



Clinical trial results:

Phase 1-2 Safety and Efficacy Study of DACOGEN in Sequential Administration With Cytarabine in Children With Relapsed or Refractory Acute Myeloid Leukemia

Summary

EudraCT number	2013-000390-70
Trial protocol	GB BE DE FR NL DK ES
Global end of trial date	28 August 2017

Results information

Result version number	v1 (current)
This version publication date	16 March 2018
First version publication date	16 March 2018

Trial information

Trial identification

Sponsor protocol code	DACOGENAML2004
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01853228
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	Archimedesweg 29, Leiden, Netherlands, 2333CM
Public contact	Clinical Registry group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000555-PIP01-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 August 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the maximum tolerable dose (MTD) of cytarabine (up to 2 gram per square meter (g/m^2) per day*5 that can be administered on Days 8 to 12 following treatment with Dacogen 20 milligram per square meter (mg/m^2) per day on Days 1 to 5 of a 28 day cycle and decitabine pharmacokinetics (PK) parameters from blood sampling on Day 5 of Cycle 1 (Phase 1 portion); to determine the response rate using international working group (IWG) criteria (complete response [CR] + complete response with incomplete blood count recovery [CRI]) in children with relapsed or refractory acute myeloid leukemia (AML) when treated with Dacogen 20 mg/m^2 per day on Days 1 to 5 followed by cytarabine at the determined MTD on Days 8 to 12 for up to 4 cycles of treatment (Phase 2 portion).

Protection of trial subjects:

Safety evaluations included monitoring of adverse events (AEs), clinical laboratory parameters (hematology, biochemistry and urinalysis) vital sign measurements, physical examination findings, and assessment of performance status.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2014
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	Belgium: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Netherlands: 1
Worldwide total number of subjects	17
EEA total number of subjects	17

Notes:

Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	14
Adolescents (12-17 years)	2
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Sixteen subjects were enrolled in Phase 1 (9 subjects in Cohort 1 [cytarabine 1 {grams per square meter} g/m²] and 7 subjects in Cohort 2 [cytarabine 2 g/m²]) and of these, 7 in Cohort 2 continued on to Phase 2. One additional patient was newly enrolled in Phase 2 of the study, making a total of 8 subjects evaluable in Phase 2.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Decitabine (Dacogen) + Cytarabine
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Arm description:

Subjects received 1 gram per square meter (g/m²), 2 g/m², and 1.5 g/m² dose levels administered by intravenous infusion over 4 hours daily for 5 consecutive days (Day 8 to Day 12 of 28-day cycle) for the determination of the maximum tolerated dose in Phase 1 and maximum tolerated dose identified in Phase 1 was administered by intravenous infusion over 4 hours daily for 5 consecutive days (Day 8 to Day 12 of 28-day cycle) in Phase 2. Followed by this subjects received 20 milligram square per gram (mg/m²) by intravenous infusion over 1 hour once daily for 5 consecutive days (Day 1 to Day 5 of 28-day cycle) in Phase 1 and Phase 2.

Arm type	Experimental
Investigational medicinal product name	Decitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Dacogen 20 mg/m²/day on Days 1 to 5 intravenously.

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received no more than 2 g/m² per day*5 days cytarabine on Days 8 to 12 intravenously.

Number of subjects in period 1	Decitabine (Dacogen) + Cytarabine
Started	17
Completed	0
Not completed	17
Physician decision	1

Proceed to transplant	3
Other	1
Progressive disease	12

Baseline characteristics

Reporting groups

Reporting group title	Decitabine (Dacogen) + Cytarabine
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Reporting group description:

Subjects received 1 gram per square meter (g/m^2), 2 g/m^2 , and 1.5 g/m^2 dose levels administered by intravenous infusion over 4 hours daily for 5 consecutive days (Day 8 to Day 12 of 28-day cycle) for the determination of the maximum tolerated dose in Phase 1 and maximum tolerated dose identified in Phase 1 was administered by intravenous infusion over 4 hours daily for 5 consecutive days (Day 8 to Day 12 of 28-day cycle) in Phase 2. Followed by this subjects received 20 milligram square per gram (mg/m^2) by intravenous infusion over 1 hour once daily for 5 consecutive days (Day 1 to Day 5 of 28-day cycle) in Phase 1 and Phase 2.

Reporting group values	Decitabine (Dacogen) + Cytarabine	Total	
Number of subjects	17	17	
Title for AgeCategorical Units: subjects			
inUtero	0	0	
pretermNewbornInfants (gestational age <37 wks)	0	0	
newborns (0-27 days)	0	0	
infants and toddlers(28 days-23 months)	1	1	
Children (2-11 years)	14	14	
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	0	0	
From 65 to 84 years	0	0	
85 years and over	0	0	
Title for AgeContinuous Units: months			
arithmetic mean	73.3		
standard deviation	± 46.26	-	
Title for Gender Units: subjects			
Female	4	4	
Male	13	13	

End points

End points reporting groups

Reporting group title	Decitabine (Dacogen) + Cytarabine
Reporting group description: Subjects received 1 gram per square meter (g/m^2), 2 g/m^2 , and 1.5 g/m^2 dose levels administered by intravenous infusion over 4 hours daily for 5 consecutive days (Day 8 to Day 12 of 28-day cycle) for the determination of the maximum tolerated dose in Phase 1 and maximum tolerated dose identified in Phase 1 was administered by intravenous infusion over 4 hours daily for 5 consecutive days (Day 8 to Day 12 of 28-day cycle) in Phase 2. Followed by this subjects received 20 milligram square per gram (mg/m^2) by intravenous infusion over 1 hour once daily for 5 consecutive days (Day 1 to Day 5 of 28-day cycle) in Phase 1 and Phase 2.	

Primary: Maximum Tolerated Dose (MTD) of Cytarabine

End point title	Maximum Tolerated Dose (MTD) of Cytarabine ^[1]
End point description: The maximum tolerated dose (MTD) for cytarabine was based on the number of subjects experiencing a dose-limiting toxicity (DLT) by the end of Cycle 1. A non-hematological DLT is defined as: any Grade 3 toxicity that persists for greater than (>) 5 days or any Grade 2 toxicity that persists for >7 days and that is intolerable to the subject. A hematological DLT is defined as Grade 4 neutropenia or thrombocytopenia due to a hypoplastic bone marrow at Day 42, in the absence of malignant infiltration. The nominal duration of each cycle was 28 days. However, patients who have not experienced bone marrow recovery at Day 28 were followed up to Day 42. Failure of marrow recovery (improvement to Grade 3) by Day 42 was considered a DLT. The maximum duration of Cycle 1 was therefore be 42 days.	
End point type	Primary
End point timeframe: Cycle 1 (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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Decitabine (Dacogen) + Cytarabine			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: gram per square meter				
number (not applicable)	2			

Statistical analyses

No statistical analyses for this end point

Primary: Clearance of Decitabine

End point title	Clearance of Decitabine ^[2]
End point description: Total clearance of drug after intravenously administration, calculated as: dose/area under the plasma concentration-time curve. Population included all enrolled subjects in this study assessed for pharmacokinetics (PK).	
End point type	Primary

End point timeframe:

Cycle 1 Day 5: pre-infusion, 0.5 h during infusion, end of infusion, +5 min, +0.5h, +1h, and +2h after end infusion

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Decitabine (Dacogen) + Cytarabine			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: liter per hour square per meter				
median (full range (min-max))				
Less than (<) 1 month to <= 2	160.6 (11.7 to 942.3)			
> 2 to <= 6 years	152.1 (19.5 to 1061)			
> 6 to <= 12 years	125.9 (13.3 to 951.3)			
> 12 to <= 16 years	123.2 (11.4 to 832.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Volume of Distribution at Steady-State (Vss) of Decitabine

End point title	Volume of Distribution at Steady-State (Vss) of Decitabine ^[3]
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End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug. Population included all enrolled subjects in this study assessed for PK.

End point type	Primary
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End point timeframe:

Cycle 1 Day 5: pre-infusion, 0.5 h during infusion, end of infusion, +5 min, +0.5h, +1h, and +2h after end infusion

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Decitabine (Dacogen) + Cytarabine			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: liter per square meter				
median (full range (min-max))				
< 1 month to <= 2 years	35.9 (2.7 to 558.4)			
> 2 to <= 6 years	36.5 (1.4 to 535.0)			

> 6 to <= 12 years	31.8 (2.0 to 645.8)			
> 12 to <= 16 years	35.9 (2.8 to 578.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Percentage of Subjects who Achieved CR or CRi

End point title	Phase 2: Percentage of Subjects who Achieved CR or CRi ^[4]
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End point description:

Response rate was measured using international working group (IWG) criteria. Response rate is defined as complete remission (CR) and complete remission with incomplete blood count recovery (CRi) in children with relapsed or refractory acute myeloid leukemia. CRi is defined as morphologic CR with residual neutropenia (less than [$<$] 1,000/microliter) or thrombocytopenia $<100,000$ / microliter). CR is defined as morphologic leukemia-free state, with less than 5 percentage (%) blasts in aspirate sample with marrow spicules and with a count of greater than or equal to (\geq) 200 nucleated cells, plus absolute neutrophil count (ANC) greater than ($>$) 1,000/ microliter platelet count of $>100,000$ /microliter and subject must be independent of transfusions for a minimum of 1 week before each marrow assessment. Here 'N' signifies number of subjects who were evaluable for this endpoint. Here 'n' signifies number of subjects analyzed for specific arm.

End point type	Primary
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End point timeframe:

Cycle 1 Day 28, Cycle 2 Day 28 and end of study treatment (approximately 3 years)

Notes:

[4] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Decitabine (Dacogen) + Cytarabine			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of subjects				
number (not applicable)				
CRi (Cycle 1 Day 28) n=5	20.0			
CRi (Cycle 2 Day 28) n=3	66.7			
CRi End of Study Treatment (EOST) n=8	12.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Decitabine

End point title	Maximum Plasma Concentration (Cmax) of Decitabine
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End point description:

The Cmax is the maximum observed plasma concentration of Decitabine. Population included all enrolled subjects in this study assessed for PK.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 5: pre-infusion, 0.5 h during infusion, end of infusion, +5 min, +0.5h, +1h, and +2h after end infusion

End point values	Decitabine (Dacogen) + Cytarabine			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: nanogram per milliliter (ng/mL)				
median (full range (min-max))				
Less than (<) 1 month to <= 2 years	118.4 (17.6 to 1621)			
Greater than (>) 2 to <= 6 years	123.1 (15.6 to 1012)			
> 6 to <= 12 years	148.7 (16.5 to 1415)			
> 12 to <= 16 years	151.4 (19.1 to 1303)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve of Decitabine

End point title	Area Under the Plasma Concentration-Time Curve of Decitabine
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End point description:

The AUC is the area under the plasma concentration-time curve of decitabine. Population included all enrolled subjects in this study assessed for PK.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 5: pre-infusion, 0.5 h during infusion, end of infusion, +5 min, +0.5h, +1h, and +2h after end infusion

End point values	Decitabine (Dacogen) + Cytarabine			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: nanogram*hour per milliliter (ng*h/mL)				
median (full range (min-max))				
< 1 month to <= 2 years	124.8 (21.3 to 1708)			
> 2 to <= 6 years	131.5 (19.3 to 1028)			
> 6 to <= 12 years	158.9 (21.0 to 1508)			

> 12 to <= 16 years	162.4 (24.2 to 1747)			
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Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Duration of Response

End point title	Phase 2: Duration of Response
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End point description:

Duration of response is defined as weeks from date of first response to earlier of date of first relapse or date of death. Population included all enrolled subjects. Here, 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

From time of response to relapse, study completion/withdrawal, or death, whichever comes first, for up to 3 years after last participant enrollment

End point values	Decitabine (Dacogen) + Cytarabine			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: weeks				
number (not applicable)				
Subject 11	44.6			
Subject 15	6.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 and Phase 2: Overall Response Rate

End point title	Phase 1 and Phase 2: Overall Response Rate
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End point description:

Overall response rate is defined as complete remission (CR) +complete remission with incomplete blood count recovery (CRi)+partial remission (PR). CRi: morphologic CR with residual neutropenia (less than [$<$] 1,000/microliter) or thrombocytopenia $<100,000$ / microliter). CR is defined as morphologic leukemia-free state, with less than 5 percentage (%) blasts in aspirate sample with marrow spicules and with a count of greater than or equal to (\geq) 200 nucleated cells, plus absolute neutrophil count (ANC) greater than ($>$) 1,000/ microliter platelet count of $>100,000$ /microliter and subject must be independent of transfusions for a minimum of 1 week before each marrow assessment. PR: all the same hematologic values of a CR, but with a decrease of $\geq 50\%$ of the percentage of blasts to 5% to 25% in the bone marrow aspirate. Here 'N' signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:
Up to approximately 4 years

End point values	Decitabine (Dacogen) + Cytarabine			
Subject group type	Reporting group			
Number of subjects analysed	8 ^[5]			
Units: Percentage of subjects				
number (not applicable)	37.5			

Notes:

[5] - Population included who achieved the MTD of cytarabine for up to 4 cycles in the Phase 1 portion.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 and Phase 2: Overall Survival (OS)

End point title	Phase 1 and Phase 2: Overall Survival (OS)
End point description: The OS is defined as the time from the date of first dose of study drug to date of death from any cause. If the participant is alive or the vital status is unknown, the participant will be censored at the date the participant will be last known to be alive. Population included all enrolled subjects.	
End point type	Secondary
End point timeframe: From enrollment to death or withdrawal, whichever comes first, for up to 3 years after last participant enrollment	

End point values	Decitabine (Dacogen) + Cytarabine			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: months				
median (confidence interval 95%)	5.1 (3.1 to 11.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 and Phase 2: Event-Free Survival

End point title	Phase 1 and Phase 2: Event-Free Survival
End point description:	
Event free survival is defined as the time from first dose of study drug to relapse from CR, death, or second malignancy for subjects who achieve CR. Population included all enrolled subjects. -99999	

indicates that the data for lower limit of CI was not estimable due to less number of participants with events. 99999 indicates that the data for lower limit of CI was not estimable due to less number of events.

End point type	Secondary
End point timeframe:	
From enrollment to progression/relapse, death, or withdrawal, whichever comes first, for up to 3 years after last subject enrollment	

End point values	Decitabine (Dacogen) + Cytarabine			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Days				
median (confidence interval 95%)	1 (-99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 and Phase 2: Number of Subjects Reporting Treatment-Emergent Adverse Events (TEAEs)

End point title	Phase 1 and Phase 2: Number of Subjects Reporting Treatment-Emergent Adverse Events (TEAEs)
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End point description:

TEAEs are defined as adverse events with onset or worsening on or after date of first dose of study treatment. An adverse event is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. The Safety Analysis Set included all enrolled subjects who received at least 1 dose of study drug (DACOGEN).

End point type	Secondary
End point timeframe:	
Approximately 4 years	

End point values	Decitabine (Dacogen) + Cytarabine			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: subjects	17			

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening up to end of treatment (approximately 4 years)

Adverse event reporting additional description:

An adverse event is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. The Safety Analysis Set included all enrolled subjects who received at least 1 dose of study drug (DACOGEN).

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Dacogen + Cytarabine
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Reporting group description:

Subjects received cytarabine on Days 8 to 12 intravenously following Dacogen 20 milligrams per square meter (mg/m²/day) on Days 1 to 5 intravenously.

Serious adverse events	Dacogen + Cytarabine		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 17 (47.06%)		
number of deaths (all causes)	14		
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile Neutropenia			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences causally related to treatment / all	9 / 10		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Complication Associated with Device			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Keratitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin Exfoliation			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin Hyperpigmentation			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung Infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	2 / 17 (11.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Dacogen + Cytarabine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Phlebitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Face Oedema			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Catheter Site Haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Oedema Peripheral			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

Pyrexia subjects affected / exposed occurrences (all)	8 / 17 (47.06%) 30		
Immune system disorders Hypogammaglobulinaemia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Reproductive system and breast disorders Vulvovaginal Inflammation subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) Hypoxia subjects affected / exposed occurrences (all) Rhinitis Atrophic subjects affected / exposed occurrences (all) Tachypnoea subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1		
Psychiatric disorders Depressed Mood subjects affected / exposed occurrences (all) Irritability subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1		
Product issues			

Device Occlusion subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Investigations			
Adenovirus Test Positive subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Aspartate Aminotransferase Increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)	5 / 17 (29.41%) 12		
Blood Albumin Decreased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2		
Gamma-Glutamyltransferase Increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Weight Decreased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Injury, poisoning and procedural complications			
Allergic Transfusion Reaction subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Fall subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Post Procedural Complication subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Procedural Pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		

Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Nervous system disorders Dizziness Postural subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2 2 / 17 (11.76%) 5		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Febrile Neutropenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	14 / 17 (82.35%) 64 5 / 17 (29.41%) 9 6 / 17 (35.29%) 14 1 / 17 (5.88%) 4 6 / 17 (35.29%) 11 10 / 17 (58.82%) 62		
Eye disorders Conjunctivitis Allergic subjects affected / exposed occurrences (all) Keratitis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1 1 / 17 (5.88%) 1		

Dry Eye			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	3		
Anal Inflammation			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Ascites			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	5		
Haematemesis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Lip Haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Mouth Haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Stomatitis			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	5		
Tongue Haemorrhage			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	9 / 17 (52.94%)		
occurrences (all)	13		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	3		
Hepatocellular Injury			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	4		
Hepatomegaly			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hyperbilirubinaemia			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	8		
Jaundice			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Decubitus Ulcer			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Butterfly Rash			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Erythema Multiforme			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Lividity			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Petechiae			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	3		
Pruritus Generalised			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Rash Maculo-Papular			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin Hyperpigmentation			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Bone Pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Back Pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Infections and infestations			

Enterobacter Infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Fungal Infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Hepatic Infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Lung Infection subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Paronychia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Pneumonia Klebsiella subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Pseudomonas Infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Staphylococcal Infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Rhinitis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Hyperferritinaemia			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hypermagnesaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Hypernatraemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Hyperphosphataemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	6 / 17 (35.29%)		
occurrences (all)	9		
Hypomagnesaemia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	9		
Hypophosphataemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2014	The overall reason for the amendment INT-1 was to facilitate enrollment into the study and provide clarity on some aspects of the protocol.
06 October 2015	The overall reason for the amendment INT-2 was to correct errors noted in the selection criteria and typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The Sponsor terminated the study earlier than planned due to lack of efficacy with 8 evaluable subjects in Phase 2 with no clinically meaningful anti-leukemic activity.
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Notes: