Clinical trial results:
Phase II two stage dose finding run-in study of SAR3419, an anti-CD19 antibody-maytansine conjugate, administered as a single agent by intravenous infusion in patients with relapsed or Refractory Acute Lymphoblastic Leukemia

Summary

EudraCT number	2012-002961-36
Trial protocol	FR
Global end of trial date	23 May 2014

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	19 July 2015

Trial information

Trial identification

Sponsor protocol code	EFC11603

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01440179
WHO universal trial number (UTN)	U1111-1118-0642

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin , France, 91380
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	24 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 May 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To define the recommended dose of SAR3419 in acute lymphoblastic leukemia (ALL) subjects and to evaluate the efficacy of SAR3419 in subjects with relapsed or refractory ALL as measured by objective response rate (ORR), at this recommended dose.

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.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	10 October 2011
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: 11
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	36
EEA total number of subjects	11

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	27
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 2 countries. A total of 45 subjects were screened between 10 October 2011 to 31 January 2014.

Pre-assignment

Screening details:

Of 45 screened subjects, 8 subjects were screen failure and 1 subject did not get any treatment. Hence, 36 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	SAR3419 55 mg/m²

Arm description:

SAR3419 55 mg/m² once weekly for up to 2 induction cycles (1 cycle= 4 weekly dose). If subject achieved objective response in any cycle, SAR3419 was to be given every other week for up to a total 6 maintenance cycles (1 maintenance cycle = 2 biweekly doses).

Arm type	Experimental
Investigational medicinal product name	Coltuximab Ravtansine
Investigational medicinal product code	SAR3419
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

55 mg/m²

Arm title	SAR3419 70 mg/m²

Arm description:

SAR3419 70 mg/m² once weekly for up to 2 induction cycles (1 cycle= 4 weekly dose). If subject achieved objective response in any cycle, SAR3419 was to be given every other week for up to a total 6 maintenance cycles (1 maintenance cycle = 2 biweekly doses).

Arm type	Experimental
Investigational medicinal product name	Coltuximab Ravtansine
Investigational medicinal product code	SAR3419
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

70 mg/m²

Arm title	SAR3419 90 mg/m²

Arm description:

SAR3419 90 mg/m² once weekly for up to 2 induction cycles (1 cycle= 4 weekly dose). If subject achieved objective response in any cycle, SAR3419 was to be given every other week for up to a total 6 maintenance cycles (1 maintenance cycle = 2 biweekly doses).

Arm type	Experimental

Investigational medicinal product name	Coltuximab Ravtansine
Investigational medicinal product code	SAR3419
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

90 mg/m²

Number of subjects in period 1	SAR3419 55 mg/m²	SAR3419 70 mg/m²	SAR3419 90 mg/m²
Started	9	19	8
Completed	0	0	0
Not completed	9	19	8
Disease progression	7	15	1
No response	-	1	5
Adverse event	1	2	2
Unspecified	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	SAR3419 55 mg/m²
Reporting group description:	
SAR3419 55 mg/m² once weekly for up to 2 induction cycles (1 cycle= 4 weekly dose). If subject achieved objective response in any cycle, SAR3419 was to be given every other week for up to a total 6 maintenance cycles (1 maintenance cycle = 2 biweekly doses).	
Reporting group title	SAR3419 70 mg/m²
Reporting group description:	
SAR3419 70 mg/m² once weekly for up to 2 induction cycles (1 cycle= 4 weekly dose). If subject achieved objective response in any cycle, SAR3419 was to be given every other week for up to a total 6 maintenance cycles (1 maintenance cycle = 2 biweekly doses).	
Reporting group title	SAR3419 90 mg/m²
Reporting group description:	
SAR3419 90 mg/m² once weekly for up to 2 induction cycles (1 cycle= 4 weekly dose). If subject achieved objective response in any cycle, SAR3419 was to be given every other week for up to a total 6 maintenance cycles (1 maintenance cycle = 2 biweekly doses).	

Reporting group values	SAR3419 55 mg/m²	SAR3419 70 mg/m²	SAR3419 90 mg/m²
Number of subjects	9	19	8
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 51.1 ± 17.1	 41.6 ± 17.5	 57 ± 24.4
Gender categorical Units: Subjects			
Female	4	7	3
Male	5	12	5

Reporting group values	Total		
Number of subjects	36		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female	14		
Male	22		

End points

End points reporting groups

Reporting group title	SAR3419 55 mg/m²

Reporting group description:

SAR3419 55 mg/m² once weekly for up to 2 induction cycles (1 cycle= 4 weekly dose). If subject achieved objective response in any cycle, SAR3419 was to be given every other week for up to a total 6 maintenance cycles (1 maintenance cycle = 2 biweekly doses).

Reporting group title	SAR3419 70 mg/m²

Reporting group description:

SAR3419 70 mg/m² once weekly for up to 2 induction cycles (1 cycle= 4 weekly dose). If subject achieved objective response in any cycle, SAR3419 was to be given every other week for up to a total 6 maintenance cycles (1 maintenance cycle = 2 biweekly doses).

Reporting group title	SAR3419 90 mg/m²

Reporting group description:

SAR3419 90 mg/m² once weekly for up to 2 induction cycles (1 cycle= 4 weekly dose). If subject achieved objective response in any cycle, SAR3419 was to be given every other week for up to a total 6 maintenance cycles (1 maintenance cycle = 2 biweekly doses).

Primary: Number of Subjects Achieving an Objective Response Rate (ORR)

End point title	Number of Subjects Achieving an Objective Response Rate (ORR)[1]

End point description:

ORR included complete remission (CR), complete response without recovery of counts (CRi) and partial remission (PR). CR defined as normalization of marrow and blood with marrow blasts <=5%, neutrophil count >1.0*10 ^9/L, platelet count >100*10^9/L. CRi defined as normalization of marrow and blood with marrow blasts <=5%, neutrophil count >1.0*10^9/L with incomplete recover of counts (platelets <100*10^9/L and/or neutrophils <1*10^9/L). PR defined peripheral blood count recovery as for CR or CRi, but with decrease in marrow blasts of >50% and not more than 25% abnormal cells in the marrow. Analysis was performed on per protocol (PP) population included all treated subjects.

End point type	Primary

End point timeframe:

Up to 8 weeks

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: Only descriptive analysis was performed for this outcome due to premature termination of the study.

End point values	SAR3419 55 mg/m²	SAR3419 70 mg/m²	SAR3419 90 mg/m²	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	17	7	
Units: subjects				
CR	2	1	0	
CRi	0	2	0	
PR	1	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameters: Plasma Levels of SAR3419 and Free Maytansinoids (DM4)

End point title	Pharmacokinetic Parameters: Plasma Levels of SAR3419 and Free Maytansinoids (DM4)

End point description:

End point type	Secondary

End point timeframe:

Up to 8 months

End point values	SAR3419 55 mg/m²	SAR3419 70 mg/m²	SAR3419 90 mg/m²	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: subjects				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[2] - No pharmacokinetic analysis was performed due to premature termination of the study.

[3] - No pharmacokinetic analysis was performed due to premature termination of the study.

[4] - No pharmacokinetic analysis was performed due to premature termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Minimal Residual Disease (MRD)

End point title	Assessment of Minimal Residual Disease (MRD)

End point description:

End point type	Secondary

End point timeframe:

Up to 8 weeks

End point values	SAR3419 55 mg/m²	SAR3419 70 mg/m²	SAR3419 90 mg/m²	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[5]	0[6]	0[7]	
Units: subjects				

Notes:

[5] - Analysis was not performed due to premature termination of the study.

[6] - Analysis was not performed due to premature termination of the study.

[7] - Analysis was not performed due to premature termination of the study.

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 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' (42 days after the last dose).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	SAR3419 55 mg/m²

Reporting group description:

SAR3419 55 mg/m² once weekly for up to 2 induction cycles (1 cycle= 4 weekly dose). If subject achieved objective response in any cycle, SAR3419 was to be given every other week for up to a total 6 maintenance cycles (1 maintenance cycle = 2 biweekly doses).

Reporting group title	SAR3419 70 mg/m²

Reporting group description:

SAR3419 70 mg/m² once in a week for 2 induction cycle (1 induction cycle = 4 weekly doses). Subjects who achieved response, SAR3419 for up to a total maintenance treatment of 6 cycles (1 maintenance cycle = 2 biweekly doses).

Reporting group title	SAR3419 90 mg/m²

Reporting group description:

SAR3419 90 mg/m² once weekly for up to 2 induction cycles (1 cycle= 4 weekly dose). If subject achieved objective response in any cycle, SAR3419 was to be given every other week for up to a total 6 maintenance cycles (1 maintenance cycle = 2 biweekly doses).

Serious adverse events	SAR3419 55 mg/m²	SAR3419 70 mg/m²	SAR3419 90 mg/m²
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 9 (22.22%)	14 / 19 (73.68%)	7 / 8 (87.50%)
number of deaths (all causes)	1	4	4
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemic Infiltration Brain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease Progression			

subjects affected / exposed	1 / 9 (11.11%)	2 / 19 (10.53%)	2 / 8 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 2
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic Shock			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug Hypersensitivity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Interstitial Lung Disease			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Infusion Related Reaction			
subjects affected / exposed	2 / 9 (22.22%)	0 / 19 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Supraventricular Tachycardia			

subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Motor Neuropathy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Disseminated Intravascular Coagulation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile Neutropenia			
subjects affected / exposed	0 / 9 (0.00%)	4 / 19 (21.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatobiliary disorders			
Acute Hepatic Failure			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone Pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 19 (10.53%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Bronchopulmonary Aspergillosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral Aspergillosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Enterococcal Sepsis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia Bacteraemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 19 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar Pneumonia			

subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 19 (10.53%)	2 / 8 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pseudomonal Sepsis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Septic Shock			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary Tract Infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection Enterococcal			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure To Thrive			

subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	SAR3419 55 mg/m²	SAR3419 70 mg/m²	SAR3419 90 mg/m²
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	18 / 19 (94.74%)	8 / 8 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemic Infiltration Brain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Neoplasm Skin			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)	2 / 19 (10.53%)	1 / 8 (12.50%)
occurrences (all)	1	2	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
Catheter Site Inflammation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Chills			
subjects affected / exposed	1 / 9 (11.11%)	3 / 19 (15.79%)	0 / 8 (0.00%)
occurrences (all)	1	3	0
Fatigue			

subjects affected / exposed	1 / 9 (11.11%)	3 / 19 (15.79%)	4 / 8 (50.00%)
occurrences (all)	1	3	4
Injection Site Reaction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 9 (0.00%)	2 / 19 (10.53%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Oedema Peripheral			
subjects affected / exposed	0 / 9 (0.00%)	3 / 19 (15.79%)	3 / 8 (37.50%)
occurrences (all)	0	3	3
Pain			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Puncture Site Pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	4 / 9 (44.44%)	3 / 19 (15.79%)	1 / 8 (12.50%)
occurrences (all)	4	3	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Vaginal Haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 9 (0.00%)	3 / 19 (15.79%)	1 / 8 (12.50%)
occurrences (all)	0	3	1
Dyspnoea			

subjects affected / exposed	0 / 9 (0.00%)	5 / 19 (26.32%)	0 / 8 (0.00%)
occurrences (all)	0	5	0
Epistaxis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Hiccups			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Lung Disorder			
subjects affected / exposed	1 / 9 (11.11%)	0 / 19 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Pulmonary Oedema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Sinus Congestion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Depression			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Insomnia			
subjects affected / exposed	1 / 9 (11.11%)	2 / 19 (10.53%)	2 / 8 (25.00%)
occurrences (all)	1	2	2
Mental Status Changes			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	2 / 8 (25.00%)
occurrences (all)	0	1	2

Nervousness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 19 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Breath Sounds Abnormal			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Weight Decreased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 19 (10.53%)	2 / 8 (25.00%)
occurrences (all)	0	2	2
Injury, poisoning and procedural complications			
Infusion Related Reaction			
subjects affected / exposed	0 / 9 (0.00%)	4 / 19 (21.05%)	1 / 8 (12.50%)
occurrences (all)	0	4	1
Cardiac disorders			
Sinus Tachycardia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 19 (10.53%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 9 (22.22%)	1 / 19 (5.26%)	1 / 8 (12.50%)
occurrences (all)	2	1	1
Dysarthria			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 9 (11.11%)	4 / 19 (21.05%)	1 / 8 (12.50%)
occurrences (all)	1	4	1
Hypoaesthesia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Lethargy			

subjects affected / exposed	1 / 9 (11.11%)	0 / 19 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Restless Legs Syndrome			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	1 / 9 (11.11%)	0 / 19 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Dry Eye			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Eye Irritation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Keratitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Lacrimation Increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Vision Blurred			
subjects affected / exposed	1 / 9 (11.11%)	4 / 19 (21.05%)	0 / 8 (0.00%)
occurrences (all)	1	4	0
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Abdominal Distension			

subjects affected / exposed	1 / 9 (11.11%)	0 / 19 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 9 (0.00%)	2 / 19 (10.53%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Diarrhoea			
subjects affected / exposed	2 / 9 (22.22%)	5 / 19 (26.32%)	1 / 8 (12.50%)
occurrences (all)	2	5	1
Dry Mouth			
subjects affected / exposed	0 / 9 (0.00%)	2 / 19 (10.53%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Impaired Gastric Emptying			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 9 (22.22%)	6 / 19 (31.58%)	0 / 8 (0.00%)
occurrences (all)	2	6	0
Stomatitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	2 / 9 (22.22%)	3 / 19 (15.79%)	1 / 8 (12.50%)
occurrences (all)	2	3	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Petechiae			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 8 (12.50%)
occurrences (all)	0	1	1

Pruritus			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	1 / 9 (11.11%)	0 / 19 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Rash Erythematous			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 9 (11.11%)	2 / 19 (10.53%)	2 / 8 (25.00%)
occurrences (all)	1	2	2
Bone Pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Muscle Spasms			
subjects affected / exposed	0 / 9 (0.00%)	3 / 19 (15.79%)	0 / 8 (0.00%)
occurrences (all)	0	3	0
Muscular Weakness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Myalgia			
subjects affected / exposed	2 / 9 (22.22%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	2	1	0

Pain In Extremity			
subjects affected / exposed	1 / 9 (11.11%)	2 / 19 (10.53%)	1 / 8 (12.50%)
occurrences (all)	1	2	1
Infections and infestations			
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 19 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Device Related Infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Labyrinthitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 19 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Oral Candidiasis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Oral Fungal Infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 9 (11.11%)	2 / 19 (10.53%)	1 / 8 (12.50%)
occurrences (all)	1	2	1
Dehydration			
subjects affected / exposed	1 / 9 (11.11%)	0 / 19 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Fluid Retention			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 19 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hyperuricaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 19 (5.26%) 1	0 / 8 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2012	1) Change to the dose administration: Maximum allowable dose changed from 70 mg/m² to 90 mg/m², when the 70 mg/m² dose level would be completed. 2) Change to secondary endpoints: Secondary endpoint "minimal residual disease (MRD)" was added. 3) Change to the exclusion criteria: An exclusion criteria was clarified in order to better define the viral profile of population.
07 September 2012	1) A Bayesian monitoring of safety was added. 2) The modified Hunsberger's design was clarified and operating characteristics were provided. 3) Clarifications on progression disease definition were provided.
23 October 2012	Pregnancy test before each cycle and electrocardiogram exam at baseline were included.
19 July 2013	1) Change to the concomitant medication with study treatment: Subjects treated or intended to be treated with drugs presented as cytochrome substrates with narrow therapeutic range were to be carefully monitored. 2) Change in the study treatment design: Administration of the second induction cycle was allowed for subjects with partial response. 3) Clarification on the partial remission and progressive disease definitions. 4) Changes in the PK samples and analyses: In the initial version of the protocol, it was planned to shift from a rich sampling approach to a sparse sampling approach at the end of the dose escalation period but preliminary PK data suggest additional PK data at 70 mg/m² were needed to characterize properly the PK profile in this population. 5) Clarification in the reporting of AE/Serious AE after end of treatment visit and during follow-up period.
22 January 2014	Change to the management of specific adverse reactions: Additional recommendations for subjects' premedication and clarification regarding the management of infusion reactions. In particular, systematic administration of steroids as premedication and the recommendation, if subjects develop anaphylactic reactions or allergic reactions grade 3-4 following or during the SAR3419 infusion, to be permanently discontinued from the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported