Clinical trial results:
Phase II Trial to Evaluate the Efficacy of Obinutuzumab (RO5072759) + Bendamustine Treatment in Patients With Refractory or Relapsed Chronic Lymphocytic Leukemia

Summary

EudraCT number	2013-003388-79
Trial protocol	ES
Global end of trial date	19 November 2018

Results information

Result version number	v1 (current)
This version publication date	27 November 2019
First version publication date	27 November 2019

Trial information

Trial identification

Sponsor protocol code	ML29167

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02071225
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, + 41 616878333, global.trial_information@roche.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	19 November 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of obinutuzumab and bendamustine treatment in subjects with refractory or relapsed chronic lymphocytic leukemia (CLL).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 April 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	55 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 72
Worldwide total number of subjects	72
EEA total number of subjects	72

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	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 72 subjects were recruited at 20 sites in Spain.

Pre-assignment

Screening details:

Subjects enrolled in the study had documented CD20-positive B-cell type relapsed or refractory chronic lymphocytic leukemia (CLL).

Period 1

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

Arms

Arm title	Obinutuzumab + Bendamustine

Arm description:

Subjects received obinutuzumab and bendamustine in 28-days cycles for a maximum of 6 cycles.

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

Dosage and administration details:

70 milligrams per square meter (mg/m^2) given by intravenous (IV) infusion on Days 2 and 3 of Cycle 1 and on Days 1 and 2 of subsequent cycles.

Investigational medicinal product name	Obinutuzmab
Investigational medicinal product code	RO5072759
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg given by IV infusion on Days 1, 8, and 15 of Cycle 1 and on Day 1 of subsequent cycles.

Number of subjects in period 1	Obinutuzumab + Bendamustine
Started	72
Completed	42
Not completed	30
Withdrawal of Consent	2
Protocol Deviation	1
Death	25
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Obinutuzumab + Bendamustine
Reporting group description:	
Subjects received obinutuzumab and bendamustine in 28-days cycles for a maximum of 6 cycles.	

Reporting group values	Obinutuzumab + Bendamustine	Total	
Number of subjects	72	72	
Age categorical Units: Subjects			
Adults (18-64 years)	26	26	
From 65-84 years	46	46	
Age Continuous Units: years			
median	67.9		
full range (min-max)	42.5 to 83.1	-	
Sex: Female, Male Units: Subjects			
Female	24	24	
Male	48	48	

End points

End points reporting groups

Reporting group title	Obinutuzumab + Bendamustine

Reporting group description:

Subjects received obinutuzumab and bendamustine in 28-days cycles for a maximum of 6 cycles.

Primary: Overall Response Rate (ORR) as Assessed by the Investigator Using the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 Criteria

End point title	Overall Response Rate (ORR) as Assessed by the Investigator Using the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 Criteria[1]

End point description:

ORR was defined as percentage of subjects achieving Complete Response (CR), incomplete CR (CRi) or Partial Response (PR). CR: lymphocytes below 4 x 10^9/L, absence of lymphadenopathy, hepatomegaly and splenomegaly, absence of disease or constitutional symptoms, neutrophils > 1.5 x 10^9/L, platelets > 100 x 10^9/L, hemoglobin > 110 g/L, bone marrow at least normocellular for age. CRi: CR with persistent cytopenia, i.e. anemia, thrombocytopenia and/or neutropenia. PR: reduction ≥ 50% of the lymphocyte count AND reduction ≥ 50% of the lymphadenopathy OR reduction ≥ 50% of the size of the liver if enlarged at baseline OR reduction ≥ 50% of the size of the spleen if enlarged at baseline PLUS one of the following: neutrophils > 1.5 x 10^9/L, platelets > 100 x 10^9/L, hemoglobin > 110 g/L or increase ≥ 50% compared to pre-treatment. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and obinutuzumab).

End point type	Primary

End point timeframe:

2-3 months after last dose of the study treatment (up to approximately 9 months)

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 were planned for this one arm study.

End point values	Obinutuzumab + Bendamustine			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: percentage of subjects				
number (confidence interval 95%)	78.6 (66.8 to 87.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Response Rate (BRR) as Assessed by the Investigator Using the IWCLL 2008 Criteria

End point title	Best Response Rate (BRR) as Assessed by the Investigator Using the IWCLL 2008 Criteria

End point description:

Best overall response was defined as percentage of subjects achieving a BR of CR, CRi and PR. CR: lymphocytes below 4x10^9/L, absence of lymphadenopathy, hepatomegaly and splenomegaly, absence

of disease or constitutional symptoms, neutrophils >1.5x10^9/L, platelets >100x10^9/L, hemoglobin >110 g/L, bone marrow at least normocellular for age. CRi: CR with persistent cytopenia, i.e. anemia, thrombocytopenia and/or neutropenia. PR: reduction ≥50% of the lymphocyte count AND reduction ≥50% of the lymphadenopathy OR reduction ≥50% of the size of liver if enlarged at baseline OR reduction ≥50% of the size of the spleen if enlarged at baseline PLUS one of the following: neutrophils >1.5x10^9/L, platelets >100x10^9/L, hemoglobin >110 g/L or increase ≥50% compared to pre-treatment. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and obinutuzumab). Reported here is the number of subjects for whom data for BR achieved were available.

End point type	Secondary

End point timeframe:

During study treatment and until 6 months after end of study treatment at approximately 12 months

End point values	Obinutuzumab + Bendamustine			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: percentage of subjects				
number (not applicable)				
CR	46.3			
CRi	1.9			
PR	42.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS is defined as the time from the start of treatment to disease progression (DP), relapse or death from any cause, whichever occurs first, as assessed by the investigator. DP: at least one of the following characteristics: increase ≥50% in lymphocytes up to at least 5x10^9/L, appearance of new palpable lymph nodes, increase ≥50% of the longest diameter of any previous area of clinically significant lymphadenopathy, increase ≥50% of the size of the liver and/or spleen, transformation to a more aggressive histology, after treatment progression of any cytopenia: decrease of hemoglobin levels of more than 20 g/L or to below 100 g/L and/or decrease of platelet counts by more than 50% or to below 100x10^9/L and/or decrease in the neutrophil counts by more than 50% or to below 1.0x10^9/L if the marrow biopsy also shows infiltration of clonal CLL cells. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and obinutuzumab).

End point type	Secondary

End point timeframe:

From start of treatment up to disease progression or relapse or death, whichever occurred first (up to approximately 4.5 years)

End point values	Obinutuzumab + Bendamustine			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: months				
median (confidence interval 95%)	24.14 (20.81 to 27.47)			

Statistical analyses

No statistical analyses for this end point

Secondary: Event Free Survival (EFS)

End point title	Event Free Survival (EFS)

End point description:

EFS was defined as the time from the start of treatment to DP/relapse, death from any cause or start of a new anti-leukemia therapy. DP: at least one of the following characteristics: increase ≥ 50% in lymphocytes up to at least 5 x 10^9/L, appearance of new palpable lymph nodes, increase ≥ 50% of the longest diameter of any previous area of clinically significant lymphadenopathy, increase ≥ 50% of the size of the liver and/or spleen, transformation to a more aggressive histology, after treatment, progression of any cytopenia: decrease of hemoglobin levels of more than 20 g/L or to below 100 g/L and/or decrease of platelet counts by more than 50% or to below 100 x 10^9/L and/or decrease in the neutrophil counts by more than 50% or to below 1.0 x 10^9/L if the marrow biopsy also shows infiltration of clonal CLL cells. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and obinutuzumab).

End point type	Secondary

End point timeframe:

From start of treatment up to disease progression or relapse or death or start of a new anti-leukemic therapy, whichever occurred first (up to approximately 4.5 years)

End point values	Obinutuzumab + Bendamustine			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: months				
median (confidence interval 95%)	24.14 (19.96 to 28.32)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the start of study treatment to death from any cause. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and

obinutuzumab). Here, 99999 indicates that median of OS for efficacy population was not reached.

End point type	Secondary

End point timeframe:

From start of treatment up to death of any cause (up to approximately 4.5 years)

End point values	Obinutuzumab + Bendamustine			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Free Survival (DFS)

End point title	Disease Free Survival (DFS)

End point description:

DFS was defined for all subjects who achieved CRi or CR. DFS lasted from the date on which CRi or CR was recorded until date on which first DP or death from any cause occurred. DP: at least one: increase ≥50% in lymphocytes up to at least 5x10^9/L, appearance of new palpable lymph nodes, increase ≥50% of longest diameter of any previous area of clinically significant lymphadenopathy, increase ≥50% of size of liver and/or spleen, transformation to a more aggressive histology, after treatment, progression of any cytopenia: decrease of hemoglobin levels of more than 20 g/L or to below 100 g/L and/or decrease of platelet counts by more than 50% or to below 100x10^9/L and/or decrease in neutrophil counts by more than 50% or to below 1.0x10^9/L if marrow biopsy also shows infiltration of clonal CLL cells. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and obinutuzumab). Included in the analysis are subjects who achieved CRi or CR.

End point type	Secondary

End point timeframe:

From occurrence of complete response up to disease progression or death, whichever occurred first (up to approximately 4.5 years)

End point values	Obinutuzumab + Bendamustine			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: months				
median (confidence interval 95%)	23.02 (21.38 to 24.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)

End point description:

DR was defined for subjects with CRi, CR or PR. DR spanned from date on which response was recorded until the date on which DP or death from any cause occurred. DP: at least one: increase ≥50% in lymphocytes up to at least 5x10^9/L, appearance of new palpable lymph nodes, increase ≥50% of the longest diameter of any previous area of clinically significant lymphadenopathy, increase ≥50% of size of liver and/or spleen, transformation to a more aggressive histology, after treatment, progression of any cytopenia: decrease of hemoglobin levels of more than 20 g/L or to below 100 g/L and/or decrease of platelet counts by more than 50% or to below 100x10^9/L and/or decrease in neutrophil counts by more than 50% or to below 1.0 x 10^9/L if marrow biopsy also shows infiltration of clonal CLL cells. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and obinutuzumab). Included in the analysis are subjects who achieved CRi, CR or PR.

End point type	Secondary

End point timeframe:

From occurrence of CR or PR up to disease progression or death, whichever occurred first (up to approximately 4.5 years)

End point values	Obinutuzumab + Bendamustine			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: months				
median (confidence interval 95%)	21.41 (17.60 to 25.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Re-treatment/New Anti-leukemia Therapy

End point title	Time to Re-treatment/New Anti-leukemia Therapy

End point description:

Time to re-treatment/new leukemia therapy was defined as the time between the start of treatment and the date of the first administration of re-treatment or new leukemia therapy. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and obinutuzumab). Here, 99999 indicates that median of time to re-treatment for efficacy population was not reached.

End point type	Secondary

End point timeframe:

Up to 4.5 years

End point values	Obinutuzumab + Bendamustine			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Minimal Residual Disease (MRD) Negativity

End point title	Percentage of Subjects With Minimal Residual Disease (MRD) Negativity

End point description:

MRD negativity was defined as the presence of less than 1 cell of CLL per 10,000 leukocytes (= category 0, <0.01%) assessed in bone marrow (BM) and peripheral blood (PB) by flow cytometry after the end of the treatment at the final response assessment. Intent-to-treat (ITT) population included all subjects, who received at least one dose of any treatment.

End point type	Secondary

End point timeframe:

At approximately 9 months

End point values	Obinutuzumab + Bendamustine			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: percentage of subjects				
number (not applicable)				
MRD in BM: Cat 0	36.4			
MRD in PB: Cat 0	53.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not

considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as AEs. An SAE was any AE that was any of the following: fatal, life-threatening, required or prolonged inpatient hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/ birth defect, and was considered a significant medical event by the investigator. Safety population included all subjects, who received at least one dose of any treatment.

End point type	Secondary

End point timeframe:

Up to approximately 4.5 years

End point values	Obinutuzumab + Bendamustine			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: percentage of subjects				
number (not applicable)				
AEs	94.4			
SAEs	51.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With AEs of Special Interest (AESIs)

End point title	Percentage of Subjects With AEs of Special Interest (AESIs)

End point description:

AESIs included any of the following: SAEs associated with the infusion of obinutuzumab: obinutuzumab serious infusion-related reactions, which were defined as AEs occurring during or within 24 hours following the administration of an infusion of obinutuzumab and considered related to obinutuzumab; serious infection; serious neutropenia; any tumor lysis syndrome (TLS); second malignancies. Safety population included all subjects, who received at least one dose of any treatment.

End point type	Secondary

End point timeframe:

Up to approximately 4.5 years

End point values	Obinutuzumab + Bendamustine			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: percentage of subjects				
number (not applicable)	45.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Infusion-related Reactions (IRRs)

End point title	Percentage of Subjects With Infusion-related Reactions (IRRs)

End point description:

IRRs were defined as AEs occurring during or within 24 hours following the administration of an infusion and considered related to drug treatment. Safety population included all subjects, who received at least one dose of any treatment.

End point type	Secondary

End point timeframe:

Up to end of treatment at 6 months

End point values	Obinutuzumab + Bendamustine			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: percentage of subjects				
number (not applicable)	20.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Discontinued Treatment Prematurely

End point title	Percentage of Subjects Who Discontinued Treatment Prematurely

End point description:

Safety population included all subjects, who received at least one dose of any treatment.

End point type	Secondary

End point timeframe:

Up to end of treatment at 6 months

End point values	Obinutuzumab + Bendamustine			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: percentage of subjects				
number (not applicable)	41.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Previous/Concomitant Diseases

End point title	Percentage of Subjects With Previous/Concomitant Diseases

End point description:

Safety population included all subjects, who received at least one dose of any treatment.

End point type	Secondary

End point timeframe:

Up to approximately 4.5 years

End point values	Obinutuzumab + Bendamustine			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: percentage of subjects				
number (not applicable)	97.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Concomitant Medication

End point title	Percentage of Subjects With Concomitant Medication

End point description:

Concomitant therapies included any medication (prescription medication, over-the-counter medications, herbal/homeopathic remedies, nutritional supplements) used by subjects in the 7 days prior to screening until the end of treatment. The following treatments were not permitted during the study treatment period: investigational or unauthorized or unapproved medicinal products, immunotherapy or radioimmunotherapy (other than the trial immunotherapy, obinutuzumab), chemotherapy (other than the trial chemotherapy, bendamustine) and radiotherapy. Safety population included all subjects, who received at least one dose of any treatment.

End point type	Secondary

End point timeframe:

From 7 days prior to screening to the end of treatment at 6 months

End point values	Obinutuzumab + Bendamustine			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: percentage of subjects				
number (not applicable)	54.2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to approximately 4.5 years	
Adverse event reporting additional description:	
Safety population included all subjects, who received at least one dose of any treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Obinutuzumab + Bendamustine
Reporting group description:	
Subjects received obinutuzumab and bendamustine in 28-days cycles for a maximum of 6 cycles.	

Serious adverse events	Obinutuzumab + Bendamustine		
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 72 (51.39%)		
number of deaths (all causes)	25		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastrointestinal stromal tumour			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Glioblastoma multiforme			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Laryngeal squamous cell carcinoma			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			

subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Squamous cell carcinoma of lung				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertensive crisis				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Dyspnoea				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Neutropenia				
subjects affected / exposed	9 / 72 (12.50%)			
occurrences causally related to treatment / all	11 / 12			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	8 / 72 (11.11%)			
occurrences causally related to treatment / all	6 / 10			
deaths causally related to treatment / all	0 / 0			
Acute myeloid leukaemia				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Acute myelomonocytic leukaemia				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			

Haemophagocytic lymphohistiocytosis				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	8 / 72 (11.11%)			
occurrences causally related to treatment / all	3 / 8			
deaths causally related to treatment / all	0 / 0			
Infusion related reaction				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Cachexia				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Mucosal inflammation				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchiolitis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 72 (11.11%)		
occurrences causally related to treatment / all	2 / 9		
deaths causally related to treatment / all	0 / 2		
Respiratory tract infection			
subjects affected / exposed	6 / 72 (8.33%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Septic shock			

subjects affected / exposed	3 / 72 (4.17%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	1 / 1			
Bronchitis				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Abdominal Sepsis				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung Infection				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Periorbital cellulitis				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rotavirus infection				

subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Serratia sepsis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tuberculosis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Obinutuzumab + Bendamustine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 72 (93.06%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		

Cardiac disorders Dyspnoea subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all)	 6 / 72 (8.33%) 7 4 / 72 (5.56%) 4		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	 4 / 72 (5.56%) 4 4 / 72 (5.56%) 4		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	 48 / 72 (66.67%) 147 30 / 72 (41.67%) 51 14 / 72 (19.44%) 35		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Infusion related reaction subjects affected / exposed occurrences (all)	 28 / 72 (38.89%) 37 27 / 72 (37.50%) 38 13 / 72 (18.06%) 14		
Gastrointestinal disorders			

Nausea subjects affected / exposed occurrences (all)	17 / 72 (23.61%) 22		
Diarrhoea subjects affected / exposed occurrences (all)	16 / 72 (22.22%) 22		
Constipation subjects affected / exposed occurrences (all)	9 / 72 (12.50%) 11		
Vomiting subjects affected / exposed occurrences (all)	8 / 72 (11.11%) 10		
Abdominal pain subjects affected / exposed occurrences (all)	5 / 72 (6.94%) 6		
Abdominal pain upper subjects affected / exposed occurrences (all)	4 / 72 (5.56%) 4		
Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all)	4 / 72 (5.56%) 4		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	11 / 72 (15.28%) 13		
Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 72 (12.50%) 9		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	9 / 72 (12.50%) 9		
Rash subjects affected / exposed occurrences (all)	6 / 72 (8.33%) 6		

Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	19 / 72 (26.39%)		
occurrences (all)	23		
Urinary tract infection			
subjects affected / exposed	6 / 72 (8.33%)		
occurrences (all)	7		
Herpes zoster			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	6		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2014	Protocol was amended to reflect changes in the safety profile of obinutuzumab with regard to a higher incidence of thrombocytopenia and haemorrhagic events during the first cycle in patients with CLL treated with obinutuzumab plus chlorambucil, as compared to patients treated with rituximab plus chlorambucil or chlorambucil alone, in the phase 3 pivotal study BO21004/2009-012476-28. Patients who experienced Grade 3 or 4 neutropenia were to be monitored until neutrophil values returned to at least Grade 2. The use of G-CSF was allowed for treatment of neutropenia in this study. Primary prophylaxis with G-CSF was recommended according to the American Society of Clinical Oncology (ASCO), the European Organisation for Research and Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO) guidelines, namely for patients who were >/= 60 years old and/or with co-morbidities. Severe and life-threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) had been observed during treatment with obinutuzumab. Fatal haemorrhagic events had also been reported in subjects treated with obinutuzumab. It seemed that the first cycle was the greatest risk of haemorrhage in obinutuzumab-treated subjects. A clear relationship between thrombocytopenia and haemorrhagic events had not been established. Subjects treated with concomitant medication, which could possibly worsen thrombocytopenia-related events such as platelet inhibitors and anticoagulants, could be at greater risk of bleeding. Subjects were to be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests were to be performed until the event resolved, and dose delays were to be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e. platelet transfusion) according to institutional practice was at the discretion of the treating physician.
29 January 2015	Protocol was amended to add clarity to elements that were causing confusion at study sites based on experiences and to correct errors. Additional guidance was added to improve management and increase the safety of patients. The amendment also sought to communicate the risk of tumor lysis syndrome (TLS) and reinforced adherence to the protocol when treating subjects in the study: Guidance was clarified to improve the management and emphasis on the monitoring of patients who were at high risk for tumor lysis syndrome (TLS). Bendamustine is contraindicated in subjects with severe blood count alterations. Therefore, subjects who received bendamustine had to have a leukocyte count > 3,000/mcL at baseline. Patients with prolymphocytic transformation could not be enrolled in the study. For Grade 3 or 4 adverse events when obinutuzumab was administered on Days 1, 2, 8 and 15, up to 2 weeks delay for infusions was allowed during Cycle 1. For subsequent obinutuzumab cycles, a maximum dose delay of 4 weeks was permitted per cycle due to toxicity. A maximum of 8 weeks of cumulative delay due to toxicity was allowed in total per subjects. In patients receiving chemotherapy, chemotherapy had to be similarly delayed matching any obinutuzumab delay and vice versa. Premedication guidance was clarified according to the recommendations for management of Infusion Related Reactions in the obinutuzumab safety reference document. In order to collect more robust data in this broader patient population, immunoglobulins and beta2-microglobulin were now to be tested. Concerning the study visits there was to be a visit of End of Treatment 28 days after last study drug administration, as well as the Final Response Assessment Visit 2-3 months after last study drug administration.

06 October 2015	Protocol was amended in order to extend the exploratory study of the prognostic markers as well as to be consistent with updated safety information regarding gastrointestinal (GI) perforation as an important identified risk associated with obinutuzumab. Cases of GI perforation were reported in patients receiving obinutuzumab, mainly in Non-Hodgkin Lymphoma (NHL). Patients with GI involvement had to be monitored for signs of GI perforation.
31 March 2016	Protocol was amended to implement additional risk minimization measures in patients with chronic lymphocytic leukemia (CLL) at risk of tumor lysis syndrome (TLS) treated with a combination of obinutuzumab and bendamustine. These measures included additional monitoring and laboratory assessments during Cycle 1. If the Howard criteria for TLS were fulfilled (two or more electrolyte laboratory abnormalities present simultaneously) or if a medically relevant laboratory abnormality in TLS-related parameters or a sign of clinical TLS (e.g. increased serum creatinine or cardiac dysrhythmia) were noted, study drugs were to be withheld and patients were to be hospitalized and adequately treated until normalisation of laboratory abnormalities. After normalisation, treatment could be restarted. Patients were to be informed about symptoms or signs of TLS and advised to contact the investigator immediately if any such symptoms occurred.
31 May 2017	Protocol was amended to consider second malignancies as an adverse event of special interest (AESI) and report these events indefinitely, regardless of relationship to study treatment (even if the study has been closed).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported