



## Clinical trial results:

### An Open Label Non-Randomized Phase 2 Study Evaluating SAR3419, an Anti-CD19 Antibody – Maytansine Conjugate, Administered as Single Agent by Intravenous Infusion to Patients With Relapsed or Refractory CD19+ Diffuse Large B Cell Lymphoma

#### Summary

EudraCT number	2011-003657-26
Trial protocol	CZ BE ES IT GB
Global end of trial date	10 October 2016

#### Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

#### Trial information

##### Trial identification

Sponsor protocol code	ARD10248
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01472887
WHO universal trial number (UTN)	U1111-1115-3349
Other trial identifiers	Study Name: STARLYTE

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	25 October 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 October 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To determine the objective response rate (ORR) produced by SAR3419 in subjects with CD19+ diffuse large B-cell lymphoma (DLBCL) after failure of at least 1 prior line of standard therapy.

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	19 January 2012
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	Poland: 4
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	61
EEA total number of subjects	48

Notes:

### Subjects enrolled per age group

In utero	0
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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)	17
From 65 to 84 years	42
85 years and over	2

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 28 sites in 9 countries between 19 January 2012 and 10 October 2016. A total of 79 subjects were screened in the study, out of which 18 were screen failures and 61 were enrolled and treated in the study.

### Pre-assignment

Screening details:

Subjects enrolled in the study to evaluate the efficacy and safety of SAR3419 in adult subjects with CD19+ DLBCL with relapsed or refractory disease after failure of at least 1 prior line of standard therapy.

### 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	SAR3419
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Arm description:

SAR3419 55 mg/m<sup>2</sup> once weekly for 4 weeks, followed by 1 week rest, and thereafter, every 2 weeks until disease progression (DP), unacceptable toxicity, or any other reason for treatment discontinuation.

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

Dosage and administration details:

SAR3419 administered at initial infusion rate of 1 mL/min for 30 minutes and then increased progressively by 0.5 mL/min increments at 15-minute intervals up to 3 mL/min.

Number of subjects in period 1	SAR3419
Started	61
Completed	0
Not completed	61
Disease progression	49
Adverse event	9
Other than specified	3

## Baseline characteristics

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### Reporting groups

Reporting group title	SAR3419
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Reporting group description:

SAR3419 55 mg/m<sup>2</sup> once weekly for 4 weeks, followed by 1 week rest, and thereafter, every 2 weeks until disease progression (DP), unacceptable toxicity, or any other reason for treatment discontinuation.

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Reporting group values	SAR3419	Total	
Number of subjects	61	61	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	68.1 ± 11.3	-	
Gender categorical Units: Subjects			
Female	30	30	
Male	31	31	

## End points

### End points reporting groups

Reporting group title	SAR3419
Reporting group description: SAR3419 55 mg/m <sup>2</sup> once weekly for 4 weeks, followed by 1 week rest, and thereafter, every 2 weeks until disease progression (DP), unacceptable toxicity, or any other reason for treatment discontinuation.	

### Primary: Percentage of Subjects with Objective Response (OR)

End point title	Percentage of Subjects with Objective Response (OR) <sup>[1]</sup>
End point description: OR reported as percentage of subjects achieving complete response (CR) or partial response (PR) relative to total number of subjects in per protocol (PP) population. As per Revised Response Criteria for Malignant Lymphoma, CR:Disappearance of all evidence of disease (nodal masses: [18F] Fluorodeoxyglucose[FDG]-avid or Positron emission tomography[PET] positive before therapy;Variably FDG-avid or if PET negative,regression to normal size; spleen/liver: not palpable,nodules disappeared; bone marrow infiltration cleared on repeat biopsy or negative immunohistochemistry) and PR: Regression of measurable disease, no new sites (≥50% decrease in sum of product of diameters of up to 6 largest dominant nodes or masses; no increase in size of other nodes, liver or spleen). PP population: all subjects who received at least 1 dose of study drug with no protocol deviation impacting efficacy at study entry & had an evaluable response assessment during treatment period or at end of treatment (EOT).	
End point type	Primary
End point timeframe: Baseline, every 12 weeks up to DP, or any other reason for treatment discontinuation (upto 95.14 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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	SAR3419			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: percentage of subjects				
number (confidence interval 90%)	43.9 (30.6 to 57.9)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of response (DOR)

End point title	Duration of response (DOR)
End point description: Duration of tumor response was defined as the time interval from the date of the first occurrence of CR or PR to the date of the first documentation of disease progression or death due to any reason, whichever occurred first. In the absence of DP or death or further anticancer therapy at the time of the data cut-off date, duration of response was censored to the earliest date of the last evaluable response assessment without evidence of progression and data cut-off date. Analysis was performed on PP	

population using Kaplan-Meier method.

End point type	Secondary
End point timeframe:	
Baseline, every 12 weeks up to DP, or any other reason for treatment discontinuation (maximum duration: 166 weeks)	

<b>End point values</b>	SAR3419			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: months				
median (full range (min-max))	4.6 (0 to 40)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
End point description:	
Progression-free survival was defined as the time interval from the date of the first study treatment infusion to the date of the first occurrence of progression or death (from any reason), whichever occurred first. In the absence of DP, death or further anticancer therapy at the time of the data cut-off date, the PFS was censored to the earliest date between the date of last evaluable response assessment without evidence of progression and the time of the data cut-off date. Analysis was performed on PP population using Kaplan-Meier method.	
End point type	Secondary
End point timeframe:	
Baseline, every 12 weeks up to DP, or any other reason for treatment discontinuation (maximum duration: 166 weeks)	

<b>End point values</b>	SAR3419			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: months				
median (confidence interval 90%)	4.4 (3.02 to 5.95)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival (OS)

End point title	Overall survival (OS)
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**End point description:**

Overall survival was defined as the time interval from the date of the first study treatment infusion to the date of death (due to any reason). Analysis was performed using Kaplan-Meier method. Analysis was performed on safety population that included all-treated population who received at least 1 dose of study treatment.

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End point type	Secondary
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**End point timeframe:**

Baseline, every 12 weeks up to death or study cut-off, whichever came first (maximum duration: 166 weeks)

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<b>End point values</b>	SAR3419			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: months				
median (confidence interval 90%)	9.2 (6.57 to 12.22)			

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**Statistical analyses**

No statistical analyses for this end point

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## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (maximum duration: 166 weeks) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are treatment emergent that is AEs that developed/worsened and deaths that occurred during 'on treatment period' (time from first study treatment infusion to last study treatment infusion + 42 days). Analysis was performed on safety population.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	SAR3419
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Reporting group description:

SAR3419 55 mg/m<sup>2</sup> once weekly for 4 weeks, followed by 1 week rest, and thereafter, every 2 weeks until DP, unacceptable toxicity, or any other reason for treatment discontinuation.

Serious adverse events	SAR3419		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 61 (44.26%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastrointestinal Stromal Tumour			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease Progression			
subjects affected / exposed	7 / 61 (11.48%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 5		
Pyrexia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Humerus Fracture			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post Procedural Haematoma			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Sinus Bradycardia			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Spinal Cord Compression			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss Of Consciousness			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile Neutropenia			

subjects affected / exposed	2 / 61 (3.28%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	1 / 1		
<b>Gastrointestinal disorders</b>			
Abdominal Pain			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis Acute			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Hepatobiliary disorders</b>			
Acute Hepatic Failure			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hepatotoxicity			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Renal and urinary disorders</b>			

Acute Kidney Injury			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Renal Failure			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral Disc Protrusion			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Herpes Zoster			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 61 (4.92%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			

subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	SAR3419		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 61 (81.97%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	6		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	8		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	6		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 61 (11.48%)		
occurrences (all)	7		
Fatigue			
subjects affected / exposed	11 / 61 (18.03%)		
occurrences (all)	13		
Oedema Peripheral			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	7		
Gastrointestinal disorders			

Abdominal Pain subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 6		
Constipation subjects affected / exposed occurrences (all)	6 / 61 (9.84%) 8		
Diarrhoea subjects affected / exposed occurrences (all)	11 / 61 (18.03%) 16		
Nausea subjects affected / exposed occurrences (all)	13 / 61 (21.31%) 18		
Vomiting subjects affected / exposed occurrences (all)	8 / 61 (13.11%) 13		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	12 / 61 (19.67%) 13		
Dyspnoea subjects affected / exposed occurrences (all)	6 / 61 (9.84%) 6		
Oropharyngeal Pain subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 7		
Back Pain subjects affected / exposed occurrences (all)	7 / 61 (11.48%) 7		

Pain In Extremity subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 6		
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4		
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	8 / 61 (13.11%) 8		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2012	Following amendments were made: <ul style="list-style-type: none"><li>• Changed the schedule for tumor assessment;</li><li>• Corrected the schedule for tumor assessment along the treatment period mixing response criteria Cheson 1999 and Cheson 2007 applying to Diffuse large B-cell lymphoma (DLBCL) being a FDG-avid, aggressive lymphoma;</li><li>• Changed to the biomarkers analysis;</li><li>• Changed the inclusion/exclusion criteria;</li><li>• Provided the study name as STARLYTE;</li><li>• Clarified the stopping rules and timing of the interim analysis;</li><li>• Changed the investigational medicinal product administration: Corrected the formulation and instruction for preparing and administering the IMP;</li><li>• Updated the safety follow-up period as a 42-day period;</li><li>• Corrected minor inconsistencies/typos throughout the protocol.</li></ul>
25 May 2012	<ul style="list-style-type: none"><li>• Changes in inclusion/exclusion criteria;</li><li>• Changed the primary objective as: to evaluate the objective response rate (ORR) of SAR3419 in subjects with CD19+ DLBCL after failure of at least one prior line of standard therapy;</li><li>• Changed the study design as: This is an open label, uncontrolled Phase 2 evaluation of the efficacy and safety of SAR3419 as single agent in subjects with CD19+DLBCL after failure of at least one prior line of standard therapy,</li><li>• Updated the study rationale.</li></ul>
12 November 2012	<ul style="list-style-type: none"><li>• Replaced 1 working day with within 24 hours in SAE reporting timelines,</li><li>• Changed minor inconsistencies/typos throughout the protocol.</li></ul>
19 July 2013	<ul style="list-style-type: none"><li>• Changed the concomitant medication with study treatment;</li><li>• Changed the IP preparation;</li><li>• Clarification on related AE/SAEs occurring during FU period or ongoing at the EOT visit.</li></ul>
22 January 2014	Updated the management of specific adverse reactions (management of potential specific toxicities).

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported