia subjects affected / exposed occurrences (all)	14 / 89 (15.73%) 34		
Hypokalemia subjects affected / exposed occurrences (all)	40 / 89 (44.94%) 129		
Hypomagnesemia subjects affected / exposed occurrences (all)	10 / 89 (11.24%) 23		
CRP increase subjects affected / exposed occurrences (all)	17 / 89 (19.10%) 61		
Other lab disorders subjects affected / exposed occurrences (all)	18 / 89 (20.22%) 36		
Cardiac disorders Cardiac arrhythmia - other subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 14		
Supraventricular arrhythmia subjects affected / exposed occurrences (all)	9 / 89 (10.11%) 19		
Hypertension subjects affected / exposed occurrences (all)	17 / 89 (19.10%) 47		
Hypotension subjects affected / exposed occurrences (all)	14 / 89 (15.73%) 23		
Pericardial effusion subjects affected / exposed occurrences (all)	6 / 89 (6.74%) 10		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	20 / 89 (22.47%) 43		
Mood alteration - agitation			

subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	8		
Mood alteration - anxiety			
subjects affected / exposed	11 / 89 (12.36%)		
occurrences (all)	20		
Mood alteration - depression			
subjects affected / exposed	12 / 89 (13.48%)		
occurrences (all)	24		
Neuropathy sensory			
subjects affected / exposed	9 / 89 (10.11%)		
occurrences (all)	16		
Pain head/Headache			
subjects affected / exposed	39 / 89 (43.82%)		
occurrences (all)	105		
Blood and lymphatic system disorders			
Hemoglobin			
subjects affected / exposed	72 / 89 (80.90%)		
occurrences (all)	358		
Leukocytes			
subjects affected / exposed	53 / 89 (59.55%)		
occurrences (all)	238		
Neutrophils			
subjects affected / exposed	27 / 89 (30.34%)		
occurrences (all)	79		
Platelets			
subjects affected / exposed	72 / 89 (80.90%)		
occurrences (all)	364		
Edema head and neck			
subjects affected / exposed	8 / 89 (8.99%)		
occurrences (all)	25		
Edema limb			
subjects affected / exposed	10 / 89 (11.24%)		
occurrences (all)	17		
Eye disorders			
Dry eye			

subjects affected / exposed	13 / 89 (14.61%)		
occurrences (all)	25		
Other ocular disorder			
subjects affected / exposed	10 / 89 (11.24%)		
occurrences (all)	13		
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	16 / 89 (17.98%)		
occurrences (all)	30		
Colitis			
subjects affected / exposed	7 / 89 (7.87%)		
occurrences (all)	10		
Constipation			
subjects affected / exposed	39 / 89 (43.82%)		
occurrences (all)	100		
Diarrhea			
subjects affected / exposed	61 / 89 (68.54%)		
occurrences (all)	162		
Enteritis			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	9		
Flatulence			
subjects affected / exposed	11 / 89 (12.36%)		
occurrences (all)	28		
Gastritis			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	5		
Other gastrointestinal disorder			
subjects affected / exposed	13 / 89 (14.61%)		
occurrences (all)	19		
Heartburn			
subjects affected / exposed	9 / 89 (10.11%)		
occurrences (all)	19		
Mucositis			
subjects affected / exposed	37 / 89 (41.57%)		
occurrences (all)	49		

Nausea			
subjects affected / exposed	74 / 89 (83.15%)		
occurrences (all)	248		
Taste alteration			
subjects affected / exposed	9 / 89 (10.11%)		
occurrences (all)	15		
Vomiting			
subjects affected / exposed	45 / 89 (50.56%)		
occurrences (all)	106		
Hemorrhage gastrointestinal			
subjects affected / exposed	6 / 89 (6.74%)		
occurrences (all)	7		
Pain - abdomen			
subjects affected / exposed	29 / 89 (32.58%)		
occurrences (all)	77		
Pain - anus			
subjects affected / exposed	7 / 89 (7.87%)		
occurrences (all)	9		
Pain - Dental / teeth			
subjects affected / exposed	8 / 89 (8.99%)		
occurrences (all)	10		
Pain - Stomach			
subjects affected / exposed	19 / 89 (21.35%)		
occurrences (all)	35		
Skin and subcutaneous tissue disorders			
Dermatology - other disorder			
subjects affected / exposed	10 / 89 (11.24%)		
occurrences (all)	14		
Dry skin			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	5		
Hand - foot syndrom			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	6		
Injection site reaction			

subjects affected / exposed	13 / 89 (14.61%)		
occurrences (all)	21		
Pruritus			
subjects affected / exposed	16 / 89 (17.98%)		
occurrences (all)	18		
Rash			
subjects affected / exposed	53 / 89 (59.55%)		
occurrences (all)	113		
Hematoma			
subjects affected / exposed	10 / 89 (11.24%)		
occurrences (all)	12		
Petechiae			
subjects affected / exposed	16 / 89 (17.98%)		
occurrences (all)	27		
Renal and urinary disorders			
Fluid retention			
subjects affected / exposed	36 / 89 (40.45%)		
occurrences (all)	95		
Other renal disorders			
subjects affected / exposed	7 / 89 (7.87%)		
occurrences (all)	9		
Renal failure			
subjects affected / exposed	7 / 89 (7.87%)		
occurrences (all)	8		
Musculoskeletal and connective tissue disorders			
Other musculoskeletal disorders			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	5		
Pain - Back			
subjects affected / exposed	28 / 89 (31.46%)		
occurrences (all)	56		
Pain - Bone			
subjects affected / exposed	10 / 89 (11.24%)		
occurrences (all)	16		
Pain - Extremity			

subjects affected / exposed	9 / 89 (10.11%)		
occurrences (all)	12		
Pain - Joint			
subjects affected / exposed	23 / 89 (25.84%)		
occurrences (all)	39		
Pain - Neck			
subjects affected / exposed	6 / 89 (6.74%)		
occurrences (all)	9		
Infections and infestations			
Colitis, Infectious			
subjects affected / exposed	6 / 89 (6.74%)		
occurrences (all)	7		
Febrile neutropenia			
subjects affected / exposed	39 / 89 (43.82%)		
occurrences (all)	81		
Sepsis			
subjects affected / exposed	24 / 89 (26.97%)		
occurrences (all)	56		
Other infection			
subjects affected / exposed	43 / 89 (48.31%)		
occurrences (all)	96		
Lip/perioral infection			
subjects affected / exposed	14 / 89 (15.73%)		
occurrences (all)	23		
Infection anal/perianal			
subjects affected / exposed	6 / 89 (6.74%)		
occurrences (all)	8		
Infection oral cavity/gums (gingivitis)			
subjects affected / exposed	8 / 89 (8.99%)		
occurrences (all)	8		
Infection catheter-related			
subjects affected / exposed	12 / 89 (13.48%)		
occurrences (all)	26		
Lung (pneumonia)			

subjects affected / exposed	31 / 89 (34.83%)		
occurrences (all)	53		
Infection upper airways			
subjects affected / exposed	22 / 89 (24.72%)		
occurrences (all)	40		
Infection urinary tract			
subjects affected / exposed	13 / 89 (14.61%)		
occurrences (all)	33		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2009	Amendment 1 (dated 17 August 2009) was issued before start of patient enrollment. There were no changes made to the protocol, but new investigational sites and investigators introduced to the study.
04 February 2010	Amendment 2 (dated 04 February 2010) to the protocol was issued after 11 patients were enrolled into the study. The major changes made to the protocol were due to integration of Austria as new country with four new investigational sites.
01 September 2010	Amendment 3 (dated 01 September 2010) to the protocol was issued after 25 patients were enrolled and initial planned study cohort was completed. The following major procedural changes (not all-inclusive) were made to the protocol: <ul style="list-style-type: none">• Increase of sample size to additional 57 patients (overall sample size = 82 patients).• Implementation of an optional second induction cycle for patients not achieving complete remission after the first induction cycle.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
22 June 2010	After the enrollment of initially planned 25 patients on 22.06.2010, recruitment was interrupted until approval of the amended protocol Version 3.1 (01.09.2010). Recruitment was restarted on 01.12.2010.	01 December 2010

Notes:

Limitations and caveats

None reported