Clinical trial results:
A MULTI-CENTER, PHASE IB/II, OPEN LABEL, SINGLE ARM STUDY OF INOTUZUMAB OZOGAMICIN PLUS RITUXIMAB (R-CMC544) ALTERNATING WITH GEMCITABINE-OXALIPLATIN PLUS RITUXIMAB (R-GEMOX) IN PATIENTS AGED FROM 18 TO 80 YEARS WITH CD20 AND CD22 POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) IN RELAPSE AFTER/REFRACTORY TO 1ST OR 2ND LINE TREATMENT, WHO ARE NO CANDIDATES FOR AUTOLOGOUS TRANSPLANT

Summary

EudraCT number	2011-003849-18
Trial protocol	BE
Global end of trial date	22 March 2016

Results information

Result version number	v1 (current)
This version publication date	13 April 2017
First version publication date	13 April 2017

Trial information

Trial identification

Sponsor protocol code	CMC-R-GEMOX

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01562990
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LYSARC
Sponsor organisation address	Secteur Sainte Eugénie - pavillon 6D, Pierre Bénite, France, 69495
Public contact	Elise Hutasse, LYSARC, +33 472669333, elise.hutasse@lysarc.org
Scientific contact	Elise Hutasse, LYSARC, +33 472669333, elise.hutasse@lysarc.org

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	22 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 March 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the phase Ib part of the study is to determine the tolerability, safety and MTD or recommended dose of R-CMC544 alternating with RGEMOX in subjects aged from 18 to 80 years with CD20 and CD22 positive DLBCL in relapse after/refractory to 1st or 2nd line treatment, who are no candidates for autologous transplant.
The primary objective of the phase II part of the study is to assess the efficacy or RCMC544 alternating with R-GEMOX as measured by the overall response rate (ORR) by IWG criteria (Cheson 1999) at the end of treatment (after complete treatment or at withdrawal).

Protection of trial subjects:

Patients have been followed for safety (adverse event) during all study duration.
If a patient does not respond to study treatment, relapses or has progressive disease, each site was free to initiate further treatment according to local guidelines

Background therapy:

R-GEMOX is one of standard therapies for patients with relapsed/refractory diffuse large B-cell lymphoma.

Evidence for comparator:

NA

Actual start date of recruitment	03 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 11
Worldwide total number of subjects	11
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)	3
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

1st patient included in France in December, 2012.
Elevent patients included in France, no patient included in Belgium.
Last patient included in phase I in February, 2014.
Phase II cancelled due to poor overall response rate and long duration of phase I which led to investigators demotivation.

Pre-assignment

Screening details:

No patient screen failed in eCRF.
- Histologically documented CD20 and CD22 positive diffuse large B-cell lymphoma, according to WHO classification.
- In 1st or 2nd relapse or refractory to 1st and/or 2nd line treatment.
- Measurable disease by bidimensional transverse CT scan assessment
- Not eligible for autologous transplantation

Period 1

Period 1 title	Induction
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	experimental

Arm description: -

Arm type	Experimental
Investigational medicinal product name	inotuzumab-ozogamicin
Investigational medicinal product code	CMC544
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

CMC544 was given by IV route over 1 hour ± 10 minutes at the fixed dose rate of 50 mL/hour.
Dose administered was 1.8mg/m²

Number of subjects in period 1	experimental
Started	11
Completed	5
Not completed	6
Physician decision	1
disease progression	4
toxicity of study treatment	1

Period 2

Period 2 title	Consolidation
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Experimental

Arm description: -

Arm type	Experimental
Investigational medicinal product name	inotuzumab-ozogamicin
Investigational medicinal product code	CMC544
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

CMC544 was given by IV route over 1 hour ± 10 minutes at the fixed dose rate of 50 mL/hour.
Dose administered was 1.8mg/m²

Number of subjects in period 2	Experimental
Started	5
Completed	1
Not completed	4
disease progression	1
toxicity of study treatment	3

Baseline characteristics

Reporting groups

Reporting group title	Induction

Reporting group description: -

Reporting group values	Induction	Total	
Number of subjects	11	11	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	71.2		
inter-quartile range (Q1-Q3)	64 to 78	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	5	5	

End points

End points reporting groups

Reporting group title	experimental
Reporting group description: -	
Reporting group title	Experimental
Reporting group description: -	
Subject analysis set title	Evaluable set
Subject analysis set type	Full analysis

Subject analysis set description:

The evaluable population includes all enrolled patients who received at least one dose of any investigational drugs. Primary endpoint of the phase II will be analyzed on this population. Secondary efficacy and safety endpoints (for both phase Ib and II) will be performed on this population.

Subject analysis set title	DLT evaluable set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The DLT evaluable population includes all patients from "Evaluable population" with a DLT assessment. It is considered that a patient have a DLT assessment if he/she performed completely the first two cycles unless a DLT occurred before the end of the cycle 2, in which case he/she remains evaluable for DLT.
Primary endpoint of the phase Ib will be analyzed on this population

Primary: Number of patients with DLT

End point title	Number of patients with DLT[1]

End point description:

Recommended dose will be identified according to the incidence of DLTs during the first 2 cycles of treatment (induction).
DLT is defined as follows (NCI CTCAE vs. 4):
- Grade 4 neutropenia ≥ 7 days
- Grade 4 thrombocytopenia ≥ 7 days
- Grade 3 or 4 thrombocytopenia associated with bleeding requiring a transfusion
- Grade 3 non-hematologic toxicity (except alopecia) ≥ 7 days or determined to be investigational product-related
- Grade 4 non-hematologic toxicity (except alopecia)
- Grade 4 AST/ALT increase irrespective of duration
- Grade 2 hyperbilirubinemia (> 1.5 x ULN) > 7 days
- Grade 3 or greater QTc prolongation (average of three ECGs)
- Delayed recovery from an investigational product-related toxicity that prevents redosing by more than 21 days

End point type	Primary

End point timeframe:

Two first induction cycles

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is performed for the primary endpoint of the phase Ib part of the study as the Recommended Dose is determined by the number of patients with at least one DLT in each cohort level.

End point values	DLT evaluable set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: patients				
1.8 mg/m²	3			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR according to Cheson 99 at the end of treatment

End point title	ORR according to Cheson 99 at the end of treatment

End point description:

ORR as defined by Cheson 99 criteria: ORR = CR/CRu/PR

End point type	Secondary

End point timeframe:

At the end of treatment defined as after complete treatment or at permanent treatment discontinuation

End point values	Evaluable set			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: percent				
number (confidence interval 95%)				
1.8 mg/m²	18.2 (2.3 to 51.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AE) occurring from the signing of the Informed Consent and until 30 days after the end of the last cycle of treatment have been recorded on the AE pages of the CRF.

Adverse event reporting additional description:

Only grade 3 and 4 toxicities (NCIC Common Toxicity Criteria grading system – version 4.03) or grade 2 for infections, and toxicities (grade 1 to 4) related to a Serious Adverse Event as described below, have been be reported as "Adverse Event" in the appropriate CRF pages.
All "Alopecia" toxicity have not been recorded as "Adverse Event".

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	4.03

Reporting groups

Reporting group title	All patients

Reporting group description: -

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 11 (36.36%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
DISEASE PROGRESSION			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Gastrointestinal disorders			
LARGE INTESTINE PERFORATION			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

RENAL FAILURE ACUTE			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
PERITONITIS			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
LACTIC ACIDOSIS			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)		
Investigations			
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	5		
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
PLATELET COUNT DECREASED			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
THROMBOCYTOPENIA			
subjects affected / exposed	6 / 11 (54.55%)		
occurrences (all)	16		
LYMPHOPENIA			
subjects affected / exposed	4 / 11 (36.36%)		
occurrences (all)	6		
NEUTROPENIA			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	4		
ANAEMIA			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
LEUKOPENIA			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
General disorders and administration site conditions			
DISEASE PROGRESSION			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Gastrointestinal disorders			
LARGE INTESTINE PERFORATION			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hepatobiliary disorders			
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Renal and urinary disorders			
RENAL FAILURE ACUTE			

subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Infections and infestations PERITONITIS subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1		
Metabolism and nutrition disorders LACTIC ACIDOSIS subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2012	• A change in the name only of the Sponsor name from Groupe d'Etude des Lymphomes de l'Adulte Recherche Clinique (GELARC) to LYSARC on 1 June 2012. • The definition of DLTs was modified slightly to specify that all grade 4 non-hematologic toxicities will be considered as DLT whatever duration or relationship to study treatment. •The sentence explaining that a copy signed consent forms would be recovered by the sponsor in a sealed envelope was deleted
25 July 2014	• Prolongation of study duration from 4 years to 5.5 years. • Addition of details on the main study objective phase-by-phase • Precision of secondary and exploratory objectives • Correction of the inconsistencies identified between the body of the text on the dose de-escalation rules and the summary table: summary table was corrected to properly describe the de-escalation process, as described in the text. • Clarification of statistical endpoints of phase I and phase II

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
24 March 2015	As written in the protocol and following the de-escalation rules, the recommended phase 2 study dose was found and confirmed by an IDMC. However, the long duration of the phase I slowed down the investigators motivation. In addition, the overall response rate was poor. Given these data, the sponsor decided not to proceed the phase 2 part of CMC-R-GEMOX study.	-

Notes:

Limitations and caveats

None reported