Clinical trial results:
Phase I-II study of F14512 in combination with cytarabine in patients 60 years old and older with acute myeloid leukemia.

Summary

EudraCT number	2012-005241-20
Trial protocol	FR IT ES
Global end of trial date	03 March 2017

Results information

Result version number	v1 (current)
This version publication date	01 April 2018
First version publication date	01 April 2018

Trial information

Trial identification

Sponsor protocol code	F14512IN102G1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	PIERRE FABRE MEDICAMENT
Sponsor organisation address	45 Place Abel Gance, Boulogne-Billancourt, France, 92100
Public contact	Clinical Trial Information Desk, PIERRE FABRE MEDICAMENT, contact_essais_cliniques@pierre-fabre.com
Scientific contact	Karim Keddad, Institut de Recherche Pierre Fabre 3 avenue Hubert Curien 31100 Toulouse, 33 534506169, karim.keddad@pierre-fabre.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	10 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2015
Global end of trial reached?	Yes
Global end of trial date	03 March 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase I part:
To determine the maximal tolerated dose (MTD) of F14512 administered as a three-hour daily infusion given for 5 consecutive days in combination with cytarabine 1 g/m²/day for 5 consecutive days in patients 60 years old or older with refractory or relapsing AML.

Phase II part:
To evaluate the efficacy of F14512 in combination with cytarabine (rate of complete remission [CR] and complete remission with incomplete blood recovery [CRi]) in AML patients 60 years old and older in first relapse or with refractory disease.

Protection of trial subjects:

This study was performed in accordance with the principles stated in current version of the Declaration of Helsinki (1964 and subsequent amendments) and with the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) (CPMP/ICH/135/95), and with related national regulations in biomedical research. All patients were informed of the aims, methods, objectives, and potential hazards of the study, and a signed informed consent form (ICF) was obtained from each patient prior to any study related procedures, or appropriate corrective actions have been implemented in case of failure. A specific patient informed consent, either on the same document or a separate document depending on the country, was also required for genetic research. The first study protocol in use (V2 : 15 February 2013), all of its 3 amendments (all substantial), and the patient information sheets, were reviewed by the appropriate IECs, including local IECs.

Background therapy:

In both phases, the test product (F14512) was administered in combination with cytarabine
F14512 (3-h daily infusion) was tested at the doses of 10 (DL 1), 15 (DL 1), 20 (DL 2), 26 (DL 3) and 34 mg/m²/day (DL 4) (Phase I) and 26 mg/m²/day (Phase II-induction) then 15 mg/m2/day (Phase II consolidation) : F14512 was administered as a 3 hour daily infusion, beginning 1 hour after the end of cytarabine infusion (1g/m2/day) for 5 consecutive days per 21-to-42-day cycle : until unacceptable toxicity/disease progression and up to a maximum of 6 cycles in phase I ; up to a maximum of 5 cycles (1 induction+4 consolidation or 2 induction+3 consolidation cycles) in phase II.

Evidence for comparator:

The non-randomised, open-label design was typical for a Phase I to II oncology study with such objectives. There was no placebo control group as this would not have been ethical in this patient population. In first relapse, there is no single approach considered as standard and treatment is selected based on the age of the patient and the duration of the first complete response. In patients who are 60 years old or older, intermediate dose cytarabine alone or associated with another cytotoxic agent is commonly used. Results of a previous Phase I study of single-agent F14512 in patients with relapsed and refractory AML, together with demonstration of synergism between F14512 and cytarabine in preclinical models, constituted the rationale for testing this combination regimen in patients with AML.

Actual start date of recruitment	09 April 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	26 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	France: 70
Worldwide total number of subjects	71
EEA total number of subjects	71

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	15
From 65 to 84 years	56
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

72 patients were registered (71 in France, 1 in Spain), and 71 patients were enrolled and treated (70 in France, 1 in Spain) :
- 18 in Phase I part in 4 cohorts (3, 3, 6 and 6 patients were administered 15mg/m2/day, 20mg/m2/day, 26mg/m2/day and 34 mg/m2/day, respectively)
- 53 in Phase II part (26mg/m2/day)

Pre-assignment

Screening details:

Eligible patients had AML (both phases) refractory after failure of 1 induction chemotherapy regimen or recurrence of disease < 3 months after CR, or (Phase I) relapsed AML, or (Phase II) first relapse after CR or CRi lasting 3 to 24 months ; were ≥60 years, with WHO PS ≤ 2, adequate liver and renal function and a LVEF≥45%.

Period 1

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

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I-15 mg

Arm description:

Patients treated with F14512 at 15 mg/m2/day during the phase I dose escalation

Arm type	Experimental
Investigational medicinal product name	F14512
Investigational medicinal product code	F14512
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

F14512 was administered as a 3-hour daily infusion, beginning 1 hour after the end of cytarabine infusion, through a central venous catheter for 5 consecutive days

Investigational medicinal product name	cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose of 1 g/m²/day as a 2-hour daily infusion for 5 consecutive days

Arm title	Phase I-20 mg

Arm description:

Patients treated with F14512 at 20 mg/m2/day during the Phase I dose escalation

Arm type	Experimental

Investigational medicinal product name	F14512
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose of 20 mg/m²/day administered as a 3-hour daily infusion, beginning 1 hour after the end of cytarabine infusion, through a central venous catheter for 5 consecutive days

Investigational medicinal product name	cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose of 1 g/m²/day administered as a 2-hour daily infusion for 5 consecutive days

Arm title	Phase I-26 mg

Arm description:

Patients treated with F14512 26 mg/m2/day during Phase I-dose escalation

Arm type	Experimental
Investigational medicinal product name	F14512
Investigational medicinal product code	F14512
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Doses of 26 mg/m²/day administered as a 3-hour daily infusion, beginning 1 hour after the end of cytarabine infusion, through a central venous catheter for 5 consecutive days

Investigational medicinal product name	cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose of 1 g/m²/day administered as a 2-hour daily infusion for 5 consecutive days.

Arm title	Phase I-34 mg

Arm description:

Patients treated with F14512 at 34 mg/m2/day in the Phase I dose escalation

Arm type	Experimental
Investigational medicinal product name	F14512
Investigational medicinal product code	F14512
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose of 34 mg/m²/day administered as a 3-hour daily infusion, beginning 1 hour after the end of cytarabine infusion, through a central venous catheter for 5 consecutive days

Investigational medicinal product name	cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose of 1 g/m²/day administered as a 2-hour daily infusion for 5 consecutive days

Arm title	Phase II (26 mg)

Arm description:

All patients treated in Phase II of the study. In this phase, all patients were treated with F14512 at the dose of 26 mg/m2/day during the induction cycle(s)

Arm type	Experimental
Investigational medicinal product name	F14512
Investigational medicinal product code	F14512
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose of 26 mg/m²/day administered as a 3-hour daily infusion, beginning 1 hour after the end of cytarabine infusion, through a central venous catheter for 5 consecutive days during the induction cycle(s) = 1st and (if haematological improvement) 2nd cycle. During the consolidation cycles, the dose was reduced to 15 mg/m2/day.

Investigational medicinal product name	cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose of 1 g/m²/day administered as a 2-hour daily infusion for 5 consecutive days

Number of subjects in period 1	Phase I-15 mg	Phase I-20 mg	Phase I-26 mg
Started	3	3	6
Completed	0	0	0
Not completed	3	3	6
Adverse event, serious fatal	-	-	-
Physician decision	-	-	-
Psychological reason	-	-	-
Adverse event, non-fatal	-	-	1
Maximum benefit obtained (complete response)	-	-	2
Maximum benefit obtained	-	-	-
Transplant	-	-	-
Lack of efficacy	3	3	3

Number of subjects in period 1	Phase I-34 mg	Phase II (26 mg)
Started	6	53
Completed	0	2
Not completed	6	51

Adverse event, serious fatal	-	1
Physician decision	-	1
Psychological reason	-	1
Adverse event, non-fatal	-	2
Maximum benefit obtained (complete response)	-	-
Maximum benefit obtained	-	10
Transplant	-	4
Lack of efficacy	6	32

Baseline characteristics

Reporting groups	
Reporting group title	Phase I-15 mg
Reporting group description:	
Patients treated with F14512 at 15 mg/m2/day during the phase I dose escalation	
Reporting group title	Phase I-20 mg
Reporting group description:	
Patients treated with F14512 at 20 mg/m2/day during the Phase I dose escalation	
Reporting group title	Phase I-26 mg
Reporting group description:	
Patients treated with F14512 26 mg/m2/day during Phase I-dose escalation	
Reporting group title	Phase I-34 mg
Reporting group description:	
Patients treated with F14512 at 34 mg/m2/day in the Phase I dose escalation	
Reporting group title	Phase II (26 mg)
Reporting group description:	
All patients treated in Phase II of the study. In this phase, all patients were treated with F14512 at the dose of 26 mg/m2/day during the induction cycle(s)	

Reporting group values	Phase I-15 mg	Phase I-20 mg	Phase I-26 mg
Number of subjects	3	3	6
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			
All patients were to be >=60 years			
Units: years			
arithmetic mean	72	67.5	67.6
standard deviation	± 4.9	± 1.7	± 4.6
Gender categorical Units: Subjects			
Female	0	1	2
Male	3	2	4

Reporting group values	Phase I-34 mg	Phase II (26 mg)	Total
Number of subjects	6	53	71
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			
All patients were to be >=60 years			
Units: years			
arithmetic mean	70.2	67.2	
standard deviation	± 4.4	± 4.0	-
Gender categorical			
Units: Subjects			
Female	1	24	28
Male	5	29	43

Subject analysis sets

Subject analysis set title	Phase II ITT set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients treated in Phase II	
Subject analysis set title	Phase II ITT subset of responders
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
ITT subset of responders after induction cycle(s) of Phase II (i.e. with CR or CRi).	

Reporting group values	Phase II ITT set	Phase II ITT subset of responders	
Number of subjects	53	20	
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			
All patients were to be >=60 years			
Units: years			
arithmetic mean	67.2		
standard deviation	± 4.0	±	

Gender categorical Units: Subjects			
Female	24		
Male	29		

End points

End points reporting groups

Reporting group title	Phase I-15 mg
Reporting group description:	
Patients treated with F14512 at 15 mg/m2/day during the phase I dose escalation	
Reporting group title	Phase I-20 mg
Reporting group description:	
Patients treated with F14512 at 20 mg/m2/day during the Phase I dose escalation	
Reporting group title	Phase I-26 mg
Reporting group description:	
Patients treated with F14512 26 mg/m2/day during Phase I-dose escalation	
Reporting group title	Phase I-34 mg
Reporting group description:	
Patients treated with F14512 at 34 mg/m2/day in the Phase I dose escalation	
Reporting group title	Phase II (26 mg)
Reporting group description:	
All patients treated in Phase II of the study. In this phase, all patients were treated with F14512 at the dose of 26 mg/m2/day during the induction cycle(s)	
Subject analysis set title	Phase II ITT set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients treated in Phase II	
Subject analysis set title	Phase II ITT subset of responders
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
ITT subset of responders after induction cycle(s) of Phase II (i.e. with CR or CRi).	

Primary: Dose limiting toxicity (DLT)-Phase I

End point title	Dose limiting toxicity (DLT)-Phase I[1][2]
End point description:	
The maximal tolerated dose (MTD) was defined as the dose at which 2 out of 3 or 2 out of 6 patients experienced a DLT during the 1st cycle of administration	
End point type	Primary
End point timeframe:	
1st cycle of administration (min 21 days, max 42 days)	

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 planned. The conclusion were based on the number of patients with DLT in each dose level

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: There was no evaluation of DLT assessed in the single arm of the Phase II part of the trial (different objective from that of Phase I). Phase II part was conducted at the recommended dose determined in phase I (defined as the dose immediately below the MTD): 34 mg/m2/day was determined to be the MTD and 26 mg/m2/day the recommended dose for Phase II.

End point values	Phase I-15 mg	Phase I-20 mg	Phase I-26 mg	Phase I-34 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	6
Units: number of patients with DLTs	0	0	0	2

Statistical analyses

No statistical analyses for this end point

Primary: Overall response rate (ORR)-Phase II

End point title	Overall response rate (ORR)-Phase II[3]

End point description:

The ORR is defined as the rate of patients in complete remission (CR) or in complete remission with incomplete blood recovery (CRi) as assessed by the Investigator.
The 95% CI was one-sided (left-sided).

End point type	Primary

End point timeframe:

The ORR was evaluated in phase II, after one or (if haematological improvement after cycle 1) two cycles of induction.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis planned. The conclusion were based on the descriptive values.

End point values	Phase II ITT set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: percentage				
number (confidence interval 95%)	37.7 (26.6 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR-Phase I

End point title	ORR-Phase I[4]

End point description:

The ORR was the rate of responders i.e. of patients in complete remission (CR) or complete remission with incomplete blood recovery (CRi) as assessed by the Investigator

End point type	Secondary

End point timeframe:

The ORR in phase I was evaluated over the treatment period i.e. until unacceptable toxicity or disease progression up to a maximum of 6 cycles.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis planned. The conclusion were based on the descriptive values.

End point values	Phase I-15 mg	Phase I-20 mg	Phase I-26 mg	Phase I-34 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	6
Units: Percentage				
number (confidence interval 95%)	33.3 (0.8 to 90.6)	0 (0 to 70.8)	50 (11.8 to 88.2)	16.7 (0.4 to 64.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse-free survival (RFS)-Phase II

End point title	Relapse-free survival (RFS)-Phase II

End point description:

Time from date of CR/CRi to relapse or death whichever occurs first, or (in progression-free patients) to last disease assessment . Relapse was defined as an increase of bone marrow blasts ≥ 5% or reappearance of blasts in the blood; or development of extramedullary disease.

End point type	Secondary

End point timeframe:

Post-remission treatment and follow-up periods.

End point values	Phase II ITT subset of responders			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Months				
median (confidence interval 95%)	7.5 (4.1 to 30.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)-Phase II

End point title	Progression-free survival (PFS)-Phase II

End point description:

Time from registration to disease progression, relapse or death whichever occurs first, or (in progression-free patients) to last disease assessment.

End point type	Secondary

End point timeframe:

Whole study period from registration.

End point values	Phase II ITT set			
Subject group type	Subject analysis set			
Number of subjects analysed	53			
Units: Months				
median (confidence interval 95%)	1.3 (1.1 to 3.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)-Phase II

End point title	Overall survival (OS)-Phase II

End point description:

Time from registration to death or date of last news if not died.

End point type	Secondary

End point timeframe:

Whole study period from registration

End point values	Phase II ITT set			
Subject group type	Subject analysis set			
Number of subjects analysed	53			
Units: Months				
median (confidence interval 95%)	6.7 (5.3 to 9.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of remission-Phase II

End point title	Duration of remission-Phase II

End point description:

Time from CR/CRi date to the date of relapse, or (in progression-free patients) of last disease assessment.

End point type	Secondary

End point timeframe:

Post-remission treatment and follow-up periods

End point values	Phase II ITT subset of responders			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Months				
median (inter-quartile range (Q1-Q3))	7.5 (5.7 to 30.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment period (including 60 days of follow-up)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Phase I-15 mg
Reporting group description:	
Patients treated with F14512 at 15 mg/m2/day during the phase I dose escalation	
Reporting group title	Phase I-20 mg
Reporting group description:	
Patients treated with F14512 mg/m2/day during the Phase I dose escalation	
Reporting group title	Phase I-26 mg
Reporting group description:	
Patients treated with F14512 26 mg/m2/day during Phase I-dose escalation	
Reporting group title	Phase I-34 mg
Reporting group description:	
Patients treated with F14512 at 34 mg/m2/day in the Phase I dose escalation	
Reporting group title	Phase II (26 mg)
Reporting group description:	
All patients treated in Phase II of the study. In this phase, all patients were treated with F14512 at the dose of 26 mg/m2/day	

Serious adverse events	Phase I-15 mg	Phase I-20 mg	Phase I-26 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	1 / 3 (33.33%)	2 / 6 (33.33%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Investigation	Additional description: Abnormal transthoracic echocardiography of the aortic and mitral valves in the patient of Phase II concerned		
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression	Additional description: Progression of the target disease (AML)		
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Injury, poisoning and procedural complications			
Septic shock			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiogenic shock			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebellar ataxia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (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
Neutropenia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (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
Bone marrow failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (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
Cholecystitis acute			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (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
Hidradenitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia fungal			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (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
Device related infection			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (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
Device related sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase I-34 mg	Phase II (26 mg)	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	27 / 53 (50.94%)	
number of deaths (all causes)	0	6	
number of deaths resulting from adverse events	0	2	
Investigations			
Investigation	Additional description: Abnormal transthoracic echocardiography of the aortic and mitral valves in the patient of Phase II concerned		
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression	Additional description: Progression of the target disease (AML)		
subjects affected / exposed	1 / 6 (16.67%)	5 / 53 (9.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 5	
Injury, poisoning and procedural complications			
Septic shock			
subjects affected / exposed	0 / 6 (0.00%)	6 / 53 (11.32%)	
occurrences causally related to treatment / all	0 / 0	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiogenic shock			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebellar ataxia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhage intracranial			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 6 (0.00%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 6 (16.67%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hidradenitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	4 / 53 (7.55%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 6 (16.67%)	8 / 53 (15.09%)	
occurrences causally related to treatment / all	1 / 1	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 6 (16.67%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Phase I-15 mg	Phase I-20 mg	Phase I-26 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm skin			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Cancer pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vascular disorders			

Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	4 / 6 (66.67%)
occurrences (all)	2	1	7
Chills			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	2	1	3
Pyrexia			
subjects affected / exposed	3 / 3 (100.00%)	0 / 3 (0.00%)	4 / 6 (66.67%)
occurrences (all)	4	0	7
Catheter site inflammation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Catheter site pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Implant site pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Fatigue			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Thrombosis in device			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Hiccups			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Epistaxis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Hypoxia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	2 / 6 (33.33%)
occurrences (all)	0	2	4

Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Hallucination			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Investigations			
Weight increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oxygen saturation decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Procedural pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Allergic transfusion reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Toxicity to various agents			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Arrhythmia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 3 (100.00%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	4	1	5
Paraesthesia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 3 (100.00%)	3 / 6 (50.00%)
occurrences (all)	0	3	9
Lymphadenopathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye disorder			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0

Eye pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 3 (66.67%)	2 / 3 (66.67%)	2 / 6 (33.33%)
occurrences (all)	5	2	4
Diarrhoea			
subjects affected / exposed	2 / 3 (66.67%)	2 / 3 (66.67%)	1 / 6 (16.67%)
occurrences (all)	2	2	2
Dry mouth			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	6 / 6 (100.00%)
occurrences (all)	4	1	10
Vomiting			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	3 / 6 (50.00%)
occurrences (all)	3	1	3
Abdominal pain upper			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	1	1	3
Dysphagia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Haemorrhoids			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	3 / 6 (50.00%)
occurrences (all)	1	1	3
Toothache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Anal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Cheilitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Oesophagitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Petechiae			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rash			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	4 / 6 (66.67%)
occurrences (all)	0	0	6
Skin lesion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Toxic skin eruption			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hidradenitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dysuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Micturition disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary tract disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Pain in jaw			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Back pain			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	2
Myalgia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Bone pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	3
Osteoarthritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Sialoadenitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
Bacteraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bacterial infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	4
Folliculitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Fungal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Laryngitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Device related infection			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	1	1	2
Pharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Anorectal infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Gingivitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Streptococcal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Anorectal cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Catheter site cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Enterocolitis infectious			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Herpes virus infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Oral infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Lung infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	2	1	2
Gout			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Tumour lysis syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Malnutrition			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Fluid retention			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2

Non-serious adverse events	Phase I-34 mg	Phase II (26 mg)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	53 / 53 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Cancer pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 6 (16.67%)	5 / 53 (9.43%)	
occurrences (all)	1	7	
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	6 / 53 (11.32%)	
occurrences (all)	0	8	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 6 (33.33%)	9 / 53 (16.98%)	
occurrences (all)	2	11	
Chills			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	

Oedema peripheral			
subjects affected / exposed	0 / 6 (0.00%)	10 / 53 (18.87%)	
occurrences (all)	0	10	
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	13 / 53 (24.53%)	
occurrences (all)	1	16	
Catheter site inflammation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Catheter site pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	1 / 6 (16.67%)	3 / 53 (5.66%)	
occurrences (all)	1	3	
Pain			
subjects affected / exposed	0 / 6 (0.00%)	4 / 53 (7.55%)	
occurrences (all)	0	4	
Implant site pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Thrombosis in device			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 6 (16.67%)	6 / 53 (11.32%)	
occurrences (all)	1	6	
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Hiccups			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	9 / 53 (16.98%)	
occurrences (all)	0	9	
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 53 (3.77%)	
occurrences (all)	0	2	
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 6 (50.00%)	12 / 53 (22.64%)	
occurrences (all)	3	12	
Insomnia			
subjects affected / exposed	1 / 6 (16.67%)	9 / 53 (16.98%)	
occurrences (all)	1	9	
Hallucination			
subjects affected / exposed	1 / 6 (16.67%)	3 / 53 (5.66%)	
occurrences (all)	1	3	
Confusional state			
subjects affected / exposed	1 / 6 (16.67%)	1 / 53 (1.89%)	
occurrences (all)	1	1	
Investigations			
Weight increased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Weight decreased			

subjects affected / exposed	1 / 6 (16.67%)	17 / 53 (32.08%)	
occurrences (all)	1	21	
Oxygen saturation decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Procedural pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Allergic transfusion reaction			
subjects affected / exposed	1 / 6 (16.67%)	4 / 53 (7.55%)	
occurrences (all)	1	4	
Toxicity to various agents			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Skin injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	5 / 53 (9.43%)	
occurrences (all)	0	7	
Arrhythmia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 6 (16.67%)	20 / 53 (37.74%)	
occurrences (all)	1	25	
Paraesthesia			

subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)	1 / 53 (1.89%)	
occurrences (all)	1	1	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	5 / 6 (83.33%)	22 / 53 (41.51%)	
occurrences (all)	5	27	
Lymphadenopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Eye disorders			
Eye disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Eye pain			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 6 (33.33%)	19 / 53 (35.85%)	
occurrences (all)	2	26	
Diarrhoea			
subjects affected / exposed	5 / 6 (83.33%)	34 / 53 (64.15%)	
occurrences (all)	5	42	
Dry mouth			
subjects affected / exposed	1 / 6 (16.67%)	2 / 53 (3.77%)	
occurrences (all)	1	2	
Nausea			

subjects affected / exposed	5 / 6 (83.33%)	35 / 53 (66.04%)	
occurrences (all)	5	52	
Vomiting			
subjects affected / exposed	2 / 6 (33.33%)	21 / 53 (39.62%)	
occurrences (all)	2	31	
Abdominal pain upper			
subjects affected / exposed	2 / 6 (33.33%)	9 / 53 (16.98%)	
occurrences (all)	2	12	
Abdominal pain			
subjects affected / exposed	3 / 6 (50.00%)	17 / 53 (32.08%)	
occurrences (all)	3	20	
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	6 / 53 (11.32%)	
occurrences (all)	0	6	
Haemorrhoids			
subjects affected / exposed	1 / 6 (16.67%)	11 / 53 (20.75%)	
occurrences (all)	1	14	
Mouth ulceration			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Stomatitis			
subjects affected / exposed	2 / 6 (33.33%)	13 / 53 (24.53%)	
occurrences (all)	2	15	
Toothache			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Anal inflammation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Cheilitis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Oesophagitis			
subjects affected / exposed	1 / 6 (16.67%)	2 / 53 (3.77%)	
occurrences (all)	1	2	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	6 / 53 (11.32%)	
occurrences (all)	0	6	
Dry skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Petechiae			
subjects affected / exposed	0 / 6 (0.00%)	2 / 53 (3.77%)	
occurrences (all)	0	2	
Rash			
subjects affected / exposed	1 / 6 (16.67%)	4 / 53 (7.55%)	
occurrences (all)	1	6	
Skin lesion			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Toxic skin eruption			
subjects affected / exposed	0 / 6 (0.00%)	4 / 53 (7.55%)	
occurrences (all)	0	4	
Alopecia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 53 (3.77%)	
occurrences (all)	1	2	
Erythema			
subjects affected / exposed	0 / 6 (0.00%)	2 / 53 (3.77%)	
occurrences (all)	0	2	
Hidradenitis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Dysuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Micturition disorder			
subjects affected / exposed	1 / 6 (16.67%)	4 / 53 (7.55%)	
occurrences (all)	1	4	
Urinary tract disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Pain in jaw			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	7 / 53 (13.21%)	
occurrences (all)	0	8	
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)	8 / 53 (15.09%)	
occurrences (all)	0	8	
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	4 / 53 (7.55%)	
occurrences (all)	1	4	
Bone pain			

subjects affected / exposed	1 / 6 (16.67%)	4 / 53 (7.55%)	
occurrences (all)	1	4	
Osteoarthritis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 53 (1.89%)	
occurrences (all)	1	1	
Infections and infestations			
Sialoadenitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Bacteraemia			
subjects affected / exposed	0 / 6 (0.00%)	5 / 53 (9.43%)	
occurrences (all)	0	8	
Bacterial infection			
subjects affected / exposed	0 / 6 (0.00%)	8 / 53 (15.09%)	
occurrences (all)	0	10	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 6 (16.67%)	7 / 53 (13.21%)	
occurrences (all)	1	7	
Folliculitis			
subjects affected / exposed	0 / 6 (0.00%)	5 / 53 (9.43%)	
occurrences (all)	0	5	
Fungal infection			
subjects affected / exposed	0 / 6 (0.00%)	8 / 53 (15.09%)	
occurrences (all)	0	9	
Oral candidiasis			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	4	
Pneumonia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 53 (5.66%)	
occurrences (all)	1	3	

Laryngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Device related infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Anorectal infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Sepsis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Gingivitis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 53 (3.77%)	
occurrences (all)	0	2	
Streptococcal infection			
subjects affected / exposed	0 / 6 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 53 (3.77%)	
occurrences (all)	0	2	
Anorectal cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Catheter site cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Enterocolitis infectious			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Herpes virus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	

Sinusitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Oral infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 53 (0.00%)	
occurrences (all)	0	0	
Lung infection			
subjects affected / exposed	1 / 6 (16.67%)	2 / 53 (3.77%)	
occurrences (all)	1	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)	16 / 53 (30.19%)	
occurrences (all)	0	18	
Gout			
subjects affected / exposed	0 / 6 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Tumour lysis syndrome			
subjects affected / exposed	0 / 6 (0.00%)	2 / 53 (3.77%)	
occurrences (all)	0	2	
Malnutrition			
subjects affected / exposed	2 / 6 (33.33%)	1 / 53 (1.89%)	
occurrences (all)	2	1	
Fluid retention			
subjects affected / exposed	1 / 6 (16.67%)	1 / 53 (1.89%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2013	Completion of the definition of DLT. Correction of a discrepancy between the synopsis and the protocol regarding the exclusion criteria number 10. Correction of the volume of rinse of the catheter following the end of F14512 infusion. Addition of specifications for F14512 preparation. Correction of the labelling of the study drugs F14512 and Cytarabine. Modification of the reporting modalities of SAEs and the SAE report form. Addition of pharmaceutical information about the non-modified associated product Cytarabine following the addition of a second supplier.
28 April 2014	combination (F14512 plus cytarabine) showed similar results in first relapsed and refractory patients. Extension of the follow-up phase until documentation of death from any cause. Modification of the PK sampling in Phase II regarding the results of Phase I and modification of the volume of bone marrow sample for Specification of the RD determined during Phase I, to be tested during Phase II (26 mg/m²/day of F14512). Definition of specific criteria allowing 1 re-induction cycle and consolidation cycles, for Phase II, as well as the rules of study drugs administration: dose of F14512 and cytarabine and number of cycles. Extension of the inclusion criteria of Phase II to patients who had refractory AML after failure of 1 induction chemotherapy regimen or who had recurrence of disease < 3 months after CR. In Phase I, the rate of response of thePD assessments (Phase I and Phase II). Withdrawal of PBMC sample collection. Study manager was appointed and head statistician was changed. Modification of the blood sampling procedures for PK assessment. Correction of the results of efficacy of the first-in-man Phase I study. Extension of the list of participating countries. The number of sites was increased in order to recruit the 50 patients in Phase II. Update of the version of the IB. Update of the version of the World Medical Association Declaration of Helsinki (October 2013).
03 February 2015	Extension of the recruitment period in order to obtain the 50 patients requested by the protocol in the ongoing Phase II part.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 March 2017	Due to the discontinuation of the development of F14512 in the indication of AML, and, as described in the study protocol, the sponsor decided to proceed with an early termination of the trial on 03 March 2017. All the patients had finished the study treatment period at time of trial early termination. The date of the last study drug administration was 24 October 2015.	-

Notes:

Limitations and caveats

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

No limitations and caveats for Phase I of the trial: 26 mg/M2/day was defined as the recommended dose for Phase II.
The early termination of Phase II is not a limitation as all patients had completed the treatment period + 60 days evaluation period.

Notes: