Clinical trial results:
RANDOMIZED PHASE III STUDY OF LENALIDOMIDE (REVLIMID®) MAINTENANCE IN RESPONDING ELDERLY PATIENTS WITH DLBCL AND TREATED WITH R-CHOP IN FIRST LINE

Summary

EudraCT number	2008-008202-52
Trial protocol	BE FR PT ES AT PL
Global end of trial date	30 September 2019

Results information

Result version number	v1 (current)
This version publication date	10 April 2021
First version publication date	10 April 2021

Trial information

Trial identification

Sponsor protocol code	REMARC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01122472
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LYSARC
Sponsor organisation address	Centre Hospitalier Lyon-Sud_Bat 2D, Pierre Bénite, France, 69495
Public contact	Anne Schuyleman, LYSARC, REMARC@lysarc.org
Scientific contact	Pr Catherine Thieblemont, APHP, catherine.thieblemont@aphp.fr

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	30 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine the benefit estimated by the progression-free survival associated with lenalidomide maintenance compared to placebo in responding patients treated with R-CHOP for diffuse large B-cell lymphoma.

Protection of trial subjects:

DSMC periodically reviewed the safety and efficacy data from the trial prepared by the independent statistician. All data presented at the meeting were confidential. Following each meeting the DSMC prepared a report and may recommended changes in trial conduct

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 May 2009
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	Poland: 27
Country: Number of subjects enrolled	Portugal: 33
Country: Number of subjects enrolled	Spain: 52
Country: Number of subjects enrolled	Austria: 19
Country: Number of subjects enrolled	Belgium: 54
Country: Number of subjects enrolled	France: 403
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Australia: 49
Worldwide total number of subjects	650
EEA total number of subjects	588

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)	177
From 65 to 84 years	473
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period per country:
- Australia: from 08MAR11 to 13MAY14
- Austria: from 01JUN11 to 19AUG13
- Belgium: from 27APR10 to 03MAR14
- France: 14MAY09 to 25MAR14
- Israel: 21DEC11 to 14JAN14
- Poland: 12SEP11 to 12FEB14
- Portugal: 15MAR10 to 18NOV13
- Spain: 17AUG10 to 01APR14
- Switzerland: 03JAN11 to 13MAR13

Pre-assignment

Screening details:

Patients aged from 60 to 80 years (>59 year and <81 years old) at time of registration and responding (CR or PR) to 1st line treatment with R-CHOP for diffuse large B-cell Lymphoma, CD 20 positive

Period 1

Period 1 title	overall trial (randomized patients) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenalidomide

Arm description:

Lenalidomide 25mg/ day

3 weeks every 4 weeks for 24 months

Arm type	Experimental
Investigational medicinal product name	Revlimid®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Dosage:
Starting dose 25mg lenalidomide (200 mg of excipient anhydrous lactose)
Dose reduction: 20, 15, 10 or 5 mg of lenalidomide and respectively 244.5, 289, 294 or 147 mg of excipient anhydrous lactose.

Administration:
Lenalidomide administered daily from D1 to D21, repeated at day 29 for 24 months (max up to 26 cycles).
Day 1 of cycle 1 of study drug treatment occured within 12 weeks (84 days) after the first day of the last R-CHOP cycle or the last Rituximab alone

Arm title	Placebo

Arm description:

Placebo 25mg/day

3 weeks every 4 weeks for 24 months

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Dosage:
Starting dose: 25mg
Placebo 25, 20, 15, 10 and 5 mg is presented in hard capsules.
Two types of placebos may be used.
- One placebo contains the excipients used for the drug product (matching placebo): Lactose Anhydrous Microcrystalline Cellulose Croscarmellose Sodium Magnesium Stearate.
- The other placebo is a standardized formulation containing microcrystalline cellulose (standardized placebo).
Capsules conform in colour and size for blinded studies

Administration:
Daily from D1 to D21, repeated at D29 for 24 months (max up to 26 cycles)
Day 1 of cycle 1 occured within 12 weeks (84 days) after the first day of last R-CHOP cycle or the last Rituximab alone

