



Clinical trial results:

An Open Label, Multicenter, Phase II Study of Intravenous SAR3419, an Anti-CD19 Antibody-Maytansine Conjugate, in Combination with Rituximab in Patients with Relapsed or Refractory Diffuse Large B Cell Lymphomas

Summary

EudraCT number	2011-002865-39
Trial protocol	SE DE AT
Global end of trial date	22 September 2014

Results information

Result version number	v1 (current)
This version publication date	20 March 2016
First version publication date	20 March 2016

Trial information

Trial identification

Sponsor protocol code	TCD12333
-----------------------	----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01470456
WHO universal trial number (UTN)	U1111-1120-0315
Other trial identifiers	Study name : SARIT

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	16 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the objective response rate (ORR) of SAR3419 in combination with rituximab.

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	22 November 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	France: 51
Worldwide total number of subjects	52
EEA total number of subjects	52

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)	21
From 65 to 84 years	30
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 12 sites in France and Norway. A total of 85 subjects were screened between 22 November 2011 and 21 February 2013.

Pre-assignment

Screening details:

Of 85 screened subjects, 32 were screen failure; the screen failures were due to failure to meet the inclusion/exclusion criteria. Of 53 included subjects, 1 was not treated due to disease progression.

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 + Rituximab
-----------	---------------------

Arm description:

SAR3419 and Rituximab administered weekly from Weeks 1 to 4, then biweekly on Weeks 6, 8, 10, and 12. One cycle was defined as a 4-week period, except Cycle 1, which was to last 5 weeks (4 weekly administrations followed by a week's rest).

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

Dosage and administration details:

SAR3419 55 mg/m² infusion, administered over approximately an hour.

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

Dosage and administration details:

Rituximab 375 mg/m² administered over approximately 4 hours.

Number of subjects in period 1	SAR3419 + Rituximab
Started	52
Completed	29
Not completed	23
disease progression	23

Baseline characteristics

Reporting groups

Reporting group title	SAR3419 + Rituximab
-----------------------	---------------------

Reporting group description:

SAR3419 and Rituximab administered weekly from Weeks 1 to 4, then biweekly on Weeks 6, 8, 10, and 12. One cycle was defined as a 4-week period, except Cycle 1, which was to last 5 weeks (4 weekly administrations followed by a week's rest).

Reporting group values	SAR3419 + Rituximab	Total	
Number of subjects	52	52	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	64.7 ± 11.2	-	
Gender categorical Units: Subjects			
Female	26	26	
Male	26	26	

End points

End points reporting groups

Reporting group title	SAR3419 + Rituximab
Reporting group description: SAR3419 and Rituximab administered weekly from Weeks 1 to 4, then biweekly on Weeks 6, 8, 10, and 12. One cycle was defined as a 4-week period, except Cycle 1, which was to last 5 weeks (4 weekly administrations followed by a week's rest).	

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR) ^[1]
End point description: ORR was defined as the percentage of subjects achieving a complete response (CR) or partial response (PR), assessed based on International Workshop Guidelines (IWG) Cheson 2007 criteria. CR was defined as disappearance of all evidence of disease. PR was defined as regression of measurable disease and no new sites. Analysis was performed on per protocol (PP) population including all treated subjects who had an evaluable response assessment during treatment or end of treatment visit and without any important protocol deviation impacting efficacy.	
End point type	Primary
End point timeframe: Baseline; end of the treatment and then every 3 months during the follow-up until progression or initiation of further anticancer therapy (24 months)	
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: The data is provided as a separate attachment.	

End point values	SAR3419 + Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	45 ^[2]			
Units: percentage of subjects				
number (confidence interval 80%)	31.1 (22 to 41.6)			

Notes:
[2] - 45 out of 52 subjects were eligible for the PP population.

Attachments (see zip file)	Statistical Analyses for ORR/Statistical Analyses for ORR.pdf
-----------------------------------	---

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response
End point description: Duration of response was defined as the time interval from the date of first occurrence of complete response or partial response to the date of first documentation of disease progression (DP) or death due to any cause, which ever occurred first. Responses were assessed based on IWG Cheson 2007 criteria. CR was defined as disappearance of all evidence of disease. PR was defined as regression of measurable disease and no new sites. DP was defined as any new lesion or increase by $\geq 50\%$ of previously involved sites from nadir. Duration of response was calculated using the Kaplan-Meier method. Number	

of subjects with duration of response ≤ 6 months and >6 months are provided. Analysis was performed on PP population.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline; end of the treatment and then every 3 months during the follow-up until progression or initiation of further anticancer therapy (24 months)

End point values	SAR3419 + Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	45 ^[3]			
Units: subjects				
≤ 6 months	7			
> 6 months	7			

Notes:

[3] - 45 out of 52 subjects were eligible for the PP population.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival
-----------------	---------------------------

End point description:

Progression-free survival was defined as the time interval (in months) from the date of first study treatment infusion to the date of first occurrence of progression or death from any cause, whichever occurred first. DP was defined as any new lesion or increase by $\geq 50\%$ of previously involved sites from nadir. Duration of response was calculated using the Kaplan Meier method. Analysis was performed on PP population.

End point type	Secondary
----------------	-----------

End point timeframe:

From the date of first study treatment infusion to the date of first occurrence of progression or death from any cause (24 months)

End point values	SAR3419 + Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	45 ^[4]			
Units: months				
median (confidence interval 80%)	3.9 (3.22 to 3.98)			

Notes:

[4] - 45 out of 52 subjects were eligible for the PP population.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival
-----------------	------------------

End point description:

Overall survival was defined as the time interval (in months) from the date of first study treatment infusion to the date of death from any cause. Analysis was performed on safety population included all treated subjects.

End point type	Secondary
----------------	-----------

End point timeframe:

From the date of first study treatment infusion to the date of death from any cause (24 months)

End point values	SAR3419 + Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: months				
median (confidence interval 80%)	9 (6.47 to 13.67)			

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 (Month 24) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events and death are treatment-emergent that is AEs that developed/worsened and death that occurred during the 'on treatment period' (from first study treatment infusion to 42 days after last study treatment infusion [i.e, last infusion of last cycle]).

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	17.0
--------------------	------

Reporting groups

Reporting group title	SAR3419 + Rituximab
-----------------------	---------------------

Reporting group description:

SAR3419 and Rituximab administered weekly from Weeks 1 to 4, then biweekly, on Weeks 6, 8, 10, and 12. One cycle was defined as a 4-week period, except Cycle 1, which was to last 5 weeks (4 weekly administrations followed by a week's rest).

Serious adverse events	SAR3419 + Rituximab		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 52 (42.31%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events			
Vascular disorders			
Superior Vena Cava Syndrome			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac Arrest			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus Tachycardia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Syncope			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease Progression			
subjects affected / exposed	9 / 52 (17.31%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 7		
General Physical Health Deterioration			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			

subjects affected / exposed	3 / 52 (5.77%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pulmonary Embolism			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal Failure Acute			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ureteric Obstruction			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Neck Pain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain In Extremity			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia Bacterial			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	1 / 52 (1.92%)		
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 %

Non-serious adverse events	SAR3419 + Rituximab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 52 (75.00%)		
Investigations			
Weight Decreased			
subjects affected / exposed	9 / 52 (17.31%)		
occurrences (all)	10		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	4		
Neuropathy Peripheral			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	4		
Paraesthesia			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	13 / 52 (25.00%)		
occurrences (all)	13		
Oedema Peripheral			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	7 / 52 (13.46%)		
occurrences (all)	7		
Eye disorders			

Dry Eye subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3		
Keratitis subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 4		
Gastrointestinal disorders Abdominal Pain subjects affected / exposed occurrences (all)	6 / 52 (11.54%) 8		
Constipation subjects affected / exposed occurrences (all)	6 / 52 (11.54%) 6		
Diarrhoea subjects affected / exposed occurrences (all)	9 / 52 (17.31%) 13		
Nausea subjects affected / exposed occurrences (all)	11 / 52 (21.15%) 11		
Vomiting subjects affected / exposed occurrences (all)	8 / 52 (15.38%) 11		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	10 / 52 (19.23%) 11		
Dyspnoea subjects affected / exposed occurrences (all)	6 / 52 (11.54%) 6		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3		
Back Pain subjects affected / exposed occurrences (all)	7 / 52 (13.46%) 8		

Myalgia subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3		
Infections and infestations Rhinitis subjects affected / exposed occurrences (all)	4 / 52 (7.69%) 4		
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 September 2011	<ul style="list-style-type: none">- Pregnancy tests which were initially required at baseline and end of treatment Visit were performed at Day 1 of each cycle.- Contraception which was required to be continued during 3 months after the last treatment administration was extended until 12 months after the last treatment administration.- To provide the study name.- To correct the formulation and instruction for preparing and administrating the investigational medicinal product in the clinical trial summary and protocol.
16 December 2011	<ul style="list-style-type: none">- To correct the schedule for tumor assessment in reference to response criteria Cheson 2007 applying to diffuse large B-cell lymphoma (DLBCL) being a fluorodeoxyglucose-avid (FDG-avid), aggressive lymphoma. Both computed tomography (CT) and positron emission tomography (PET) scans were performed for any subject at baseline and at the end of treatment Visit (42 days after the last treatment administration). For non-progressing subjects at the end of treatment, surveillance CT scans were performed 3 months during the follow-up period.- To remove the central reviews for both histology confirmation and disease response in this phase II Proof of Concept study.- To add the option of retrospectively using archived diagnostic biopsies in case of missing material for exploratory endpoint at study entry.- To answer the exploratory endpoint of the study, all subjects must have had either a recent biopsy or a free needle aspiration (FNA) at study entry. Any effort should be done in order to obtain fresh biopsies. At the end of the study, the diagnosis biopsy might be retrospectively collected and used for the centralized analysis of the selected biomarkers defined in Hans and Choi algorithms. If necessary, a specific informed consent was to be obtained.- To revise the reporting of biological results in the safety follow-up period after further anticancer therapy was administered.- To add the pharmacokinetic (PK) parameters as an endpoint of the interim analysis on the first 20 subjects.- To clarify the stopping rules and timing of the interim analysis.- To harmonize the safety follow-up period as a 42-day period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported