



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/m ² |

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/m ² |
|------------------|------------------------------|

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/m ² |
|------------------|------------------------------|

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/m ² | SAR3419 70 mg/m ² | SAR3419 90 mg/m ² |
|---------------------------------------|------------------------------|------------------------------|------------------------------|
| 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/m ² |
|-----------------------|------------------------------|

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/m ² |
|-----------------------|------------------------------|

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/m ² |
|-----------------------|------------------------------|

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/m ² | SAR3419 70 mg/m ² | SAR3419 90 mg/m ² |
|------------------------------------|------------------------------|------------------------------|------------------------------|
| 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/m ² |
| Reporting group description: SAR3419 55 mg/m ² 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/m ² |
| Reporting group description: SAR3419 70 mg/m ² 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/m ² |
| Reporting group description: SAR3419 90 mg/m ² 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/m ² | SAR3419 70 mg/m ² | SAR3419 90 mg/m ² | |
|-----------------------------|------------------------------|------------------------------|------------------------------|--|
| 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/m ² | SAR3419 70 mg/m ² | SAR3419 90 mg/m ² | |
|--------------------------------------|------------------------------|------------------------------|------------------------------|--|
| 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/m ² | SAR3419 70 mg/m ² | SAR3419 90 mg/m ² | |
|-----------------------------|------------------------------|------------------------------|------------------------------|--|
| 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/m ² |
|-----------------------|------------------------------|

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/m ² |
|-----------------------|------------------------------|

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/m ² |
|-----------------------|------------------------------|

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/m ² | SAR3419 70 mg/m ² | SAR3419 90 mg/m ² |
|---|------------------------------|------------------------------|------------------------------|
| 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/m ² | SAR3419 70 mg/m ² | SAR3419 90 mg/m ² |
|---|------------------------------|------------------------------|------------------------------|
| 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 occurrences (all) | 1 / 9 (11.11%) 1 | 3 / 19 (15.79%) 3 | 4 / 8 (50.00%) 4 |
| Injection Site Reaction subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Non-Cardiac Chest Pain subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 19 (10.53%) 2 | 0 / 8 (0.00%) 0 |
| Oedema Peripheral subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 3 / 19 (15.79%) 3 | 3 / 8 (37.50%) 3 |
| Pain subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Puncture Site Pain subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 4 / 9 (44.44%) 4 | 3 / 19 (15.79%) 3 | 1 / 8 (12.50%) 1 |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Reproductive system and breast disorders Menorrhagia subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Vaginal Haemorrhage subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 3 / 19 (15.79%) 3 | 1 / 8 (12.50%) 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 occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Investigations | | | |
| Alanine Aminotransferase Increased subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 19 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Breath Sounds Abnormal subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Weight Decreased subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 19 (10.53%) 2 | 2 / 8 (25.00%) 2 |
| Injury, poisoning and procedural complications | | | |
| Infusion Related Reaction subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 4 / 19 (21.05%) 4 | 1 / 8 (12.50%) 1 |
| Cardiac disorders | | | |
| Sinus Tachycardia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 19 (10.53%) 2 | 0 / 8 (0.00%) 0 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 9 (22.22%) 2 | 1 / 19 (5.26%) 1 | 1 / 8 (12.50%) 1 |
| Dysarthria subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 4 / 19 (21.05%) 4 | 1 / 8 (12.50%) 1 |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Lethargy | | | |

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

| | | | |
|---|---------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 19 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 19 (10.53%) 2 | 1 / 8 (12.50%) 1 |
| Diarrhoea subjects affected / exposed occurrences (all) | 2 / 9 (22.22%) 2 | 5 / 19 (26.32%) 5 | 1 / 8 (12.50%) 1 |
| Dry Mouth subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 19 (10.53%) 2 | 0 / 8 (0.00%) 0 |
| Gastroesophageal Reflux Disease subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Impaired Gastric Emptying subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | 2 / 9 (22.22%) 2 | 6 / 19 (31.58%) 6 | 0 / 8 (0.00%) 0 |
| Stomatitis subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 9 (22.22%) 2 | 3 / 19 (15.79%) 3 | 1 / 8 (12.50%) 1 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Petechiae subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 1 / 8 (12.50%) 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 occurrences (all) | 1 / 9 (11.11%) 1 | 2 / 19 (10.53%) 2 | 1 / 8 (12.50%) 1 |
| Infections and infestations | | | |
| Clostridium Difficile Colitis subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 19 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Device Related Infection subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Labyrinthitis subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 19 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Oral Candidiasis subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Oral Fungal Infection subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 19 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Metabolism and nutrition disorders | | | |
| Decreased Appetite subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 2 / 19 (10.53%) 2 | 1 / 8 (12.50%) 1 |
| Dehydration subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 19 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Fluid Retention subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 19 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 19 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 19 (5.26%) 1 | 0 / 8 (0.00%) 0 |
| Hypocalcaemia | | | |

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 06 August 2012 | <ol style="list-style-type: none">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 | <ol style="list-style-type: none">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 | <ol style="list-style-type: none">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