Number of subjects in period 1	Lenalidomide	Placebo
Started	323	327
Completed	204	219
Not completed	119	108
Consent withdrawn by subject	11	4
Death	97	91
Lost to follow-up	11	13

Baseline characteristics

Reporting groups	
Reporting group title	Lenalidomide
Reporting group description: Lenalidomide 25mg/ day 3 weeks every 4 weeks for 24 months	

Reporting group title	Placebo
Reporting group description: Placebo 25mg/day 3 weeks every 4 weeks for 24 months	

Reporting group values	Lenalidomide	Placebo	Total
Number of subjects	323	327	650
Age categorical Units: Subjects			
Adults (18-64 years)	81	96	177
From 65-84 years	242	231	473
Age continuous Units: years			
arithmetic mean	69	68.5	
standard deviation	± 5.52	± 5.58	-
Gender categorical Units: Subjects			
Female	140	147	287
Male	183	180	363

End points

End points reporting groups

Reporting group title	Lenalidomide

Reporting group description:

Lenalidomide 25mg/ day

3 weeks every 4 weeks for 24 months

Reporting group title	Placebo

Reporting group description:

Placebo 25mg/day

3 weeks every 4 weeks for 24 months

Primary: PFS-FAS maintenance

End point title	PFS-FAS maintenance[1]

End point description:

Remark : The Median-PFS was not reached for Lenalidomide Arm at the end of study

End point type	Primary

End point timeframe:

From the date of randomization to the date of first documented disease progression or relapse assessed by a blinded independent response adjudication committee, or death from any cause whichever occurs first.

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: Median PFS not reached at the end of the study in LEN arm
Median OS not reached at the end of the study in both arms

End point values	Lenalidomide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	327		
Units: months				
number (not applicable)	0	88.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Remark : The Median-OSwas not reached for both Arms at the end of study

End point type	Secondary

End point timeframe:

OS measured from the date of randomization to the date of death from any cause.

End point values	Lenalidomide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	327		
Units: months				
number (not applicable)				
OS_FAS maintenance	0000000	0000000		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AE) regardless of seriousness or relationship to Investigational Product that occurred after the informed consent up to 60 days after the last study drug administration

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Lenalidomide

Reporting group description:

Lenalidomide 25mg/ day

3 weeks every 4 weeks for 24 months

Reporting group title	Placebo

Reporting group description:

Placebo 25mg/day

3 weeks every 4 weeks for 24 months

Serious adverse events	Lenalidomide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	99 / 322 (30.75%)	92 / 323 (28.48%)	
number of deaths (all causes)	98	91	
number of deaths resulting from adverse events	0	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subjects affected / exposed	9 / 322 (2.80%)	27 / 323 (8.36%)	
occurrences causally related to treatment / all	7 / 15	5 / 40	
deaths causally related to treatment / all	0 / 0	0 / 3	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	4 / 322 (1.24%)	6 / 323 (1.86%)	
occurrences causally related to treatment / all	3 / 4	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures			

subjects affected / exposed	1 / 322 (0.31%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
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	3 / 322 (0.93%)	5 / 323 (1.55%)	
occurrences causally related to treatment / all	1 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Immune system disorders			
subjects affected / exposed	1 / 322 (0.31%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 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 / 322 (0.00%)	1 / 323 (0.31%)	
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	12 / 322 (3.73%)	7 / 323 (2.17%)	
occurrences causally related to treatment / all	5 / 12	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	3 / 322 (0.93%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Investigations			
subjects affected / exposed	1 / 322 (0.31%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	9 / 322 (2.80%)	6 / 323 (1.86%)	
occurrences causally related to treatment / all	3 / 9	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	19 / 322 (5.90%)	14 / 323 (4.33%)	
occurrences causally related to treatment / all	14 / 23	8 / 18	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	11 / 322 (3.42%)	5 / 323 (1.55%)	
occurrences causally related to treatment / all	2 / 12	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	13 / 322 (4.04%)	7 / 323 (2.17%)	
occurrences causally related to treatment / all	9 / 18	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	0 / 322 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorders			
subjects affected / exposed	0 / 322 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	10 / 322 (3.11%)	7 / 323 (2.17%)	
occurrences causally related to treatment / all	7 / 13	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	6 / 322 (1.86%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	3 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	8 / 322 (2.48%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	6 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	2 / 322 (0.62%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Endocrine disorders			
subjects affected / exposed	3 / 322 (0.93%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	5 / 322 (1.55%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	3 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	25 / 322 (7.76%)	15 / 323 (4.64%)	
occurrences causally related to treatment / all	17 / 29	2 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Metabolism and nutrtion disorders			
subjects affected / exposed	2 / 322 (0.62%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	2 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lenalidomide	Placebo	
Total subjects affected by non-serious adverse events subjects affected / exposed	197 / 322 (61.18%)	176 / 323 (54.49%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Neoplasms benign, malignant and unspecified (incl cysts and polyps) subjects affected / exposed occurrences (all)	1 / 322 (0.31%) 1	1 / 323 (0.31%) 1	
Vascular disorders Vascular disorders subjects affected / exposed occurrences (all)	14 / 322 (4.35%) 14	9 / 323 (2.79%) 9	
Surgical and medical procedures Surgical and medical procedures subjects affected / exposed occurrences (all)	2 / 322 (0.62%) 2	7 / 323 (2.17%) 10	
General disorders and administration site conditions General disorders and administration site conditions subjects affected / exposed occurrences (all)	31 / 322 (9.63%) 36	19 / 323 (5.88%) 20	
Immune system disorders Immune system disorders subjects affected / exposed occurrences (all)	2 / 322 (0.62%) 2	2 / 323 (0.62%) 2	
Reproductive system and breast disorders Reproductive system and breast disorders subjects affected / exposed occurrences (all)	4 / 322 (1.24%) 4	1 / 323 (0.31%) 1	
Respiratory, thoracic and mediastinal disorders			

Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	16 / 322 (4.97%)	8 / 323 (2.48%)	
occurrences (all)	19	8	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	7 / 322 (2.17%)	14 / 323 (4.33%)	
occurrences (all)	9	15	
Investigations			
Investigations			
subjects affected / exposed	10 / 322 (3.11%)	17 / 323 (5.26%)	
occurrences (all)	11	22	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	34 / 322 (10.56%)	32 / 323 (9.91%)	
occurrences (all)	49	50	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	9 / 322 (2.80%)	2 / 323 (0.62%)	
occurrences (all)	11	4	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	42 / 322 (13.04%)	35 / 323 (10.84%)	
occurrences (all)	55	45	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	193 / 322 (59.94%)	93 / 323 (28.79%)	
occurrences (all)	719	194	
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	2 / 322 (0.62%)	6 / 323 (1.86%)	
occurrences (all)	2	7	
Eye disorders			
Eye disorders			
subjects affected / exposed	6 / 322 (1.86%)	2 / 323 (0.62%)	
occurrences (all)	6	2	
Gastrointestinal disorders			

Gastrointestinal disorders			
subjects affected / exposed	32 / 322 (9.94%)	20 / 323 (6.19%)	
occurrences (all)	43	32	
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	0 / 322 (0.00%)	1 / 323 (0.31%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	47 / 322 (14.60%)	12 / 323 (3.72%)	
occurrences (all)	64	13	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	2 / 322 (0.62%)	1 / 323 (0.31%)	
occurrences (all)	2	2	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	23 / 322 (7.14%)	16 / 323 (4.95%)	
occurrences (all)	28	20	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	114 / 322 (35.40%)	107 / 323 (33.13%)	
occurrences (all)	244	176	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	7 / 322 (2.17%)	5 / 323 (1.55%)	
occurrences (all)	10	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2009	Protocol V2 and ICF V2.1
13 April 2010	Protocol V3 and ICF V3
30 August 2011	Protocol V4 and ICF V4
06 July 2012	Protocol V5 and ICF V5 and ICF Bio V3
03 May 2013	Protocol V6 and ICF V6
20 November 2014	Protocol V7 and additional patient information V1
10 October 2017	Protocol V8
13 February 2019	Protocol V9

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported