Clinical trial results:
PHASE IB STUDY OF IBRUTINIB COMBINED WITH R-DHAP OR R-DHAOX IN PATIENTS WITH B-CELL LYMPHOMAS

Summary

EudraCT number	2013-000771-33
Trial protocol	BE
Global end of trial date	22 December 2018

Results information

Result version number	v1 (current)
This version publication date	02 January 2021
First version publication date	02 January 2021

Trial information

Trial identification

Sponsor protocol code	BIBLOS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02055924
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LYSARC
Sponsor organisation address	Centre Hospitalier Lyon-Sud Secteur Sainte Eugénie - Pavillon 6D , PIERRE-BENITE, France, 69495
Public contact	Julie ASSEMAT, LYSARC, 0033 472669333,
Scientific contact	Gilles SALLES, LYSA, 0033 472669333,

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	29 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 December 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine the recommended dose of ibrutinib when administered in combination with R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin) or with R-DHAOx (rituximab + dexametasone + cytarabine + oxaliplatin) in patients with relapsed or refractory B-cell malignancies eligible for autologous stem cell transplantation (ASCT) by assessing the maximum tolerated dose (MTD) observed during the dose escalation part of the study. Assessment of the MTD will be performed by the analysis of the dose-limiting toxicities (DLTs).

Protection of trial subjects:

Salvage therapy planned if patients withdraw from protocol and study treatment.

Background therapy:

R-DHAOx
R-DHAP

Evidence for comparator: -

Actual start date of recruitment	26 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	France: 71
Worldwide total number of subjects	81
EEA total number of subjects	81

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)	53

From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

France: from 26-MAY-2014 to 23-MAR-2018
Belgium: from 13-OCT-2014 to 12-MAR-2018

Pre-assignment

Screening details:

Demographics/Medical History: age, gender, height, relevant medical history, concomitant treatments, history of the NHL, Physical exam, Weight, BSA, Vital signs, ECOG PS, Presence of B symptoms,Tumor and Bone Marrow biopsies, cardiac exam, biochemistry & haematology lab tests, CT/PET scans
Nb of screened pts: 94
Nb of included pts: 85
Rando: NA

Period 1

Period 1 title	overall-trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

NA

Arms

Are arms mutually exclusive?	Yes
Arm title	R-DHAOx

Arm description:

R-DHAOx + ibrutinib

Arm type	Experimental
Investigational medicinal product name	R-DHAOx + Ibrutinib
Investigational medicinal product code	R-DHAOx + Ibrutinib
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

rituximab, oxaliplatin, cytosine arabinoside, dexamethasone IV + ibrutininb PO

Investigational medicinal product name	R-DHAP + Ibrutinib
Investigational medicinal product code	R-DHAP
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

rituximab, cisplatin, cytosine arabinoside, dexamethasone IV + ibrutininb PO

Arm title	R-DHAP

Arm description:

R-DHAP + ibrutinib

Arm type	Experimental
Investigational medicinal product name	R-DHAP + Ibrutinib
Investigational medicinal product code	R-DHAP
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
rituximab, cisplatin, cytosine arabinoside, dexamethasone IV + ibrutininb PO

Number of subjects in period 1	R-DHAOx	R-DHAP
Started	56	25
Completed	43	14
Not completed	13	11
Consent withdrawn by subject	2	1
Following to security alert	5	-
Adverse event, non-fatal	2	6
Progression	4	3
Concurrent illness	-	1

Baseline characteristics

Reporting groups	
Reporting group title	R-DHAOx
Reporting group description:	
R-DHAOx + ibrutinib	
Reporting group title	R-DHAP
Reporting group description:	
R-DHAP + ibrutinib	

Reporting group values	R-DHAOx	R-DHAP	Total
Number of subjects	56	25	81
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			
geometric mean	57.2	59.3	
full range (min-max)	25 to 70	25 to 70	-
Gender categorical			
Units: Subjects			
Female	19	8	27
Male	37	17	54

Subject analysis sets	
Subject analysis set title	Safety analysis
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set includes all patients who took at least one dose of ibrutinib.	

Reporting group values	Safety analysis		
Number of subjects	81		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years geometric mean full range (min-max)	 58.4 25 to 70		
Gender categorical Units: Subjects			
Female Male	27 54		

End points

End points reporting groups

Reporting group title	R-DHAOx
Reporting group description: R-DHAOx + ibrutinib	
Reporting group title	R-DHAP
Reporting group description: R-DHAP + ibrutinib	
Subject analysis set title	Safety analysis
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety Set includes all patients who took at least one dose of ibrutinib.	

Primary: Overall response

End point title	Overall response[1]
End point description:	
End point type	Primary
End point timeframe: 3 or 4 cycles of chemotherapy + ibrutinib = 9 or 12 weeks	

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 analyses since there is no comparison between cohorts

End point values	R-DHAOx	R-DHAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	25		
Units: OR				
Escalation	24	25		
Expansion	32	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AE of grade ≥ 2 for cardiac, renal, neuropathic and hemorrhagic toxicities regardless relationship to investigational product occurring from the date of informed consent form signature to end of treatment evaluation (30 days after last drug adm.)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	1

Reporting groups

Reporting group title	total population

Reporting group description: -

Serious adverse events	total population		
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 81 (53.09%)		
number of deaths (all causes)	26		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences causally related to treatment / all	5 / 8		
deaths causally related to treatment / all	1 / 1		
Immune system disorders			
Iodine allergy			

subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood phosphorus decreased			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
drug administration error			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Neuropathy peripheral			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	15 / 81 (18.52%)		
occurrences causally related to treatment / all	18 / 24		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	11 / 81 (13.58%)		
occurrences causally related to treatment / all	0 / 15		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Venoocclusive liver disease			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	12 / 81 (14.81%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	14 / 81 (17.28%)		
occurrences causally related to treatment / all	0 / 17		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

hyponatremia			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	total population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 81 (92.59%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	6		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	11 / 81 (13.58%)		
occurrences (all)	12		
Immune system disorders			
Iodine allergy			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Investigations			

Blood phosphorus decreased subjects affected / exposed occurrences (all)	3 / 81 (3.70%) 3		
Injury, poisoning and procedural complications drug administration error subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2		
Congenital, familial and genetic disorders Aplasia subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	9 / 81 (11.11%) 12		
Nervous system disorders Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	12 / 81 (14.81%) 14		
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	75 / 81 (92.59%) 336		
Ear and labyrinth disorders Hypoacusis subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	19 / 81 (23.46%) 27		
Hepatobiliary disorders Venoocclusive liver disease subjects affected / exposed occurrences (all)	8 / 81 (9.88%) 10		
Skin and subcutaneous tissue disorders			

Rash subjects affected / exposed occurrences (all)	4 / 81 (4.94%) 4		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all)	16 / 81 (19.75%) 17		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	19 / 81 (23.46%) 28		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2014	Update of protocol with modifications on end of treatment evaluation, abnormal lab ranges declaration and description of IMP + new IB of Ibrutinib v8.0
05 October 2015	New design of escalation phase, updated protocol and new IB of ibrutinib v9.0
14 February 2017	Adding of antiviral prophylaxis, update of protocol and new IB of ibrutinib v10.0
29 June 2017	Slight changes in the design of expansion phase and update of protocol
19 October 2017	Update of protocol Following observation of HBV reactivation, update of dexamethasone administration, and update of SAE reporting rules
10 April 2018	Update of protocol with adding of an exclusion criterion: history of liver chronic disease or venoocclusive syndrome, and new IB of ibrutinib v11.0

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 March 2018	Following to 3 cases of venoocclusive syndrome in the trial, ANSM and LYSARC decided to stop recruitment prematurely.	-

Notes:

Limitations and caveats

None reported