Clinical trial results:
A prospective phase II study of bendamustine in patients aged over 60 years with classical Hodgkin lymphoma treated by prednisone, vinblastine, and doxorubicin

Summary

EudraCT number	2014-001002-17
Trial protocol	BE
Global end of trial date	10 November 2020

Results information

Result version number	v1 (current)
This version publication date	04 June 2022
First version publication date	04 June 2022

Trial information

Trial identification

Sponsor protocol code	PVAB

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02414568
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LYSARC
Sponsor organisation address	Centre hospitalier Lyon Sud, 165 chemin du grand Revoyet, LYON, France, 69495
Public contact	Fabienne Morand (Project Manager), LYSARC , 33 (0)472 66 38 53, fabienne.morand@lysarc.org
Scientific contact	Fabienne Morand (Project Manager), LYSARC , 33 (0)472 66 38 53, fabienne.morand@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	10 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary endpoint of the study is to assess the Complete Metabolic Response (CMR) rate at the final evaluation after completion of study treatment (after 6 cycles of study treatment or at premature treatment discontinuation) defined according to Lugano Classification (PET-CT-Based response).

Protection of trial subjects:

An ICF explaining the procedures of the study, including the potential hazards, was reviewed and approved by the IEC prior to its use. Before entering the study, the ICF was read by and explained to all subjects. Each subject had ample opportunity to ask questions and was assured of the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision.
Each subject was required to sign an ICF to participate in the study. Two specific ICFs, for the collection of biological samples and for a genetic study for medical purposes, were also required to be signed by each subject willing to participate in these studies. Each subject received a copy of each signed and dated ICF.

Background therapy:

Prednisone, vinblastine and doxorubicin were not tested and were given to patients as standard treatment.

Evidence for comparator:

No comparator was used.

Actual start date of recruitment	17 July 2015
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	Belgium: 10
Country: Number of subjects enrolled	France: 80
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	26
From 65 to 84 years	60
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Date of recrutement :
First inclusion : France 17JUL2015 / Belgium 18DEC2015
Last inclusion : France 31JUL2018 / Belgium 16MAY2018

Pre-assignment

Screening details:

Number of patients screened : 99 patients
- 9 patient not included
Number of patients included: 90 patients
- 1 patient with no study drug administration
Number of patients in the Full Analysis Set : 89 patients

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	Experimental

Arm description:

Patients with at least one administration of study treatment

Arm type	Experimental
Investigational medicinal product name	Bendamustine Hydrochloride
Investigational medicinal product code	3543-75-7
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

bendamustine is injected via IV only at J1 with a dose at 120mg/m2 every 3 week during 4 or 6 cycles

Number of subjects in period 1[1]	Experimental
Started	89
Completed	78
Not completed	11
Adverse event, serious fatal	2
Consent withdrawn by subject	1
Adverse event, non-fatal	6
concurrent illness	1
Lack of efficacy	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 90 patients were included in the study. However, one patient had no study drug administration and was not included in the full analysis set. This is the reason why only 89 patients were analyzed.

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	89	89	
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)	26	26	
From 65-84 years	59	59	
85 years and over	4	4	
Age continuous Units: years			
median	68		
full range (min-max)	61 to 88	-	
Gender categorical Units: Subjects			
Female	31	31	
Male	58	58	

End points

End points reporting groups

Reporting group title	Experimental

Reporting group description:

Patients with at least one administration of study treatment

Primary: Complete metabolic response rate at the end of study treatment

End point title	Complete metabolic response rate at the end of study treatment[1]

End point description:

According to Lugano Classification (PET-CT based response)

End point type	Primary

End point timeframe:

At the end of study treatment (after 6 cycles of study treatment or at premature treatment discontinuation)

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: Non-comparative phase II study. The confidence interval is included in the primary endpoint.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: Percentage				
CMR	69			
Not CMR	20			

Statistical analyses

No statistical analyses for this end point

Secondary: PFS at 4 years

End point title	PFS at 4 years

End point description:

End point type	Secondary

End point timeframe:

From the date of inclusion to the date of first documented disease progression, relapse or death from any cause, whatever the event that occurs first.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: percentage				
number (confidence interval 50%)	50.3 (38.9 to 60.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: DFS at 4 years

End point title	DFS at 4 years

End point description:

End point type	Secondary

End point timeframe:

From the time of attainment of CMR (according to the Lugano Classification; PET-CT-Based response) to the date of first documented disease progression, relapse or death from any cause.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: percentage				
number (confidence interval 62.8%)	62.8 (49.4 to 73.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: OS at 4 years

End point title	OS at 4 years

End point description:

End point type	Secondary

End point timeframe:

from the date of inclusion to the date of death from any cause. Alive patients will be censored at their last date of contact.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: percentage				
number (confidence interval 69%)	69 (56.6 to 78.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of informed consent signature to 30 days after last study drug administration

Adverse event reporting additional description:

After the last drug administration, only the SAEs with the AEs corresponding are reported

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Safety analysis

Reporting group description: -

Serious adverse events	Safety analysis		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 89 (31.46%)		
number of deaths (all causes)	24		
number of deaths resulting from adverse events	4		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal carcinoma			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			

subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac valve disease			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiogenic shock			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			
Brain stem haematoma			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Febrile bone marrow aplasia			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Leukopenia				
subjects affected / exposed	2 / 89 (2.25%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Bone marrow failure				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
histiocytosis hematophagic				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
General physical health deterioration				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mucosal inflammation				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Strangulated hernia				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obstructive defaecation			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Pneumonitis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Suicide attempt				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pyelonephritis				
subjects affected / exposed	2 / 89 (2.25%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	2 / 89 (2.25%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	2 / 89 (2.25%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Bacterial prostatitis				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Citrobacter sepsis				

subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia bacteraemia				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia infection				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia pyelonephritis				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fungal infection				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Prostatitis Escherichia coli				

subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety analysis		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 89 (96.63%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Oesophageal carcinoma			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	5		
General physical health deterioration			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Mucosal inflammation			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Strangulated hernia			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Acute respiratory distress syndrome subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Pneumonitis subjects affected / exposed occurrences (all) Pulmonary embolism subjects affected / exposed occurrences (all) Pulmonary oedema subjects affected / exposed occurrences (all)	1 / 89 (1.12%) 1 1 / 89 (1.12%) 1 1 / 89 (1.12%) 1 1 / 89 (1.12%) 1 1 / 89 (1.12%) 1		
Psychiatric disorders Suicide attempt subjects affected / exposed occurrences (all)	1 / 89 (1.12%) 1		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Infusion related reaction subjects affected / exposed occurrences (all)	1 / 89 (1.12%) 1 1 / 89 (1.12%) 1		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all) Cardiac valve disease subjects affected / exposed occurrences (all) Cardiogenic shock subjects affected / exposed occurrences (all)	2 / 89 (2.25%) 3 1 / 89 (1.12%) 1 1 / 89 (1.12%) 1		

Nervous system disorders			
Brain stem haematoma			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Polyneuropathy			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	73 / 89 (82.02%)		
occurrences (all)	125		
Leukopenia			
subjects affected / exposed	29 / 89 (32.58%)		
occurrences (all)	75		
Neutropenia			
subjects affected / exposed	25 / 89 (28.09%)		
occurrences (all)	71		
Anaemia			
subjects affected / exposed	12 / 89 (13.48%)		
occurrences (all)	15		
Thrombocytopenia			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	8		
Febrile neutropenia			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences (all)	5		
Febrile bone marrow aplasia			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Bone marrow failure			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Histiocytosis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Gastrointestinal disorders			

Inguinal hernia			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Obstructive defaecation			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Oesophagitis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Renal failure			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences (all)	4		
Urinary tract infection			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences (all)	6		
cystitis			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Fungal infection			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Pyelonephritis			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Rhinitis			

subjects affected / exposed	2 / 89 (2.25%)			
occurrences (all)	2			
Septic shock				
subjects affected / exposed	2 / 89 (2.25%)			
occurrences (all)	2			
Bacterial prostatitis				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences (all)	1			
Bacterial sepsis				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences (all)	1			
Citrobacter sepsis				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences (all)	1			
Clostridium difficile colitis				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences (all)	1			
Device related infection				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences (all)	1			
Escherichia bacteraemia				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences (all)	1			
Escherichia infection				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences (all)	1			
Escherichia pyelonephritis				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences (all)	1			
Escherichia sepsis				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences (all)	1			
Infection				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences (all)	1			
Lung infection				

subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Prostatitis Escherichia coli			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Pseudomonas infection			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Tuberculosis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Hypokalaemia			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Hyperkalaemia			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2018	This amendment was due to a safety alert for bendamustine. A warning and a course of action regarding the risk of opportunistic infections reported during the safety alert have been added to the protocol.
22 September 2020	Addition of 2 exploratory objectives, to analyze centrally and independently of the first results obtained, the PET scans of the patients included in the study. Furthermore, the efficacy population, on which the sensitivity analyses of the primary endpoint was performed, was modified to include patients with non-evaluable responses at the end of treatment, in order to limit the bias of the analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No limitations and caveats.

Notes: