Clinical trial results:
A Multicenter, Phase III, Open-Label, Randomized Study in Relapsed/Refractory Patients With Chronic Lymphocytic Leukemia to Evaluate the Benefit of Venetoclax (GDC-0199/ABT-199) Plus Rituximab Compared With Bendamustine Plus Rituximab

Summary

EudraCT number	2013-002110-12
Trial protocol	CZ SE BE GB AT IT FR NL HU DK DE ES PL
Global end of trial date	

Results information

Result version number	v1
This version publication date	19 May 2018
First version publication date	19 May 2018

Trial information

Trial identification

Sponsor protocol code	GO28667

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02005471
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 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, 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	Interim
Date of interim/final analysis	08 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 May 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of venetoclax and rituximab compared with bendamustine and rituximab in participants with relapsed or refractory chronic lymphocytic leukemia (CLL) as measured by investigator-assessed progression-free survival (PFS)

Protection of trial subjects:

This study was conducted in full conformance with the International Council on Harmonization (ICH) E6 guideline for Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study complied with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). The study complied with U.S. FDA regulations and applicable local, state, and federal laws. In the EU/EEA the study complied with the EU Clinical Trial Directive (2001/20/EC).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 March 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Australia: 73
Country: Number of subjects enrolled	New Zealand: 13
Country: Number of subjects enrolled	Czech Republic: 44
Country: Number of subjects enrolled	Hungary: 26
Country: Number of subjects enrolled	Poland: 46
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	France: 29

Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Sweden: 3
Worldwide total number of subjects	389
EEA total number of subjects	247

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)	186
From 65 to 84 years	201
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 489 participants were screened, out of which, 389 participants were enrolled into the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Bendamustine + Rituximab

Arm description:

Participants received bendamustine at a dose of 70 milligrams per meter squared (mg/m^2) via intravenous (IV) infusion on Days 1 and 2 of each 28-day cycle for 6 cycles, in combination with rituximab at a dose of 375 mg/m^2 via IV infusion on Day 1 of Cycle 1 and at a dose of 500 mg/m^2 on Day 1 of Cycles 2-6.

Arm type	Active comparator
Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bendamustine was administered at a dose of 70 mg/m^2 via IV infusion on Days 1 and 2 of each 28-day cycle, for 6 cycles.

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

Dosage and administration details:

Rituximab was administered at a dose of 375 mg/m^2 via IV infusion on Day 1 of Cycle 1 and at a dose of 500 mg/m^2 on Day 1 of Cycles 2-6.

Arm title	Venetoclax + Rituximab

Arm description:

Participants were initially placed on a venetoclax ramp-up period of 5 weeks, and received an initial dose of 20 milligrams (mg) via tablet orally once daily (QD) for initial 1 to 7 days, then venetoclax dose was incremented weekly up to a maximum dose of 400 mg via tablet orally QD. Participants continued receiving venetoclax at a dose of 400 mg via tablet orally QD from Week 6 (Day 1 of Cycle 1 of combination therapy) onwards up to disease progression (PD) or 2 years, whichever occurred first, as directed by the investigator, in combination with rituximab at a dose of 375 mg/m^2 via IV infusion on Day 1 of Cycle 1 and at a dose of 500 mg/m^2 on Day 1 of Cycles 2-6.

Arm type	Experimental

Investigational medicinal product name	Venetoclax
Investigational medicinal product code	
Other name	GDC-0199, ABT-199
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Venetoclax was administered at an initial dose of 20 mg via tablet orally QD, incremented weekly up to a maximum dose of 400 mg during 4-5 weeks ramp-up period. Venetoclax was continued at 400 mg QD from Week 6 (Day 1 of Cycle 1 of combination therapy) onwards up to PD or 2 years, whichever occurred first.

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

Dosage and administration details:

Rituximab was administered at a dose of 375 mg/m^2 via IV infusion on Day 1 of Cycle 1 and at a dose of 500 mg/m^2 on Day 1 of Cycles 2-6.

Number of subjects in period 1	Bendamustine + Rituximab	Venetoclax + Rituximab
Started	195	194
Treated	188	194
Completed	0	0
Not completed	195	194
Ongoing in Study	144	171
Physician decision	2	1
Consent withdrawn by subject	18	7
Adverse Event	1	-
Death	26	15
Progressive Disease	3	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Bendamustine + Rituximab
Reporting group description:	
Participants received bendamustine at a dose of 70 milligrams per meter squared (mg/m^2) via intravenous (IV) infusion on Days 1 and 2 of each 28-day cycle for 6 cycles, in combination with rituximab at a dose of 375 mg/m^2 via IV infusion on Day 1 of Cycle 1 and at a dose of 500 mg/m^2 on Day 1 of Cycles 2-6.	
Reporting group title	Venetoclax + Rituximab
Reporting group description:	
Participants were initially placed on a venetoclax ramp-up period of 5 weeks, and received an initial dose of 20 milligrams (mg) via tablet orally once daily (QD) for initial 1 to 7 days, then venetoclax dose was incremented weekly up to a maximum dose of 400 mg via tablet orally QD. Participants continued receiving venetoclax at a dose of 400 mg via tablet orally QD from Week 6 (Day 1 of Cycle 1 of combination therapy) onwards up to disease progression (PD) or 2 years, whichever occurred first, as directed by the investigator, in combination with rituximab at a dose of 375 mg/m^2 via IV infusion on Day 1 of Cycle 1 and at a dose of 500 mg/m^2 on Day 1 of Cycles 2-6.	

Reporting group values	Bendamustine + Rituximab	Venetoclax + Rituximab	Total
Number of subjects	195	194	389
Age Categorical Units: Subjects			
Age Continuous			
Analysis was performed on intent-to-treat (ITT) population, which included all randomized participants, with participants grouped according to randomized treatment group, regardless of the actual treatment received.			
Units: years			
arithmetic mean	64.4	63.9	
standard deviation	± 9.6	± 10.5	-
Gender Categorical Units: Subjects			
Female	44	58	102
Male	151	136	287

End points

End points reporting groups

Reporting group title	Bendamustine + Rituximab

Reporting group description:

Participants received bendamustine at a dose of 70 milligrams per meter squared (mg/m^2) via intravenous (IV) infusion on Days 1 and 2 of each 28-day cycle for 6 cycles, in combination with rituximab at a dose of 375 mg/m^2 via IV infusion on Day 1 of Cycle 1 and at a dose of 500 mg/m^2 on Day 1 of Cycles 2-6.

Reporting group title	Venetoclax + Rituximab

Reporting group description:

Participants were initially placed on a venetoclax ramp-up period of 5 weeks, and received an initial dose of 20 milligrams (mg) via tablet orally once daily (QD) for initial 1 to 7 days, then venetoclax dose was incremented weekly up to a maximum dose of 400 mg via tablet orally QD. Participants continued receiving venetoclax at a dose of 400 mg via tablet orally QD from Week 6 (Day 1 of Cycle 1 of combination therapy) onwards up to disease progression (PD) or 2 years, whichever occurred first, as directed by the investigator, in combination with rituximab at a dose of 375 mg/m^2 via IV infusion on Day 1 of Cycle 1 and at a dose of 500 mg/m^2 on Day 1 of Cycles 2-6.

Subject analysis set title	Bendamustine + Rituximab 17p Del. Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received bendamustine at a dose of 70 mg/m^2 via IV infusion on Days 1 and 2 of each 28-day cycle for 6 cycles, in combination with rituximab at a dose of 375 mg/m^2 via IV infusion on Day 1 of Cycle 1 and at a dose of 500 mg/m^2 on Day 1 of Cycles 2-6. Only participants with 17p deletion as identified by Fluorescence in-situ Hybridization (FISH) test were included.

Subject analysis set title	Venetoclax + Rituximab 17p Del. Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were initially placed on a venetoclax ramp-up period of 5 weeks, and received an initial dose of 20 mg via tablet orally QD for initial 1 to 7 days, then venetoclax dose was incremented weekly up to a maximum dose of 400 mg via tablet orally QD. Participants continued receiving venetoclax at a dose of 400 mg via tablet orally QD from Week 6 (Day 1 of Cycle 1 of combination therapy) onwards up to PD or 2 years, whichever occurred first, as directed by the investigator, in combination with rituximab at a dose of 375 mg/m^2 via IV infusion on Day 1 of Cycle 1 and at a dose of 500 mg/m^2 on Day 1 of Cycles 2-6. Only participants with 17p deletion as identified by FISH test were included.

Primary: Percentage of Participants With PD as Assessed by the Investigator Using Standard International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Guidelines or Death

End point title	Percentage of Participants With PD as Assessed by the Investigator Using Standard International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Guidelines or Death[1]

End point description:

Assessment of response was performed by the investigator according to the iwCLL guidelines. PD was defined as occurrence of one of the following events: appearance of any new extra nodal lesion; new palpable lymph node (greater than [>] 1.5 centimeters [cm]); unequivocal progression of non-target lesion; an increase of greater than or equal to (>/=) 50 percent (%) compared to baseline in splenomegaly, hepatomegaly, number of blood lymphocytes with lymphocyte count >/=5000 per microliter (mcL), or in longest diameter of any extra nodal lesion; transformation to a more aggressive histology; decrease of >/=50% compared to baseline in platelet or neutrophil count; or decrease in hemoglobin level by >2 gram per deciliter (g/dL) or to less than [<] 10 g/dL. Analysis was performed on ITT population.

End point type	Primary

End point timeframe:

Baseline up to PD or death from any cause, whichever occurred first (up to approximately 3 years)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Results for this outcome were reported descriptively and were not planned to be analyzed

for statistically significant differences between groups

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	194		
Units: percentage of participants				
number (not applicable)	58.5	16.5		

Statistical analyses

No statistical analyses for this end point

Primary: PFS as Assessed by the Investigator Using Standard iwCLL Guidelines

End point title	PFS as Assessed by the Investigator Using Standard iwCLL Guidelines

End point description:

PFS was defined as the time from randomization until first occurrence of PD/relapse as assessed by the investigator using iwCLL guidelines, or death from any cause, whichever occurred first. PD: occurrence of one of the following: new lesion; new palpable lymph node (>1.5 cm); unequivocal progression of non-target lesion; increase of >/=50% in splenomegaly, hepatomegaly, blood lymphocytes with count >/=5000/mcL, longest diameter of any lesion; transformation to more aggressive histology; decrease of >/=50% in platelet or neutrophil count, or hemoglobin level by >2 g/dL or to <10 g/dL. Participants who had not progressed, relapsed, or died at the time of analysis, were censored on the date of last assessment. In case of no disease assessment after baseline, PFS was censored at the time of randomization+1 day. The median PFS was estimated using Kaplan-Meier method and the 95% confidence interval (CI) was computed using method of Brookmeyer and Crowley.

End point type	Primary

End point timeframe:

Baseline up to PD or death from any cause, whichever occurred first (up to approximately 3 years)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[2]	194[3]		
Units: months				
median (confidence interval 95%)	17.0 (15.5 to 21.6)	99999 (99999 to 99999)		

Notes:

[2] - Analysis was performed on ITT population.

[3] - '99999' signifies that data could not be estimated due to low number of participants with an event.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis; Stratification factors: 17p deletion, risk status, geographic region.

Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab

Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.25

Notes:

[4] - Hazard ratio was estimated by Cox regression model.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Unstratified Analysis

Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.26

Notes:

[5] - Hazard ratio was estimated by Cox regression model.

Secondary: Percentage of Participants With PD or Death as Assessed by the Independent Review Committee (IRC) Using Standard iwCLL Guidelines

End point title	Percentage of Participants With PD or Death as Assessed by the Independent Review Committee (IRC) Using Standard iwCLL Guidelines

End point description:

Assessment of response was performed by the IRC according to the iwCLL guidelines. PD was defined as occurrence of one of the following events: appearance of any new extra nodal lesion; new palpable lymph node (>1.5 cm); unequivocal progression of non-target lesion; an increase of >/=50% compared to baseline in splenomegaly, hepatomegaly, number of blood lymphocytes with lymphocyte count >/=5000/mcL, or in longest diameter of any extra nodal lesion; transformation to a more aggressive histology; decrease of >/=50% compared to baseline in platelet or neutrophil count; or decrease in hemoglobin level by >2 g/dL or to <10 g/dL. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline up to PD or death from any cause, whichever occurred first (up to approximately 3 years)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	194		
Units: percentage of participants				
number (not applicable)	54.4	18.0		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Assessed by the IRC Using Standard iwCLL Guidelines

End point title	PFS as Assessed by the IRC Using Standard iwCLL Guidelines

End point description:

PFS was defined as the time from randomization until first occurrence of PD/relapse as assessed by the IRC using iwCLL guidelines, or death from any cause, whichever occurred first. PD: occurrence of one of the following: new lesion; new palpable lymph node (>1.5 cm); unequivocal progression of non-target lesion; increase of >/=50% in splenomegaly, hepatomegaly, blood lymphocytes with count >/=5000/mcL, longest diameter of any lesion; transformation to more aggressive histology; decrease of >/=50% in platelet or neutrophil count, or hemoglobin level by >2 g/dL or to <10 g/dL. Participants who had not progressed, relapsed, or died at the time of analysis, were censored on the date of last assessment. In case of no disease assessment after baseline, PFS was censored at the time of randomization+1 day. The median PFS was estimated using Kaplan-Meier method and the 95% CI was computed using method of Brookmeyer and Crowley.

End point type	Secondary

End point timeframe:

Baseline up to PD or death from any cause, whichever occurred first (up to approximately 3 years)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[6]	194[7]		
Units: months				
median (confidence interval 95%)	18.1 (15.8 to 22.3)	99999 (99999 to 99999)		

Notes:

[6] - Analysis was performed on ITT population.

[7] - '99999' signifies that data could not be estimated due to low number of participants with an event.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis; Stratification factors: 17p deletion, risk status, geographic region.

Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab

Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	0.28

Notes:

[8] - Hazard ratio was estimated by Cox regression model.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Unstratified Analysis

Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.3

Notes:

[9] - Hazard ratio was estimated by Cox regression model.

Secondary: Percentage of Participants With PD or Death as Assessed by the Investigator Using Standard iwCLL Guidelines in Participants With 17p Deletion as Identified by FISH Test

End point title	Percentage of Participants With PD or Death as Assessed by the Investigator Using Standard iwCLL Guidelines in Participants With 17p Deletion as Identified by FISH Test

End point description:

Assessment of response was performed by the investigator according to the iwCLL guidelines. PD was defined as occurrence of one of the following events: appearance of any new extra nodal lesion; new palpable lymph node (>1.5 cm); unequivocal progression of non-target lesion; an increase of >/=50% compared to baseline in splenomegaly, hepatomegaly, number of blood lymphocytes with lymphocyte count >/=5000/mcL, or in longest diameter of any extra nodal lesion; transformation to a more aggressive histology; decrease of >/=50% compared to baseline in platelet or neutrophil count; or decrease in hemoglobin level by >2 g/dL or to <10 g/dL. Analysis was performed on ITT population participants with 17p deletion as identified by FISH test.

End point type	Secondary

End point timeframe:

Baseline up to PD or death from any cause, whichever occurred first (up to approximately 3 years)

End point values	Bendamustine + Rituximab 17p Del. Population	Venetoclax + Rituximab 17p Del. Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	46		
Units: percentage of participants				
number (not applicable)	58.7	15.2		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Assessed by the Investigator Using Standard iwCLL Guidelines in Participants With 17p Deletion as Identified by FISH Test

End point title	PFS as Assessed by the Investigator Using Standard iwCLL Guidelines in Participants With 17p Deletion as Identified by FISH Test

End point description:

PFS was defined as the time from randomization until first occurrence of PD/relapse as assessed by the investigator using iwCLL guidelines, or death from any cause, whichever occurred first. PD: occurrence of one of the following: new lesion; new palpable lymph node (>1.5 cm); unequivocal progression of non-target lesion; increase of >/=50% in splenomegaly, hepatomegaly, blood lymphocytes with count >/=5000/mcL, longest diameter of any lesion; transformation to more aggressive histology; decrease of >/=50% in platelet or neutrophil count, or hemoglobin level by >2 g/dL or to <10 g/dL. Participants who had not progressed, relapsed, or died at the time of analysis, were censored on the date of last assessment. In case of no disease assessment after baseline, PFS was censored at the time of randomization+1 day. The median PFS was estimated using Kaplan-Meier method and the 95% CI was computed using method of Brookmeyer and Crowley.

End point type	Secondary

End point timeframe:

Baseline up to PD or death from any cause, whichever occurred first (up to approximately 3 years)

End point values	Bendamustine + Rituximab 17p Del. Population	Venetoclax + Rituximab 17p Del. Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[10]	46[11]		
Units: months				
median (confidence interval 95%)	15.4 (10.0 to 21.0)	99999 (27.6 to 99999)		

Notes:

[10] - Analysis was performed on ITT population participants with 17p deletion as identified by FISH test.

[11] - '99999' signifies that data could not be estimated due to low number of participants with an event.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Stratified Analysis; Stratification factor: geographic region.	
Comparison groups	Bendamustine + Rituximab 17p Del. Population v Venetoclax + Rituximab 17p Del. Population
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.31

Notes:

[12] - Hazard ratio was estimated by Cox regression model.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Unstratified Analysis	
Comparison groups	Bendamustine + Rituximab 17p Del. Population v Venetoclax + Rituximab 17p Del. Population
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.29

Notes:

[13] - Hazard ratio was estimated by Cox regression model.

Secondary: Percentage of Participants With PD or Death as Assessed by the IRC Using Standard iwCLL Guidelines in Participants With 17p Deletion as Identified by FISH Test

End point title	Percentage of Participants With PD or Death as Assessed by the IRC Using Standard iwCLL Guidelines in Participants With 17p Deletion as Identified by FISH Test

End point description:

Assessment of response was performed by the IRC according to the iwCLL guidelines. PD was defined as occurrence of one of the following events: appearance of any new extra nodal lesion; new palpable lymph node (>1.5 cm); unequivocal progression of non-target lesion; an increase of >/=50% compared to baseline in splenomegaly, hepatomegaly, number of blood lymphocytes with lymphocyte count

>/=5000/mcL, or in longest diameter of any extra nodal lesion; transformation to a more aggressive histology; decrease of >/=50% compared to baseline in platelet or neutrophil count; or decrease in hemoglobin level by >2 g/dL or to <10 g/dL. Analysis was performed on ITT population participants with 17p deletion as identified by FISH test.

End point type	Secondary

End point timeframe:

Baseline up to PD or death, whichever occurred first (up to approximately 3 years)

End point values	Bendamustine + Rituximab 17p Del. Population	Venetoclax + Rituximab 17p Del. Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	46		
Units: percentage of participants				
number (not applicable)	47.8	19.6		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Assessed by the IRC Using Standard iwCLL Guidelines in Participants With 17p Deletion as Identified by FISH Test

End point title	PFS as Assessed by the IRC Using Standard iwCLL Guidelines in Participants With 17p Deletion as Identified by FISH Test

End point description:

PFS was defined as the time from randomization until first occurrence of PD/relapse as assessed by the IRC using iwCLL guidelines, or death from any cause, whichever occurred first. PD: occurrence of one of the following: new lesion; new palpable lymph node (>1.5 cm); unequivocal progression of non-target lesion; increase of >/=50% in splenomegaly, hepatomegaly, blood lymphocytes with count >/=5000/mcL, longest diameter of any lesion; transformation to more aggressive histology; decrease of >/=50% in platelet or neutrophil count, or hemoglobin level by >2 g/dL or to <10 g/dL. Participants who had not progressed, relapsed, or died at the time of analysis, were censored on the date of last assessment. In case of no disease assessment after baseline, PFS was censored at the time of randomization+1 day. The median PFS was estimated using Kaplan-Meier method and the 95% CI was computed using method of Brookmeyer and Crowley.

End point type	Secondary

End point timeframe:

Baseline up to PD or death, whichever occurred first (up to approximately 3 years)

End point values	Bendamustine + Rituximab 17p Del. Population	Venetoclax + Rituximab 17p Del. Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[14]	46[15]		
Units: months				
median (confidence interval 95%)	16.1 (13.6 to 22.3)	99999 (27.6 to 99999)		

Notes:

[14] - Analysis was performed on ITT population participants with 17p deletion as identified by FISH test.
[15] - '99999' signifies that data could not be estimated due to low number of participants with an event.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Stratified Analysis; Stratification factor: geographic region.	
Comparison groups	Bendamustine + Rituximab 17p Del. Population v Venetoclax + Rituximab 17p Del. Population
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.49

Notes:

[16] - Hazard ratio was estimated by Cox regression model.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Unstratified Analysis	
Comparison groups	Bendamustine + Rituximab 17p Del. Population v Venetoclax + Rituximab 17p Del. Population
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.46

Notes:

[17] - Hazard ratio was estimated by Cox regression model.

Secondary: Percentage of Participants With Best Overall Response of Complete Response (CR), CR with Incomplete Bone Marrow Recovery (CRi), Nodular Partial Response (nPR), or Partial Response (PR) as Assessed by the Investigator Using

iwCLL Guidelines

End point title	Percentage of Participants With Best Overall Response of Complete Response (CR), CR with Incomplete Bone Marrow Recovery (CRi), Nodular Partial Response (nPR), or Partial Response (PR) as Assessed by the Investigator Using iwCLL Guidelines

End point description:

Response was assessed by the investigator according to the iwCLL guidelines and was confirmed by repeat assessment >/=4 weeks after initial documentation. CR: peripheral blood lymphocytes <4000/mcL; absence of any new lesion, nodal disease, lymphadenopathy, hepatomegaly, splenomegaly, and constitutional symptoms; neutrophils >1500/mcL, platelets >100000/mcL, hemoglobin >11.0 g/dL without need for transfusion or exogenous growth factors; normocellular bone marrow with <30% lymphocytes; no lymphoid nodules. CRi: fulfilling all CR criteria but persistent cytopenia. PR: >/=50% reduction in two of the following: peripheral blood lymphocytes, lymphadenopathy, spleen and/or liver enlargement; and one of the following: neutrophils >1500/mcL, platelets >100000/mcL, hemoglobin >11.0 g/dL or >/=50% improvement without need for transfusion or exogenous growth factors. nPR: fulfilling all CR criteria but presence of lymphoid nodules. The 95% CI was computed using Pearson-Clopper method.

End point type	Secondary

End point timeframe:

Baseline up to last follow-up visit (FUV) (maximum up to data cut-off date, overall approximately 3 years)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[18]	194[19]		
Units: percentage of participants				
number (confidence interval 95%)	67.7 (60.64 to 74.20)	93.3 (88.81 to 96.38)		

Notes:

[18] - Analysis was performed on ITT population.

[19] - Participants without post-baseline response assessment were considered as non-responders.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	25.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.88
upper limit	33.33

Notes:

[20] - The 95% CI was computed using Anderson-Hauck method.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[21]
Parameter estimate	Odds ratio (OR)
Point estimate	7.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.97
upper limit	15.37

Notes:

[21] - Odds Ratio (OR) was estimated using logistic regression model. The 95% CI was computed using Wald test.

Secondary: Percentage of Participants With Best Overall Response of CR, CRi, nPR, or PR as Assessed by the IRC Using iwCLL Guidelines

End point title	Percentage of Participants With Best Overall Response of CR, CRi, nPR, or PR as Assessed by the IRC Using iwCLL Guidelines

End point description:

Response was assessed by the IRC according to the iwCLL guidelines and was confirmed by repeat assessment >/=4 weeks after initial documentation. CR: peripheral blood lymphocytes <4000/mcL; absence of any new lesion, nodal disease, lymphadenopathy, hepatomegaly, splenomegaly, and constitutional symptoms; neutrophils >1500/mcL, platelets >100000/mcL, hemoglobin >11.0 g/dL without need for transfusion or exogenous growth factors; normocellular bone marrow with <30% lymphocytes; no lymphoid nodules. CRi: fulfilling all CR criteria but persistent cytopenia. PR: >/=50% reduction in two of the following: peripheral blood lymphocytes, lymphadenopathy, spleen and/or liver enlargement; and one of the following: neutrophils >1500/mcL, platelets >100000/mcL, hemoglobin >11.0 g/dL or >/=50% improvement without need for transfusion or exogenous growth factors. nPR: fulfilling all CR criteria but presence of lymphoid nodules. The 95% CI was computed using Pearson-Clopper method.

End point type	Secondary

End point timeframe:

Baseline up to last FUV (maximum up to data cut-off date, overall approximately 3 years)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[22]	194[23]		
Units: percentage of participants				
number (confidence interval 95%)	72.3 (65.46 to 78.46)	92.3 (87.57 to 95.61)		

Notes:

[22] - Analysis was performed on ITT population.

[23] - Participants without post-baseline response assessment were considered as non-responders.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab

Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	19.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.36
upper limit	27.56

Notes:

[24] - The 95% CI was computed using Anderson-Hauck method.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[25]
Parameter estimate	Odds ratio (OR)
Point estimate	4.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.56
upper limit	8.99

Notes:

[25] - OR was estimated using logistic regression model. The 95% CI was computed using Wald test.

Secondary: Percentage of Participants With Overall Response of CR, Cri, nPR, or PR at end of Combination Treatment Visit as Assessed by the Investigator Using iwCLL Guidelines

End point title	Percentage of Participants With Overall Response of CR, Cri, nPR, or PR at end of Combination Treatment Visit as Assessed by the Investigator Using iwCLL Guidelines

End point description:

Response was assessed by the investigator according to the iwCLL guidelines and was confirmed by repeat assessment >/=4 weeks after initial documentation. CR: peripheral blood lymphocytes <4000/mcL; absence of any new lesion, nodal disease, lymphadenopathy, hepatomegaly, splenomegaly, and constitutional symptoms; neutrophils >1500/mcL, platelets >100000/mcL, hemoglobin >11.0 g/dL without need for transfusion or exogenous growth factors; normocellular bone marrow with <30% lymphocytes; no lymphoid nodules. CRi: fulfilling all CR criteria but persistent cytopenia. PR: >/=50% reduction in two of the following: peripheral blood lymphocytes, lymphadenopathy, spleen and/or liver enlargement; and one of the following: neutrophils >1500/mcL, platelets >100000/mcL, hemoglobin >11.0 g/dL or >/=50% improvement without need for transfusion or exogenous growth factors. nPR: fulfilling all CR criteria but presence of lymphoid nodules. The 95% CI was computed using Pearson-Clopper method.

End point type	Secondary

End point timeframe:

End of combination treatment response (EoCTR) visit (8 to 12 weeks after Cycle [C] 6 Day [1]); Cycle length = 28 days

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[26]	194[27]		
Units: percentage of participants				
number (confidence interval 95%)	62.6 (55.37 to 69.37)	88.1 (82.74 to 92.33)		

Notes:

[26] - Analysis was performed on ITT population.

[27] - Participants without post-baseline response assessment were considered as non-responders.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	25.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.13
upper limit	34.03

Notes:

[28] - The 95% CI was computed using Anderson-Hauck method.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[29]
Parameter estimate	Odds ratio (OR)
Point estimate	4.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.76
upper limit	8.16

Notes:

[29] - OR was estimated using logistic regression model. The 95% CI was computed using Wald test.

Secondary: Percentage of Participants With Overall Response of CR, Cri, nPR, or PR at end of Combination Treatment Visit as Assessed by the IRC Using iwCLL Guidelines

End point title	Percentage of Participants With Overall Response of CR, Cri, nPR, or PR at end of Combination Treatment Visit as Assessed by the IRC Using iwCLL Guidelines

End point description:

Response was assessed by the IRC according to the iwCLL guidelines and was confirmed by repeat assessment >/=4 weeks after initial documentation. CR: peripheral blood lymphocytes <4000/mcL; absence of any new lesion, nodal disease, lymphadenopathy, hepatomegaly, splenomegaly, and constitutional symptoms; neutrophils >1500/mcL, platelets >100000/mcL, hemoglobin >11.0 g/dL without need for transfusion or exogenous growth factors; normocellular bone marrow with <30% lymphocytes; no lymphoid nodules. CRi: fulfilling all CR criteria but persistent cytopenia. PR: >/=50% reduction in two of the following: peripheral blood lymphocytes, lymphadenopathy, spleen and/or liver enlargement; and one of the following: neutrophils >1500/mcL, platelets >100000/mcL, hemoglobin >11.0 g/dL or >/=50% improvement without need for transfusion or exogenous growth factors. nPR: fulfilling all CR criteria but presence of lymphoid nodules. The 95% CI was computed using Pearson-Clopper method.

End point type	Secondary

End point timeframe:

EoCTR visit (8 to 12 weeks after C6D1); Cycle length = 28 days

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[30]	194[31]		
Units: percentage of participants				
number (confidence interval 95%)	62.6 (55.37 to 69.37)	87.1 (81.57 to 91.48)		

Notes:

[30] - Analysis was performed on ITT population.

[31] - Participants without post-baseline response assessment were considered as non-responders.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	24.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	16
upper limit	33.1

Notes:

[32] - The 95% CI was computed using Anderson-Hauck method.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab

Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[33]
Parameter estimate	Odds ratio (OR)
Point estimate	4.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.68
upper limit	7.85

Notes:

[33] - OR was estimated using logistic regression model. The 95% CI was computed using Wald test.

Secondary: Percentage of Participants Who Died

End point title	Percentage of Participants Who Died

End point description:

Percentage of participants who died from any cause, during the study, was reported. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline up to last FUV (maximum up to Data Cut-off date, overall approximately 3 years)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	194		
Units: percentage of participants				
number (not applicable)	13.8	7.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomization to the date of death from any cause. Participants alive at the time of the analysis were censored at the date when they were last known to be alive as documented by the investigator. The median OS was estimated using Kaplan-Meier method and the 95% CI was computed using method of Brookmeyer and Crowley. Analysis was performed on ITT population. The data '99999 (99999 to 99999)' in the results signifies that median and corresponding 95% CI could not be estimated due to low number of participants with an event.

End point type	Secondary

End point timeframe:

Baseline up to last FUV (maximum up to Data Cut-off date, overall approximately 3 years)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	194		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Stratified Analysis; Stratification factors: 17p deletion, risk status, geographic region.	
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.0186
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.9

Notes:
[34] - Hazard ratio was estimated by Cox regression model.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Unstratified Analysis	
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.019
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.9

Notes:

[35] - Hazard ratio was estimated by Cox regression model.

Secondary: Percentage of Participants With PD/Relapse, Start of a new Anti-Chronic Lymphocytic Leukemia (CLL) Therapy, or Death as Assessed by the Investigator Using iwCLL Guidelines

End point title	Percentage of Participants With PD/Relapse, Start of a new Anti-Chronic Lymphocytic Leukemia (CLL) Therapy, or Death as Assessed by the Investigator Using iwCLL Guidelines

End point description:

Percentage of participants with PD/relapse, death from any cause, or start of a new non-protocol-specified anti-CLL therapy as assessed by the investigator, during the study, was reported. PD was defined as occurrence of one of the following events: appearance of any new extra nodal lesion; new palpable lymph node (>1.5 cm); unequivocal progression of non-target lesion; an increase of >/=50% compared to baseline in splenomegaly, hepatomegaly, number of blood lymphocytes with lymphocyte count >/=5000/mcL, or in longest diameter of any extra nodal lesion; transformation to a more aggressive histology; decrease of >/=50% compared to baseline in platelet or neutrophil count; or decrease in hemoglobin level by >2 g/dL or to <10 g/dL. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline up to PD/relapse, start of a new anti-CLL therapy, or death from any cause, whichever occurred first (maximum up to Data Cut-off date, overall approximately 3 years)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	194		
Units: percentage of participants				
number (not applicable)	60.5	17.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS) as Assessed by the Investigator Using iwCLL Guidelines

End point title	Event-Free Survival (EFS) as Assessed by the Investigator Using iwCLL Guidelines

End point description:

EFS was defined as the time from date of randomization until the date of PD/relapse, start of a new non-protocol-specified anti-CLL therapy, or death from any cause, whichever occurred first, as assessed by the investigator. PD: occurrence of one of the following: new lesion; new palpable lymph node (>1.5 cm); unequivocal progression of non-target lesion; increase of >/=50% in splenomegaly, hepatomegaly, blood lymphocytes with count >/=5000/mcL, longest diameter of any lesion; transformation to more aggressive histology; decrease of >/=50% in platelet or neutrophil count, or hemoglobin level by >2 g/dL or to <10 g/dL. Participants without any of the specified event at the time of analysis were censored at the date of last adequate response assessment. In case of no post-baseline response assessment, participants were censored at the randomization date. The median EFS was estimated using Kaplan-Meier method and the 95% CI was computed using method of Brookmeyer and Crowley.

End point type	Secondary

End point timeframe:

Baseline up to PD/relapse, start of a new anti-CLL therapy, or death from any cause, whichever occurred first (maximum up to Data Cut-off date, overall approximately 3 years)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[36]	194[37]		
Units: months				
median (confidence interval 95%)	16.4 (14.6 to 21.2)	99999 (99999 to 99999)		

Notes:

[36] - Analysis was performed on ITT population.

[37] - '99999' signifies that data could not be estimated due to low number of participants with an event.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Stratified Analysis; Stratification factors: 17p deletion, risk status, geographic region.	
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.25

Notes:

[38] - Hazard ratio was estimated by Cox regression model.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Unstratified Analysis	
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.26

Notes:

[39] - Hazard ratio was estimated by Cox regression model.

Secondary: Percentage of Participants With PD or Death Among Participants With Best Overall Response of CR, CRi, nPR, or PR as Assessed by the Investigator Using iwCLL Guidelines

End point title	Percentage of Participants With PD or Death Among Participants With Best Overall Response of CR, CRi, nPR, or PR as Assessed by the Investigator Using iwCLL Guidelines

End point description:

Percentage of participants with PD as assessed by the investigator according to the iwCLL guidelines, or death from any cause, during the study, was reported. PD was defined as occurrence of one of the following events: appearance of any new extra nodal lesion; new palpable lymph node (>1.5 cm); unequivocal progression of non-target lesion; an increase of >/=50% compared to baseline in splenomegaly, hepatomegaly, number of blood lymphocytes with lymphocyte count >/=5000/mcL, or in longest diameter of any extra nodal lesion; transformation to a more aggressive histology; decrease of >/=50% compared to baseline in platelet or neutrophil count; or decrease in hemoglobin level by >2 g/dL or to <10 g/dL. Analysis was performed on ITT population participants who had best overall response of CR, CRi, nPR, or PR.

End point type	Secondary

End point timeframe:

From time of achieving best overall response until PD or death from any cause, whichever occurred first (up to approximately 3 years)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	181		
Units: percentage of participants				
number (not applicable)	53.8	11.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Responses (DOR) as Assessed by the Investigator Using iwCLL Guidelines

End point title	Duration of Responses (DOR) as Assessed by the Investigator Using iwCLL Guidelines

End point description:

DOR was defined as the time from first occurrence of a documented response of CR, CRi, nPR, or PR until PD/relapse, as assessed by the investigator according to the iwCLL guidelines, or death from any cause. PD: occurrence of one of the following: new lesion; new palpable lymph node (>1.5 cm); unequivocal progression of non-target lesion; increase of >/=50% in splenomegaly, hepatomegaly, blood lymphocytes with count >/=5000/mcL, longest diameter of any lesion; transformation to more aggressive histology; decrease of >/=50% in platelet or neutrophil count, or hemoglobin level by >2 g/dL or to <10 g/dL. Participants without PD or death after response were censored at the last date of

adequate response assessment. The median DOR was estimated using Kaplan-Meier method and the 95% CI was computed using method of Brookmeyer and Crowley. Analysis was performed on ITT population participants who had best overall response of CR, CRi, nPR, or PR.

End point type	Secondary

End point timeframe:

From time of achieving best overall response until PD or death from any cause, whichever occurred first (up to approximately 3 years)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	181[40]		
Units: months				
median (confidence interval 95%)	19.4 (16.1 to 22.6)	99999 (99999 to 99999)		

Notes:

[40] - '99999' signifies that data could not be estimated due to low number of participants with an event.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Start of New Anti-CLL Treatment or Death as Assessed by the Investigator

End point title	Percentage of Participants With Start of New Anti-CLL Treatment or Death as Assessed by the Investigator

End point description:

Percentage of participants with start of new non-protocol-specified anti-CLL therapy, as assessed by the investigator, or death from any cause, during the study, was reported. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline up to start of new ani-CLL therapy or death, whichever occurred first (up to approximately 3 years)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	194		
Units: percentage of participants				
number (not applicable)	42.6	11.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to New Anti-CLL Treatment (TTNT) as Assessed by the Investigator

End point title	Time to New Anti-CLL Treatment (TTNT) as Assessed by the Investigator

End point description:

TTNT was defined as the time from randomization until start of new non-protocol-specified anti-CLL treatment or death from any cause. Participants without the event at the time of analysis were censored at the last visit date for this outcome measure analysis. The median TTNT was estimated using Kaplan-Meier method and the 95% CI was computed using method of Brookmeyer and Crowley. Analysis was performed on ITT population. The data '99999 (99999 to 99999)' in the results signifies that median and corresponding 95% CI could not be estimated due to low number of participants with an event.

End point type	Secondary

End point timeframe:

Baseline up to start of new ani-CLL therapy or death, whichever occurred first (up to approximately 3 years)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	194		
Units: months				
median (confidence interval 95%)	26.4 (21.9 to 33.1)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis; Stratification factors: 17p deletion, risk status, geographic region.

Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.31

Notes:

[41] - Hazard ratio was estimated by Cox regression model.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Unstratified Analysis

Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab

Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.31

Notes:

[42] - Hazard ratio was estimated by Cox regression model.

Secondary: Percentage of Participants With Minimal Residual Disease (MRD) Negativity at the EoCTR Visit

End point title	Percentage of Participants With Minimal Residual Disease (MRD) Negativity at the EoCTR Visit

End point description:

MRD-negativity was defined as the presence of <1 malignant B-cell per 10000 normal B-cells in a sample of at least 200000 B-cells, as assessed by the allele specific oligonucleotide polymerase chain reaction (ASO-PCR) and/or flow cytometry technique. Percentage of participants with MRD-negativity at the EoCTR visit was reported. The 95% CI was computed using Pearson-Clopper method. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

EoCTR visit (8 to 12 weeks after C6D1); Cycle length = 28 days

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	194		
Units: percentage of participants				
number (confidence interval 95%)	13.3 (8.90 to 18.92)	62.4 (55.15 to 69.21)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Difference in MRD Negativity Rates
Point estimate	49.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	40.44
upper limit	57.64

Notes:

[43] - The 95% CI was computed using Anderson-Hauck method.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[44]
Parameter estimate	Odds ratio (OR)
Point estimate	10.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.5
upper limit	17.85

Notes:

[44] - OR was estimated using logistic regression model. The 95% CI was computed using Wald test.

Secondary: Plasma Venetoclax Concentrations

End point title	Plasma Venetoclax Concentrations[45]

End point description:

Analysis was performed on Pharmacokinetic (PK)-Evaluable population, which included all participants in the 'Venetoclax + Rituximab' arm and who received at least one dose of venetoclax with at least one post-dose PK concentration result available. Here, 'Number of Subject Analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour, anytime before venetoclax administeration) and 4 hours post-dose on D1 of Cycles 1 and 4; Cycle length = 28 days

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reported analysis was planned to be carried out in the indicated arm(s) only

End point values	Venetoclax + Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	184			
Units: micrograms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
C1D1, Pre-dose (n=151)	0.626 (± 0.540)			
C1D1, 4 hours Post-Dose (n=159)	1.34 (± 0.881)			
C4D1, Pre-dose (n=112)	0.681 (± 0.745)			
C4D1, 4 hours Post-Dose (n=121)	1.34 (± 0.905)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Lymphocyte Subset Counts at Specified Time Points

End point title	Change From Baseline in Lymphocyte Subset Counts at Specified Time Points

End point description:

End point type	Secondary

End point timeframe:

Baseline, C4D14-28, Study Treatment Completion/Early Withdrawal (STC/EW, up to C6D28), EoCTR visit (8 to 12 weeks after C6D1), and at FUVs (every 12 weeks after EoCTR up to 3 years); Cycle length = 28 days

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[46]	0[47]		
Units: lymphocyte counts				

Notes:

[46] - Anticipated Posting Date: Sep 2019

[47] - Anticipated Posting Date: Sep 2019

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Monroe Dunaway (MD) Anderson Symptom Inventory (MDASI) Core Symptom Severity, Module Symptom Severity, and Interference Scores

End point title	Change From Baseline in Monroe Dunaway (MD) Anderson Symptom Inventory (MDASI) Core Symptom Severity, Module Symptom Severity, and Interference Scores

End point description:

MDASI is a 25-item validated questionnaire consisting of 2 parts. Part 1: 19-items divided into 2 scales, Core Symptom Severity (average of Questions 1 to 13) and Module Symptom Severity (average of Questions 14 to 19). Part 2: 6-items to assess Interference (symptom distress) (average of Questions 20 to 25). Each item was rated from 0 to 10, with lower scores indicating better outcome. Total score for Core Symptom Severity, Module Symptom Severity, and Interference are reported which range from 0 to 10, with lower scores indicating better health-related quality of life (HRQoL). Analysis was performed on patient reported outcome (PRO)-evaluable population, which included all participants with baseline and at least one post-baseline PRO assessment. '99999' = either data were not available because no participant was evaluable or standard deviation (SD) was not available because only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

Baseline, Days 1, 8, and 15 of Cycles 1, 2, and 3; Cycle length = 28 days

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117[48]	42[49]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline; Core symptom severity (n=116,42)	1.76 (± 1.55)	1.55 (± 1.31)		
Change at C1D1; Core symptom severity (n=116,36)	0.0 (± 0.0)	-0.08 (± 0.98)		
Change at C1D8; Core symptom severity (n=107,36)	0.26 (± 1.34)	-0.30 (± 0.84)		
Change at C1D15; Core symptom severity (n=104,33)	0.00 (± 1.31)	-0.27 (± 0.93)		
Change at C2D1; Core symptom severity (n=101,35)	-0.23 (± 1.30)	-0.33 (± 0.91)		
Change at C2D8; Core symptom severity (n=91,36)	0.17 (± 1.59)	-0.45 (± 0.91)		
Change at C2D15; Core symptom severity (n=90,37)	-0.13 (± 1.53)	-0.53 (± 0.90)		
Change at C3D1; Core symptom severity (n=89,36)	-0.26 (± 1.60)	-0.40 (± 1.13)		
Change at C3D8; Core symptom severity (n=72,30)	-0.13 (± 1.63)	-0.66 (± 1.20)		
Change at C3D15; Core symptom severity (n=73,32)	-0.42 (± 1.52)	-0.53 (± 1.05)		
Baseline; Module symptom severity (n=116,42)	1.60 (± 1.46)	1.57 (± 1.11)		
Change at C1D1; Module symptom severity (n=116,36)	0.00 (± 0.00)	-0.19 (± 0.96)		
Change at C1D8;Module symptom severity(n=107,36)	-0.22 (± 1.40)	-0.53 (± 0.96)		
Change atC1D15;Module symptom severity(n=104,33)	-0.43 (± 1.51)	-0.73 (± 1.13)		
Change at C2D1; Module symptom severity (n=101,34)	-0.49 (± 1.46)	-0.65 (± 0.92)		
Change at C2D8; Module symptom severity (n=91,35)	-0.46 (± 1.63)	-0.77 (± 0.87)		
Change at C2D15; Module symptom severity (n=90,36)	-0.69 (± 1.47)	-0.94 (± 0.93)		
Change at C3D1; Module symptom severity (n=86,35)	-0.65 (± 1.48)	-0.81 (± 0.97)		
Change at C3D8; Module symptom severity (n=72,30)	-0.51 (± 1.58)	-0.83 (± 0.97)		
Change at C3D15; Module symptom severity (n=73,32)	-0.83 (± 1.51)	-0.92 (± 0.97)		
Baseline; Interference (n=116,41)	1.81 (± 2.05)	1.90 (± 2.25)		
Change at C1D1; Interference (n=116,35)	0.00 (± 0.00)	-0.13 (± 1.49)		
Change at C1D8; Interference (n=107,33)	0.45 (± 1.78)	-0.29 (± 2.14)		
Change at C1D15; Interference (n=104,32)	0.36 (± 1.85)	0.01 (± 2.04)		

Change at C2D1; Interference (n=101,33)	0.01 (± 1.73)	-0.34 (± 1.78)		
Change at C2D8; Interference (n=91,34)	0.58 (± 2.20)	-0.58 (± 1.81)		
Change at C2D15; Interference (n=89,35)	0.06 (± 1.84)	-0.64 (± 1.59)		
Change at C3D1; Interference (n=86,34)	-0.02 (± 2.02)	-0.73 (± 2.06)		
Change at C3D8; Interference (n=72,29)	0.15 (± 1.91)	-0.82 (± 2.09)		
Change at C3D15; Interference (n=72,30)	-0.07 (± 2.01)	-0.55 (± 2.18)		

Notes:

[48] - 'Number of Subject Analysed' = participants evaluable for this outcome measure

[49] - 'n' = participants evaluable at specified time point, for each arm respectively

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in HRQoL as Measured by European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) Functional Scales Score and Global Health Status/Global Quality-of-Life (QoL) Scale Score

End point title	Change from Baseline in HRQoL as Measured by European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) Functional Scales Score and Global Health Status/Global Quality-of-Life (QoL) Scale Score

End point description:

EORTC QLQ-C30 is a validated self-report measure consisting of 30 questions incorporated into five functional scales (Physical, Role, Cognitive, Emotional, and Social scales), three symptom scales (fatigue, pain, nausea, and vomiting scales), a global health status/global QoL scale, and single items (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea). Most questions used 4-point scale (1='Not at all' to 4='Very much'), while 2 questions used 7-point scale (1='very poor' to 7='Excellent'). Functional scales score and global health status/global QoL scale score are reported. Scores were averaged, transformed to 0-100 scale; where higher score for functional scales=poor level of functioning; higher score for global health status/global QoL=better HRQoL. Analysis was performed on PRO-evaluable population. '99999'=either data were not available because no participant was evaluable or SD was not available because only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

Baseline, D1 of Cycles 1, 2, 3, 4, 5, 6, STC/EW visit (up to C6D28), EoCTR visit (8 to 12 weeks after C6D1), and FUVs (every 12 weeks after EoCTR up to 3 years); Cycle length = 28 days

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[50]	69[51]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline; Physical functioning (n=177,69)	82.59 (± 17.46)	83.77 (± 15.27)		
Change at C1D1; Physical functioning (n=177,67)	0.0 (± 0.0)	1.39 (± 12.90)		
Change at C2D1; Physical functioning (n=172,67)	0.31 (± 15.81)	2.99 (± 12.83)		

Change at C3D1; Physical functioning (n=160,64)	0.22 (± 16.43)	1.46 (± 14.76)		
Change at C4D1; Physical functioning (n=154,65)	2.11 (± 14.95)	5.54 (± 14.17)		
Change at C5D1; Physical functioning (n=149,65)	2.44 (± 18.19)	4.62 (± 15.27)		
Change at C6D1; Physical functioning (n=143,65)	2.25 (± 16.82)	4.51 (± 16.59)		
Change at STC/EW; Physical functioning (n=162,64)	1.68 (± 18.76)	4.53 (± 16.04)		
Change at EoCTR; Physical functioning (n=142,63)	2.92 (± 18.03)	4.34 (± 16.12)		
Change at FUV1; Physical functioning (n=124,63)	2.27 (± 18.86)	3.81 (± 16.27)		
Change at FUV2; Physical functioning (n=114,63)	2.40 (± 19.21)	2.75 (± 17.17)		
Change at FUV3; Physical functioning (n=95,62)	2.54 (± 17.83)	3.44 (± 17.31)		
Change at FUV4; Physical functioning (n=77,47)	4.74 (± 20.14)	0.85 (± 21.06)		
Change at FUV5; Physical functioning (n=57,19)	1.90 (± 17.68)	-1.75 (± 19.35)		
Change at FUV6; Physical functioning (n=33,5)	-1.41 (± 15.34)	1.33 (± 5.58)		
Change at FUV7; Physical functioning (n=13,1)	-3.08 (± 11.74)	0.00 (± 99999)		
Change at FUV8; Physical functioning (n=5,1)	-9.33 (± 23.38)	0.00 (± 99999)		
Change at FUV9; Physical functioning (n=2,0)	-10.00 (± 33.0)	99999 (± 99999)		
Baseline; Role functioning (n=177,69)	78.25 (± 25.67)	83.82 (± 21.00)		
Change at C1D1; Role functioning (n=177,67)	0.0 (± 0.0)	-1.74 (± 23.23)		
Change at C2D1; Role functioning (n=172,67)	-1.26 (± 27.45)	2.49 (± 23.07)		
Change at C3D1; Role functioning (n=160,64)	-0.10 (± 29.64)	1.82 (± 26.08)		
Change at C4D1; Role functioning (n=154,65)	0.87 (± 29.01)	5.13 (± 22.03)		
Change at C5D1; Role functioning (n=149,65)	0.45 (± 30.75)	4.36 (± 23.44)		
Change at C6D1; Role functioning (n=143,65)	0.70 (± 29.92)	1.79 (± 25.71)		
Change at STC/EW; Role functioning (n=162,64)	-0.41 (± 32.91)	2.60 (± 25.58)		
Change at EoCTR; Role functioning (n=143,63)	3.26 (± 29.95)	2.12 (± 26.69)		
Change at FUV1; Role functioning (n=125,63)	2.93 (± 32.31)	2.65 (± 27.47)		
Change at FUV2; Role functioning (n=114,63)	3.07 (± 32.63)	-1.85 (± 31.84)		
Change at FUV3; Role functioning (n=95,62)	5.26 (± 31.16)	1.88 (± 28.17)		
Change at FUV4; Role functioning (n=77,47)	5.41 (± 33.16)	-0.35 (± 30.39)		
Change at FUV5; Role functioning (n=57,19)	2.34 (± 29.79)	1.75 (± 34.20)		
Change at FUV6; Role functioning (n=33,5)	-4.04 (± 27.01)	-13.33 (± 32.06)		
Change at FUV7; Role functioning (n=13,1)	2.56 (± 29.54)	-16.67 (± 99999)		

Change at FUV8; Role functioning (n=5,1)	0.00 (± 23.57)	16.67 (± 99999)		
Change at FUV9; Role functioning (n=2,0)	-16.67 (± 23.57)	99999 (± 99999)		
Baseline; Emotional functioning (n=176,69)	78.98 (± 22.47)	82.13 (± 15.80)		
Change at C1D1; Emotional functioning (n=176,67)	0.0 (± 0.0)	4.35 (± 15.17)		
Change at C2D1; Emotional functioning (n=171,67)	2.24 (± 20.07)	5.60 (± 14.68)		
Change at C3D1; Emotional functioning (n=158,64)	2.99 (± 20.06)	5.34 (± 19.09)		
Change at C4D1; Emotional functioning (n=151,65)	2.61 (± 18.35)	4.19 (± 15.45)		
Change at C5D1; Emotional functioning (n=146,65)	1.14 (± 18.79)	3.97 (± 17.37)		
Change at C6D1; Emotional functioning (n=143,65)	2.06 (± 18.74)	3.08 (± 17.96)		
Change at STC/EW; Emotional functioning (n=160,64)	2.43 (± 20.61)	5.34 (± 18.69)		
Change at EoCTR; Emotional functioning (n=142,62)	2.58 (± 19.45)	3.49 (± 17.83)		
Change at FUV1; Emotional functioning (n=124,63)	3.49 (± 20.91)	4.37 (± 18.50)		
Change at FUV2; Emotional functioning (n=114,63)	4.39 (± 20.33)	0.66 (± 21.02)		
Change at FUV3; Emotional functioning (n=92,62)	0.63 (± 19.97)	2.82 (± 17.66)		
Change at FUV4; Emotional functioning (n=76,47)	4.82 (± 19.73)	1.95 (± 18.41)		
Change at FUV5; Emotional functioning (n=56,19)	3.13 (± 17.95)	2.63 (± 20.61)		
Change at FUV6; Emotional functioning (n=33,5)	2.27 (± 21.78)	5.00 (± 17.28)		
Change at FUV7; Emotional functioning (n=13,1)	5.77 (± 17.48)	-8.33 (± 99999)		
Change at FUV8; Emotional functioning (n=5,1)	3.33 (± 28.01)	0.00 (± 99999)		
Change at FUV9; Emotional functioning (n=2,0)	-16.67 (± 11.79)	99999 (± 99999)		
Baseline; Cognitive functioning (n=176,69)	86.55 (± 16.78)	89.86 (± 14.91)		
Change at C1D1; Cognitive functioning (n=176,67)	0.0 (± 0.0)	-1.24 (± 14.01)		
Change at C2D1; Cognitive functioning (n=171,67)	-0.19 (± 15.34)	0.25 (± 14.06)		
Change at C3D1; Cognitive functioning (n=158,64)	-0.32 (± 16.34)	-1.56 (± 17.50)		
Change at C4D1; Cognitive functioning (n=152,65)	-1.54 (± 17.41)	-0.26 (± 17.05)		
Change at C5D1; Cognitive functioning (n=146,65)	-1.94 (± 18.10)	-0.26 (± 14.28)		
Change at C6D1; Cognitive functioning (n=143,65)	-2.68 (± 16.97)	-0.77 (± 15.98)		
Change at STC/EW; Cognitive functioning (n=160,64)	-2.19 (± 17.65)	1.04 (± 18.28)		
Change at EoCTR; Cognitive functioning (n=142,62)	-2.23 (± 18.11)	-0.27 (± 16.94)		
Change at FUV1; Cognitive functioning (n=124,63)	-2.02 (± 17.21)	-0.26 (± 15.98)		
Change at FUV2; Cognitive functioning (n=114,63)	1.32 (± 16.16)	-2.38 (± 18.17)		

Change at FUV3; Cognitive functioning (n=92,62)	-1.63 (± 14.84)	-2.96 (± 18.24)		
Change at FUV4; Cognitive functioning (n=76,47)	0.44 (± 17.63)	-1.77 (± 19.11)		
Change at FUV5; Cognitive functioning (n=56,19)	-1.49 (± 15.66)	-6.14 (± 21.67)		
Change at FUV6; Cognitive functioning (n=33,5)	-0.51 (± 14.72)	0.00 (± 0.00)		
Change at FUV7; Cognitive functioning (n=13,1)	-1.28 (± 14.37)	0.00 (± 99999)		
Change at FUV8; Cognitive functioning (n=5,1)	0.00 (± 23.57)	0.00 (± 99999)		
Change at FUV9; Cognitive functioning (n=2,0)	16.67 (± 23.57)	99999 (± 99999)		
Baseline; Social functioning (n=176,69)	82.48 (± 22.06)	85.51 (± 21.18)		
Change at C1D1; Social functioning (n=176,67)	0.0 (± 0.0)	-1.74 (± 19.92)		
Change at C2D1; Social functioning (n=171,67)	-2.44 (± 21.44)	0.25 (± 18.46)		
Change at C3D1; Social functioning (n=158,64)	-2.32 (± 22.61)	3.65 (± 25.45)		
Change at C4D1; Social functioning (n=151,65)	-0.55 (± 22.15)	4.62 (± 20.09)		
Change at C5D1; Social functioning (n=146,65)	-5.48 (± 26.49)	2.56 (± 20.46)		
Change at C6D1; Social functioning (n=143,65)	-5.13 (± 24.80)	3.85 (± 24.61)		
Change at STC/EW; Social functioning (n=160,64)	-4.06 (± 27.71)	1.04 (± 19.22)		
Change at EoCTR; Social functioning (n=142,62)	-0.47 (± 24.95)	1.88 (± 20.49)		
Change at FUV1; Social functioning (n=124,63)	-1.08 (± 26.09)	1.59 (± 24.27)		
Change at FUV2; Social functioning (n=114,63)	0.58 (± 24.68)	1.32 (± 27.97)		
Change at FUV3; Social functioning (n=92,62)	-0.91 (± 24.00)	1.88 (± 25.98)		
Change at FUV4; Social functioning (n=76,47)	1.97 (± 27.35)	1.06 (± 32.12)		
Change at FUV5; Social functioning (n=56,19)	1.79 (± 26.72)	0.00 (± 33.79)		
Change at FUV6; Social functioning (n=33,5)	1.52 (± 29.27)	10.00 (± 14.91)		
Change at FUV7; Social functioning (n=13,1)	-2.56 (± 23.42)	33.33 (± 99999)		
Change at FUV8; Social functioning (n=5,1)	-10.00 (± 22.36)	33.33 (± 99999)		
Change at FUV9; Social functioning (n=2,0)	-25.00 (± 35.36)	99999 (± 99999)		
Baseline; Global health status/QoL (n=176,69)	63.02 (± 21.45)	67.39 (± 22.17)		
Change at C1D1;Global health status/QoL(n=176,67)	0.0 (± 0.0)	6.34 (± 18.41)		
Change at C2D1;Global health status/QoL (n=171,67)	2.73 (± 21.69)	5.35 (± 20.14)		
Change at C3D1;Global health status/QoL (n=157,64)	2.34 (± 24.66)	2.21 (± 23.58)		
Change at C4D1;Global health status/QoL (n=152,65)	3.84 (± 22.26)	7.05 (± 21.05)		
Change at C5D1;Global health status/QoL (n=146,65)	7.36 (± 24.20)	7.18 (± 21.94)		

Change at C6D1;Global health status/QoL (n=143,65)	4.25 (± 25.00)	5.90 (± 25.16)		
Change at STC/EW;Global health status/QoL;n=160,64	4.32 (± 26.20)	6.51 (± 23.22)		
Change at EoCTR;Global health status/QoL(n=142,62)	6.10 (± 23.65)	7.66 (± 24.11)		
Change at FUV1;Global health status/QoL (n=124,63)	5.91 (± 24.57)	7.01 (± 25.01)		
Change at FUV2;Global health status/QoL (n=114,63)	6.94 (± 24.81)	4.50 (± 26.51)		
Change at FUV3; Global health status/QoL (n=92,62)	4.80 (± 25.30)	6.32 (± 27.36)		
Change at FUV4; Global health status/QoL (n=76,47)	7.35 (± 26.77)	6.38 (± 27.60)		
Change at FUV5; Global health status/QoL (n=56,19)	4.46 (± 23.89)	4.39 (± 18.08)		
Change at FUV6; Global health status/QoL (n=33,5)	1.01 (± 24.00)	5.00 (± 7.45)		
Change at FUV7; Global health status/QoL (n=13,1)	8.33 (± 25.69)	16.67 (± 99999)		
Change at FUV8; Global health status/QoL (n=5,1)	6.67 (± 16.03)	8.33 (± 99999)		
Change at FUV9; Global health status/QoL (n=2,0)	0.00 (± 0.00)	99999 (± 99999)		

Notes:

[50] - 'Number of Subject Analysed' = participants evaluable for this outcome measure

[51] - 'n' = participants evaluable at specified time point, for each arm respectively

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HRQoL as Measured by Quality of Life Questionnaire Associated CLL Module (QLQ-CLL16) Multi-Item Scales Score

End point title	Change From Baseline in HRQoL as Measured by Quality of Life Questionnaire Associated CLL Module (QLQ-CLL16) Multi-Item Scales Score

End point description:

The EORTC QLQ-CLL16 module is designed for participants with Stage 0 to Stage 4 CLL. It is composed of 16 questions and there are four multi-item scales on Fatigue (2 items), Treatment-related side effects (TRSE, 4 items), Disease-related symptoms (DRS, 4 items), and Infection (4 items); and two single-item scales on social activities and future health worries. Multi-item scales score are reported and the total score for each multi-item scale was transformed to result in a total score range of 0 to 100, where higher score = poor HRQoL. Analysis was performed on PRO-evaluable population. 'Number of Subject Analysed' = participants evaluable for this outcome measure; 'n' = participants evaluable at specified time point; '99999' = either mean was not available because no participant was evaluable or SD was not available because only 1 participant was evaluable at indicated time points.

End point type	Secondary

End point timeframe:

Baseline, D1 of Cycles 1, 2, 3, 4, 5, 6, STC/EW visit (up to C6D28), EoCTR visit (8 to 12 weeks after C6D1), and FUVs (every 12 weeks after EoCTR up to 3 years); Cycle length = 28 days

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	69		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline; TRSE (n=175,69)	14.29 (± 13.95)	9.42 (± 8.80)		
Change at C1D1; TRSE (n=175,67)	0.0 (± 0.0)	0.12 (± 10.10)		
Change at C2D1; TRSE (n=170,67)	1.62 (± 13.82)	0.62 (± 12.76)		
Change at C3D1; TRSE (n=159,63)	-0.26 (± 13.76)	1.98 (± 14.72)		
Change at C4D1; TRSE (n=152,64)	-0.49 (± 13.97)	0.52 (± 11.87)		
Change at C5D1; TRSE (n=147,65)	-0.51 (± 14.57)	0.64 (± 10.02)		
Change at C6D1; TRSE (n=144,65)	0.46 (± 15.51)	-0.13 (± 10.04)		
Change at STC/EW; TRSE (n=161,64)	0.81 (± 18.11)	0.13 (± 10.76)		
Change at EoCTR; TRSE (n=142,63)	-0.88 (± 16.06)	0.26 (± 12.61)		
Change at FUV1; TRSE (n=123,63)	-1.20 (± 14.87)	1.19 (± 12.24)		
Change at FUV2; TRSE (n=113,63)	-1.70 (± 15.28)	2.65 (± 14.03)		
Change at FUV3; TRSE (n=95,62)	-2.08 (± 12.64)	-0.13 (± 13.70)		
Change at FUV4; TRSE (n=76,47)	-1.97 (± 12.76)	2.84 (± 15.18)		
Change at FUV5; TRSE (n=56,19)	-2.68 (± 11.02)	1.32 (± 10.49)		
Change at FUV6; TRSE (n=33,5)	-1.01 (± 12.10)	-1.67 (± 3.73)		
Change at FUV7; TRSE (n=13,1)	2.56 (± 22.67)	-8.33 (± 99999)		
Change at FUV8; TRSE (n=5,1)	1.67 (± 13.69)	0.00 (± 99999)		
Change at FUV9; TRSE (n=2,0)	8.33 (± 11.79)	99999 (± 99999)		
Baseline; DRS (n=175,69)	19.57 (± 16.81)	16.95 (± 17.37)		
Change at C1D1; DRS (n=175,67)	0.0 (± 0.0)	-2.74 (± 16.18)		
Change at C2D1; DRS (n=170,67)	-3.33 (± 16.05)	-4.77 (± 16.84)		
Change at C3D1; DRS (n=159,63)	-4.77 (± 16.49)	-3.35 (± 17.48)		
Change at C4D1; DRS (n=152,64)	-6.03 (± 16.51)	-5.12 (± 17.72)		
Change at C5D1; DRS (n=147,65)	-5.90 (± 16.73)	-4.79 (± 17.50)		
Change at C6D1; DRS (n=144,65)	-6.40 (± 17.26)	-5.30 (± 16.72)		
Change at STC/EW; DRS (n=161,64)	-5.80 (± 18.52)	-6.51 (± 18.45)		
Change at EoCTR; DRS (n=142,63)	-6.57 (± 17.21)	-5.86 (± 20.38)		
Change at FUV1; DRS (n=123,63)	-6.55 (± 15.73)	-5.82 (± 19.20)		
Change at FUV2; DRS (n=113,63)	-8.63 (± 14.39)	-3.57 (± 18.31)		

Change at FUV3; DRS (n=95,62)	-7.37 (± 14.88)	-3.76 (± 19.25)		
Change at FUV4; DRS (n=76,47)	-8.55 (± 18.56)	-2.66 (± 20.49)		
Change at FUV5; DRS (n=56,19)	-8.33 (± 16.13)	-2.19 (± 19.41)		
Change at FUV6; DRS (n=33,5)	-6.31 (± 16.01)	-3.33 (± 13.94)		
Change at FUV7; DRS (n=13,1)	-15.38 (± 20.08)	-8.33 (± 99999)		
Change at FUV8; DRS (n=5,1)	-10.00 (± 16.03)	-8.33 (± 99999)		
Change at FUV9; DRS (n=2,0)	-4.17 (± 5.89)	99999 (± 99999)		
Baseline; Fatigue (n=175,69)	28.76 (± 24.66)	21.74 (± 20.67)		
Change at C1D1; Fatigue (n=175,67)	0.0 (± 0.0)	-2.24 (± 20.29)		
Change at C2D1; Fatigue (n=170,67)	-2.55 (± 22.86)	-5.47 (± 21.40)		
Change at C3D1; Fatigue (n=159,63)	-2.83 (± 25.17)	-3.17 (± 23.73)		
Change at C4D1; Fatigue (n=152,64)	-3.18 (± 23.23)	-4.17 (± 22.02)		
Change at C5D1; Fatigue (n=147,65)	-2.38 (± 27.52)	-4.36 (± 20.89)		
Change at C6D1; Fatigue (n=144,65)	-2.66 (± 26.35)	-2.31 (± 21.42)		
Change at STC/EW; Fatigue (n=161,64)	-3.11 (± 28.64)	-4.69 (± 21.30)		
Change at EoCTR; Fatigue (n=142,63)	-6.69 (± 26.78)	-3.97 (± 24.27)		
Change at FUV1; Fatigue (n=123,63)	-6.37 (± 26.61)	-4.23 (± 22.99)		
Change at FUV2; Fatigue (n=113,63)	-6.64 (± 24.55)	-1.85 (± 24.70)		
Change at FUV3; Fatigue (n=95,62)	-5.79 (± 23.29)	-2.42 (± 23.73)		
Change at FUV4; Fatigue (n=76,47)	-9.65 (± 26.84)	-0.35 (± 25.18)		
Change at FUV5; Fatigue (n=56,19)	-6.55 (± 25.56)	3.51 (± 23.95)		
Change at FUV6; Fatigue (n=33,5)	-5.05 (± 24.82)	3.33 (± 24.72)		
Change at FUV7; Fatigue (n=13,1)	-10.26 (± 30.08)	-33.33 (± 99999)		
Change at FUV8; Fatigue (n=5,1)	-6.67 (± 19.00)	0.00 (± 99999)		
Change at FUV9; Fatigue (n=2,0)	-8.33 (± 11.79)	99999 (± 99999)		
Baseline; Infection (n=175,69)	15.92 (± 17.63)	14.01 (± 18.99)		
Change at C1D1; Infection (n=175,67)	0.0 (± 0.0)	-2.24 (± 20.03)		
Change at C2D1; Infection (n=170,67)	-0.02 (± 19.98)	-3.61 (± 21.72)		
Change at C3D1; Infection (n=159,63)	-1.66 (± 19.21)	-1.32 (± 20.48)		
Change at C4D1; Infection (n=152,64)	-1.44 (± 22.07)	-3.13 (± 21.28)		
Change at C5D1; Infection (n=147,65)	-1.91 (± 24.00)	-2.56 (± 23.47)		

Change at C6D1; Infection (n=143,65)	-1.09 (± 20.66)	-2.95 (± 20.54)		
Change at STC/EW; Infection (n=161,64)	-0.12 (± 23.28)	-1.69 (± 23.34)		
Change at EoCTR; Infection (n=142,63)	-0.55 (± 21.73)	-3.44 (± 25.78)		
Change at FUV1; Infection (n=121,63)	1.08 (± 18.77)	-2.65 (± 26.51)		
Change at FUV2; Infection (n=113,63)	0.05 (± 23.29)	-0.53 (± 25.74)		
Change at FUV3; Infection (n=95,62)	-1.90 (± 16.97)	-0.54 (± 26.48)		
Change at FUV4; Infection (n=76,47)	-4.24 (± 16.71)	0.53 (± 25.56)		
Change at FUV5; Infection (n=56,19)	-4.51 (± 22.66)	7.46 (± 27.20)		
Change at FUV6; Infection (n=33,5)	-1.60 (± 18.90)	8.33 (± 15.59)		
Change at FUV7; Infection (n=13,1)	-0.43 (± 21.84)	-16.67 (± 99999)		
Change at FUV8; Infection (n=5,1)	8.89 (± 23.36)	-25.00 (± 99999)		
Change at FUV9; Infection (n=2,0)	-2.78 (± 3.93)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Euro QoL 5 Dimension (EQ-5D) Questionnaire Score

End point title	Euro QoL 5 Dimension (EQ-5D) Questionnaire Score

End point description:

End point type	Post-hoc

End point timeframe:

Baseline, D1 of Cycles 1, 2, 3, 4, 5, 6, STC/EW visit (up to C6D28), EoCTR visit (8 to 12 weeks after C6D1), and FUVs (every 12 weeks after EoCTR up to 3 years); Cycle length = 28 days

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[52]	0[53]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[52] - Anticipated Posting Date: Sep 2019

[53] - Anticipated Posting Date: Sep 2019

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Follow-up (maximum up to Data Cut-off date, overall approximately 3 years)

Adverse event reporting additional description:

Analysis was performed on safety evaluable (SE) population, which included all randomized participants who received at least one dose of study treatment (venetoclax, rituximab, or bendamustine), with participants grouped according to the actual treatment received.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Venetoclax + Rituximab

Reporting group description:

Participants were initially placed on a venetoclax ramp-up period of 5 weeks, and received an initial dose of 20 mg via tablet orally once daily (QD) for initial 1 to 7 days, then venetoclax dose was incremented weekly up to a maximum dose of 400 mg via tablet orally QD. Participants continued receiving venetoclax at a dose of 400 mg via tablet orally QD from Week 6 (Day 1 of Cycle 1 of combination therapy) onwards up to disease progression or 2 years, whichever occurred first, as directed by the investigator, in combination with rituximab at a dose of 375 mg/m^2 via IV infusion on Day 1 of Cycle 1 and at a dose of 500 mg/m^2 on Day 1 of Cycles 2-6.

Reporting group title	Bendamustine + Rituximab

Reporting group description:

Participants received bendamustine at a dose of 70 milligrams per meter square (mg/m^2) via intravenous (IV) infusion on Days 1 and 2 of each 28-day cycle for 6 cycles, in combination with rituximab at a dose of 375 mg/m^2 via IV infusion on Day 1 of Cycle 1 and at a dose of 500 mg/m^2 on Day 1 of Cycles 2-6.

Serious adverse events	Venetoclax + Rituximab	Bendamustine + Rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	90 / 194 (46.39%)	81 / 188 (43.09%)	
number of deaths (all causes)	15	27	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Adenocarcinoma gastric			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Adenocarcinoma of colon			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	2 / 194 (1.03%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 194 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Lymphoma			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant melanoma			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medullary thyroid cancer			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			

subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	2 / 194 (1.03%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	3 / 194 (1.55%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			

subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 194 (0.52%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
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 / 194 (0.00%)	5 / 188 (2.66%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperpyrexia			
subjects affected / exposed	1 / 194 (0.52%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 194 (2.58%)	13 / 188 (6.91%)	
occurrences causally related to treatment / all	2 / 5	11 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			

subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden death			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Unevaluable event			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchiectasis			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (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 / 194 (0.52%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (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 / 194 (0.52%)	6 / 188 (3.19%)	
occurrences causally related to treatment / all	1 / 1	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (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	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 194 (1.03%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lacunar infarction			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			

subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Syncope			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 194 (1.55%)	5 / 188 (2.66%)	
occurrences causally related to treatment / all	3 / 4	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 194 (1.55%)	3 / 188 (1.60%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 194 (1.03%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Autoimmune haemolytic anaemia			
subjects affected / exposed	3 / 194 (1.55%)	3 / 188 (1.60%)	
occurrences causally related to treatment / all	3 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	7 / 194 (3.61%)	16 / 188 (8.51%)	
occurrences causally related to treatment / all	7 / 7	14 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anal fistula			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 194 (1.03%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			

subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 194 (0.52%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 194 (0.52%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess neck			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 194 (1.03%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 194 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (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	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			

subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (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	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex otitis externa			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	3 / 194 (1.55%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeria sepsis			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Localised infection			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	3 / 194 (1.55%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Moraxella infection			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal tuberculosis			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 194 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal bacteraemia			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	16 / 194 (8.25%)	15 / 188 (7.98%)	
occurrences causally related to treatment / all	6 / 20	5 / 17	
deaths causally related to treatment / all	0 / 3	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 194 (1.03%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection fungal			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scedosporium infection			

subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	1 / 194 (0.52%)	4 / 188 (2.13%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	1 / 1	1 / 2	
Septic shock			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	2 / 194 (1.03%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 194 (1.55%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 194 (0.52%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			

subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 194 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 194 (1.03%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 194 (0.52%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 194 (1.03%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperphosphataemia			
subjects affected / exposed	2 / 194 (1.03%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	4 / 194 (2.06%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Venetoclax + Rituximab	Bendamustine + Rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	190 / 194 (97.94%)	176 / 188 (93.62%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 194 (6.19%)	7 / 188 (3.72%)	
occurrences (all)	13	7	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	8 / 194 (4.12%)	16 / 188 (8.51%)	
occurrences (all)	10	20	
Fatigue			

subjects affected / exposed	34 / 194 (17.53%)	39 / 188 (20.74%)	
occurrences (all)	40	44	
Oedema peripheral			
subjects affected / exposed	11 / 194 (5.67%)	7 / 188 (3.72%)	
occurrences (all)	15	11	
Pyrexia			
subjects affected / exposed	27 / 194 (13.92%)	33 / 188 (17.55%)	
occurrences (all)	39	44	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	35 / 194 (18.04%)	31 / 188 (16.49%)	
occurrences (all)	49	37	
Dyspnoea			
subjects affected / exposed	11 / 194 (5.67%)	14 / 188 (7.45%)	
occurrences (all)	14	17	
Oropharyngeal pain			
subjects affected / exposed	10 / 194 (5.15%)	7 / 188 (3.72%)	
occurrences (all)	12	7	
Productive cough			
subjects affected / exposed	12 / 194 (6.19%)	4 / 188 (2.13%)	
occurrences (all)	14	5	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	21 / 194 (10.82%)	12 / 188 (6.38%)	
occurrences (all)	22	13	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 194 (4.64%)	10 / 188 (5.32%)	
occurrences (all)	15	11	
Neutrophil count decreased			
subjects affected / exposed	11 / 194 (5.67%)	13 / 188 (6.91%)	
occurrences (all)	26	27	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	15 / 194 (7.73%)	40 / 188 (21.28%)	
occurrences (all)	19	54	

Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 194 (6.19%)	10 / 188 (5.32%)	
occurrences (all)	14	13	
Headache			
subjects affected / exposed	21 / 194 (10.82%)	19 / 188 (10.11%)	
occurrences (all)	21	21	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	28 / 194 (14.43%)	40 / 188 (21.28%)	
occurrences (all)	48	68	
Neutropenia			
subjects affected / exposed	118 / 194 (60.82%)	82 / 188 (43.62%)	
occurrences (all)	288	181	
Thrombocytopenia			
subjects affected / exposed	24 / 194 (12.37%)	42 / 188 (22.34%)	
occurrences (all)	31	56	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	13 / 194 (6.70%)	6 / 188 (3.19%)	
occurrences (all)	14	7	
Constipation			
subjects affected / exposed	27 / 194 (13.92%)	39 / 188 (20.74%)	
occurrences (all)	30	47	
Diarrhoea			
subjects affected / exposed	76 / 194 (39.18%)	31 / 188 (16.49%)	
occurrences (all)	115	43	
Nausea			
subjects affected / exposed	41 / 194 (21.13%)	64 / 188 (34.04%)	
occurrences (all)	57	82	
Vomiting			
subjects affected / exposed	15 / 194 (7.73%)	22 / 188 (11.70%)	
occurrences (all)	18	29	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	10 / 194 (5.15%)	8 / 188 (4.26%)	
occurrences (all)	10	8	

Rash			
subjects affected / exposed	14 / 194 (7.22%)	24 / 188 (12.77%)	
occurrences (all)	17	30	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 194 (6.19%)	10 / 188 (5.32%)	
occurrences (all)	17	13	
Back pain			
subjects affected / exposed	15 / 194 (7.73%)	11 / 188 (5.85%)	
occurrences (all)	15	11	
Muscle spasms			
subjects affected / exposed	4 / 194 (2.06%)	11 / 188 (5.85%)	
occurrences (all)	4	11	
Infections and infestations			
Bronchitis			
subjects affected / exposed	20 / 194 (10.31%)	13 / 188 (6.91%)	
occurrences (all)	31	15	
Conjunctivitis			
subjects affected / exposed	10 / 194 (5.15%)	5 / 188 (2.66%)	
occurrences (all)	11	5	
Lower respiratory tract infection			
subjects affected / exposed	11 / 194 (5.67%)	4 / 188 (2.13%)	
occurrences (all)	15	4	
Nasopharyngitis			
subjects affected / exposed	22 / 194 (11.34%)	10 / 188 (5.32%)	
occurrences (all)	27	14	
Oral herpes			
subjects affected / exposed	8 / 194 (4.12%)	12 / 188 (6.38%)	
occurrences (all)	11	12	
Pharyngitis			
subjects affected / exposed	13 / 194 (6.70%)	1 / 188 (0.53%)	
occurrences (all)	16	1	
Pneumonia			
subjects affected / exposed	5 / 194 (2.58%)	11 / 188 (5.85%)	
occurrences (all)	6	13	
Sinusitis			

subjects affected / exposed	17 / 194 (8.76%)	5 / 188 (2.66%)	
occurrences (all)	22	5	
Upper respiratory tract infection			
subjects affected / exposed	41 / 194 (21.13%)	28 / 188 (14.89%)	
occurrences (all)	71	39	
Urinary tract infection			
subjects affected / exposed	11 / 194 (5.67%)	7 / 188 (3.72%)	
occurrences (all)	21	9	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 194 (4.12%)	17 / 188 (9.04%)	
occurrences (all)	11	18	
Hyperkalaemia			
subjects affected / exposed	11 / 194 (5.67%)	0 / 188 (0.00%)	
occurrences (all)	16	0	
Hypokalaemia			
subjects affected / exposed	12 / 194 (6.19%)	7 / 188 (3.72%)	
occurrences (all)	14	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2013	An exclusion of participants who had received potent cytochrome (CYP3A4) inhibitors was clarified to make consistent with the rest of the protocol; An exclusion criterion was added for participants with recent major surgery in line with the prescribing information for bendamustine; The pregnancy testing procedure was modified such that testing was required at each cycle of combination therapy and every 3 months thereafter until the end of treatment in order to obtain a more timely diagnosis of pregnancy.
10 June 2014	Modifications to the tumor lysis syndrome prophylaxis measures for participants with CLL were implemented following analysis of participants enrolled in different venetoclax trials: All participants randomized to the 'Venetoclax + Rituximab' arm were to initiate dosing with 20 mg venetoclax daily for at least 7 days; Outpatient dosing and monitoring for the first venetoclax dose at all dose levels (20 mg, 50 mg, 100 mg, 200 mg, 400 mg) was introduced for low- and medium-risk participants, if there was no indication to hospitalize; Outpatient IV hydration prior to the first venetoclax dose was introduced for medium-risk participants at 20 and 50 mg; Inpatient dosing and monitoring was introduced for high-risk participants prior to the first venetoclax dose only at the 20 mg and 50 mg dose levels; Outpatient dosing and IV hydration prior to the first venetoclax dose was introduced for high-risk participants at dose levels of 100 mg and above, if there was no indication to hospitalize; Reduced frequency of laboratory assessments after dosing; Prophylaxis with rasburicase had to be administered prior to the first dose of venetoclax only for high-risk participants with high uric acid levels and per regional standards/guidelines; Dose Modification for venetoclax + rituximab in case of non-hematologic toxicity was clarified globally.
16 October 2014	The recruitment of participants with occult or prior hepatitis B virus (HBV) infection if HBV deoxy-ribonucleic acid (DNA) was undetectable was allowed; In order to collect appropriate MRD information, bone marrow aspiration was added. This was previously only mandated in participants with CR. To synchronize with other venetoclax development studies MRD in peripheral blood was to be monitored for up to 1 year after completion of venetoclax single-agent therapy.
22 December 2015	The interim analysis was changed to be information-fraction-based as opposed to time-based (that is, percentage of total PFS) events; A secondary objective of best overall response rate as assessed by the investigator was added; Details regarding multiplicity adjustment and order for testing the key secondary endpoints were added; The secondary outcome measure of MRD response rate was clarified that this assessment was based on the EoCTR visit. MRD response rate at other disease response assessment timepoints were designated as exploratory outcome measures; Additional details were provided on the use of strong, moderate and weak CYP3A4 inhibitors and inducers as well as cautionary medications; Timings for the baseline QoL questionnaires for the 'Venetoclax + Rituximab' arm were incorporated; PK outcome measures were further defined to include concentrations of venetoclax.
21 November 2016	Allowed for a change in the clinical prioritization of the secondary efficacy endpoints to mirror the evolving relapsed/refractory CLL therapeutic and scientific landscape.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported