Clinical trial results:
A multicenter pilot phase II study for the preliminary evaluation of feasibility, activity and safety of the administration of Bendamustine and Ofatumumab in combination in marginal zone B-cell lymphomas (MZL)

Summary

EudraCT number	2011-003495-36
Trial protocol	IT
Global end of trial date	26 September 2016

Results information

Result version number	v1 (current)
This version publication date	15 October 2017
First version publication date	15 October 2017

Trial information

Trial identification

Sponsor protocol code	S10BEOF01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	CLinical Organization for Strategies and Solutions S.r.l. - CLIOSS S.r.l.
Sponsor organisation address	Viale Pasteur 10, Nerviano (Mi), Italy, 20014
Public contact	Direzione Scientifica, CLIOSS Srl, 0039 0331581482, cristina.davite@clioss.com
Scientific contact	Direzione Scientifica, CLIOSS Srl, 0039 0331581482, cristina.davite@clioss.com

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	03 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 September 2016
Global end of trial reached?	Yes
Global end of trial date	26 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy (Overall Remission Rate) of ofatumumab and bendamustine in relapsed or refractory marginal zone B-cell lymphomas

Protection of trial subjects:

Study Protocol foresees that therapies considered necessary for the patient's well being might be given at the discretion of the Investigator, i.e. chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems.

Background therapy:

Study Protocol foresees that pre-medication with paracetamol, antihistamine and glicocorticoids had to be performed before each ofatumumab infusion.

Evidence for comparator:

NA

Actual start date of recruitment	13 March 2012
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	Switzerland: 8
Country: Number of subjects enrolled	Italy: 8
Worldwide total number of subjects	16
EEA total number of subjects	8

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)	9

From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment lasted from 28 March 2012 to 03 April 2014.

Pre-assignment

Screening details:

All 16 patients were elegible and treated with bendamustine and ofatumumab.

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	Arm 1

Arm description:

All patients treated with ofatumumab and bendamustine

Arm type	Experimental
Investigational medicinal product name	OFATUMUMAB
Investigational medicinal product code	GSK1841157
Other name	NA
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were treated with Ofatumumab iv 1000 mg on day 1 every 28 days for 6 cycles. The initial rate of the first infusion of 1000 mg ofatumumab (1 mg/mL) had to be 12 mL/h. If no infusion reactions occurred the infusion rate had to be increased every 30 minutes, to a maximum of 400 mL/h. If an infusion reaction developed, the infusion had to be temporarily slowed or interrupted. If the previous infusion were completed without grade ≥ 3 infusion-associated AEs, the subsequent infusion of the 1000 mg ofatumumab (1 mg/mL) could start at a rate of 25 mL/h and had to be doubled every 30 minutes up to a maximum of 400 mL/h.

Investigational medicinal product name	BENDAMUSTINE HYDROCHLORIDE
Investigational medicinal product code	NA
Other name	NA
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bendamustine 90 mg/m2 was administered on days 1 and 2 by iv infusion over 30-60 minutes. I

Number of subjects in period 1	Arm 1
Started	16
Completed	11
Not completed	5
Start new therapy	3
Death	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1
Reporting group description:	
All patients treated with ofatumumab and bendamustine	

Reporting group values	Arm 1	Total	
Number of subjects	16	16	
Age categorical			
Alla treated patients			
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)	9	9	
From 65-84 years	7	7	
85 years and over	0	0	
Age continuous			
All treated patients			
Units: years			
median	63.5		
full range (min-max)	46 to 78	-	
Gender categorical			
Units: Subjects			
Female	7	7	
Male	9	9	
Race			
Units: Subjects			
Caucasian	16	16	
Performance Status (ECOG)			
Units: Subjects			
Zero	15	15	
One	1	1	
Tumor Stage at Study Entry			
Units: Subjects			
Stage I	1	1	
Stage II	2	2	
Stage III	1	1	
Stage IV	12	12	
Primary Tumor Site			
One patient enrolled with the diagnosis of mediastinic marginal zone B-cell lymphoma at stage IV was actually suffering from neuroendocrin tumor.			
Units: Subjects			
Dist. Oesophagus, L. Orbit	1	1	

Gastric	2	2	
Gastric Fundus	1	1	
Left Orbit	1	1	
Lung	2	2	
Lymphonodes	1	1	
Mediastinum	1	1	
Right Thigh Radix	1	1	
Spleen	5	5	
Stomach	1	1	
Prior Antitumor Therapies Units: Subjects			
1-3	11	11	
4-6	3	3	
7-9	2	2	
Type of Prior Therapies Units: Subjects			
Systemic	7	7	
Sistemic + Surgery	9	9	

End points

End points reporting groups

Reporting group title	Arm 1

Reporting group description:

All patients treated with ofatumumab and bendamustine

Subject analysis set title	Evaluable patients
Subject analysis set type	Per protocol

Subject analysis set description:

Efficacy Evaluable (EE) population defined as all treated patients, with no major deviations from the eligibility criteria affecting efficacy evaluation, for whom the tumor response could be evaluated at least once while on treatment. These patients should have received at least 2 cycles after treatment starts, unless disease progression occurred at cycle 1.

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)[1]

End point description:

Overall Remission Rate (ORR) was defined as the percentage of patients with a CR or PR as per Cheson criteria (2007) . For patients with splenic MZL response was defined according to Matutes et al. (2008) and for patients with gastric lymphomas histological response was evaluated according to GELA scoring system (Copie-Bergman et al 2003). A patient with unknown or missing response was to be treated as a non-responder, i.e., the patient was to be included in the denominator when calculating the percentage. Exact methods for calculated confidence intervals were to be utilized.

End point type	Primary

End point timeframe:

CT-scan at the end of cycle 2 and at FU1 (4 months), FU2 (8 months) and FU3 (24 months) after the 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: An ORR of at least 90% was obtained, as expected. The p-value given by the exact binomial test (<.001) lead the rejection of the null hyphotesis (p=0.55) in favour of the althernative one (p=0.90).

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: percentage				
number (not applicable)				
CR + PR	92.9			
SD	7.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

Progression Free Survival was defined as the time from the first treatment administration to documentation of disease progression, start of a new antitumor therapy or death (for any cause).

Patients not known to have progressed or started a new antitumor therapy or died (for any cause) were to be censored for PFS at the time of last tumor assessment.

End point type	Secondary

End point timeframe:

Two years after the end of the treatment.

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: months				
median (confidence interval 95%)				
Progression Free Survival	33 (21.9 to 999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of Response was defined, for the subset of patients with a CR or PR, as the time from when criteria for response were first met until first documented relapse or progression or death due to any cause. If sample size permitted, duration of response had to be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of patients who showed a CR or PR were to be included in this summary.

End point type	Secondary

End point timeframe:

Time to relapse.

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed	13[2]			
Units: months				
median (confidence interval 95%)				
Duration of Response	30.4 (15.5 to 999999)			

Notes:

[2] - Only patients showing CR and PR

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During all study period and followed until 28 days following the last dose of investigational product.

Adverse event reporting additional description:

Drug-related and serious adverse events ongoing at the end of this observation period had to be recorded until they were resolved or the investigator assessed them as chronic or the subject was lost to follow-up or started a new anti-cancer treatment, whichever occurred earlier.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Arm 1

Reporting group description:

All patients treated with ofatumumab and bendamustine

Serious adverse events	Arm 1		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 16 (25.00%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Troponin I increased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Infusion related reaction			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Fistula			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anal abscess			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Arm 1		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Phlebitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Thrombophlebitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 16 (50.00%)		
occurrences (all)	15		
Infusion related reaction			
subjects affected / exposed	8 / 16 (50.00%)		
occurrences (all)	12		
Asthenia			

subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Face oedema			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	3		
Infusion site extravasation			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Infusion site pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Localised oedema			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Pneumonitis			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	14 / 16 (87.50%)		
occurrences (all)	21		
Weight decreased			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	5		
Neutrophil count decreased			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	4		
White blood cell count decereased			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		
Haemoglobin decreased			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
Platelet count decreased			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
Blood bilirubin decreased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Blood glucose decreased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Blood magnesium decreased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Blood potassium decreased			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Blood sodium decreased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
Ataxia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Cognitive disorder			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Dysaesthesia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Eye disorders			

Conjunctivitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Eyelid oedema			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 16 (37.50%)		
occurrences (all)	16		
Abdominal pain upper			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	5		
Abdominal pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Stomatitis			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Onychoclasis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Pain of skin			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Palmar erythema			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Pityriasis rosea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Rash macular			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Skin reaction			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Trichorrhexis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Musculoskeletal chest pain subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Myalgia subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Pain in extremity subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Arthralgia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Back pain subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Groin pain subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Infections and infestations Oral herpes subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Central line infection subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Herpes zoster subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported