Clinical trial results:
A phase III, open label, randomized, multicenter trial of Ofatumumab added to Chlorambucil vs. Chlorambucil Monotherapy in previously untreated patients with Chronic Lymphocytic Leukemia

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2008-004932-19
Trial protocol	NL IE DE ES SE BE CZ FR IT GR GB
Global end of trial date	17 May 2018

Results information

Result version number	v2 (current)
This version publication date	31 May 2019
First version publication date	13 November 2014
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	COMB157B2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00748189
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	17 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 May 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate PFS of ofatumumab added to chlorambucil for previously untreated (front-line) CLL compared to chlorambucil monotherapy.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 2008
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	Brazil: 6
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	Germany: 43
Country: Number of subjects enrolled	United Kingdom: 58
Country: Number of subjects enrolled	Greece: 21
Country: Number of subjects enrolled	India: 42
Country: Number of subjects enrolled	Belgium: 60
Country: Number of subjects enrolled	Ireland: 15
Country: Number of subjects enrolled	Italy: 35
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Poland: 41
Country: Number of subjects enrolled	Russian Federation: 28
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Sweden: 16
Country: Number of subjects enrolled	United States: 38

Worldwide total number of subjects	447
EEA total number of subjects	329

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)	139
From 65 to 84 years	301
85 years and over	7

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eligible participants (par.) were stratified by age (<65 years vs. >=65years), stage (Binet A vs. B vs. C) and Eastern Cooperative Oncology Group (ECOG) performance status (0-1 vs. 2). Participants in each stratum were then centrally randomized in a 1:1 ratio to receive ofatumumab plus chlorambucil (O+CHL) or chlorambucil alone (CHL).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Chlorambucil

Arm description:

Participants with previously untreated chronic lymphocytic leukemia (CLL) received chlorambucil monotherapy 10 milligram (mg)/meter squared (m^2) orally on Days 1-7 of every 28-day cycle for a minimum of 3 cycles until best response or a maximum of 12 cycles.

Arm type	Active comparator
Investigational medicinal product name	Chlorambucil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Chlorambucil was administered as 2-mg tablets. The treatment dose was 10 mg/m² given on Days 1-7 every 28 days. For patients suffering from nausea or vomiting, dose splitting to 2 or 3 daily administrations was permitted. Dose delays or reductions were allowed in the event of toxicity

Arm title	Ofatumumab + Chlorambucil

Arm description:

Participants with CLL received intravenous (IV) infusions of ofatumumab on Day 1 (300 mg) and Day 8 (1000 mg) in the first cycle, followed by IV infusions of 1000 mg on the first day of each subsequent 28-day cycle in combination with chlorambucil 10 mg/m^2 orally on Days 1-7 of every 28-day cycle for a minimum of 3 cycles until best response or a maximum of 12 cycles.

Arm type	Experimental
Investigational medicinal product name	Ofatumumab
Investigational medicinal product code	OMB157
Other name	
Pharmaceutical forms	Cutaneous liquid, Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ofatumumab (GSK1841157) was provided as clear, colorless, liquid 100-mg/mL concentrate in 5-mL glass vials. The ofatumumab infusions were prepared in 1000 mL sterile, to yield a 0.3 mg/mL ofatumumab concentration for the first 300-mg infusion and to yield a 1 mg/mL concentration for subsequent 1000-mg infusions. Ofatumumab was infused IV on Day 1 (300 mg) and Day 8 (1000 mg) in the first cycle,
followed by infusions of 1000 mg on the first day of each subsequent 28-day cycle.

Investigational medicinal product name	Chlorambucil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

hlorambucil was administered as 2-mg tablets. The treatment dose was 10 mg/m² given on Days 1-7 every 28 days. For patients suffering from nausea or vomiting, dose splitting to 2 or 3 daily administrations was permitted. Dose delays or reductions were allowed in the event of toxicity

Number of subjects in period 1	Chlorambucil	Ofatumumab + Chlorambucil
Started	226	221
Completed	10	9
Not completed	216	212
Adverse event, serious fatal	99	84
Consent withdrawn by subject	23	29
Physician decision	16	5
Study terminated by Sponsor	70	79
Lost to follow-up	8	15

Baseline characteristics

Reporting groups	
Reporting group title	Chlorambucil
Reporting group description:	
Participants with previously untreated chronic lymphocytic leukemia (CLL) received chlorambucil monotherapy 10 milligram (mg)/meter squared (m^2) orally on Days 1-7 of every 28-day cycle for a minimum of 3 cycles until best response or a maximum of 12 cycles.	
Reporting group title	Ofatumumab + Chlorambucil
Reporting group description:	
Participants with CLL received intravenous (IV) infusions of ofatumumab on Day 1 (300 mg) and Day 8 (1000 mg) in the first cycle, followed by IV infusions of 1000 mg on the first day of each subsequent 28-day cycle in combination with chlorambucil 10 mg/m^2 orally on Days 1-7 of every 28-day cycle for a minimum of 3 cycles until best response or a maximum of 12 cycles.	

Reporting group values	Chlorambucil	Ofatumumab + Chlorambucil	Total
Number of subjects	226	221	447
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	70	69	139
From 65-84 years	151	150	301
85 years and over	5	2	7
Sex: Female, Male Units: Subjects			
Female	86	79	165
Male	140	142	282
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	2	4	6
American Indian or Alaskan Native	1	0	1
Asian - Central/South Asian Heritage	22	19	41
Asian - Mixed Race	0	2	2
White	201	196	397
AgeCategoricalOther Units: Years			
median	70	69	
full range (min-max)	36 to 91	35 to 92	-

End points

End points reporting groups

Reporting group title	Chlorambucil

Reporting group description:

Participants with previously untreated chronic lymphocytic leukemia (CLL) received chlorambucil monotherapy 10 milligram (mg)/meter squared (m^2) orally on Days 1-7 of every 28-day cycle for a minimum of 3 cycles until best response or a maximum of 12 cycles.

Reporting group title	Ofatumumab + Chlorambucil

Reporting group description:

Participants with CLL received intravenous (IV) infusions of ofatumumab on Day 1 (300 mg) and Day 8 (1000 mg) in the first cycle, followed by IV infusions of 1000 mg on the first day of each subsequent 28-day cycle in combination with chlorambucil 10 mg/m^2 orally on Days 1-7 of every 28-day cycle for a minimum of 3 cycles until best response or a maximum of 12 cycles.

Subject analysis set title	Chlorambucil
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants with previously untreated chronic lymphocytic leukemia (CLL) received chlorambucil monotherapy 10 milligram (mg)/meter squared (m^2) orally on Days 1-7 of every 28-day cycle for a minimum of 3 cycles until best response or a maximum of 12 cycles.

Subject analysis set title	Ofatumumab + Chlorambucil
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants with CLL received intravenous (IV) infusions of ofatumumab on Day 1 (300 mg) and Day 8 (1000 mg) in the first cycle, followed by IV infusions of 1000 mg on the first day of each subsequent 28-day cycle in combination with chlorambucil 10 mg/m^2 orally on Days 1-7 of every 28-day cycle for a minimum of 3 cycles until best response or a maximum of 12 cycles.

Subject analysis set title	Study OMB110911: Ofatumumab + Chlorambucil
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with CLL received intravenous (IV) infusions of ofatumumab on Day 1 (300 mg) and Day 8 (1000 mg) in the first cycle, followed by IV infusions of 1000 mg on the first day of each subsequent 28-day cycle in combination with chlorambucil 10 mg/m^2 orally on Days 1-7 of every 28-day cycle for a minimum of 3 cycles until best response or a maximum of 12 cycles.

Subject analysis set title	Study LEUA1001: Chlorambucil
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with CLL, Non-Hodgkin’s lymphoma or other refractory malignancies received three different formulations of a 0.2 mg/kilogram(kg) chlorambucil tablet orally with a two-day interval between drug administration.

Primary: Progression-Free Survival (PFS), as assessed by the Independent Review Committee (IRC)

End point title	Progression-Free Survival (PFS), as assessed by the Independent Review Committee (IRC)

End point description:

PFS is defined as the interval of time between the date of randomization and the earlier of the date of disease progression (PD) and the date of death due to any cause. PD requires at least one of the following: lymphadenopathy, appearance of any new lesion such as enlarged lymph nodes (>1.5 cm) spleen or liver or other infiltrates or an increase by 50% or more in the greatest diameter of any previous site; an increase by 50% or more in the previously noted enlargement of the liver or spleen, an increase by 50% or more in the numbers of blood lymphocytes with at least 5000 lymphocytes per microliter, transformation to a more aggressive histology, or occurrence of cytopenia attributable to chronic lymphocytic leukaemia. Par. who were alive and had not progressed at the time of analysis or if a progression event or death occurred after extensive lost-to-follow-up time or if new anti-cancer therapy was started were censored at the date of the last visit with adequate assessment.

End point type	Primary

End point timeframe:

From randomization to the date of first documented disease progression or death due to any cause, whichever occured first, reported between day of first patient randomized up to about 49 months

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	221		
Units: Months				
median (confidence interval 95%)	13.1 (10.6 to 13.8)	22.4 (19.0 to 25.2)		

Statistical analyses

Statistical analysis title	PFS as assessed by IRC
Comparison groups	Chlorambucil v Ofatumumab + Chlorambucil
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.72

Secondary: Number of participants with the best overall response (OR), as assessed by the IRC

End point title	Number of participants with the best overall response (OR), as assessed by the IRC

End point description:

OR is defined as the number of participants achieving an objective response (complete response [CR], CR with incomplete bone marrow recovery [CRi], partial response [PR], and nodular PR [nPR]). CR (all the criteria at least 2 months after last treatment): no lymphadenopathy (Ly) > 1.5 cm/ hepatomegaly/ splenomegaly/ constitutional symptoms; neutrophils >1500 per microliter (µL), platelets (PL) >100,000/µL, hemoglobin (Hb) >11 grams/deciliter (g/dL), lymphocytes (LC) <4000/µL, bone marrow (BM) sample must be normocellular for age, <30% LC, no lymphoid nodule. CRi: CR criteria, persistent anemia/thrombocytopenia/neutropenia unrelated to CLL but related to drug toxicity. PR: >=50% decrease in LC, Ly, size of liver and spleen and at least one of the following results: PL >100,000/µL or 50% improvement over Baseline (BL), Hb >11 g/dL or 50% improvement over BL. nPR: persistent nodules BM.

End point type	Secondary

End point timeframe:

From randomization until the 259th PFS event occurred, up to about 49 months

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	221		
Units: Participants				
CR	3	27		
CRi	0	5		
nPR	0	1		
PR	152	149		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who were negative for minimal residual disease (MRD)

End point title	Number of participants who were negative for minimal residual disease (MRD)

End point description:

MRD was performed by flow cytometry on a bone marrow or peripheral blood sample taken at least 2 months after final treatment. MRD negative was defined as less than one CLL cell per 10000 leukocytes.

End point type	Secondary

End point timeframe:

From randomization until the 259th PFS event occurred (Median follow-up approximately 28.9 months)

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	221		
Units: Participants				
MRD negative, irrespective of response	8	26		
MRD negative, with an IRC-assessed CR	0	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival is defined as the time from randomization to death due to any cause. Each participant was followed at the time when the total IRC-assessed PFS events occurred. Participants who had not

died were censored at the date of last contact.

End point type	Secondary

End point timeframe:

From randomization up to about 111 months

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	221		
Units: Months				
median (confidence interval 95%)	84.67 (74.25 to 999)	999 (84.50 to 999)		

Statistical analyses

Statistical analysis title	Overall survival

Statistical analysis description:

hazard ratios are
obtained using the Pike estimator. A hazard ratio <1 indicates a lower risk with O+CHL treatment compared with chlorambucil

Comparison groups	Chlorambucil v Ofatumumab + Chlorambucil
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.363
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.17

Secondary: Time to response, as assessed by the IRC

End point title	Time to response, as assessed by the IRC

End point description:

Time to response is defined as the time from randomization to the first response (CR, CRi, nPR, or PR). CR (all the criteria at least 2 months after last treatment): no lymphadenopathy (Ly) > 1.5 cm/ hepatomegaly/ splenomegaly/ constitutional symptoms; neutrophils >1500 per microliter (µL), platelets (PL) >100,000/µL, hemoglobin (Hb) >11 grams/deciliter (g/dL), lymphocytes (LC) <4000/µL, bone marrow (BM) sample must be normocellular for age, <30% LC, no lymphoid nodule. CRi: CR criteria, persistent anemia/thrombocytopenia/neutropenia unrelated to CLL but related to drug toxicity. PR: >=50% decrease in LC, Ly, size of liver and spleen and at least one of the following results: PL >100,000/µL or 50% improvement over Baseline (BL), Hb >11 g/dL or 50% improvement over BL. nPR: persistent nodules BM. Participants with unknown or missing responses were considered as non-responders. Only responders (CR, CRi, PR, nPR) were included in the analysis.

End point type	Secondary

End point timeframe:

From randomization uo to about 27 months

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	182		
Units: Months				
median (confidence interval 95%)	1.9 (1.2 to 1.9)	1.2 (1.0 to 1.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR), as assessed by the IRC

End point title	Duration of response (DOR), as assessed by the IRC

End point description:

DOR is defined as the time from the initial response (CR, CRi, nPR, or PR) to the first documented sign of PD or death due to any cause. PD requires at least one of the following: lymphadenopathy, appearance of any new lesion such as enlarged lymph nodes (>1.5 cm) spleen or liver or other infiltrates or an increase by 50% or more in the greatest diameter of any previous site; an increase by 50% or more in the previously noted enlargement of the liver or spleen, an increase by 50% or more in the numbers of blood lymphocytes with at least 5000 lymphocytes per microliter, transformation to a more aggressive histology, or occurrence of cytopenia attributable to chronic lymphocytic leukaemia. Par. who were alive and had not progressed at the time of analysis or if a progression event occurred after extensive lost-to-follow-up time (>= 12 weeks) were censored at the date of the last visit with adequate assessment. Par. with unknown or missing responses were considered as non-responders.

End point type	Secondary

End point timeframe:

From randomization up to about 43 months

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	182		
Units: Months				
median (confidence interval 95%)	13.2 (10.8 to 16.4)	22.1 (19.1 to 24.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression, as assessed by the IRC

End point title	Time to progression, as assessed by the IRC

End point description:

Time to progression is defined as the time from the date of randomization to disease progression (PD). PD requires at least one of the following: lymphadenopathy, appearance of any new lesion such as enlarged lymph nodes (>1.5 cm) spleen or liver or other infiltrates or an increase by 50% or more in the greatest diameter of any previous site; an increase by 50% or more in the previously noted enlargement of the liver or spleen, an increase by 50% or more in the numbers of blood lymphocytes with at least 5000 lymphocytes per microliter, transformation to a more aggressive histology, or occurrence of cytopenia attributable to chronic lymphocytic leukaemia. Participants who were alive and had not progressed at the time of analysis or if a progression event occurred after extensive lost-to-follow-up time were censored at the date of the last visit with adequate assessment.

End point type	Secondary

End point timeframe:

From randomization up to about 49 months

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	221		
Units: Months				
median (confidence interval 95%)	13.6 (11.2 to 14.6)	23.1 (21.2 to 25.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to next therapy

End point title	Time to next therapy

End point description:

Time to next therapy is defined as the time from randomization until the start of the next-line of treatment.

End point type	Secondary

End point timeframe:

From randomization up to about 49 months

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	64		
Units: Months				
median (confidence interval 95%)	24.67 (22.57 to 29.08)	39.82 (34.69 to 48.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with improvement in ECOG performance status of 0 or 1

End point title	Number of participants with improvement in ECOG performance status of 0 or 1

End point description:

The ECOG performance status scales and criteria are used by doctors and researchers to assess how a participant's disease is progressing, how the disease affects the daily living, and determines appropriate treatment and prognosis. Grade 0, fully active, able to carry on all pre-disease performance without restriction. Grade 1, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. Grade 2, ambulatory and capable of all selfcare, but unable to carry out any work activities; up and about more than 50% of waking hours. Grade 3, capable of only limited selfcare; confined to bed or chair more than 50% of waking hours. Grade 4, completely disabled; cannot carry on any selfcare; totally confined to bed or chair. Grade 5, dead. Participants with an ECOG performance status of 0 or 1 are shown..

End point type	Secondary

End point timeframe:

Baseline, Cycle 3 Day 1, 1 month Follow-up

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	227	217		
Units: Participants				
ECOG (0, 1) at Baseline	209	200		
ECOG (0, 1) at Cycle 3 Day 1	184	189		
ECOG (0, 1) 1 Month Follow-up	183	191		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with improvement in constitutional symptoms (CS)

End point title	Number of participants with improvement in constitutional symptoms (CS)

End point description:

Assessment for the presence of the following symptoms were performed at Screening, Day 1 of each treatment cycle and at every Follow-up visit: night sweats (without signs of infection); unexplained, unintentional weight loss >= 10% within the previous 6 months; recurrent, unexplained fever of greater than 38 degrees celsius or 100.5 degrees fahrenheit for 2 weeks; and extreme fatigue. The best

response refers to overall best response in terms of CR, CRi, PR or nPR. Data are presented for constitutional response= yes and no.

End point type	Secondary

End point timeframe:

Baseline, Cycle 3 Day 1, and 1 month Follow-up

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	221		
Units: Participants				
CS present, Baseline, n=226, 221	120	118		
CS present, Cycle 3 Day 1, n=198, 199	44	33		
CS present, 1 Month Follow-up, n=198, 200	23	22		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with a human anti-human antibody (HAHA) positive result

End point title	Number of participants with a human anti-human antibody (HAHA) positive result

End point description:

Serum samples for analysis of HAHA were collected at Baseline (Screening), Cycle 4 Day 1 (after 3 months of treatment), and at 1 month and 6 months post last dose of ofatumumab. All samples were first tested in a screening step; positive samples from the screening were further evaluated in a confirmation test. The confirmed positive samples were reported as HAHA-positive and further evaluated in the titration test to obtain a titer of HAHA.

End point type	Secondary

End point timeframe:

Baseline, Cycle 4 Day 1, 1 Month Follow-up, and 6 Month Follow-up

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	202		
Units: Participants		0		

Notes:

[1] - not analyzed for anti-ofatumumab antibody.

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax and Ctrough of ofatumumab

End point title	Cmax and Ctrough of ofatumumab

End point description:

Blood samples were collected to assess the plasma concentration of ofatumumab. Maximum concentration (Cmax) and observed drug concentration prior to the next dose (Ctrough) were determined. Blood samples were collected from participants who received ofatumumab plus chlorambucil at pre-dose and 0.5 hours after the end of the ofatumumab infusion at treatment Cycle 1 and Cycle 4 (Days 1, 8, and 85). In addition, pre-dose samples were collected prior to ofatumumab administration at Cycles 2, 3, 5, 6, 9 and 12 (Days 29, 57, 113, 141, 225 and 309), depending on the duration of treatment.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1,Cycle 1 Day 8, Cycle 2 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, and Cycle 9 Day 1

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	193		
Units: Micrograms/Milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
Cmax, Cycle 1 Day 1, n=0, 176	()	51.8 (± 1.03)		
Cmax, Cycle 1 Day 8, n=0, 193	()	241 (± 0.46)		
Cmax, Cycle 4 Day 1, n=0, 169	()	285 (± 0.44)		
Ctrough, Cycle 1 Day 8, n=0, 99	()	2.5 (± 5.85)		
Ctrough, Cycle 2 Day 1, n=0, 138	()	5.2 (± 15.37)		
Ctrough, Cycle 3 Day 1, n=0, 142	()	6.2 (± 17.06)		
Ctrough, Cycle 4 Day 1, n=0, 147	()	15.5 (± 7.99)		
Ctrough, Cycle 5 Day 1, n=0, 149	()	33.5 (± 3.61)		
Ctrough, Cycle 6 Day 1, n=0, 155	()	45.9 (± 2.77)		
Ctrough, Cycle 9 Day 1, n=0, 56	()	55.6 (± 3.50)		

Notes:

[2] - Cmax and Ctrough were not collected for this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Total plasma clearance (CL) of ofatumumab

End point title	Total plasma clearance (CL) of ofatumumab

End point description:

Plasma clearance is defined as the plasma volume which is totally cleared of drug per unit of time. Blood samples were collected from participants who received ofatumumab plus chlorambucil at pre-dose and 0.5 hours after the end of the ofatumumab infusion at treatment Cycle 1 and Cycle 4 (Days 1, 8, and 85). In addition, pre-dose samples were collected prior to the ofatumumab administration at Cycles 2, 3, 5, 6, 9 and 12 (Days 29, 57, 113, 141, 225 and 309), depending on duration of treatment. Samples were also collected during clinic visits on Day 15 (during Cycle 1) and Day 43 (during Cycle 2) and at 1, 3, and 6 months post-treatment.

End point type	Secondary

End point timeframe:

Cycle 4 Day 1

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	183		
Units: Milliliter/hour (mL/h)				
geometric mean (geometric coefficient of variation)	()	15.4 (± 0.73)		

Notes:

[3] - total plasma clearance was not collected for this arm/drug.

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-tau) of ofatumumab

End point title	AUC(0-tau) of ofatumumab

End point description:

Area under the concentration time curve over the dosing interval [AUC(0-tau)] is a measure of drug exposure over time. AUC(0-tau) is defined as the area under the ofatumumab plasma concentration-time curve from dosing to time tau, where tau is the length of the dosing interval of ofatumumab. For estimation of AUC(0-tau), blood samples were collected from participants who received ofatumumab plus chlorambucil at pre-dose and 0.5 hous after the end of the ofatumumab infusion at treatment Cycle 1 and Cycle 4 (Days 1, 8, and 85). In addition, pre-dose samples were collected prior to the ofatumumab administration at Cycles 2, 3, 5, 6, 9 and 12 (Days 29, 57, 113, 141, 225 and 309), depending on duration of treatment. Samples were also collected during clinic visits on Day 15 (during Cycle 1) and Day 43 (during Cycle 2) and at 1, 3, and 6 months post-treatment.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 4 Day 1

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	208		
Units: µg x hours/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1, n=0, 193	()	2621 (± 0.76)		
Cycle 1 Day 8, n=0, 208	()	25369 (± 0.87)		
Cycle 4 Day 1, n=0, 183	()	65100 (± 0.73)		

Notes:

[4] - AUC was not collected for this arm/drug

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of distribution at steady state (Vss) of ofatumumab

End point title	Volume of distribution at steady state (Vss) of ofatumumab

End point description:

Volume of distribution at steady state (Vss) is defined as the distribution of a drug between plasma and the rest of the body at steady state. Blood samples were collected from participants who received ofatumumab plus chlorambucil at predose and 0.5 hour after the end of the ofatumumab infusion at treatment Cycle 1 and Cycle 4 (Days 1, 8, and 85). In addition, pre-dose samples were collected prior to ofatumumab administration at Cycles 2, 3, 5, 6, 9 and 12 (Days 29, 57, 113, 141, 225 and 309), depending on the duration of the treatment. Samples were also collected during clinic visits on Day 15 (during Cycle 1) and Day 43 (during Cycle 2) and at 1, 3, and 6 months post-treatment.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 4 Day 1

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	208		
Units: Liters				
geometric mean (geometric coefficient of variation)				
Vss, Cycle 1 Day 1, n=0, 193	()	7.78 (± 0.55)		
Vss, Cycle 1 Day 8, n=0, 208	()	7.77 (± 0.54)		
Vss, Cycle 4 Day 1, n=0, 183	()	8.06 (± 0.53)		

Notes:

[5] - Vss was not collected for this arm/drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma half life (t1/2) of ofatumumab

End point title	Plasma half life (t1/2) of ofatumumab

End point description:

The terminal half-life (t1/2) of ofatumumab is defined as the time required for the plasma concentration of ofatumumab to reach half of its original concentration. Blood samples were collected to assess the plasma half-life of ofatumumab. Blood samples were collected from participants who received ofatumumab plus chlorambucil pre-dose and 0.5 hours after the end of the ofatumumab infusion at treatment Cycle 1 and Cycle 4 (Days 1, 8, and 85). In addition, pre-dose samples were collected prior to ofatumumab administration at Cycles 2, 3, 5, 6, 9 and 12 (Days 29, 57, 113, 141, 225 and 309), depending on the duration of the treatment. Samples were also collected during clinic visits on Day 15 (during Cycle 1) and Day 43 (during Cycle 2) and at 1, 3, and 6 months post-treatment.

End point type	Secondary

End point timeframe:

Cycle 4 Day 1

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	183		
Units: hours				
geometric mean (geometric coefficient of variation)	()	445 (± 1.05)		

Notes:

[6] - t1/2 was not collected for this arm/drug

Statistical analyses

No statistical analyses for this end point

Secondary: Dose-normalized Cmax of chlorambucil and phenylacetic acid mustard (PAAM)

End point title	Dose-normalized Cmax of chlorambucil and phenylacetic acid mustard (PAAM)

End point description:

Blood samples for the determination of serum concentrations of chlorambucil and its metabolite PAAM were collected from participants in a substudy on Cycle 3 Day 1. The maximum observed concentration (Cmax) of chlorambucil and PAAM normalized to the administered dose was determined as a measure of exposure and compared to reference data from a prior study (LEUA1001) [No NCT number available for this study; GlaxoSmithKline Document Number RM1998/00449/00].

End point type	Secondary

End point timeframe:

Cycle 3 Day 1

End point values	Study OMB110911: Ofatumumab + Chlorambucil	Study LEUA1001: Chlorambucil		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	12		
Units: nanograms per milliliter per milligram				
geometric mean (standard deviation)				
Chlorambucil Cmax/Dose	27.1 (± 0.32)	38.4 (± 0.36)		
PAAM Cmax/Dose	19.3 (± 0.23)	24.3 (± 0.30)		

Statistical analyses

Statistical analysis title	Dose-normalized Cmax of chlorambucil and PAAM
Comparison groups	Study OMB110911: Ofatumumab + Chlorambucil v Study LEUA1001: Chlorambucil

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of Cmax/Dose
Point estimate	0.71
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.53
upper limit	0.94

Statistical analysis title	Dose-normalized Cmax of chlorambucil and PAAM
Comparison groups	Study OMB110911: Ofatumumab + Chlorambucil v Study LEUA1001: Chlorambucil
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of Cmax/Dose
Point estimate	0.79
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.63
upper limit	0.99

Secondary: Dose-normalized AUC(0-6) and AUC(0-inf) of chlorambucil and dose-normalized AUC(0-6) of phenylacetic acid mustard (PAAM)

End point title	Dose-normalized AUC(0-6) and AUC(0-inf) of chlorambucil and dose-normalized AUC(0-6) of phenylacetic acid mustard (PAAM)

End point description:

Blood samples for the determination of serum concentrations of chlorambucil and its metabolite PAAM were collected from participants in a substudy on Cycle 3 Day 1. The area under the plasma concentration-time curve from time zero (pre-dose) extrapolated to infinite time (AUC[0-inf]) and over 6 hours (AUC[0-6]) of chlorambucil and AUC(0-6) of PAAM normalized to the administered dose was determined as a measure of exposure and compared to reference data from a prior study (LEUA1001) [No NCT number available for this study; GlaxoSmithKline Document Number RM1998/00449/00].

End point type	Secondary

End point timeframe:

Cycle 3 Day 1

End point values	Study OMB110911: Ofatumumab + Chlorambucil	Study LEUA1001: Chlorambucil		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	12		
Units: Hours*nanogram/milliliter/milligram				
geometric mean (standard deviation)				
Chlorambucil AUC(0-6)/Dose	67.84 (± 0.24)	65.43 (± 0.44)		
Chlorambucil AUC(0-inf)/Dose	74.42 (± 0.23)	67.10 (± 0.45)		
PAAM AUC(0-6)/Dose	71.52 (± 0.26)	80.32 (± 0.26)		

Statistical analyses

Statistical analysis title	Dose-normalized AUC of PAAM
Comparison groups	Study OMB110911: Ofatumumab + Chlorambucil v Study LEUA1001: Chlorambucil
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of AUC(0-6)/Dose
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.77
upper limit	1.4

Statistical analysis title	Dose-normalized AUC of PAAM
Comparison groups	Study OMB110911: Ofatumumab + Chlorambucil v Study LEUA1001: Chlorambucil
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of AUC(0-inf)/Dose
Point estimate	1.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.82
upper limit	1.5

Statistical analysis title	Dose-normalized AUC of PAAM
Comparison groups	Study OMB110911: Ofatumumab + Chlorambucil v Study LEUA1001: Chlorambucil

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of AUC(0-6)/Dose
Point estimate	0.89
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.72
upper limit	1.1

Secondary: Change from Baseline in health related quality of life (HRQOL)

End point title	Change from Baseline in health related quality of life (HRQOL)

End point description:

HRQOL was assessed using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTCQLQC30), Chronic Lymphocytic Leukemia module (EORTC QLQ-CLL16), EuorQoL-Five Dimension (EQ-5D), and HCQ. Period (P)1 (Day 85, Day 169, Day 253) and P2 (scheduled follow-up (FU) and withdrawal visits) analysis were considered. Baseline (BL) for P1 was defined as score from screening visit and BL for P2 was defined as the last on-treatment score. The 2 principal QoL outcomes were pre-specified as the Global Health scale (GHS/QOL) of the EORTC QLQ-C30 and fatigue scale of the EORTC QLQ-CLL16. For EORTC QLQ-C30,GHS/Qol, the possible scale range was 0-100 (with 100 being 'best') and a positive difference from BL is indicative of better functioning (range -100 to +100). For the EORTC QLQ-CLL16 fatigue scale, the possible scale range was 0-100 (with 0 being 'best') and a negative difference from BL represents an improvement in fatigue (range -100 to +100).

End point type	Secondary

End point timeframe:

Baseline, Cycle 4 day 1, cycle 7 day 1, 1 month follow-up, 6 month follow-up, 12 month follow-up

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	221		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
P1, Cycle 4 Day 1, QLQC30 GHS/QoL score, n=139,159	1.92 (± 21.22)	6.08 (± 21.08)		
P1, Cycle 7 Day 1, QLQC30 GHS/QoL score, n=52, 55	8.01 (± 22.20)	6.97 (± 17.55)		
P1,Cycle 4 Day 1,QLQCLL16 fatigue score, n=145,163	-4.71 (± 27.48)	-4.60 (± 24.23)		
P1, Cycle 7 Day 1,QLQCLL16 fatigue score, n=55,57	-1.21 (± 25.43)	-9.36 (± 22.93)		
P2,1 month FU, QLQC30 GHS/QoL score, n=118, 150	4.79 (± 23.13)	0.56 (± 18.31)		
P2, 6 month FU, QLQC30 GHS/QoL score, n=83, 129	3.01 (± 22.07)	3.75 (± 20.83)		
P2, 12 month FU, QLQC30 GHS/QoL score, n=48, 96	3.82 (± 18.27)	1.22 (± 17.69)		
P2, 1 month FU, QLQCLL16 fatigue score, n=121, 152	-1.24 (± 21.75)	-0.33 (± 19.13)		
P2, 6 month FU, QLQCLL16 fatigue score, n=85, 131	-7.06 (± 18.96)	-2.93 (± 19.34)		

P2, 12 month FU, QLQCLL16 fatigue score, n=51, 95	-2.94 (± 17.86)	0.88 (± 16.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any adverse event (AE) or serious adverse event (SAE)

End point title	Number of participants with any adverse event (AE) or serious adverse event (SAE)

End point description:

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury. Refer to the general Adverse AE/SAE module for a complete list of AEs and SAEs.

End point type	Secondary

End point timeframe:

From the first dose of study medication to 60 days after the last dose of study medication and until follow-up for SAEs unless initiation of subsequent anti-CLL therapy

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	227	217		
Units: Participants				
Any AE	205	208		
Any SAE	84	97		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with AEs and SAEs of maximum severity of grade 3 or higher

End point title	Number of participants with AEs and SAEs of maximum severity of grade 3 or higher

End point description:

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury. Refer to the general Adverse AE/SAE module for a complete list of AEs and SAEs. Maximum severity grades were evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 (1, mild; 2, moderate; 3, severe; 4, life-

threatening/disabling; 5, death).

End point type	Secondary

End point timeframe:

From the first dose of study medication to 60 days after the last dose of study medication and until follow-up for SAEs unless initiation of subsequent anti-CLL therapy

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	227	217		
Units: Participants				
Any AE, Grade 3	54	67		
Any AE, Grade 4	31	36		
Any AE, Grade 5	25	36		
Any SAE, Grade 3	36	34		
Any SAE, Grade 4	13	19		
Any SAE, Grade 5	25	36		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with at least one Grade 3/Grade 4 myelosuppression (anemia, neutropenia, and thrombocytopenia)

End point title	Number of participants with at least one Grade 3/Grade 4 myelosuppression (anemia, neutropenia, and thrombocytopenia)

End point description:

Participants with a Grade 3 or Grade 4 myelosuppression (anemia, neutropenia, and thrombocytopenia) are presented by treatment cycle. Myelosuppression is defined as the decrease in the ability of the bone marrow to produce blood cells. AEs were graded according to NCI common terminology criteria for adverse events (CTCAE) grade, version 3.0 (1, mild; 2, moderate; 3, severe; 4, life-threatening/disabling; 5, death).

End point type	Secondary

End point timeframe:

From the first dose of study medication to 60 days after the last dose of study medication and until follow-up for SAEs unless initiation of subsequent anti-CLL therapy

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	227	217		
Units: Participants	92	83		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with autoimmune hemolytic anaemia (AIHA) disease

End point title	Number of participants with autoimmune hemolytic anaemia (AIHA) disease

End point description:

AIHA is a disease where the body's immune system fails to recognize red blood cells as "self" and begins destroying these red blood cells. The number of participants diagnosed with AIHA are presented.

End point type	Secondary

End point timeframe:

From the first dose of study medication to 60 days after the last dose of study medication and until follow-up for SAEs unless initiation of subsequent anti-CLL therapy

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	227	217		
Units: Participants	6	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who received no transfusion or at least one transfusion during the study

End point title	Number of participants who received no transfusion or at least one transfusion during the study

End point description:

Participants who received no transfusion and at least one transfusion during the study are presented. Participants who took any blood products are counted in this table.

End point type	Secondary

End point timeframe:

From start of treatment to the last study visit/withdrawal visit (Median follow-up approximately 28.9 months)

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	227	217		
Units: Participants				
No transfusions	159	168		
At least one transfusion	68	49		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in the Immunoglobulin (Ig) antibodies IgA, IgG, and IgM

End point title	Mean change from Baseline in the Immunoglobulin (Ig) antibodies IgA, IgG, and IgM

End point description:

Immunoglobulins, or antibodies, are large proteins used by the immune system to identify and neutralize foreign particles such as bacteria and viruses. Their normal blood levels indicate proper immune status. Low levels indicate immuno-suppression. IgA, IgG, and IgM were measured in the blood samples of the participants. Baseline IgA, IgG, and IgM values are the last pre-dose assessment values performed on Cycle 1 Day 1. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From start of treatment up to 30 days after last treatment

End point values	Chlorambucil	Ofatumumab + Chlorambucil		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	227	217		
Units: Gram per liter				
arithmetic mean (standard deviation)				
IgA, n=175, 186	0.047 (± 0.5706)	0.048 (± 0.4257)		
IgG, n=175, 186	-0.458 (± 3.6177)	-0.268 (± 2.5430)		
IgM n=175, 186	-0.398 (± 4.7864)	-0.031 (± 0.2507)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events and Serious Adverse Events were collected for the maximum actual duration of treatment exposure and follow up for a participant per the protocol for approximately 111 months

Adverse event reporting additional description:

All cause mortality (deaths) was collected for as long as participants could be contacted from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV) up to a maximum of 111 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Chlorambucil

Reporting group description:

Participants with previously untreated chronic lymphocytic leukemia (CLL) received chlorambucil monotherapy 10 milligram (mg)/meter squared (m^2) orally on Days 1-7 of every 28-day cycle for a minimum of 3 cycles until best response or a maximum of 12 cycles.

Reporting group title	Ofatumumab 1000 mg + Chlorambucil

Reporting group description:

Participants with CLL received intravenous (IV) infusions of ofatumumab on Day 1 (300 mg) and Day 8 (1000 mg) in the first cycle, followed by IV infusions of 1000 mg on the first day of each subsequent 28-day cycle in combination with chlorambucil 10 mg/m^2 orally on Days 1-7 of every 28-day cycle for a minimum of 3 cycles until best response or a maximum of 12 cycles.

Reporting group title	Total

Reporting group description:

All patients.

Serious adverse events	Chlorambucil	Ofatumumab 1000 mg + Chlorambucil	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	57 / 227 (25.11%)	53 / 217 (24.42%)	110 / 444 (24.77%)
number of deaths (all causes)	99	84	183
number of deaths resulting from adverse events	2	3	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Prostate cancer			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Peripheral artery stenosis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 227 (0.44%)	5 / 217 (2.30%)	6 / 444 (1.35%)
occurrences causally related to treatment / all	1 / 1	5 / 5	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent restenosis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			

subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiectasis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	2 / 227 (0.88%)	2 / 217 (0.92%)	4 / 444 (0.90%)
occurrences causally related to treatment / all	2 / 2	2 / 2	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	4 / 227 (1.76%)	2 / 217 (0.92%)	6 / 444 (1.35%)
occurrences causally related to treatment / all	5 / 5	2 / 2	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 227 (0.00%)	2 / 217 (0.92%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 227 (0.00%)	4 / 217 (1.84%)	4 / 444 (0.90%)
occurrences causally related to treatment / all	0 / 0	4 / 4	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Psychiatric disorders			
Confusional state			

subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mycobacterium test			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Subarachnoid haemorrhage			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Traumatic ulcer			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 227 (0.00%)	2 / 217 (0.92%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 227 (0.00%)	2 / 217 (0.92%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	1 / 2	1 / 2
Cardio-respiratory arrest			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			

subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Supraventricular tachycardia			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Central nervous system haemorrhage			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar ischaemia			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cognitive disorder			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			

subjects affected / exposed	1 / 227 (0.44%)	1 / 217 (0.46%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrapyramidal disorder			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 227 (0.00%)	2 / 217 (0.92%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial haematoma			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 227 (0.00%)	2 / 217 (0.92%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	1 / 227 (0.44%)	1 / 217 (0.46%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	5 / 227 (2.20%)	3 / 217 (1.38%)	8 / 444 (1.80%)
occurrences causally related to treatment / all	6 / 6	4 / 4	10 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune haemolytic anaemia			
subjects affected / exposed	3 / 227 (1.32%)	0 / 217 (0.00%)	3 / 444 (0.68%)
occurrences causally related to treatment / all	4 / 4	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eosinophilia			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	5 / 227 (2.20%)	3 / 217 (1.38%)	8 / 444 (1.80%)
occurrences causally related to treatment / all	5 / 5	3 / 3	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			
subjects affected / exposed	1 / 227 (0.44%)	1 / 217 (0.46%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic anaemia			
subjects affected / exposed	2 / 227 (0.88%)	0 / 217 (0.00%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	4 / 227 (1.76%)	6 / 217 (2.76%)	10 / 444 (2.25%)
occurrences causally related to treatment / all	4 / 4	7 / 7	11 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	3 / 227 (1.32%)	1 / 217 (0.46%)	4 / 444 (0.90%)
occurrences causally related to treatment / all	3 / 3	1 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Aphthous ulcer			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholestasis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis cholestatic			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis allergic			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	2 / 227 (0.88%)	1 / 217 (0.46%)	3 / 444 (0.68%)
occurrences causally related to treatment / all	2 / 2	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 227 (0.00%)	2 / 217 (0.92%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nephrolithiasis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis			
subjects affected / exposed	1 / 227 (0.44%)	1 / 217 (0.46%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilus infection			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 227 (0.44%)	3 / 217 (1.38%)	4 / 444 (0.90%)
occurrences causally related to treatment / all	1 / 1	3 / 3	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	3 / 227 (1.32%)	2 / 217 (0.92%)	5 / 444 (1.13%)
occurrences causally related to treatment / all	3 / 3	2 / 2	5 / 5
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Oral herpes			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			

subjects affected / exposed	1 / 227 (0.44%)	1 / 217 (0.46%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis bacterial			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal sepsis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Pneumonia			
subjects affected / exposed	11 / 227 (4.85%)	8 / 217 (3.69%)	19 / 444 (4.28%)
occurrences causally related to treatment / all	12 / 12	8 / 8	20 / 20
deaths causally related to treatment / all	1 / 2	1 / 1	2 / 3
Pneumonia legionella			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pneumonia staphylococcal			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 227 (0.00%)	2 / 217 (0.92%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Septic shock			
subjects affected / exposed	1 / 227 (0.44%)	1 / 217 (0.46%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			

subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 217 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 227 (0.00%)	1 / 217 (0.46%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	0 / 227 (0.00%)	2 / 217 (0.92%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Chlorambucil	Ofatumumab 1000 mg + Chlorambucil	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	175 / 227 (77.09%)	183 / 217 (84.33%)	358 / 444 (80.63%)
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 227 (0.00%)	17 / 217 (7.83%)	17 / 444 (3.83%)
occurrences (all)	0	29	1
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 227 (0.44%)	11 / 217 (5.07%)	12 / 444 (2.70%)
occurrences (all)	1	11	2
Hypertension			
subjects affected / exposed	1 / 227 (0.44%)	11 / 217 (5.07%)	12 / 444 (2.70%)
occurrences (all)	1	12	6
Hypotension			

subjects affected / exposed	2 / 227 (0.88%)	12 / 217 (5.53%)	14 / 444 (3.15%)
occurrences (all)	3	16	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	15 / 227 (6.61%)	10 / 217 (4.61%)	25 / 444 (5.63%)
occurrences (all)	21	13	29
Headache			
subjects affected / exposed	7 / 227 (3.08%)	18 / 217 (8.29%)	25 / 444 (5.63%)
occurrences (all)	7	30	26
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	27 / 227 (11.89%)	16 / 217 (7.37%)	43 / 444 (9.68%)
occurrences (all)	31	25	58
Leukopenia			
subjects affected / exposed	4 / 227 (1.76%)	14 / 217 (6.45%)	18 / 444 (4.05%)
occurrences (all)	4	22	27
Neutropenia			
subjects affected / exposed	36 / 227 (15.86%)	57 / 217 (26.27%)	93 / 444 (20.95%)
occurrences (all)	55	103	161
Thrombocytopenia			
subjects affected / exposed	56 / 227 (24.67%)	30 / 217 (13.82%)	86 / 444 (19.37%)
occurrences (all)	69	41	114
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 227 (4.85%)	18 / 217 (8.29%)	29 / 444 (6.53%)
occurrences (all)	11	19	28
Chills			
subjects affected / exposed	1 / 227 (0.44%)	18 / 217 (8.29%)	19 / 444 (4.28%)
occurrences (all)	1	20	3
Fatigue			
subjects affected / exposed	40 / 227 (17.62%)	35 / 217 (16.13%)	75 / 444 (16.89%)
occurrences (all)	46	36	85
Oedema peripheral			
subjects affected / exposed	12 / 227 (5.29%)	15 / 217 (6.91%)	27 / 444 (6.08%)
occurrences (all)	13	17	30
Pyrexia			

subjects affected / exposed	18 / 227 (7.93%)	36 / 217 (16.59%)	54 / 444 (12.16%)
occurrences (all)	26	45	41
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	5 / 227 (2.20%)	11 / 217 (5.07%)	16 / 444 (3.60%)
occurrences (all)	5	12	10
Constipation			
subjects affected / exposed	13 / 227 (5.73%)	10 / 217 (4.61%)	23 / 444 (5.18%)
occurrences (all)	14	11	25
Diarrhoea			
subjects affected / exposed	31 / 227 (13.66%)	38 / 217 (17.51%)	69 / 444 (15.54%)
occurrences (all)	37	44	70
Nausea			
subjects affected / exposed	57 / 227 (25.11%)	43 / 217 (19.82%)	100 / 444 (22.52%)
occurrences (all)	72	66	105
Vomiting			
subjects affected / exposed	24 / 227 (10.57%)	23 / 217 (10.60%)	47 / 444 (10.59%)
occurrences (all)	30	26	25
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	25 / 227 (11.01%)	33 / 217 (15.21%)	58 / 444 (13.06%)
occurrences (all)	29	38	65
Dyspnoea			
subjects affected / exposed	10 / 227 (4.41%)	25 / 217 (11.52%)	35 / 444 (7.88%)
occurrences (all)	10	32	23
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	2 / 227 (0.88%)	11 / 217 (5.07%)	13 / 444 (2.93%)
occurrences (all)	2	14	5
Hyperhidrosis			
subjects affected / exposed	5 / 227 (2.20%)	12 / 217 (5.53%)	17 / 444 (3.83%)
occurrences (all)	6	13	14
Pruritus			
subjects affected / exposed	11 / 227 (4.85%)	26 / 217 (11.98%)	37 / 444 (8.33%)
occurrences (all)	11	33	28
Rash			

subjects affected / exposed	21 / 227 (9.25%)	53 / 217 (24.42%)	74 / 444 (16.67%)
occurrences (all)	25	67	44
Urticaria			
subjects affected / exposed	2 / 227 (0.88%)	22 / 217 (10.14%)	24 / 444 (5.41%)
occurrences (all)	2	30	7
Psychiatric disorders			
Insomnia			
subjects affected / exposed	17 / 227 (7.49%)	12 / 217 (5.53%)	29 / 444 (6.53%)
occurrences (all)	17	13	27
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 227 (3.52%)	11 / 217 (5.07%)	19 / 444 (4.28%)
occurrences (all)	8	11	18
Back pain			
subjects affected / exposed	12 / 227 (5.29%)	11 / 217 (5.07%)	23 / 444 (5.18%)
occurrences (all)	13	13	18
Infections and infestations			
Bronchitis			
subjects affected / exposed	10 / 227 (4.41%)	11 / 217 (5.07%)	21 / 444 (4.73%)
occurrences (all)	11	11	22
Nasopharyngitis			
subjects affected / exposed	19 / 227 (8.37%)	9 / 217 (4.15%)	28 / 444 (6.31%)
occurrences (all)	21	9	30
Upper respiratory tract infection			
subjects affected / exposed	16 / 227 (7.05%)	12 / 217 (5.53%)	28 / 444 (6.31%)
occurrences (all)	17	13	30
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	20 / 227 (8.81%)	13 / 217 (5.99%)	33 / 444 (7.43%)
occurrences (all)	20	15	34

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2008	1) Clarification of translational research and consent language to comply with local Institutional Review Board / Ethics Committee requirements. 2) The steroid pre-infusion schedule was modified to allow dose reduction for patients where steroid administration was not medically indicated (U.S. FDA request). 3) DoR and PROs were removed as inferential secondary endpoints because a formal comparison of these endpoints was not considered feasible with the proposed study design. Instead, OS was added as an inferential secondary endpoint (U.S. FDA/EMA request).
10 August 2009	1) Addition of inclusion criterion, 'considered inappropriate for fludarabine-based therapy, for reasons that include, but not limited to, advanced age or presence of comorbidities' to further define patient population (U.S. FDA request). 2) Addition of a CT scan at time of progression to provide the IRC a means of objective assessment of progressive disease by lymphadenopathy, for sensitivity analysis (U.S. FDA request). 3) Update of CLL diagnosis definition and response assessment criteria in alignment with the IWCLL updated (NCI-WG) guidelines.
25 November 2009	1) Implementation of Hepatitis B virus DNA monitoring for HBcAb-positive patients to monitor for potential hepatitis reactivation. 2) Addition of a drug-drug interaction and ECG substudy to evaluate potential ofatumumab/chlorambucil interaction and any effect of ofatumumab on QTc intervals (FDA request).
23 May 2014	1) Change of Medical Monitor. 2) Removal of CT scan at time of progression 3) Extension of follow-up period from 5 to up to 10 years 4) Clarification of data collection period for concomitant medication in follow-up 5) Update Data Disclosure information
24 September 2015	1) Delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents. 2) Make administrative changes to align with Novartis processes and procedures.

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.

The study was terminated early because the majority of patients (62%) had been treated with next line therapies, including new highly effective therapies confounding the interpretation of the OS results.

Notes: