Clinical trial results:
A PHASE IB/II STUDY OF ESCALATING DOSES OF REVLIMID IN ASSOCIATION WITH R-CHOP (R2-CHOP) IN THE TREATMENT OF B-CELL LYMPHOMA

Summary

EudraCT number	2007-007698-22
Trial protocol	FR
Global end of trial date	23 November 2015

Results information

Result version number	v1 (current)
This version publication date	14 January 2018
First version publication date	14 January 2018
Summary attachment (see zip file)	CSR Synopsis (CSR_synopsis_R2CHOP_V1_LYSARC 20171221.pdf)

Trial information

Trial identification

Sponsor protocol code	R2-CHOP

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00901615
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LYSARC
Sponsor organisation address	CH Lyon Sud – Secteur Sainte Eugénie – Pav 6D, PIERRE-BENITE Cedex, France, 69495
Public contact	Yvain ROBREAU, LYSARC, 33 4 72 66 93 33,
Scientific contact	Prof Hervé TILLY, LYSA, 33 2 32 08 22 00,
Sponsor organisation name	Centre Henri Becquerel
Sponsor organisation address	rue d'Amiens, ROUEN, France, 76038
Public contact	Yvain ROBREAU, LYSARC CH Lyon Sud – Secteur Sainte Eugénie – Pav 6D - 69495 PIERRE-BENITE Cedex - France, +33 4 72 66 93 33,
Scientific contact	Prof. Hervé TILLY, LYSA CH Lyon Sud - Service d'Hématologie – Bâtiment 1 F 69495 PIERRE-BENITE Cedex , +33 2 32 08 22 00,

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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 November 2015
Was the trial ended prematurely?	No

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 recommended dose (RD) of lenalinomide (Revlimid) when administered in association with R-CHOP.
The primary objective of the Phase II part of the study is to assess the efficacy of the association of Revlimid and R-CHOP in a population of patients with follicular lymphoma as measured by the response rate at the end of treatment.

Protection of trial subjects:

salavge therapy if necessary

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 January 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 108
Worldwide total number of subjects	108
EEA total number of subjects	108

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)	108
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Fom 06-Jan-2009 to 25-Jan-2012

Pre-assignment

Screening details:

- Phase IB: Patients with one of the following B-cell Lymphoma, CD 20 positive:
  - Mantle cell, Marginal zone, follicular
  - Histological transformation from low grade to high grade
  - Diffuse large B cell
- Phase II: Patients with follicular lymphoma, WHO grade 1, 2 or 3a with at least one of the following signs requiring initiation of treatment

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	R2-CHOP
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Revlimid
Investigational medicinal product code	Lenalidomide
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2.5 mg, 5 mg and 10 mg strengths.
All patients were treated with R2-CHOP at a three-week interval for 6 cycles.

Number of subjects in period 1	R2-CHOP
Started	108
Completed	101
Not completed	7
Consent withdrawn by subject	2
Adverse event, non-fatal	1
concurrent illness	2
Protocol deviation	1
Lack of efficacy	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	108	108	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	108	108	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	59		
full range (min-max)	24 to 77	-	
Gender categorical Units: Subjects			
Female	52	52	
Male	56	56	

Subject analysis sets

Subject analysis set title	Phase I part
Subject analysis set type	Full analysis

Subject analysis set description:
Subjects included in Phase I part

Subject analysis set title	Phase II part
Subject analysis set type	Full analysis

Subject analysis set description:
Subjects included in phase II part

Reporting group values	Phase I part	Phase II part	
Number of subjects	28	80	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	

Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	28	80	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	58	60	
full range (min-max)	24 to 77	29 to 71	
Gender categorical			
Units: Subjects			
Female	12	40	
Male	16	40	

End points

End points reporting groups

Reporting group title	R2-CHOP
Reporting group description: -	
Subject analysis set title	Phase I part
Subject analysis set type	Full analysis
Subject analysis set description: Subjects included in Phase I part	
Subject analysis set title	Phase II part
Subject analysis set type	Full analysis
Subject analysis set description: Subjects included in phase II part	

Primary: Complete Response Rate at the End of Treatment According to Cheson 99

End point title	Complete Response Rate at the End of Treatment According to Cheson 99[1]
End point description:	
End point type	Primary
End point timeframe: end of treatment	

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: Included in figure

End point values	R2-CHOP	Phase II part		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[2]			
Units: Subjects with CR or CRu				
CR or CRu		59		
Other		21		

Notes:

[2] - Not applicable

Statistical analyses

No statistical analyses for this end point

Primary: Dose limiting toxicities (DLT)

End point title	Dose limiting toxicities (DLT)[3]
End point description:	
End point type	Primary
End point timeframe: End of cycle 2	

Notes:

[3] - 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: Descriptive analysis

End point values	R2-CHOP	Phase I part		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[4]			
Units: Subject presenting DLT				
with DLT		6		
without DLT		21		

Notes:

[4] - Not applicable

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate at the End of Treatment

End point title	Overall Response Rate at the End of Treatment

End point description:

End point type	Secondary

End point timeframe:

End of treatment

End point values	R2-CHOP	Phase II part		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[5]			
Units: Subjects with response				
response (CR, CRu, PR)		75		
Other (SD, PD)		5		

Notes:

[5] - Not applicable

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

End point type	Secondary

End point timeframe:

60 months

End point values	R2-CHOP	Phase II part		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[6]			
Units: Subjects presenting event				
Event		18		
Censored		62		

Notes:

[6] - Not applicable

Attachments (see zip file)	PFS.png

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

60 months

End point values	R2-CHOP	Phase II part		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[7]			
Units: Deaths				
Dead		4		
Censored		76		

Notes:

[7] - Not applicable

Attachments (see zip file)	OS.png

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	Phase I
Reporting group description: -	
Reporting group title	Phase II
Reporting group description: -	

Serious adverse events	Phase I	Phase II	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 27 (25.93%)	21 / 80 (26.25%)	
number of deaths (all causes)	0	4	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified			
subjects affected / exposed	1 / 27 (3.70%)	6 / 80 (7.50%)	
occurrences causally related to treatment / all	1 / 1	6 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	0 / 27 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	2 / 27 (7.41%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Immune system disorders (			
subjects affected / exposed	1 / 27 (3.70%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	0 / 27 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	1 / 27 (3.70%)	3 / 80 (3.75%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Investigations			
subjects affected / exposed	0 / 27 (0.00%)	2 / 80 (2.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	0 / 27 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	0 / 27 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorders			

subjects affected / exposed	0 / 27 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	2 / 27 (7.41%)	5 / 80 (6.25%)	
occurrences causally related to treatment / all	1 / 2	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorders			
subjects affected / exposed	0 / 27 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	0 / 27 (0.00%)	3 / 80 (3.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	1 / 27 (3.70%)	2 / 80 (2.50%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders (			
subjects affected / exposed	0 / 27 (0.00%)	4 / 80 (5.00%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	2 / 27 (7.41%)	6 / 80 (7.50%)	
occurrences causally related to treatment / all	2 / 2	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Phase I	Phase II	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)	68 / 80 (85.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
subjects affected / exposed	0 / 27 (0.00%)	7 / 80 (8.75%)	
occurrences (all)	0	7	
Vascular disorders			
VASCULAR DISORDERS			
subjects affected / exposed	2 / 27 (7.41%)	4 / 80 (5.00%)	
occurrences (all)	2	7	
Surgical and medical procedures			
SURGICAL AND MEDICAL PROCEDURES			
subjects affected / exposed	0 / 27 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
subjects affected / exposed	3 / 27 (11.11%)	2 / 80 (2.50%)	
occurrences (all)	3	2	
Immune system disorders			
IMMUNE SYSTEM DISORDERS			
subjects affected / exposed	1 / 27 (3.70%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
subjects affected / exposed	0 / 27 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
subjects affected / exposed	3 / 27 (11.11%)	3 / 80 (3.75%)	
occurrences (all)	3	4	

Investigations INVESTIGATIONS subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0	 4 / 80 (5.00%) 5	
Injury, poisoning and procedural complications INJURY, POISONING AND PROCEDURAL COMPLICATIONS subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0	 1 / 80 (1.25%) 2	
Cardiac disorders CARDIAC DISORDERS subjects affected / exposed occurrences (all)	 1 / 27 (3.70%) 1	 2 / 80 (2.50%) 3	
Nervous system disorders NERVOUS SYSTEM DISORDERS subjects affected / exposed occurrences (all)	 3 / 27 (11.11%) 3	 7 / 80 (8.75%) 8	
Blood and lymphatic system disorders BLOOD AND LYMPHATIC SYSTEM DISORDERS subjects affected / exposed occurrences (all)	 27 / 27 (100.00%) 88	 68 / 80 (85.00%) 420	
Eye disorders EYE DISORDERS subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0	 2 / 80 (2.50%) 3	
Gastrointestinal disorders GASTROINTESTINAL DISORDERS subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0	 8 / 80 (10.00%) 12	
Hepatobiliary disorders HEPATOBILIARY DISORDERS subjects affected / exposed occurrences (all)	 2 / 27 (7.41%) 2	 1 / 80 (1.25%) 1	
Skin and subcutaneous tissue disorders SKIN AND SUBCUTANEOUS TISSUE DISORDERS subjects affected / exposed occurrences (all)	 1 / 27 (3.70%) 1	 4 / 80 (5.00%) 5	
Renal and urinary disorders			

RENAL AND URINARY DISORDERS subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	4 / 80 (5.00%) 4	
Infections and infestations INFECTIONS AND INFESTATIONS subjects affected / exposed occurrences (all)	14 / 27 (51.85%) 14	29 / 80 (36.25%) 42	
Metabolism and nutrition disorders METABOLISM AND NUTRITION DISORDERS subjects affected / exposed occurrences (all)	6 / 27 (22.22%) 6	3 / 80 (3.75%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2008	The first one concerns form corrections in the research protocol (mainly harmonizations between the synopsis and the text of the protocol and corrections of translation errors of measurement units), the submission of a patient booklet which was be distributed to the participants in the study and aimed at ensuring compliance with the test treatment, the collection of safety data (version 1 of 15 October 2008) and the modification of the investigator coordinator of the study, Professor Bertrand COIFFIER, by Professor Hervé TILLY and the modification of the principal investigator of the René Huguenin center of St Cloud, Dr. Maud JANVIER, by Dr. Carole SOUSSAIN. These modifications has been implemented in Protocol version 3 dated October 15, 2008.
01 October 2009	Second amendment concerns the addition of a dose level in Phase IB at 25 mg (indeed, the initially planned maximum level of 20 mg was well tolerated in the trial as in other trials studying the combination of Lenalidomide and Rituximab) and the addition of a cut-off date concerning the analysis of the primary criterion of Phase IB prior to that concerning the analysis of secondary criteria due to the earlier availability of data. These modifications has been implemented in Protocol version 4 dated October 1st, 2009.
27 October 2010	Third amendment concerns: 1. The transfer of the trial promotion to the Centre Henri Becquerel (Rouen, France). 2. Following the inclusion of all patients in Phase I, the primary endpoint data were analyzed. The Research Monitoring Committee recommended the 25 mg dose for Phase II with a schedule of dose adjustments for toxicity. 3. Five search locations are added and another has changed address. 4. In order to take into account the evolution of the practices, the protocol plan foreseen two cycles of rituximab alone for the end of the induction treatment and recommended the establishment of a maintenance treatment for the answering patients. 5. The PET-scan exam was added to the efficacy evaluation criteria as it now corresponds to the usual care of the patients involved in the research. 6. The safety information of the investigational drug was updated following the updating of the Investigator's Brochure. These modifications has been implemented in Protocol version 5 dated October 27, 2010.
30 August 2011	Fourth amendment concerns 1. The conditions for reporting secondary malignancies and the conditions for reviewing the data by the DSMC following the recommendations of the AFSSAPS concerning the suspicion of risk of occurrence of secondary cancers dear to patients receiving lenalidomide. 2. The change of principal investigators in three research sites: the Principal Investigator of the Nancy Center, that of Paris St Louis and that of the Institut Curie have been modified. 3. The safety information of the investigational drug has been updated following updates to the Investigator Brochure version 14 and RCP version 20 of Revlimid. These modifications has been implemented in Protocol version 6 dated August 30, 2011.

16 December 2011	Last amendment to the protocol concerns the updating of the product's safety information following the transmission of the new version of Investigator's Brochure No. 15 and RCP 22 by the product owner. For this purpose, a supplement of information leaflet of the patients has been written. These modifications has been implemented in Protocol version 6.2 dated December 16, 2011.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22733106