



Clinical trial results:

A Randomized Phase IIIb Study of Rituximab Added to a Chemotherapy, Bendamustine or Chlorambucil, in Patients With Chronic Lymphocytic Leukemia

Summary

EudraCT number	2009-012072-28
Trial protocol	ES SE FR FI PT GB
Global end of trial date	31 March 2014

Results information

Result version number	v1 (current)
This version publication date	14 July 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	MO22468
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01056510
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	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, 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	09 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2014
Global end of trial reached?	Yes
Global end of trial date	31 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to compare the confirmed complete response (CR) rate after 6 cycles of treatment between the two treatment arms for the first-line participants with chronic lymphocytic leukemia (CLL).

Protection of trial subjects:

The investigator has ensured that this study was conducted in full conformance with the principles of the Declaration of Helsinki (2008) or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study was designed to fully adhere to the principles outlined in the Guideline for Good Clinical Practice, International Conference on Harmonisation (ICH) Tripartite Guideline (January 1997), or with local law if it affords greater protection to the participant. For studies conducted in the European Union (EU) or the European Economic Area (EEA) countries, the investigator has ensured compliance with the EU Clinical Trial Directive (2001/20/EC). In other countries where a Guideline for Good Clinical Practice exists, F. Hoffmann-La Roche and the investigators has strictly ensured adherence to the stated provisions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 February 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Tunisia: 23
Country: Number of subjects enrolled	Turkey: 80
Country: Number of subjects enrolled	Portugal: 24
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	Sweden: 23
Country: Number of subjects enrolled	United Kingdom: 68
Country: Number of subjects enrolled	Finland: 11
Country: Number of subjects enrolled	France: 106
Worldwide total number of subjects	357
EEA total number of subjects	254

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)	85
From 65 to 84 years	258
85 years and over	14

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening examination was performed within 28 days before randomization. Participants who fulfilled all the inclusion and none of the exclusion criteria were randomized to one of the two treatment groups.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab + Bendamustine

Arm description:

Participants received a specialized first-line or second-line regimen based upon prior chemotherapy exposure. Participants received intravenous (IV) rituximab 375 milligrams per square meter (mg/m^2) on Day 1 of Cycle 1 and 500 mg/m^2 on Day 1 of Cycles 2 to 6. In those requiring a first-line regimen, bendamustine was administered IV at a dose of 90 mg/m^2 on Days 1 and 2 of Cycles 1 to 6. In those requiring a second-line regimen, the bendamustine dose was lowered to 70 mg/m^2 . Each cycle was 4 weeks in duration. Treatment was discontinued early in participants who experienced progressive disease (PD).

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received IV rituximab 375 mg/m^2 on Day 1 of Cycle 1 and 500 mg/m^2 on Day 1 every 4 weeks for Cycles 2 to 6.

Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

In those requiring a first-line regimen, bendamustine was administered IV at a dose of 90 mg/m^2 on Days 1 and 2 every 4 weeks for Cycles 1 to 6. In those requiring a second-line regimen, the bendamustine dose was lowered to 70 mg/m^2 .

Arm title	Rituximab + Chlorambucil
------------------	--------------------------

Arm description:

Participants received IV rituximab 375 mg/m^2 on Day 1 of Cycle 1 and 500 mg/m^2 on Day 1 of Cycles 2 to 6. Chlorambucil was administered orally (PO) at a dose of 10 mg/m^2 on Days 1 to 7, beginning with Cycle 1 and continuing for up to 12 cycles or until CR was achieved. Each cycle was 4 weeks in duration. Treatment was discontinued early in participants who experienced PD.

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received IV rituximab 375 mg/m² on Day 1 of Cycle 1 and 500 mg/m² on Day 1 every 4 weeks for Cycles 2 to 6.

Investigational medicinal product name	Chlorambucil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Chlorambucil was administered PO at a dose of 10 mg/m² on Days 1 to 7 every 4 weeks, beginning with Cycle 1 and continuing for up to 12 cycles or until CR was achieved.

Number of subjects in period 1	Rituximab + Bendamustine	Rituximab + Chlorambucil
Started	178	179
Completed	124	115
Not completed	54	64
Consent withdrawn by subject	4	2
Physician decision	4	5
Death	29	34
Not specified	10	12
Dropout before start of treatment	1	1
Lost to follow-up	5	6
Missing	-	1
Noncompliance	1	3

Baseline characteristics

Reporting groups

Reporting group title	Rituximab + Bendamustine
-----------------------	--------------------------

Reporting group description:

Participants received a specialized first-line or second-line regimen based upon prior chemotherapy exposure. Participants received intravenous (IV) rituximab 375 milligrams per square meter (mg/m²) on Day 1 of Cycle 1 and 500 mg/m² on Day 1 of Cycles 2 to 6. In those requiring a first-line regimen, bendamustine was administered IV at a dose of 90 mg/m² on Days 1 and 2 of Cycles 1 to 6. In those requiring a second-line regimen, the bendamustine dose was lowered to 70 mg/m². Each cycle was 4 weeks in duration. Treatment was discontinued early in participants who experienced progressive disease (PD).

Reporting group title	Rituximab + Chlorambucil
-----------------------	--------------------------

Reporting group description:

Participants received IV rituximab 375 mg/m² on Day 1 of Cycle 1 and 500 mg/m² on Day 1 of Cycles 2 to 6. Chlorambucil was administered orally (PO) at a dose of 10 mg/m² on Days 1 to 7, beginning with Cycle 1 and continuing for up to 12 cycles or until CR was achieved. Each cycle was 4 weeks in duration. Treatment was discontinued early in participants who experienced PD.

Reporting group values	Rituximab + Bendamustine	Rituximab + Chlorambucil	Total
Number of subjects	178	179	357
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	70.6	70.1	
standard deviation	± 9.87	± 9.88	-
Gender categorical Units: Subjects			
Female	73	61	134
Male	105	118	223

End points

End points reporting groups

Reporting group title	Rituximab + Bendamustine
Reporting group description:	
Participants received a specialized first-line or second-line regimen based upon prior chemotherapy exposure. Participants received intravenous (IV) rituximab 375 milligrams per square meter (mg/m ²) on Day 1 of Cycle 1 and 500 mg/m ² on Day 1 of Cycles 2 to 6. In those requiring a first-line regimen, bendamustine was administered IV at a dose of 90 mg/m ² on Days 1 and 2 of Cycles 1 to 6. In those requiring a second-line regimen, the bendamustine dose was lowered to 70 mg/m ² . Each cycle was 4 weeks in duration. Treatment was discontinued early in participants who experienced progressive disease (PD).	
Reporting group title	Rituximab + Chlorambucil
Reporting group description:	
Participants received IV rituximab 375 mg/m ² on Day 1 of Cycle 1 and 500 mg/m ² on Day 1 of Cycles 2 to 6. Chlorambucil was administered orally (PO) at a dose of 10 mg/m ² on Days 1 to 7, beginning with Cycle 1 and continuing for up to 12 cycles or until CR was achieved. Each cycle was 4 weeks in duration. Treatment was discontinued early in participants who experienced PD.	

Primary: Percentage of Participants Achieving Confirmed CR According to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 Guidelines in the First-Line Subpopulation After 6 Cycles of Therapy

End point title	Percentage of Participants Achieving Confirmed CR According to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 Guidelines in the First-Line Subpopulation After 6 Cycles of Therapy
End point description:	
The definition of confirmed CR required the following at least 2 months after completion of therapy: peripheral blood lymphocytes less than (<) 4 times 10 ⁹ cells per liter (cells/L); absence of significant lymphadenopathy, hepatomegaly, or splenomegaly due to CLL involvement; absence of constitutional symptoms; normal complete blood count (CBC) without need for transfusion or exogenous growth factors, with neutrophils at least (>=) 1.5 times 10 ⁹ cells/L, platelets greater than (>) 100 times 10 ⁹ cells/L, and hemoglobin > 11.0 grams per deciliter (g/dL); normocellular bone marrow (BM) aspirate with < 30 percent (%) lymphocytes; absence of lymphoid nodules; and BM biopsy without CLL. The percentage of participants achieving confirmed CR was calculated as the number of participants meeting the above criteria divided by the number analyzed, multiplied by 100. Intent-to-Treat (ITT) Population (First-Line Subpopulation): All randomized participants requiring a first-line regimen for CLL.	
End point type	Primary
End point timeframe:	
At least 2 months after completion of therapy (up to 32 weeks)	

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	120		
Units: percentage of participants				
number (not applicable)				
Confirmed CR with biopsy	24	9.2		
CR without biopsy	2.5	5.8		
No confirmed CR	73.6	85		

Statistical analyses

Statistical analysis title	Rituximab+Bendamustine v Rituximab+Chlorambucil
Statistical analysis description:	
The first-line subpopulation became the focus of the primary statistical analysis following the protocol amendment dated 21-May-2012.	
Comparison groups	Rituximab + Bendamustine v Rituximab + Chlorambucil
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 ^[1]
Method	Chi-squared corrected

Notes:

[1] - Based on one-sided continuity corrected Chi-Square Test for participants achieving CR confirmed with biopsy versus those not achieving CR confirmed with biopsy

Secondary: Percentage of Participants Achieving Confirmed CR According to IWCLL 2008 Guidelines in the Pooled Population After 6 Cycles of Therapy

End point title	Percentage of Participants Achieving Confirmed CR According to IWCLL 2008 Guidelines in the Pooled Population After 6 Cycles of Therapy
-----------------	---

End point description:

The definition of confirmed CR required all of the following criteria as assessed at least 2 months after completion of therapy: peripheral blood lymphocytes < 4 times 10⁹ cells/L; absence of significant lymphadenopathy, hepatomegaly, or splenomegaly due to CLL involvement; absence of constitutional symptoms; normal CBC without need for transfusion or exogenous growth factors, as exhibited by neutrophils ≥ 1.5 times 10⁹ cells/L, platelets > 100 times 10⁹ cells/L, and hemoglobin > 11.0 g/dL; normocellular BM aspirate with < 30% lymphocytes; absence of lymphoid nodules; and BM biopsy without CLL activity. The percentage of participants achieving confirmed CR was calculated as the number of participants meeting the above criteria divided by the number of participants analyzed, multiplied by 100. ITT Population.

End point type	Secondary
----------------	-----------

End point timeframe:

At least 2 months after completion of therapy (up to 32 weeks)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	179		
Units: percentage of participants				
number (not applicable)				
Confirmed CR with biopsy	21.3	6.7		
CR without biopsy	2.8	4.5		
No confirmed CR	75.8	88.8		

Statistical analyses

Statistical analysis title	Rituximab+Bendamustine v Rituximab+Chlorambucil
Comparison groups	Rituximab + Bendamustine v Rituximab + Chlorambucil
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [2]
Method	Chi-squared corrected

Notes:

[2] - Based on one-sided continuity corrected Chi-Square Test for participants achieving CR confirmed with biopsy versus those not achieving CR confirmed with biopsy

Secondary: Percentage of Participants Achieving Confirmed CR According to IWCLL 2008 Guidelines in the Second-Line Subpopulation After 6 Cycles of Therapy

End point title	Percentage of Participants Achieving Confirmed CR According to IWCLL 2008 Guidelines in the Second-Line Subpopulation After 6 Cycles of Therapy
-----------------	---

End point description:

The definition of confirmed CR required all of the following criteria as assessed at least 2 months after completion of therapy: peripheral blood lymphocytes < 4 times 10^9 cells/L; absence of significant lymphadenopathy, hepatomegaly, or splenomegaly due to CLL involvement; absence of constitutional symptoms; normal CBC without need for transfusion or exogenous growth factors, as exhibited by neutrophils ≥ 1.5 times 10^9 cells/L, platelets > 100 times 10^9 cells/L, and hemoglobin > 11.0 g/dL; normocellular BM aspirate with < 30% lymphocytes; absence of lymphoid nodules; and BM biopsy without CLL activity. The percentage of participants achieving confirmed CR was calculated as the number of participants meeting the above criteria divided by the number of participants analyzed, multiplied by 100. ITT Population (Second-Line Subpopulation): All randomized participants requiring a second-line regimen for CLL.

End point type	Secondary
----------------	-----------

End point timeframe:

At least 2 months after completion of therapy (up to 32 weeks)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	59		
Units: percentage of participants				
number (not applicable)				
Confirmed CR with biopsy	15.8	1.7		
CR without biopsy	3.5	1.7		
No confirmed CR	80.7	96.6		

Statistical analyses

Statistical analysis title	Rituximab+Bendamustine v Rituximab+Chlorambucil
Comparison groups	Rituximab + Bendamustine v Rituximab + Chlorambucil
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009 ^[3]
Method	Chi-squared corrected

Notes:

[3] - Based on one-sided continuity corrected Chi-Square Test for participants achieving CR confirmed with biopsy versus those not achieving CR confirmed with biopsy

Secondary: Percentage of Participants Achieving a Best Overall Response of CR, CR With Incomplete Marrow Recovery (CRi), Partial Response (PR), or Nodular PR (nPR) in the First-Line Subpopulation

End point title	Percentage of Participants Achieving a Best Overall Response of CR, CR With Incomplete Marrow Recovery (CRi), Partial Response (PR), or Nodular PR (nPR) in the First-Line Subpopulation
-----------------	--

End point description:

The criteria for CR are identified in previous outcome measure(s). Those fulfilling CR criteria with persistent anemia, thrombocytopenia, or neutropenia were considered CRi. The definition of PR required the following for minimum 2 months: $\geq 50\%$ decrease in peripheral blood lymphocytes from Baseline; reduction in lymphadenopathy; $\geq 50\%$ reduction in spleen or liver enlargement, and CBC with one of the following without need for transfusion or exogenous growth factors: polymorphonuclear leukocytes ≥ 1.5 times 10^9 cells/L, platelets > 100 times 10^9 cells/L or $\geq 50\%$ improvement from Baseline, or hemoglobin > 11.0 g/dL or $\geq 50\%$ improvement from Baseline. Those with lymphoid nodules who otherwise met CR criteria were considered nPR. The percentage of participants achieving each level of response was calculated as the number of participants meeting the above criteria divided by the number of participants analyzed, multiplied by 100. ITT Population (First-Line Subpopulation).

End point type	Secondary
----------------	-----------

End point timeframe:

After 3 and 6 treatment cycles and from Baseline to the end-of-treatment (EOT) visit, completed within 10 days before cutoff for data collection

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	120		
Units: percentage of participants				
number (confidence interval 95%)				
After 3 cycles	78.5 (70.1 to 85.5)	80 (71.7 to 86.7)		
After 6 cycles	75.2 (66.5 to 82.6)	79.2 (70.8 to 86)		
At the EOT visit	90.9 (84.3 to 95.4)	85.8 (78.3 to 91.5)		

Statistical analyses

Statistical analysis title	Rituximab+Bendamustine v Rituximab+Chlorambucil
Statistical analysis description: After 3 cycles	
Comparison groups	Rituximab + Bendamustine v Rituximab + Chlorambucil
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9 ^[4]
Method	Chi-squared corrected

Notes:

[4] - Based on two-sided continuity corrected Chi-Square Test

Statistical analysis title	Rituximab+Bendamustine v Rituximab+Chlorambucil
Statistical analysis description: After 6 cycles	
Comparison groups	Rituximab + Bendamustine v Rituximab + Chlorambucil
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.563 ^[5]
Method	Chi-squared corrected

Notes:

[5] - Based on two-sided continuity corrected Chi-Square Test

Statistical analysis title	Rituximab+Bendamustine v Rituximab+Chlorambucil
Statistical analysis description: At the EOT visit	
Comparison groups	Rituximab + Bendamustine v Rituximab + Chlorambucil
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.304 ^[6]
Method	Chi-squared corrected

Notes:

[6] - Based on two-sided continuity corrected Chi-Square Test

Secondary: Percentage of Participants by Disease Response Category in the First-Line Subpopulation

End point title	Percentage of Participants by Disease Response Category in the First-Line Subpopulation
-----------------	---

End point description:

The criteria for CR, CRi, PR, and nPR are identified in previous outcome measure(s). PD was defined by at least one of the following: the presence of lymphadenopathy; an increase in the previously noted enlargement of the liver or spleen by $\geq 50\%$ or the de novo appearance of hepatomegaly or splenomegaly; an increase in the number of blood lymphocytes by $\geq 50\%$ with ≥ 5000 B-cells per microliter (B-cells/mcL); transformation to a more aggressive histology; or occurrence of cytopenia attributable to CLL. Participants not achieving a CR or PR, and who did not exhibit PD, were considered to have stable disease (SD). The percentage of participants achieving each level of response was calculated as the number of participants meeting the above criteria divided by the number of participants analyzed. The rows below are labeled first by the level of response at the end of 6 cycles (C6), then by level of response at the confirmation assessment. ITT Population (First-Line Subpopulation).

End point type	Secondary
----------------	-----------

End point timeframe:

After 6 treatment cycles and at the confirmation of response assessment at least 12 weeks later (up to 36 weeks)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	120		
Units: percentage of participants				
number (not applicable)				
CR with biopsy (C6), CR (confirmed)	21.5	9.2		
CR with biopsy (C6), CRi (confirmed)	2.5	0		
CR with biopsy (C6), nPR (confirmed)	1.7	6.7		
CR with biopsy (C6), PR (confirmed)	19	17.5		
CR with biopsy (C6), SD (confirmed)	0	1.7		
CR with biopsy (C6), PD (confirmed)	0	0		
CR with biopsy (C6), Missing (confirmed)	0	0		
CR without biopsy (C6), CR (confirmed)	2.5	5.8		
CR without biopsy (C6), CRi (confirmed)	0	0		
CR without biopsy (C6), nPR (confirmed)	0	0		
CR without biopsy (C6), PR (confirmed)	16.5	10		
CR without biopsy (C6), SD (confirmed)	0	0		
CR without biopsy (C6), PD (confirmed)	0	0		
CR without biopsy (C6), Missing (confirmed)	0.8	0		
PR (C6), CR (confirmed)	1.7	4.2		
PR (C6), CRi (confirmed)	0	0		
PR (C6), nPR (confirmed)	0	0		
PR (C6), PR (confirmed)	8.3	21.7		
PR (C6), SD (confirmed)	0	0		
PR (C6), PD (confirmed)	0.8	2.5		
PR (C6), Missing (confirmed)	0	0		
SD (C6), CR (confirmed)	0	0		
SD (C6), CRi (confirmed)	0	0		
SD (C6), nPR (confirmed)	0	0		
SD (C6), PR (confirmed)	0	0		
SD (C6), SD (confirmed)	0	0.8		
SD (C6), PD (confirmed)	0	0.8		
SD (C6), Missing (confirmed)	0	0		
Missing (C6), CR (confirmed)	0.8	0		
Missing (C6), CRi (confirmed)	0	0		
Missing (C6), nPR (confirmed)	0	0		
Missing (C6), PR (confirmed)	0	0		
Missing (C6), SD (confirmed)	0	0		
Missing (C6), PD (confirmed)	0	0		
Missing (C6), Missing (confirmed)	24	19.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) in the First-Line Subpopulation

End point title	Progression-Free Survival (PFS) in the First-Line Subpopulation
-----------------	---

End point description:

The criteria for PD are identified in previous outcome measure(s). PFS was defined as the time from the first dose of trial treatment to the first documentation of PD or death, whichever occurred first. PFS was calculated in months as [first event date minus first dose date plus 1] divided by 30.44. ITT Population (First-Line Subpopulation). 99999 equals (=) not estimable due to insufficient follow-up among participants assigned to Rituximab + Bendamustine in the first-line subpopulation.

End point type	Secondary
----------------	-----------

End point timeframe:

End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	120		
Units: months				
median (confidence interval 95%)	39.6 (34.3 to 99999)	29.9 (22.4 to 34.4)		

Statistical analyses

Statistical analysis title	Rituximab+Bendamustine v Rituximab+Chlorambucil
----------------------------	---

Statistical analysis description:

Unstratified analysis

Comparison groups	Rituximab + Bendamustine v Rituximab + Chlorambucil
-------------------	---

Number of subjects included in analysis	241
---	-----

Analysis specification	Pre-specified
------------------------	---------------

Analysis type	other
---------------	-------

P-value	= 0.003
---------	---------

Method	Logrank
--------	---------

Parameter estimate	Hazard ratio (HR)
--------------------	-------------------

Point estimate	0.525
----------------	-------

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.341
upper limit	0.809

Statistical analysis title	Rituximab+Bendamustine v Rituximab+Chlorambucil
Statistical analysis description:	
Stratified analysis: by baseline Binet stage	
Comparison groups	Rituximab + Bendamustine v Rituximab + Chlorambucil
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.523
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.339
upper limit	0.806

Secondary: Disease-Free Survival (DFS) in the First-Line Subpopulation

End point title	Disease-Free Survival (DFS) in the First-Line Subpopulation
End point description:	
The criteria for CR, CRi, and PD are identified in previous outcome measure(s). DFS was defined as the time from the first assessment of CR or CRi to the first documentation of PD or death, whichever occurred first. DFS was calculated in months as [first event date minus first assessment date of CR/CRi plus 1] divided by 30.44. ITT Population (First-Line Subpopulation). 99999 = not estimable because data for > 50% of participants were censored in each arm, and thus a confidence interval upper limit was not reached.	
End point type	Secondary
End point timeframe:	
End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years)	

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90 ^[7]	77 ^[8]		
Units: months				
median (confidence interval 95%)	36.8 (32 to 99999)	32 (22.2 to 99999)		

Notes:

[7] - Only participants with CR or CRi during or within 4 months after study treatment were considered.

[8] - Only participants with CR or CRi during or within 4 months after study treatment were considered.

Statistical analyses

Statistical analysis title	Rituximab+Bendamustine v Rituximab+Chlorambucil
Comparison groups	Rituximab + Bendamustine v Rituximab + Chlorambucil
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.029
Method	Logrank

Secondary: Event-Free Survival (EFS) in the First-Line Subpopulation

End point title	Event-Free Survival (EFS) in the First-Line Subpopulation
End point description: The criteria for PD and SD are identified in previous outcome measure(s). EFS was defined as the time from the first dose of trial treatment to the first documentation of PD, the beginning of new treatment for any hematologic malignancy, or death from any cause. Those with SD were considered event-free. EFS was calculated in months as [first event date minus first dose date plus 1] divided by 30.44. ITT Population (First-Line Subpopulation). 99999 = not estimable because data for > 50% of participants were censored, and thus a confidence interval upper limit was not reached.	
End point type	Secondary
End point timeframe: End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years)	

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	120		
Units: months				
median (confidence interval 95%)	39.6 (34.3 to 99999)	29.9 (21.9 to 34.4)		

Statistical analyses

Statistical analysis title	Rituximab+Bendamustine v Rituximab+Chlorambucil
Comparison groups	Rituximab + Bendamustine v Rituximab + Chlorambucil

Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.006
Method	Logrank

Secondary: Time to Next Leukemia Treatment (TNLT) in the First-Line Subpopulation

End point title	Time to Next Leukemia Treatment (TNLT) in the First-Line Subpopulation
-----------------	--

End point description:

TNLT was defined as the time from the first dose of trial treatment to the first documentation of any new leukemia treatment. TNLT was calculated in months as [first new treatment date minus first dose date plus 1] divided by 30.44. ITT Population (First-Line Subpopulation). 99999 = not estimable due to the low number of participants who received new leukemia treatment. Data for > 90% of participants were censored in the Rituximab + Bendamustine arm, and for > 80% of participants in the Rituximab + Chlorambucil arm.

End point type	Secondary
----------------	-----------

End point timeframe:

During Cycles 1 to 6 (both treatment arms), Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	120		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Rituximab+Bendamustine v Rituximab+Chlorambucil
Comparison groups	Rituximab + Bendamustine v Rituximab + Chlorambucil
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.037
Method	Logrank

Secondary: Duration of Response in the First-Line Subpopulation

End point title	Duration of Response in the First-Line Subpopulation
-----------------	--

End point description:

The criteria for CR, CRi, PR, nPR, and PD are identified in previous outcome measure(s). Duration of response was defined as the time from the first assessment of CR, CRi, PR, or nPR to the first documentation of PD or death, whichever occurred first. Duration of response was calculated in months as [first event date minus first assessment date of CR/CRi/PR/nPR plus 1] divided by 30.44. ITT Population (First-Line Subpopulation). 99999 = not estimable because data for > 75% of participants were censored, and thus a confidence interval upper limit was not reached.

End point type	Secondary
----------------	-----------

End point timeframe:

End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114 ^[9]	107 ^[10]		
Units: months				
median (confidence interval 95%)	36.8 (31 to 99999)	27.7 (20.8 to 40.9)		

Notes:

[9] - Only participants with CR, CRi, PR, or nPR were considered in the analysis.

[10] - Only participants with CR, CRi, PR, or nPR were considered in the analysis.

Statistical analyses

Statistical analysis title	Rituximab+Bendamustine v Rituximab+Chlorambucil
Comparison groups	Rituximab + Bendamustine v Rituximab + Chlorambucil
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.007
Method	Logrank

Secondary: Overall Survival (OS) in the First-Line Subpopulation

End point title	Overall Survival (OS) in the First-Line Subpopulation
-----------------	---

End point description:

OS was defined as the time from recorded diagnosis to death from any cause. OS was calculated in months as [death date or last-known alive date minus diagnosis date plus 1] divided by 30.44. ITT Population (First-Line Subpopulation). 99999 = not estimable due to insufficient follow-up among participants assigned to Rituximab + Chlorambucil in the first-line subpopulation.

End point type	Secondary
----------------	-----------

End point timeframe:

End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	120		
Units: months				
median (confidence interval 95%)	43.8 (39.6 to 43.8)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Rituximab+Bendamustine v Rituximab+Chlorambucil
Statistical analysis description:	
Unstratified analysis	
Comparison groups	Rituximab + Bendamustine v Rituximab + Chlorambucil
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.986
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.994
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.517
upper limit	1.911

Statistical analysis title	Rituximab+Bendamustine v Rituximab+Chlorambucil
Statistical analysis description:	
Stratified analysis: by baseline Binet stage	
Comparison groups	Rituximab + Bendamustine v Rituximab + Chlorambucil
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.939
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.975
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.505
upper limit	1.88

Secondary: Percentage of Participants Achieving Molecular Response in the First-

Line Subpopulation

End point title	Percentage of Participants Achieving Molecular Response in the First-Line Subpopulation
-----------------	---

End point description:

Molecular response was defined as negative minimal residual disease (MRD) during study treatment or within 4 months after the end of treatment. Negative MRD was defined as a proportion of malignant B-cells in normal B-cells < 0.0001. The percentage of participants achieving molecular response was calculated as the number of participants with negative MRD divided by the number of participants analyzed. ITT Population (First-Line Subpopulation).

End point type	Secondary
----------------	-----------

End point timeframe:

Up to 4 months after the last treatment cycle (up to 40 weeks)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112 ^[11]	106 ^[12]		
Units: percentage of participants				
number (not applicable)				
Molecular response	57.1	16		
No molecular response	42.9	84		

Notes:

[11] - Only those with CR, CRi, PR, or nPR during or within 4 months after study treatment were considered.

[12] - Only those with CR, CRi, PR, or nPR during or within 4 months after study treatment were considered.

Statistical analyses

Statistical analysis title	Rituximab+Bendamustine v Rituximab+Chlorambucil
Comparison groups	Rituximab + Bendamustine v Rituximab + Chlorambucil
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 ^[13]
Method	Chi-squared corrected

Notes:

[13] - Based on two-sided continuity corrected Chi-Square Test

Secondary: Number of Participants With Positive and Negative Outcome for MRD in the First-Line Subpopulation

End point title	Number of Participants With Positive and Negative Outcome for MRD in the First-Line Subpopulation
-----------------	---

End point description:

Negative MRD was defined as a proportion of malignant B-cells in normal B-cells < 0.0001, and positive MRD was defined as a proportion of malignant B-cells in normal B-cells \geq 0.0001. ITT Population (First-Line Subpopulation).

End point type	Secondary
----------------	-----------

End point timeframe:

After 6 treatment cycles (up to 24 weeks)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78 ^[14]	78 ^[15]		
Units: participants				
Positive outcome	30	64		
Negative outcome	48	14		

Notes:

[14] - Only participants with available MRD data (MRD-evaluable participants) were considered.

[15] - Only participants with available MRD data (MRD-evaluable participants) were considered.

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Malignant B-cells in Normal B-cells Among Participants With a Positive Outcome for MRD in the First-Line Subpopulation

End point title	Proportion of Malignant B-cells in Normal B-cells Among Participants With a Positive Outcome for MRD in the First-Line Subpopulation
-----------------	--

End point description:

The proportion of malignant B-cells in normal B-cells was quantitatively determined, and was calculated as the number of malignant B-cells divided by the number of normal B-cells observed. ITT Population (First-Line Subpopulation).

End point type	Secondary
----------------	-----------

End point timeframe:

After 6 treatment cycles (up to 24 weeks)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30 ^[16]	64 ^[17]		
Units: proportion				
arithmetic mean (standard deviation)	0.0836 (± 0.22739)	0.1125 (± 0.27662)		

Notes:

[16] - Only participants with a positive outcome for MRD were included in the analysis.

[17] - Only participants with a positive outcome for MRD were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing PD or Death in the First-Line Subpopulation

End point title	Percentage of Participants Experiencing PD or Death in the First-Line Subpopulation
-----------------	---

End point description:

The criteria for PD are identified in previous outcome measure(s). The percentage of participants experiencing PD or death was calculated as the number of participants with event divided by the number of participants analyzed, multiplied by 100. ITT Population (First-Line Subpopulation).

End point type	Secondary
----------------	-----------

End point timeframe:

End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	120		
Units: percentage of participants				
number (not applicable)	27.3	46.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Tumor Response of CR or CRi Experiencing PD or Death in the First-Line Subpopulation

End point title	Percentage of Participants With Tumor Response of CR or CRi Experiencing PD or Death in the First-Line Subpopulation
-----------------	--

End point description:

The criteria for CR, CRi, and PD are identified in previous outcome measure(s). The percentage of participants experiencing PD or death was calculated as the number of participants with event divided by the number of participants analyzed, multiplied by 100. ITT Population (First-Line Subpopulation).

End point type	Secondary
----------------	-----------

End point timeframe:

End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90 ^[18]	77 ^[19]		
Units: percentage of participants				
number (not applicable)	17.8	33.8		

Notes:

[18] - Only participants with CR or CRi during or within 4 months after study treatment were considered.

[19] - Only participants with CR or CRi during or within 4 months after study treatment were considered.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing PD, Documented Intake of New Leukemia Therapy, or Death in the First-Line Subpopulation

End point title	Percentage of Participants Experiencing PD, Documented Intake of New Leukemia Therapy, or Death in the First-Line Subpopulation
-----------------	---

End point description:

The criteria for PD are identified in previous outcome measure(s). The percentage of participants experiencing PD, intake of new (post-trial) leukemia therapy, or death was calculated as the number of participants with event divided by the number of participants analyzed, multiplied by 100. ITT Population (First-Line Subpopulation).

End point type	Secondary
----------------	-----------

End point timeframe:

End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	120		
Units: percentage of participants				
number (not applicable)	29.8	49.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Documented Intake of New Leukemia Therapy in the First-Line Subpopulation

End point title	Percentage of Participants With Documented Intake of New Leukemia Therapy in the First-Line Subpopulation
-----------------	---

End point description:

The percentage of participants with documented intake of new (post-trial) leukemia therapy was calculated as the number of participants with new therapy divided by the number of participants analyzed, multiplied by 100. ITT Population (First-Line Subpopulation).

End point type	Secondary
----------------	-----------

End point timeframe:

During Cycles 1 to 6 (both treatment arms), Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	120		
Units: percentage of participants				
number (not applicable)	9.1	18.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Tumor Response of CR, CRi, PR, or nPR Experiencing PD or Death in the First-Line Subpopulation

End point title	Percentage of Participants With Tumor Response of CR, CRi, PR, or nPR Experiencing PD or Death in the First-Line Subpopulation
-----------------	--

End point description:

The criteria for CR, CRi, PR, nPR, and PD are identified in previous outcome measure(s). The percentage of participants experiencing PD or death was calculated as the number of participants with event divided by the number of participants analyzed, multiplied by 100. ITT Population (First-Line Subpopulation).

End point type	Secondary
----------------	-----------

End point timeframe:

End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114 ^[20]	107 ^[21]		
Units: percentage of participants				
number (not applicable)	24.6	43.9		

Notes:

[20] - Only participants with CR, CRi, PR, or nPR were considered.

[21] - Only participants with CR, CRi, PR, or nPR were considered.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Death in the First-Line Subpopulation

End point title	Percentage of Participants Experiencing Death in the First-Line Subpopulation
-----------------	---

End point description:

The percentage of participants experiencing death was calculated as the number of participants with event divided by the number of participants analyzed, multiplied by 100. ITT Population (First-Line Subpopulation).

End point type	Secondary
----------------	-----------

End point timeframe:

End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years)

End point values	Rituximab + Bendamustine	Rituximab + Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	120		
Units: percentage of participants				
number (not applicable)	14.9	15		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to 8 weeks after the start of the last treatment cycle (nonserious adverse events [AEs]; up to 56 weeks) or until the EOT visit (serious AEs; up to 4.5 years)

Adverse event reporting additional description:

Based upon the pooled population including both first-line and second line participants

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	17.0
--------------------	------

Reporting groups

Reporting group title	Rituximab + Bendamustine
-----------------------	--------------------------

Reporting group description:

Participants received a specialized first-line or second-line regimen based upon prior chemotherapy exposure. Participants received intravenous (IV) rituximab 375 mg/m² on Day 1 of Cycle 1 and 500 mg/m² on Day 1 of Cycles 2 to 6. In those requiring a first-line regimen, bendamustine was administered IV at a dose of 90 mg/m² on Days 1 and 2 of Cycles 1 to 6. In those requiring a second-line regimen, the bendamustine dose was lowered to 70 mg/m². Each cycle was repeated every 4 weeks. Treatment was discontinued early in participants who experienced progressive disease (PD).

Reporting group title	Rituximab + Chlorambucil
-----------------------	--------------------------

Reporting group description:

Participants received IV rituximab 375 mg/m² on Day 1 of Cycle 1 and 500 mg/m² on Day 1 of Cycles 2 to 6. Chlorambucil was administered orally (PO) at a dose of 10 mg/m² on Days 1 to 7, beginning with Cycle 1 and continuing for up to 12 cycles or until complete response (CR) was achieved. Each cycle was repeated every 4 weeks. Treatment was discontinued early in participants who experienced PD.

Serious adverse events	Rituximab + Bendamustine	Rituximab + Chlorambucil	
Total subjects affected by serious adverse events			
subjects affected / exposed	73 / 177 (41.24%)	56 / 178 (31.46%)	
number of deaths (all causes)	30	35	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Leiomyosarcoma			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bladder transitional cell carcinoma subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular occlusion			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	5 / 177 (2.82%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	3 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ill-defined disorder			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Pneumonitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 177 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 177 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			

subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Liver function test abnormal subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 177 (0.56%)	4 / 178 (2.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	2 / 177 (1.13%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute myocardial infarction			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 177 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 177 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac fibrillation			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrhythmia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	11 / 177 (6.21%)	7 / 178 (3.93%)	
occurrences causally related to treatment / all	8 / 11	7 / 7	
deaths causally related to treatment / all	0 / 0	1 / 1	
Neutropenia			
subjects affected / exposed	6 / 177 (3.39%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	6 / 6	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	3 / 177 (1.69%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 177 (1.13%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 177 (1.13%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	2 / 2	1 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 177 (1.69%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Constipation			
subjects affected / exposed	1 / 177 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 177 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 177 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholecystitis			
subjects affected / exposed	2 / 177 (1.13%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin reaction			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin toxicity			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			

subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 177 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 177 (4.52%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	4 / 9	1 / 2	
deaths causally related to treatment / all	1 / 2	0 / 0	
Herpes zoster			

subjects affected / exposed	5 / 177 (2.82%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	4 / 177 (2.26%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	3 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 177 (1.69%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	3 / 177 (1.69%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	3 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Infection			
subjects affected / exposed	2 / 177 (1.13%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 177 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeria sepsis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 177 (0.56%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Tumour lysis syndrome			

subjects affected / exposed	4 / 177 (2.26%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	2 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Rituximab + Bendamustine	Rituximab + Chlorambucil	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	165 / 177 (93.22%)	159 / 178 (89.33%)	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	8 / 177 (4.52%)	11 / 178 (6.18%)	
occurrences (all)	11	21	
Weight decreased			
subjects affected / exposed	13 / 177 (7.34%)	5 / 178 (2.81%)	
occurrences (all)	13	5	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	12 / 177 (6.78%)	18 / 178 (10.11%)	
occurrences (all)	12	23	
Vascular disorders			

Hypotension subjects affected / exposed occurrences (all)	9 / 177 (5.08%) 11	5 / 178 (2.81%) 6	
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	10 / 177 (5.65%) 10	14 / 178 (7.87%) 16	
Dizziness subjects affected / exposed occurrences (all)	7 / 177 (3.95%) 7	12 / 178 (6.74%) 12	
Blood and lymphatic system disorders			
Neutropenia subjects affected / exposed occurrences (all)	97 / 177 (54.80%) 231	86 / 178 (48.31%) 187	
Leukopenia subjects affected / exposed occurrences (all)	42 / 177 (23.73%) 103	31 / 178 (17.42%) 54	
Thrombocytopenia subjects affected / exposed occurrences (all)	35 / 177 (19.77%) 66	41 / 178 (23.03%) 73	
Anaemia subjects affected / exposed occurrences (all)	40 / 177 (22.60%) 44	27 / 178 (15.17%) 34	
Lymphopenia subjects affected / exposed occurrences (all)	30 / 177 (16.95%) 43	21 / 178 (11.80%) 32	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	29 / 177 (16.38%) 35	34 / 178 (19.10%) 40	
Pyrexia subjects affected / exposed occurrences (all)	33 / 177 (18.64%) 36	16 / 178 (8.99%) 21	
Fatigue subjects affected / exposed occurrences (all)	17 / 177 (9.60%) 19	18 / 178 (10.11%) 25	

Chills			
subjects affected / exposed	16 / 177 (9.04%)	15 / 178 (8.43%)	
occurrences (all)	20	20	
Oedema peripheral			
subjects affected / exposed	9 / 177 (5.08%)	10 / 178 (5.62%)	
occurrences (all)	9	11	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	53 / 177 (29.94%)	46 / 178 (25.84%)	
occurrences (all)	77	66	
Diarrhoea			
subjects affected / exposed	29 / 177 (16.38%)	20 / 178 (11.24%)	
occurrences (all)	37	26	
Constipation			
subjects affected / exposed	27 / 177 (15.25%)	22 / 178 (12.36%)	
occurrences (all)	34	22	
Vomiting			
subjects affected / exposed	18 / 177 (10.17%)	20 / 178 (11.24%)	
occurrences (all)	23	24	
Abdominal pain			
subjects affected / exposed	3 / 177 (1.69%)	11 / 178 (6.18%)	
occurrences (all)	3	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 177 (9.60%)	18 / 178 (10.11%)	
occurrences (all)	18	19	
Dyspnoea			
subjects affected / exposed	10 / 177 (5.65%)	12 / 178 (6.74%)	
occurrences (all)	11	12	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	28 / 177 (15.82%)	9 / 178 (5.06%)	
occurrences (all)	34	9	
Pruritus			
subjects affected / exposed	14 / 177 (7.91%)	8 / 178 (4.49%)	
occurrences (all)	14	8	

Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	5 / 177 (2.82%) 6	12 / 178 (6.74%) 12	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all)	10 / 177 (5.65%) 11 8 / 177 (4.52%) 9	9 / 178 (5.06%) 9 9 / 178 (5.06%) 10	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	14 / 177 (7.91%) 15	8 / 178 (4.49%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2010	The confirmation of response assessment visit was changed from 8 weeks to 12 weeks after initial diagnosis of CR. Additionally, participants in the second-line subpopulation were permitted to have received any first-line chemotherapy prior to enrollment unless explicitly prohibited under the exclusion criteria. The method of investigational drug dosing was also specified as the DuBois formula for body surface area (BSA). The amendment also stipulated a second set of screening examinations within 7 days of treatment start. Splitting of the rituximab dose was permitted for participants with a high absolute lymphocyte count ($\geq 25 \times 10^9$ cells/mL). Bendamustine dose adaptation and reconstitution technique were also specified to reflect start criteria per the manufacturer. The reporting period for AEs was updated, where only serious AEs were to be followed until premature withdrawal or the EOT visit.
21 May 2012	The relapsed (second-line) participant cohort was closed in order to focus on enrollment of participants into the first-line subpopulation. Previous treatment for CLL became an exclusion criterion. Participants already enrolled into the second-line subpopulation continued to receive treatment and perform routine study assessments as specified by the protocol. Analyses of the first-line subpopulation became the focus of the primary endpoint; however, the interim analysis was unaffected by the protocol amendment and was applied to the pooled population of first-line and second-line participants. Confirmed CR assessment was based on IWCLL2008 criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported