Clinical trial results:
A Phase II, Open-Label Study of Clofarabine in Paediatric Patients with Refractory / Relapsed Acute Lymphoblastic Leukaemia

Summary

EudraCT number	2004-001853-27
Trial protocol	AT IT
Global end of trial date	26 July 2007

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	18 July 2015

Trial information

Trial identification

Sponsor protocol code	BIOV-111

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00930098
WHO universal trial number (UTN)	-
Other trial identifiers	UKCCSG Number: NAG 2003 06

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 January 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 July 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the overall response (OR) rate in paediatric subjects with refractory or relapsed acute lymphoblastic leukaemia (ALL) after 1 or more courses of clofarabine treatment.

Protection of trial subjects:

Pediatric 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 may have been used to minimize distress and discomfort.
Adult subjects: Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.
Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2003
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	France: 29
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	74
EEA total number of subjects	74

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	2
Infants and toddlers (28 days-23 months)	2
Children (2-11 years)	38
Adolescents (12-17 years)	21
Adults (18-64 years)	11
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 30 sites in 5 countries. A total of 74 subjects were enrolled between 1 December 2003 and 5 July 2007.

Pre-assignment

Screening details:

Of 74 enrolled subjects, 71 subjects were treated. 3 subjects were not treated due to death prior to first administration.

Period 1

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

Arms

Arm title	Clofarabine

Arm description:

Clofarabine for 5 consecutive days and repeated every 21±7 days.

Arm type	Experimental
Investigational medicinal product name	Clofarabine
Investigational medicinal product code	
Other name	Clolar, Evoltra, 2-chloro-9-(2.-deoxy-2.-fluoro-ß-D-arabinofuranosyl)-9H-purine-6-amine
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Clofarabine 52 mg/m^2 or 1.7 mg/kg (for subjects under 1 year of age) over 2 hours.

Number of subjects in period 1	Clofarabine
Started	74
Treated	71
Completed	65
Not completed	9
Disease relapse/progression	2
Death prior to first administration	3
Adverse event	2
Investigator decision	1
Treatment not allowed by protocol	1

Baseline characteristics

Reporting groups	
Reporting group title	Clofarabine
Reporting group description:	
Clofarabine for 5 consecutive days and repeated every 21±7 days.	

Reporting group values	Clofarabine	Total	
Number of subjects	74	74	
Age categorical Units: Subjects			
Newborns (0-27 days)	2	2	
Infants and toddlers (28 days-23 months)	2	2	
Children (2-11 years)	38	38	
Adolescents (12-17 years)	21	21	
Adults (18-64 years)	11	11	
Gender categorical Units: Subjects			
Female	26	26	
Male	48	48	

End points

End points reporting groups

Reporting group title	Clofarabine

Reporting group description:

Clofarabine for 5 consecutive days and repeated every 21±7 days.

Primary: Overall Response Rate After 1 Course or More

End point title	Overall Response Rate After 1 Course or More[1]

End point description:

The overall response (OR) rate was defined as the sum of the number of subjects with complete response (CR) or complete response in the absence of total platelet recovery (CRp) with 1 or more courses of clofarabine treatment divided by the total number of subjects with 1 or more courses of clofarabine treatment. Analysis was carried out on one-course efficacy-evaluable (C1EE) population defined as all registered subjects whose diagnosis of ALL and best response was confirmed by independent response review panel (IRRP), who received at least 1 full course (5 consecutive daily infusions) of clofarabine treatment.

End point type	Primary

End point timeframe:

Day 21 up to Day 203

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:
Due to EudraCT format constraint, the statistical analysis could not be provided for single arm study.

End point values	Clofarabine			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: percentage of subjects				
number (confidence interval 95%)	23.1 (13.5 to 35.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate After 2 Courses or More

End point title	Overall Response Rate After 2 Courses or More

End point description:

OR rate was defined as in primary endpoint. Analysis was carried out in two-course efficacy-evaluable (C2EE) population defined as all registered subjects whose diagnosis of ALL and best response was confirmed by IRRP, who received at least 2 full courses (each course consisting of 5 consecutive daily infusions) of clofarabine treatment.

End point type	Secondary

End point timeframe:

Day 37 up to Day 203

End point values	Clofarabine			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: percentage of subjects				
number (confidence interval 95%)	31.3 (16.1 to 50)			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Response After 1 Course or More

End point title	Rate of Response After 1 Course or More

End point description:

Analysis was carried out on C1EE population. In this section, -99999 and 99999 represent data not applicable as only one subject had partial response.

End point type	Secondary

End point timeframe:

Day 21 up to Day 203

End point values	Clofarabine			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: percentage of subjects				
number (confidence interval 95%)				
CR	4.6 (1 to 12.9)			
CRp	18.5 (9.9 to 30)			
Partial Response (PR)	1.5 (-99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-Event Parameters

End point title	Time-to-Event Parameters

End point description:

Time to event parameters included time to response (CR, CRp or PR) duration of remission (response) and survival. Analysis was carried out on C1EE population. In this section, 99999 represents data not applicable for upper limit of 95% CI. In this section, 'n' signifies number of subjects with available data

for specified category.

End point type	Secondary

End point timeframe:

Up to death of subject or end of treatment (Day 203)

End point values	Clofarabine			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: days				
median (confidence interval 95%)				
Time to Response (n=47)	68 (50 to 93)			
Duration of Response (n=16)	108 (43 to 99999)			
Survival Time (n=65)	85 (62 to 120)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Transplant Bone Marrow or Peripheral Blood Stem Cell Following Commencement of Clofarabine

End point title	Time to Transplant Bone Marrow or Peripheral Blood Stem Cell Following Commencement of Clofarabine

End point description:

Analysis was carried out on mITT population defined as all registered subjects with IRRP confirmed diagnosis of ALL who received at least one dose of clofarabine treatment. Here the number of subjects analyzed were those who received bone marrow or peripheral blood stem cell transplantation.

End point type	Secondary

End point timeframe:

Up to death of subject or end of treatment (Day 203)

End point values	Clofarabine			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: days				
median (full range (min-max))	40 (31 to 97)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Clofarabine Concentration

End point title	Plasma Clofarabine Concentration

End point description:

In this section, 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

0 hour (pre-infusion); 2, 24, 26, 48, 50, 72, 74, 96, 98 hours post-infusion on Day 1

End point values	Clofarabine			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: uM				
arithmetic mean (standard deviation)				
0 h (n=28)	0.02 (± 0.04)			
2 h (n=29)	1.75 (± 0.9)			
24 h (n=27)	0.06 (± 0.07)			
26 h (n=28)	2 (± 1.12)			
48 h (n=27)	0.07 (± 0.07)			
50 h (n=27)	2.28 (± 1.4)			
72 h (n=21)	0.06 (± 0.07)			
74 h (n=20)	2.08 (± 0.92)			
96 h (n=16)	0.07 (± 0.11)			
98 h (n=16)	2.25 (± 0.88)			

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 203) regardless of seriousness or relationship to investigational product

Adverse event reporting additional description:

Reported adverse events and deaths are treatment-emergent that is AEs that developed/worsened and deaths that occurred during the 'on treatment period' (time from first infusion of study drug up to 30 days after the last dose of study drug). Safety population included all registered subjects who received at least one infusion of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Clofarabine

Reporting group description:

Clofarabine for 5 consecutive days and repeated every 21±7 days.

Serious adverse events	Clofarabine		
Total subjects affected by serious adverse events			
subjects affected / exposed	59 / 71 (83.10%)		
number of deaths (all causes)	59		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Leukaemia Recurrent			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Malignant Neoplasm Progression			
subjects affected / exposed	13 / 71 (18.31%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 13		
Neoplasm Malignant			

subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Vascular disorders				
Hypertension				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	4 / 71 (5.63%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	1 / 1			
Necrosis				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mucosal Inflammation				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Hypersensitivity				
subjects affected / exposed	3 / 71 (4.23%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Oedema			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatic Enzyme Abnormal			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fibrin D Dimer Increased			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood Amylase Increased			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Alanine Aminotransferase Increased			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pericardial Effusion			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Failure			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			
Convulsion			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Tremor			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	1 / 1		

Leukopenia				
subjects affected / exposed	2 / 71 (2.82%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Febrile Neutropenia				
subjects affected / exposed	34 / 71 (47.89%)			
occurrences causally related to treatment / all	52 / 64			
deaths causally related to treatment / all	1 / 2			
Febrile Bone Marrow Aplasia				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	2 / 71 (2.82%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Haematemesis				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	5 / 71 (7.04%)			
occurrences causally related to treatment / all	4 / 6			
deaths causally related to treatment / all	0 / 0			
Proctitis				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				

subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hyperbilirubinaemia				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Vasculitic Rash				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Palmar-Plantar Erythrodysaesthesia Syndrome				
subjects affected / exposed	4 / 71 (5.63%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal Failure				
subjects affected / exposed	2 / 71 (2.82%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 2			
Renal Failure Acute				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal Impairment				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Back Pain			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain In Extremity			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Bone Pain			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 1		
Infections and infestations			
Escherichia Sepsis			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchopulmonary Aspergillosis			
subjects affected / exposed	4 / 71 (5.63%)		
occurrences causally related to treatment / all	6 / 7		
deaths causally related to treatment / all	1 / 1		
Bacterial Sepsis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Bacteraemia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Aspergillosis				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Fungal Skin Infection				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung Infection				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic Sepsis				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Otitis Media				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes Simplex				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes Zoster				
subjects affected / exposed	2 / 71 (2.82%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				

subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Mycosis				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Streptococcal Sepsis				
subjects affected / exposed	2 / 71 (2.82%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Staphylococcal Infection				
subjects affected / exposed	2 / 71 (2.82%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Staphylococcal Bacteraemia				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Septic Shock				
subjects affected / exposed	2 / 71 (2.82%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Sepsis				
subjects affected / exposed	6 / 71 (8.45%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	1 / 1			
Pneumonia Fungal				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyperglycaemia				

subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic Acidosis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperuricaemia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Clofarabine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 71 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Lysis Syndrome			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Vascular disorders			
Haematoma			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Flushing			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences (all)	7		
Haemorrhage			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	7 / 71 (9.86%)		
occurrences (all)	9		
Peripheral Circulatory Failure			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Pallor			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	10 / 71 (14.08%)		
occurrences (all)	10		
Surgical and medical procedures			
Tooth Extraction			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences (all)	7		
Catheter Site Pain			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Catheter Site Rash			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Chest Pain			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences (all)	6		
Generalised Oedema			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Feeling Abnormal			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	3		
Face Oedema			

subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Crepitations			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	11 / 71 (15.49%)		
occurrences (all)	14		
Pain			
subjects affected / exposed	7 / 71 (9.86%)		
occurrences (all)	7		
Hypothermia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Irritability			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Localised Oedema			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	4		
Malaise			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Mucosal Inflammation			
subjects affected / exposed	12 / 71 (16.90%)		
occurrences (all)	15		
Oedema			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	4		
Oedema Peripheral			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	35 / 71 (49.30%)		
occurrences (all)	72		
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	4 / 71 (5.63%)		
occurrences (all)	4		
Reproductive system and breast disorders			
Vaginal Discharge			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bradypnoea			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	13 / 71 (18.31%)		
occurrences (all)	18		
Dyspnoea			
subjects affected / exposed	4 / 71 (5.63%)		
occurrences (all)	4		
Pulmonary Oedema			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	2		
Hypoxia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	2		
Pharyngolaryngeal Pain			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences (all)	7		
Pleuritic Pain			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	10 / 71 (14.08%)		
occurrences (all)	13		
Respiratory Distress			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Wheezing			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Psychiatric disorders			
Agitation			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Anxiety			
subjects affected / exposed	7 / 71 (9.86%)		
occurrences (all)	7		
Confusional State			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Depressed Mood			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Personality Change			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	2		
Emotional Distress			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Mood Altered			
subjects affected / exposed	7 / 71 (9.86%)		
occurrences (all)	11		
Depression			
subjects affected / exposed	6 / 71 (8.45%)		
occurrences (all)	7		
Psychotic Disorder			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Investigations			
Alanine Aminotransferase			

subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Alanine Aminotransferase Increased				
subjects affected / exposed	5 / 71 (7.04%)			
occurrences (all)	10			
Aspartate Aminotransferase Increased				
subjects affected / exposed	4 / 71 (5.63%)			
occurrences (all)	12			
Blood Alkaline Phosphatase Increased				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	2			
Blood Amylase				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Blood Bilirubin Increased				
subjects affected / exposed	2 / 71 (2.82%)			
occurrences (all)	2			
Blood Creatinine Increased				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Blood Magnesium Decreased				
subjects affected / exposed	2 / 71 (2.82%)			
occurrences (all)	4			
Blood Potassium Decreased				
subjects affected / exposed	2 / 71 (2.82%)			
occurrences (all)	5			
Blood Urine Present				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Body Temperature Increased				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Haemoglobin				

subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Haemoglobin Decreased			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	4		
Weight Increased			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Oxygen Consumption			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Platelet Count Decreased			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences (all)	6		
Weight Decreased			
subjects affected / exposed	6 / 71 (8.45%)		
occurrences (all)	7		
Neutrophil Count			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
White Blood Cell Count Decreased			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Procedural Pain			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Post Procedural Haemorrhage			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	3		
Periorbital Haematoma			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Chemical Eye Injury			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Left Ventricular Dysfunction			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	2		
Bradycardia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Arrhythmia Supraventricular			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Sinus Arrhythmia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences (all)	5		
Nervous system disorders			
Headache			
subjects affected / exposed	38 / 71 (53.52%)		
occurrences (all)	71		
Ataxia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Convulsion			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Hyperaesthesia			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Lethargy			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Trigeminal Nerve Disorder			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	2		
Peripheral Sensory Neuropathy			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Sinus Headache			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	3		
Speech Disorder			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 71 (5.63%)		
occurrences (all)	4		
Febrile Bone Marrow Aplasia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Febrile Neutropenia			
subjects affected / exposed	11 / 71 (15.49%)		
occurrences (all)	17		
Leukopenia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		

Neutropenia			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	4		
Pancytopenia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	4 / 71 (5.63%)		
occurrences (all)	4		
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	4 / 71 (5.63%)		
occurrences (all)	4		
Ear Haemorrhage			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Hearing Impaired			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	2		
Hypoacusis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Eye disorders			
Abnormal Sensation In Eye			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Conjunctival Haemorrhage			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Eye Oedema			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	2		
Diplopia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Conjunctivitis			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Eye Swelling			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Photophobia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Eyelid Oedema			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	3		
Abdominal Pain			
subjects affected / exposed	26 / 71 (36.62%)		
occurrences (all)	37		
Abdominal Distension			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Anal Fissure			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	3		
Anorectal Disorder			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Anal Haemorrhage			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	25 / 71 (35.21%)		
occurrences (all)	40		
Constipation			
subjects affected / exposed	10 / 71 (14.08%)		
occurrences (all)	12		

Colitis				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Dry Mouth				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Gastrointestinal Pain				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Dysphagia				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Gastrointestinal Haemorrhage				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	2			
Gastrointestinal Oedema				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Dyspepsia				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Pancreatitis				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	37 / 71 (52.11%)			
occurrences (all)	66			
Lip Swelling				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Proctalgia				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Vomiting				
subjects affected / exposed	52 / 71 (73.24%)			
occurrences (all)	100			

Toothache			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Hepatobiliary disorders			
Cytolytic Hepatitis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	6		
Hepatotoxicity			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Hepatomegaly			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	2		
Ecchymosis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Erythema Multiforme			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Exfoliative Rash			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Generalised Erythema			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Erythema			

subjects affected / exposed	4 / 71 (5.63%)			
occurrences (all)	4			
Melanodermia				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Nail Disorder				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Night Sweats				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Palmar-Plantar Erythrodysaesthesia Syndrome				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Rash Macular				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Petechiae				
subjects affected / exposed	4 / 71 (5.63%)			
occurrences (all)	4			
Pruritus				
subjects affected / exposed	20 / 71 (28.17%)			
occurrences (all)	28			
Rash				
subjects affected / exposed	27 / 71 (38.03%)			
occurrences (all)	37			
Periorbital Oedema				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Rash Maculo-Papular				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Rash Pruritic				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			

Skin Exfoliation			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	3		
Skin Lesion			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Renal and urinary disorders			
Haemorrhage Urinary Tract			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Pollakiuria			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Urinary Tract Inflammation			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Urinary Bladder Haemorrhage			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Urinary Retention			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Renal Impairment			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences (all)	7		
Back Pain			
subjects affected / exposed	8 / 71 (11.27%)		
occurrences (all)	10		
Bone Pain			

subjects affected / exposed	9 / 71 (12.68%)		
occurrences (all)	11		
Musculoskeletal Pain			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences (all)	16		
Muscle Spasms			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Muscular Weakness			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Lower Extremity Mass			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Musculoskeletal Stiffness			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Neck Pain			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Pain In Extremity			
subjects affected / exposed	17 / 71 (23.94%)		
occurrences (all)	22		
Infections and infestations			
Central Line Infection			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	4		
Cellulitis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Catheter Related Infection			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		

Abscess				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Herpes Zoster				
subjects affected / exposed	3 / 71 (4.23%)			
occurrences (all)	5			
Herpes Simplex				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Gastrointestinal Candidiasis				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Enterococcal Infection				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Cystitis				
subjects affected / exposed	2 / 71 (2.82%)			
occurrences (all)	2			
Infection				
subjects affected / exposed	2 / 71 (2.82%)			
occurrences (all)	2			
Nasopharyngitis				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Staphylococcal Infection				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Skin Infection				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Sepsis				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			
Respiratory Tract Infection Viral				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences (all)	1			

Pyelonephritis subjects affected / exposed occurrences (all)	 1 / 71 (1.41%) 1			
Otitis Media subjects affected / exposed occurrences (all)	 1 / 71 (1.41%) 1			
Oral Herpes subjects affected / exposed occurrences (all)	 2 / 71 (2.82%) 2			
Urinary Tract Infection subjects affected / exposed occurrences (all)	 1 / 71 (1.41%) 2			
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	 1 / 71 (1.41%) 1			
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	 11 / 71 (15.49%) 12			
Decreased Appetite subjects affected / exposed occurrences (all)	 1 / 71 (1.41%) 1			
Dehydration subjects affected / exposed occurrences (all)	 1 / 71 (1.41%) 1			
Hyponatraemia subjects affected / exposed occurrences (all)	 2 / 71 (2.82%) 2			
Hypoalbuminaemia subjects affected / exposed occurrences (all)	 1 / 71 (1.41%) 2			
Hypokalaemia subjects affected / exposed occurrences (all)	 3 / 71 (4.23%) 4			
Hypomagnesaemia				

subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Hypernatraemia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2003	- The criterion for evaluability was changed from having received a minimum of 4 courses to having received a minimum of 2 courses. - The following secondary endpoint was added: Bone marrow transplant (BMT)/ peripheral blood stem cell transplant (PBSCT) rate was to be determined by dividing the number of subjects receiving BMT/PBSCT by the total number of subjects evaluable for response. - The following was added to the preamble to the inclusion criteria: The trial would recruit subjects who had failed to achieve remission by standard first line therapy or following first relapse, failed to achieve remission by standard relapse therapy. Subjects with multiple relapses would be eligible provided their prior salvage therapy did not include BMT or PBSCT. - Following Inclusion criterion was removed: National and local ethical approval for the protocol. - The criterion for subject discontinuation was changed from "lead investigator's discretion" to "investigator's discretion". - It was specified that off-study (end of study) assessments were to be performed within 14 days of the last dose of clofarabine. No time-frame had been specified in version 1 of the protocol. - A definition of "end of study" for analysis purposes was added, being the completion of course 4 of clofarabine treatment, including the bone marrow aspirate (BMA) taken at the end of course 4 to assess disease status and response to clofarabine treatments. - The confidence interval for characterising the overall response (OR) was changed from 99% to 95%.
28 October 2003	- The lead Clinical Research Organization (Tessman Technology Limited) was removed. - The preamble to the inclusion criteria was amended to specify that: Children who had received an allogeneic progenitor cell transplant must be at least 6 months post-transplant. - Following inclusion criterion was amended to: Subjects with 2 or more relapses of acute lymphoblastic leukaemia (ALL) Children who had received an allogeneic progenitor cell transplant, must be a. At least 6-months post transplant b. Had good organ function c. Stable with no major complications. - The requirement that subjects' prior salvage therapy did not include BMT or PBSCT was deleted from inclusion criterion. - Exclusion criterion was amended to allow the inclusion of subjects with prior BMT or PBSCT provided this happened more than 6 months previously. As a result, a new exclusion criterion was added, with all subsequent criteria being renumbered, to exclude subjects with prior BMT or PBSCT and poor organ function.

08 March 2005	- Overall remission, complete remission, partial remission, etc were changed to OR, etc. However the term "duration of remission" was not changed. - Secondary objective "To document an OR rate of ≥ 20% in children with refractory or relapsed ALL" was removed. - The following new secondary objective was inserted with all subsequent secondary objectives being renumbered; the modified overall response (MOR) rate was also defined as a secondary endpoint. To document the MOR rate in paediatric subjects with refractory or relapsed ALL. The MOR rate was defined as the sum of the number of subjects with either complete response (CR), complete response in the absence of platelet recovery (CRp) or partial response (PR) divided by the total number of subjects evaluable for response. - The option to reduce the dose in the event of "significant haematological toxicity" was introduced. - Exclusion criterion was amended to read: Had an active or uncontrolled systemic infection considered opportunistic, life threatening, or clinically significant at the time of treatment. Subjects who had a recent (< 30 days) history of fungal or bacterial infection or who were receiving therapeutic doses of antibiotics or antifungals. - A new exclusion criterion was introduced: Had recent history of significant renal, hepatic or pulmonary dysfunction, or cardiac dysfunction, or on treatment to support cardiac function. - A new criterion for subject discontinuation was introduced: No MOR after 4 courses of clofarabine treatment. - Metabolism studies (urine sampling) were added for the subset of subjects that consented to these investigations. - The definition of serious adverse events (SAEs) was changed to include "any medically important event" and all National Cancer Institute common toxicity criteria (NCI-CTC) grade 4 events. - Information on capillary leak syndrome and instructions to the investigators in the event of such a case occurring were added.
30 November 2006	- The primary objective was amended to determine OR only in subjects that had completed at least one full course of clofarabine treatment. -Determination of OR after 2 or more courses, which was the primary objective in the previous versions, was changed to secondary objective. - Secondary endpoint was amended to: The OR rate after 2 courses or more will be determined by the sum of the number of subjects with either a CR or CRp with 2 courses or more of clofarabine divided by the total number of subjects who received 2 courses or more of clofarabine. - The inclusion of subjects without primary refractory disease was permitted if they had relapsed or refractory disease after a minimum of 2 prior blocks of treatment.- Inclusion criterion was reworded to include definitions of adequate cardiac function. - The definition of adequate hepatic function for inclusion were amended to specify AST and ALT of ≤ 5 x ULN. - Reasons for discontinuation were amended to remove the option for discontinuation at the investigator's discretion, and to remove the exclusion from discontinuation due to non-haematological toxicities for elevated liver function tests.- Dosage, Administration, and Storage section was amended to state that the diluted clofarabine was to be used immediately or that if not used immediately, would normally not exceed 24 hours at 2 to 8°C unless reconstitution/dilution (etc) had taken place in controlled and validated aseptic conditions.- Repetition of clofarabine courses was to be at 21 ± 7 day intervals, and that subjects were to receive a minimum of 1 course and a maximum of 12 courses.- Criteria for dose reduction in subjects experiencing haematological toxicities were introduced.- The requirement for absolute neutrophil count (ANC) recovery to 0.75 × 10 9 /L for the third and subsequent courses of treatment was removed.- Criteria for bone marrow or blood sampling for molecular pharmacology studies were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported