Clinical trial results:
An Open-Label, Multi-Center Safety and Tolerability Pilot Combination Study of Clofarabine, Etoposide, Cyclophosphamide, PEG-asparaginase, and Vincristine in Pediatric Patients with Acute Lymphoblastic Leukemia (ALL) in First Relapse

Summary

EudraCT number	2015-001173-41
Trial protocol	Outside EU/EEA
Global end of trial date	26 April 2011

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	CLO08808

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00991133
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	26 April 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 April 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the safety of 1 cycle of the 5-drug regimen in pediatric subjects with acute lymphoblastic leukemia (ALL) who were in first bone marrow relapse.

Protection of trial 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.
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.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	08 January 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	8
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)	4
Adolescents (12-17 years)	2
Adults (18-64 years)	2
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 6 centers in United States of America. A total of 8 subjects were screened between 08 January 2010 and 10 November 2010.

Pre-assignment

Screening details:

All 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

Arm title	Overall Population

Arm description:

Subjects received 5 drug regimen: clofarabine, etoposide, cyclophosphamide (Days 1-5), PEG-asparaginase (Day 15) and vincristine (Days 15-22) in each 28 day cycle for maximum 2 cycles. Subjects who achieved complete remission (CR) or complete remission with incomplete platelet recovery (CRp) after 1 cycle of study drugs were eligible to receive a second cycle of study drugs upon recovery of peripheral blood counts, and subjects who did not have leukemic progression were eligible to receive a second treatment cycle at the investigator's discretion.

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

Dosage and administration details:

40 mg/m²

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	VP-16
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

100 mg/m²

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	Cytoxan
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

440 mg/m²

Investigational medicinal product name	PEG-asparaginase
Investigational medicinal product code	
Other name	PEGaspar-aginase
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details: 2500 IU/m²	
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	Oncovin
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1.5 mg/m² (maximum dose 2 mg)

Number of subjects in period 1	Overall Population
Started	8
Completed	0
Not completed	8
Consent withdrawn by subject	2
Sponsor or Investigator decision	2
Adverse event or treatment toxicity	2
Subject scheduled to receive transplant or therapy	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall Population

Reporting group description:

Subjects received 5 drug regimen: clofarabine, etoposide, cyclophosphamide (Days 1-5), PEG-asparaginase (Day 15) and vincristine (Days 15-22) in each 28 day cycle for maximum 2 cycles. Subjects who achieved complete remission (CR) or complete remission with incomplete platelet recovery (CRp) after 1 cycle of study drugs were eligible to receive a second cycle of study drugs upon recovery of peripheral blood counts, and subjects who did not have leukemic progression were eligible to receive a second treatment cycle at the investigator's discretion.

Reporting group values	Overall Population	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
Children (2-11 years)	4	4	
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	2	2	
Gender categorical Units: Subjects			
Female	6	6	
Male	2	2	

End points

End points reporting groups

Reporting group title	Overall Population

Reporting group description:

Subjects received 5 drug regimen: clofarabine, etoposide, cyclophosphamide (Days 1-5), PEG-asparaginase (Day 15) and vincristine (Days 15-22) in each 28 day cycle for maximum 2 cycles. Subjects who achieved complete remission (CR) or complete remission with incomplete platelet recovery (CRp) after 1 cycle of study drugs were eligible to receive a second cycle of study drugs upon recovery of peripheral blood counts, and subjects who did not have leukemic progression were eligible to receive a second treatment cycle at the investigator's discretion.

Primary: Number of Subjects Who Experienced Dose Limiting Toxicity

End point title	Number of Subjects Who Experienced Dose Limiting Toxicity[1]

End point description:

All enrolled subjects were analysed.

End point type	Primary

End point timeframe:

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: No statistical analysis was performed as the analysis was descriptive.

End point values	Overall Population			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: subjects	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Complete Remission (CR)

End point title	Number of Subjects with Complete Remission (CR)

End point description:

All enrolled subjects were analysed.

End point type	Secondary

End point timeframe:

Cycle 1

End point values	Overall Population			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: subjects	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Remission and Duration of Remission

End point title	Time to Remission and Duration of Remission

End point description:

Time to remission was defined as time from date of first administration of study drugs until date of first objective documentation of CR. Analysis was performed on subjects who achieved CR.

End point type	Secondary

End point timeframe:

Baseline up to first objective documentation of CR

End point values	Overall Population			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: weeks				
number (not applicable)				

Notes:

[2] - No summary analyses performed. No efficacy conclusion could be drawn due to small number of subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival (DFS)

End point title	Disease-Free Survival (DFS)

End point description:

DFS was defined as time from date of first objective documentation of CR until the earlier of date of objective documentation of disease relapse or date of death due to any cause, regardless of intervening alternative anti-leukemic therapy (including hematopoietic stem cell transplant).
Analysis was performed on subjects who achieved CR.

End point type	Secondary

End point timeframe:

First objective documentation of CR until the earlier of date of objective documentation of disease relapse or date of death due to any cause

End point values	Overall Population			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: weeks				
number (not applicable)				

Notes:

[3] - No summary analyses performed. No efficacy conclusion could be drawn due to small number of subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS)

End point title	Event-Free Survival (EFS)

End point description:

EFS was defined as time from date of first administration of study drugs until the earliest date of death due to any cause, occurrence of a treatment-related secondary neoplasm, first response assessment confirming relapse (for subjects who achieved CR); or final response assessment that failed to confirm response (CR). All enrolled subjects were analysed

End point type	Secondary

End point timeframe:

Baseline up to death due to any cause, treatment-related secondary neoplasm, first response assessment confirming relapse (for subjects who achieved CR); or final response assessment that failed to confirm response, whichever occurred first

End point values	Overall Population			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: weeks				
number (not applicable)				

Notes:

[4] - No summary analyses performed. No efficacy conclusion could be drawn due to small number of subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who achieved 4-Months EFS

End point title	Number of subjects who achieved 4-Months EFS

End point description:

Four-month events free survival: Duration of EFS was at least 4 months post initial administration of the 5-drug regimen. All enrolled subjects were analysed.

End point type	Secondary

End point timeframe:

Baseline up to 4 months

End point values	Overall Population			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: subjects	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Time from date of first administration of study drugs until date of death due to any cause. All enrolled subjects were analysed.

End point type	Secondary

End point timeframe:

Baseline up to death due to any cause

End point values	Overall Population			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: weeks				
number (not applicable)				

Notes:

[5] - No summary analyses performed. No efficacy conclusion could be drawn due to small number of subjects

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 (cycle 1) 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 during the 'on treatment period' (from the first dose study drugs up to last dose of study drug).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Overall Population

Reporting group description:

Subjects received 5 drug regimen: clofarabine, etoposide, cyclophosphamide (Days 1-5), PEG-asparaginase (Day 15) and vincristine (Days 15-22) in each 28 day cycle for maximum 2 cycles. Subjects who achieved complete remission (CR) or complete remission with incomplete platelet recovery (CRp) after 1 cycle of study drugs were eligible to receive a second cycle of study drugs upon recovery of peripheral blood counts, and subjects who did not have leukemic progression were eligible to receive a second treatment cycle at the investigator's discretion.

Serious adverse events	Overall Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
Investigations			
Blood Bilirubin Increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lipase Increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombosis			

subjects affected / exposed	1 / 8 (12.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac Failure Congestive				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Leukoencephalopathy				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Bone Marrow Failure				
subjects affected / exposed	2 / 8 (25.00%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Febrile Neutropenia				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute Respiratory Distress Syndrome				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				

subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Fungal Skin Infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Enterococcal Bacteraemia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia Respiratory Syncytial Viral			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia Fungal			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Tumour Pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Haematoma			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Thrombosis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Poor Peripheral Circulation			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
General disorders and administration site conditions			
Generalised Oedema			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Chills			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Chest Pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	5		
Mucosal Inflammation			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Pyrexia			

subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	4		
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Ovarian Cyst			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vulvovaginal Pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Haemoptysis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Pleural Effusion			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Tachypnoea			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Anxiety			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Confusional State			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Disorientation			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Aspartate Aminotransferase Increased			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood Creatinine Increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood Bilirubin Increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood Amylase Increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	3		
Blood Triglycerides Increased			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Enterococcus Test Positive			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Gallop Rhythm Present			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Mycobacterium Test Positive			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Specific Gravity Urine Abnormal			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Lipase Increased			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Weight Increased			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Allergic Transfusion Reaction			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Transfusion Reaction			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Pericardial Haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	4		
Dizziness			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Neuropathy Peripheral			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 8 (87.50%)		
occurrences (all)	17		
Leukopenia			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	4		
Febrile Neutropenia			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	5		
Lymphopenia			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Pancytopenia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	4		
Splenic Necrosis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	6 / 8 (75.00%)		
occurrences (all)	9		
Ear and labyrinth disorders			
Ear Pain			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Eye disorders			
Ocular Hyperaemia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Diplopia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vitreous Floaters			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Photophobia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	6 / 8 (75.00%)		
occurrences (all)	7		
Chapped Lips			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Anal Erosion			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Abdominal Pain Upper			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	5		
Gastrointestinal Haemorrhage			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	8 / 8 (100.00%)		
occurrences (all)	10		
Pancreatitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Gingival Bleeding			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Rectal Fissure			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Proctalgia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	7 / 8 (87.50%)		
occurrences (all)	10		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	3		
Hepatomegaly			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Drug Eruption			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Alopecia			

subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Blister			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	7		
Palmar Erythema			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Dry Skin			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Night Sweats			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Pruritus Generalised			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Rash Generalised			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Purpura			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	6		
Skin Exfoliation			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Haematuria subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Dysuria subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Haemoglobinuria subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Pollakiuria subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Proteinuria subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 4		
Musculoskeletal and connective tissue disorders			
Back Pain subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 3		
Arthralgia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Musculoskeletal Pain subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 3		
Pain In Extremity subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Infections and infestations			
Bk Virus Infection subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Endocarditis subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Cystitis			

subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Sinusitis subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Psoas Abscess subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Urinary Tract Infection Bacterial subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Metabolism and nutrition disorders Hyperamylasaemia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 2		
Decreased Appetite subjects affected / exposed occurrences (all)	7 / 8 (87.50%) 9		
Hyperuricaemia subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Hyperglycaemia subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 5		
Hypocalcaemia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 5		
Hypomagnesaemia subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		

Hypokalaemia subjects affected / exposed occurrences (all)	4 / 8 (50.00%) 5		
Hyponatraemia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Hypophosphataemia subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 July 2010	Seven subjects were enrolled under the original protocol, and 1 subject was enrolled under the amended protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported