Clinical trial results:
A Phase 1, Open-label, Multi-center Study of Clofarabine in Japanese Pediatric Patients with Relapsed or Refractory Acute Lymphoblastic Leukemia

Summary

EudraCT number	2015-001172-21
Trial protocol	Outside EU/EEA
Global end of trial date	23 May 2011

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	25 July 2015

Trial information

Trial identification

Sponsor protocol code	CLO05908

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01196013
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Genzyme Corporation
Sponsor organisation address	500 Kendall Street, Cambridge, MA, United States, 02142
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 September 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 May 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety, tolerability and pharmacokinetics (PK) of clofarabine administered intravenously to pediatric subjects with relapsed or refractory acute lymphoblastic leukemia (ALL) or for whom no other therapy with greater potential clinical benefit exists. The dosing regimen for the intravenous (IV) clofarabine was 30 or 52 mg/m^2/day for 5 days.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia might have been used to minimize distress and discomfort.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	18 August 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 7
Worldwide total number of subjects	7
EEA total number of subjects	0

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)	5
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:

The study was conducted at 9 sites in Japan. A total of 7 subjects were enrolled between 18 August 2010 and 23 May 2011.

Pre-assignment

Screening details:

All enrolled subjects were treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Clofarabine 30 mg/m²/day

Arm description:

Clofarabine 30 mg/m²/day from Day 1 to Day 5 in Cycle 1 (14 days). If no subject developed dose limiting toxicity (DLT), subjects received 52 mg/m²/day from Cycle 2 up to a total of 6 cycles.

Arm type	Experimental
Investigational medicinal product name	Clofarabine
Investigational medicinal product code	JC0707
Other name	Evoltra®, Clolar
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Clofarabine administered once daily over 2 hours infusion. If 2 DLTs occurred, dose was reduced to 22.5 mg/m²/day.

Arm title	Clofarabine 52 mg/m²/day

Arm description:

Clofarabine 52 mg/m²/day from Day 1 to Day 5 in Cycle 1 (14 days) up to a total of 6 cycles.

Arm type	Experimental
Investigational medicinal product name	Clofarabine
Investigational medicinal product code	JC0707
Other name	Evoltra®, Clolar
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Clofarabine administered once daily over 2 hours infusion. If 2 DLTs occurred, dose was reduced to 40 mg/m²/day.

Number of subjects in period 1	Clofarabine 30 mg/m²/day	Clofarabine 52 mg/m²/day
Started	3	4
Completed	3	4

Baseline characteristics

Reporting groups	
Reporting group title	Clofarabine 30 mg/m²/day
Reporting group description:	
Clofarabine 30 mg/m²/day from Day 1 to Day 5 in Cycle 1 (14 days). If no subject developed dose limiting toxicity (DLT), subjects received 52 mg/m²/day from Cycle 2 up to a total of 6 cycles.	
Reporting group title	Clofarabine 52 mg/m²/day
Reporting group description:	
Clofarabine 52 mg/m²/day from Day 1 to Day 5 in Cycle 1 (14 days) up to a total of 6 cycles.	

Reporting group values	Clofarabine 30 mg/m²/day	Clofarabine 52 mg/m²/day	Total
Number of subjects	3	4	7
Age categorical Units: Subjects			
Children (2-11 years)	3	2	5
Adolescents (12-17 years)	0	2	2
Age continuous Units: years			
arithmetic mean	4	12.8	
standard deviation	± 1	± 2.75	-
Gender categorical Units: Subjects			
Female	1	2	3
Male	2	2	4

End points

End points reporting groups

Reporting group title	Clofarabine 30 mg/m²/day
Reporting group description:	
Clofarabine 30 mg/m²/day from Day 1 to Day 5 in Cycle 1 (14 days). If no subject developed dose limiting toxicity (DLT), subjects received 52 mg/m²/day from Cycle 2 up to a total of 6 cycles.	
Reporting group title	Clofarabine 52 mg/m²/day
Reporting group description:	
Clofarabine 52 mg/m²/day from Day 1 to Day 5 in Cycle 1 (14 days) up to a total of 6 cycles.	
Subject analysis set title	Clofarabine
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects (Clofarabine 30 mg/m^2/day + Clofarabine 52 mg/m^2/day) included in the study and who received at least 1 dose of clofarabine.	

Primary: Maximum Tolerated Dose (MTD)

End point title	Maximum Tolerated Dose (MTD)[1]
End point description:	
The MTD was defined as the highest dose at which < 2/6 subjects experience a DLT during the first cycle. Analysis was carried out on safety population comprised of all subjects who received at least 1 dose of the study drug. Here '99999' represents 'not applicable' as no subject experienced any DLT.	
End point type	Primary
End point timeframe:	
Baseline up to 14 days (Cycle 1)	

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: Since analysis is descriptive in nature, statistical data could not be provided.

End point values	Clofarabine			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: mg				
number (not applicable)	99999			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Drug Plasma Concentration (Cmax)

End point title	Maximum Drug Plasma Concentration (Cmax)[2]
End point description:	
Analysis was carried out on pharmacokinetic (PK) analysis set which included subjects who received at least 1 dose of clofarabine and had measurable drug concentrations. 'Here 'n' signifies number of subjects with available data for specified category.	
End point type	Primary
End point timeframe:	
0 hour (Predose) on Day 1-5 of Cycle 1; >0 to 1, 2 (end of infusion), >2.5 to 4, >4.5 to 7, >7.5 to 10 hours after infusion; on Day 1 and Day 5 of Cycle 1	

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: Since analysis is descriptive in nature, statistical data could not be provided.

End point values	Clofarabine 30 mg/m²/day	Clofarabine 52 mg/m²/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: percent of coefficient of variation				
geometric mean (geometric coefficient of variation)				
On Day 1 (n=3,4)	221 (± 6.6)	675.4 (± 18.1)		
On Day 5 (n=2,4)	229.7 (± 35.5)	578.8 (± 30.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Time to Maximum Plasma Concentration (Tmax) and Elimination Half-life (t1/2)

End point title	Time to Maximum Plasma Concentration (Tmax) and Elimination Half-life (t1/2)[3]

End point description:

Analysis was carried out on pharmacokinetic (PK) analysis set which included subjects who received at least 1 dose of clofarabine and had measurable drug concentrations. Here 'n' signifies number of subjects with available data for specified category.

End point type	Primary

End point timeframe:

0 hour (Predose) on Day 1-5 of Cycle 1; >0 to 1, 2 (end of infusion), >2.5 to 4, >4.5 to 7, >7.5 to 10 hours after infusion; on Day 1 and Day 5 of Cycle 1

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: Since analysis is descriptive in nature, statistical data could not be provided.

End point values	Clofarabine 30 mg/m²/day	Clofarabine 52 mg/m²/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: percent of coefficient of variation				
geometric mean (geometric coefficient of variation)				
Tmax: On Day 1 (n=3,4)	1.822 (± 1.1)	1.914 (± 5.8)		
Tmax: On Day 5 (n=2,4)	1.925 (± 0.6)	1.974 (± 4.4)		
t1/2: On Day 1 (n=3,4)	5.504 (± 42.1)	3.901 (± 14.6)		
t1/2: On Day 5 (n=2,4)	2.459 (± 2.3)	1.968 (± 10.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Drug-Concentration Curve (AUC)

End point title	Area Under the Drug-Concentration Curve (AUC)[4]

End point description:

Analysis was carried out on pharmacokinetic (PK) analysis set which included subjects who received at least 1 dose of clofarabine and had measurable drug concentrations. Here 'n' signifies number of subjects with available data for specified category.

End point type	Primary

End point timeframe:

0 hour (Predose) on Day 1-5 of Cycle 1; >0 to 1, 2 (end of infusion), >2.5 to 4, >4.5 to 7, >7.5 to 10 hours after infusion; on Day 1 and Day 5 of Cycle 1

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: Since analysis is descriptive in nature, statistical data could not be provided.

End point values	Clofarabine 30 mg/m²/day	Clofarabine 52 mg/m²/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: percent of coefficient of variation				
geometric mean (geometric coefficient of variation)				
AUC0-24 h: On Day 1 (n=3,4)	885.9 (± 29.2)	2325.2 (± 20)		
AUC0-10 h: On Day 5 (n=2,4)	619.1 (± 42.5)	1446.6 (± 17.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Renal Clearance (CLr)

End point title	Renal Clearance (CLr)[5]

End point description:

Analysis was carried out on pharmacokinetic (PK) analysis set which included subjects who received at least 1 dose of clofarabine and had measurable drug concentrations.

End point type	Primary

End point timeframe:

Pre-dose; 0 to 6, >6 to 12, >12 to 24 hours after infusion; on Day 1 of Cycle 1

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Since analysis is descriptive in nature, statistical data could not be provided.

End point values	Clofarabine 30 mg/m²/day	Clofarabine 52 mg/m²/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: percent of coefficient of variation				
geometric mean (geometric coefficient of variation)				

CLr	13.16 (± 73.7)	23.69 (± 30.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Day 45) regardless of seriousness or relationship to investigational product

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that are AEs that developed/worsened during the 'on treatment period' (time from first infusion of study drug up to 45 days after the last infusion of study drug). Analysis was done on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Clofarabine 30 mg/m²/day

Reporting group description:

Clofarabine 30 mg/m²/day from Day 1 to Day 5 in Cycle 1 (14 days). If no subject developed DLT, subjects received 52 mg/m²/day from Cycle 2 up to a total of 6 cycles.

Reporting group title	Clofarabine 52 mg/m²/day

Reporting group description:

Clofarabine 52 mg/m²/day from Day 1 to Day 5 in Cycle 1 (14 days) up to a total of 6 cycles.

Serious adverse events	Clofarabine 30 mg/m²/day	Clofarabine 52 mg/m²/day	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Clofarabine 30 mg/m²/day	Clofarabine 52 mg/m²/day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	4 / 4 (100.00%)	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	3 / 3 (100.00%)	2 / 4 (50.00%)	
occurrences (all)	5	2	
Activated Partial Thromboplastin Time Prolonged			

subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	3 / 3 (100.00%)	2 / 4 (50.00%)	
occurrences (all)	5	2	
Bilirubin Conjugated Increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Platelet Count Decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Liver Function Test Abnormal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Blood Bilirubin Increased			
subjects affected / exposed	1 / 3 (33.33%)	2 / 4 (50.00%)	
occurrences (all)	1	2	
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram Qt Prolonged			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	2	
Haemoglobin Decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Pain			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Cardiac disorders			
Pericardial Effusion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	3 / 3 (100.00%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Anaemia			
subjects affected / exposed	2 / 3 (66.67%)	2 / 4 (50.00%)	
occurrences (all)	2	2	
Neutropenia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Thrombocytopenia			
subjects affected / exposed	2 / 3 (66.67%)	1 / 4 (25.00%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Malaise			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Injection Site Reaction			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Generalised Oedema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Discomfort			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Perianal Erythema			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	3 / 4 (75.00%)	
occurrences (all)	1	5	
Oral Disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	2 / 4 (50.00%)	
occurrences (all)	2	2	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Infections and infestations			
Sinusitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			

Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Hypoalbuminaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Decreased Appetite			
subjects affected / exposed	1 / 3 (33.33%)	3 / 4 (75.00%)	
occurrences (all)	2	3	
Hypokalaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2010	- Addition of exclusion criteria (had any other investigational agent received within 30 days prior to the first dose of the study drug). - Reprint of the description of the pharmacogenetic analysis method.
04 February 2011	- Edit of comment in exclusion criteria (In the case of a false positive of Hepatitis B surface [HBs] antibody, the subjects were eligible only if proved to be negative by for Hepatitis B Virus [HBV] Polymerase Chain Reaction [PCR] methods.) - Prolongation of study period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported