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	03 August 2022

Results information

Result version number	v3 (current)
This version publication date	28 October 2023
First version publication date	19 May 2018
Version creation reason	

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	Final
Date of interim/final analysis	03 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 May 2017
Global end of trial reached?	Yes
Global end of trial date	03 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of venetoclax (V) and rituximab (R) compared with bendamustine (B) 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	Czechia: 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	237

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:

A total 389 participants took part in the study across 109 investigative sites in 20 countries from 17 March 2014 to 03 August 2022. The trial consisted of a main study and an optional Retreatment/Crossover (R/C) sub study.

Pre-assignment

Screening details:

Of the 389 participants enrolled 7 participants in the bendamustine + rituximab (BR) arm did not receive a valid dose of study treatment.

Period 1

Period 1 title	Main Study
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	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.

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.

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 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, orally, QD. Participants continued receiving venetoclax at a dose of 400 mg, 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.

Arm type	Experimental

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.

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.

Number of subjects in period 1	Bendamustine + Rituximab	Venetoclax + Rituximab
Started	195	194
Safety evaluable (SE) population	188	194
Completed	71	118
Not completed	124	76
Physician decision	3	1
Consent withdrawn by subject	26	11
Adverse Event	-	1
Death	83	52
Randomized but not Dosed	8	-
Lost to follow-up	4	5
Reason not Specified	-	6

Period 2

Period 2 title	Re-treatment/Crossover (R/C) Substudy
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	Bendamustine + Rituximab Crossover Substudy

Arm description:

Participants who entered the crossover substudy had a 5-week venetoclax dose ramp-up period to reach the target dose of 400 mg QD. Following the venetoclax ramp-up period, participants received 6 cycles of rituximab, 375 mg/m^2, as IV infusion on the Day 1 of each 28-day cycle. Participants who did not progress following the completion of the 6 cycles continued to receive venetoclax monotherapy until disease progression or for a maximum of 2 years from Cycle 1 crossover Day 1 of the substudy.

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 to reach the target dose of 400 mg during 5 weeks ramp-up period. Venetoclax was continued at 400 mg QD Day 1 of Cycle 1 of substudy 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, single IV infusion for 6 cycles on the first day of each 28-day cycle.

Arm title	Venetoclax + Rituximab Re-Treatment Substudy

Arm description:

Participants who entered the re-treatment substudy had a 5-week venetoclax dose ramp-up period to reach the target dose of 400 mg QD. Following the venetoclax ramp-up period, participants received 6 cycles of rituximab consisting of a single infusion on the first day of each 28-day cycle. Participants who did not progress following the completion of the 6 cycles continued to receive venetoclax monotherapy until disease progression or for a maximum of 2 year from Cycle 1 re-treatment Day 1 of the substudy.

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 to reach the target dose of 400 mg during 5 weeks ramp-up period. Venetoclax was continued at 400 mg QD Day 1 of Cycle 1 of substudy 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, single IV infusion for 6 cycles on the first day of each 28-day cycle.

Number of subjects in period 2[1]	Bendamustine + Rituximab Crossover Substudy	Venetoclax + Rituximab Re-Treatment Substudy
Started	9	25
Completed	7	15
Not completed	2	10
Consent withdrawn by subject	-	1
Death	1	8
Lost to follow-up	1	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 9 participants from BR arm and 25 participants from VR arm entered R/C substudy.

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 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, orally, QD. Participants continued receiving venetoclax at a dose of 400 mg, 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.	

Reporting group values	Bendamustine + Rituximab	Venetoclax + Rituximab	Total
Number of subjects	195	194	389
Age Categorical Units: Subjects			
Age Continuous			
Intent-to-treat (ITT) population, 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 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, orally, QD. Participants continued receiving venetoclax at a dose of 400 mg, 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.

Reporting group title	Bendamustine + Rituximab Crossover Substudy

Reporting group description:

Participants who entered the crossover substudy had a 5-week venetoclax dose ramp-up period to reach the target dose of 400 mg QD. Following the venetoclax ramp-up period, participants received 6 cycles of rituximab, 375 mg/m^2, as IV infusion on the Day 1 of each 28-day cycle. Participants who did not progress following the completion of the 6 cycles continued to receive venetoclax monotherapy until disease progression or for a maximum of 2 years from Cycle 1 crossover Day 1 of the substudy.

Reporting group title	Venetoclax + Rituximab Re-Treatment Substudy

Reporting group description:

Participants who entered the re-treatment substudy had a 5-week venetoclax dose ramp-up period to reach the target dose of 400 mg QD. Following the venetoclax ramp-up period, participants received 6 cycles of rituximab consisting of a single infusion on the first day of each 28-day cycle. Participants who did not progress following the completion of the 6 cycles continued to receive venetoclax monotherapy until disease progression or for a maximum of 2 year from Cycle 1 re-treatment Day 1 of the substudy.

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. ITT population included all randomized participants, with participants grouped according to randomized treatment group, regardless of the actual treatment received.

End point type	Primary

End point timeframe:

Baseline up to PD or death from any cause, whichever occurred first (up to approximately 8 years 5 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned to be analyzed for this endpoint.

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)	88.7	70.1		

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= 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/neutrophil count, 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. ITT population included all randomized participants, with participants grouped according to randomized treatment group, regardless of the actual treatment received.

End point type	Primary

End point timeframe:

Baseline up to PD or death, whichever occurred first (up to approximately 8 years 5 months)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[2]	194		
Units: months				
median (confidence interval 95%)	17.0 (15.5 to 21.7)	54.7 (52.3 to 59.9)		

Notes:

[2] - Analysis was performed on ITT population.

Statistical analyses

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[3]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.31

Notes:

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

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	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.29

Notes:

[4] - 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. ITT population included all randomized participants, with participants grouped according to randomized treatment group, regardless of the actual treatment received.

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	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= 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/neutrophil count, 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. ITT population included all randomized participants, with participants grouped according to randomized treatment group, regardless of the actual treatment received.

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	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[5]	194[6]		
Units: months				
median (confidence interval 95%)	18.1 (15.8 to 22.3)	99999 (99999 to 99999)		

Notes:

[5] - Analysis was performed on ITT population.

[6] - '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[7]
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:

[7] - 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[8]
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:

[8] - 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 Fluorescence in-situ Hybridization (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 Fluorescence in-situ Hybridization (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, whichever occurred first (up to approximately 8 years 5 months)

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)	80.4	80.4		

Statistical analyses

No statistical analyses for this end point

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 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 = 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. 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 8 years 5 months)

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[9]	46		
Units: months				
median (confidence interval 95%)	15.4 (10.0 to 21.0)	47.9 (37.4 to 59.9)		

Notes:

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

Statistical analyses

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[10]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.56

Notes:

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

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[11]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	0.57

Notes:

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

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 = 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. 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[12]	46[13]		
Units: months				
median (confidence interval 95%)	16.1 (13.6 to 22.3)	99999 (27.6 to 99999)		

Notes:

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

[13] - '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[14]
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:

[14] - 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[15]
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:

[15] - 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 per investigator per 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. ITT population = all randomized participants.

End point type	Secondary

End point timeframe:

Baseline up to approximately 8 years 5 months

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[16]	194[17]		
Units: percentage of participants				
number (confidence interval 95%)				
CR	8.2 (4.76 to 12.98)	26.3 (20.24 to 33.07)		
CRi	0.5 (0.01 to 2.82)	1.5 (0.32 to 4.45)		
nPR	6.2 (3.22 to 10.50)	3.6 (1.46 to 7.29)		
PR	52.8 (45.56 to 59.99)	61.9 (54.62 to 68.72)		

Notes:

[16] - Analysis was performed on ITT population.

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

Statistical analyses

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[18]
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:

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

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[19]
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:

[19] - 95% CI for rates were constructed using Pearson- Clopper method. 95% CI for difference in rates were constructed using Anderson-Hauck method.

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 per 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. ITT population = all randomized participants.

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[20]	194[21]		
Units: percentage of participants				
number (confidence interval 95%)	63.1 (55.89 to 69.86)	88.1 (82.74 to 92.33)		

Notes:

[20] - Analysis was performed on ITT population.

[21] - 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[22]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	25.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.63
upper limit	33.51

Notes:

[22] - 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[23]
Parameter estimate	Odds ratio (OR)
Point estimate	4.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.68
upper limit	7.88

Notes:

[23] - 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 per 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. ITT population = all randomized participants.

End point type	Secondary

End point timeframe:

Baseline up to last FUV (up to approximately 3 years)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[24]	194[25]		
Units: percentage of participants				
number (confidence interval 95%)	67.7 (60.64 to 74.20)	93.3 (88.81 to 96.38)		

Notes:

[24] - Analysis was performed on ITT population.

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

Statistical analyses

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[26]
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:

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

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[27]
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:

[27] - 95% CI for rates were constructed using Pearson- Clopper method. 95% CI for difference in rates were constructed using Anderson-Hauck method.

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 per 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. ITT population = all randomized participants.

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[28]	194[29]		
Units: percentage of participants				
number (confidence interval 95%)	62.6 (55.37 to 69.37)	87.1 (81.57 to 91.48)		

Notes:

[28] - Analysis was performed on ITT population.

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

Statistical analyses

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[30]
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:

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

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[31]
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:

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

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. ITT population included all randomized participants, with participants grouped according to randomized treatment group, regardless of the actual treatment received.

End point type	Secondary

End point timeframe:

Baseline up to approximately 8 years 5 months

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)	43.1	30.9		

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. ITT population included all randomized participants, with participants grouped according to randomized treatment group, regardless of the actual treatment received. '9999' = upper limit was not estimable due to low number of participants with event. '99999' = median, lower limit and upper limit were not estimable due to low number of participants with event.

End point type	Secondary

End point timeframe:

Baseline up to approximately 8 years 5 months

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%)	87.8 (70.1 to 9999)	99999 (99999 to 99999)		

Statistical analyses

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[32]
P-value	= 0.0003
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.76

Notes:

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

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[33]
P-value	= 0.0002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.74

Notes:

[33] - 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. ITT population included all randomized participants, with participants grouped according to randomized treatment group, regardless of the actual treatment received.

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 (approximately 8 years 5 months)

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)	89.2	71.1		

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. 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 8 years 5 months)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	181		
Units: months				
median (confidence interval 95%)	19.1 (16.1 to 23.6)	53.6 (49.1 to 57.0)		

Statistical analyses

No statistical analyses for this end point

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 8 years 5 months)

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)	95.5	68.5		

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. ITT population included all randomized participants, with participants grouped according to randomized treatment group, regardless of the actual treatment received.

End point type	Secondary

End point timeframe:

Baseline up to start of new ani-CLL therapy or death, whichever occurred first (up to approximately 8 years 5 months)

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)	81.5	62.4		

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. ITT population = all randomized participants.

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 (approximately 8 years 5 months)

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[34]	194		
Units: months				
median (confidence interval 95%)	16.4 (14.2 to 21.0)	53.7 (48.5 to 59.3)		

Notes:

[34] - Analysis was performed on ITT population.

Statistical analyses

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	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.31

Notes:

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

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[36]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.29

Notes:

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

Secondary: Percentage of Participants With MRD Negativity in Bone Marrow

End point title	Percentage of Participants With MRD Negativity in Bone Marrow

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 flow cytometry technique. Percentage of participants with MRD-negativity was reported. The 95% CI was computed using Pearson-Clopper method. ITT population included all randomized participants, with participants grouped according to randomized treatment group, regardless of the actual treatment received.

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: participants				
number (confidence interval 95%)	1.0 (0.12 to 3.66)	14.4 (9.81 to 20.18)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
OR was estimated using logistic regression model. The 95% CI was computed using Wald test.	
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	16.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.82
upper limit	69.35

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[37]
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Difference in MRD negative rates
Point estimate	16.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.99
upper limit	18.82

Notes:

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

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. ITT population included all randomized participants, with participants grouped according to randomized treatment group, regardless of the actual treatment received.

End point type	Secondary

End point timeframe:

Baseline up to start of new ani-CLL therapy or death, whichever occurred first (up to approximately 8 years 5 months)

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%)	24.0 (20.7 to 29.5)	63.0 (56.1 to 73.6)		

Statistical analyses

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[38]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.41

Notes:

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

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[39]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.39

Notes:

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

Secondary: Percentage of Participants With Minimal Residual Disease (MRD) Negativity in Peripheral Blood

End point title	Percentage of Participants With Minimal Residual Disease (MRD) Negativity in Peripheral Blood

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. ITT population included all randomized participants, with participants grouped according to randomized treatment group, regardless of the actual treatment received.

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 2
Comparison groups	Bendamustine + Rituximab v Venetoclax + Rituximab

Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority[40]
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:

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

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[41]
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:

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

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). Patient reported outcome (PRO) evaluable population, included all participants with baseline and at least one post-baseline PRO assessment.

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[42]	42[43]		
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:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Venetoclax Concentrations

End point title	Plasma Venetoclax Concentrations[44]

End point description:

Pharmacokinetic (PK) evaluable population, included all participants in the 'Venetoclax + Rituximab' arm 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 administration) and 4 hours post-dose on D1 of Cycles 1 and 4; Cycle length = 28 days

Notes:

[44] - 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: Plasma venetoclax concentrations was only analyzed for VR arm of the study.

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 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 5 functional scales (Physical, Role, Cognitive, Emotional, and Social), 3 symptom scales (fatigue, pain, nausea, and vomiting), 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'). 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. PRO evaluable population = all participants with baseline and at least one post-baseline PRO assessment. '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[45]	69[46]		
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:

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

[46] - '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. PRO evaluable population, included all participants with baseline and at least one post-baseline PRO assessment. '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

Secondary: Number of Participants with Grade 3 or higher Tumor Lysis Syndrome (TLS) and Infusion-related Reactions (IRRs)

End point title	Number of Participants with Grade 3 or higher Tumor Lysis Syndrome (TLS) and Infusion-related Reactions (IRRs)

End point description:

An AE was defined as any untoward medical occurrence in a participant administered with Mircera and which does not necessarily have a causal relationship with Mircera. A SAE is any significant hazard, contraindication, side effect that is fatal or life threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; is medically significant or requires intervention to prevent one or other of the outcomes listed above. TLS and IRRs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0). Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe or medically significant; Grade 4 = Life-threatening; Grade 5 = Death. A higher grade indicates a worse outcome. SE population.

End point type	Secondary

End point timeframe:

From signing of informed consent form up to approximately 8 years 5 months

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	194		
Units: participants				
TLS	2	6		
IRRs	10	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was defined as any untoward medical occurrence in a participant administered with Mircera and which does not necessarily have a causal relationship with Mircera. A Serious Adverse Event (SAE) is any significant hazard, contraindication, side effect that is fatal or life threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; is medically significant or requires intervention to prevent one or other of the outcomes listed above. AEs were assessed using National

Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v4.0). SE population included all randomized participants who received at least one dose of study treatment with participants grouped according to the actual treatment received.

End point type	Secondary

End point timeframe:

From signing of informed consent form up to approximately 8 years 5 months

End point values	Bendamustine + Rituximab	Venetoclax + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	194		
Units: participants				
AEs	185	194		
SAEs	84	101		

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:

PRO evaluable population included all participants with baseline and at least one post-baseline PRO assessment. Here, 'Overall Number of Participants Analyzed' = participants evaluable for this outcome measure and 'Number Analyzed' = participants evaluable at specified time point.

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[47]	0[48]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[47] - Data were not presented as this is not an primary or secondary endpoint.

[48] - Data were not presented as this is not an primary or secondary endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent form up to approximately 8 years 5 months

Adverse event reporting additional description:

SE population included all randomized participants who received at least one dose of study treatment with participants grouped according to the actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Bendamustine + Rituximab Main Study

Reporting group 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.

Reporting group title	Venetoclax + Rituximab Re-Treatment Substudy

Reporting group description:

Participants who entered the re-treatment substudy had a 5-week venetoclax dose ramp-up period to reach the target dose of 400 mg QD. Following the venetoclax ramp-up period, participants received 6 cycles of rituximab consisting of a single infusion on the first day of each 28-day cycle. Participants who did not progress following the completion of the 6 cycles continued to receive venetoclax monotherapy until disease progression or for a maximum of 2 year from Cycle 1 re-treatment Day 1 of the substudy.

Reporting group title	Bendamustine + Rituximab Crossover Substudy

Reporting group description:

Participants who entered the crossover substudy had a 5-week venetoclax dose ramp-up period to reach the target dose of 400 mg QD. Following the venetoclax ramp-up period, participants received 6 cycles of rituximab, 375 mg/m^2, as IV infusion on the Day 1 of each 28-day cycle. Participants who did not progress following the completion of the 6 cycles continued to receive venetoclax monotherapy until disease progression or for a maximum of 2 years from Cycle 1 crossover Day 1 of the substudy.

Reporting group title	Venetoclax + Rituximab Main Study

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 QD for initial 1 to 7 days, then venetoclax dose was incremented weekly up to a maximum dose of 400 mg, orally, QD. Participants continued receiving venetoclax at a dose of 400 mg, 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.

Serious adverse events	Bendamustine + Rituximab Main Study	Venetoclax + Rituximab Re-Treatment Substudy	Bendamustine + Rituximab Crossover Substudy
Total subjects affected by serious adverse events			
subjects affected / exposed	84 / 188 (44.68%)	13 / 25 (52.00%)	5 / 9 (55.56%)
number of deaths (all causes)	84	8	1
number of deaths resulting from adverse events	4	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			

subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Adenocarcinoma gastric			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	3 / 188 (1.60%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Colorectal cancer			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoma			
subjects affected / exposed	1 / 188 (0.53%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Malignant melanoma			

subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Medullary thyroid cancer			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic malignant melanoma			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic adenoma			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			

subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 188 (0.00%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastasis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sebaceous adenoma			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin squamous cell carcinoma recurrent			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			

subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Colorectal adenocarcinoma			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	5 / 188 (2.66%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	4 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 188 (0.00%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hyperpyrexia			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	13 / 188 (6.91%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	11 / 15	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiectasis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical observation			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Humerus fracture			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	6 / 188 (3.19%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	8 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scar			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			

subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 188 (0.00%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 188 (0.00%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			

subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 188 (2.66%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	4 / 6	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	3 / 188 (1.60%)	0 / 25 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	2 / 188 (1.06%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune haemolytic anaemia			

subjects affected / exposed	3 / 188 (1.60%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	16 / 188 (8.51%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	14 / 16	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenia			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Eye haemorrhage			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal fistula			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 188 (0.00%)	1 / 25 (4.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal obstruction			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary obstruction			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 188 (0.00%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	0 / 188 (0.00%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Dermatitis allergic			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot			
subjects affected / exposed	0 / 188 (0.00%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Actinic keratosis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 188 (0.00%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 188 (0.00%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 188 (1.06%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abscess neck			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 188 (0.53%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilus infection			

subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex otitis externa			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	2 / 188 (1.06%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Listeria sepsis			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			

subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal bacteraemia			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal tuberculosis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	2 / 188 (1.06%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Moraxella infection			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	15 / 188 (7.98%)	3 / 25 (12.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	5 / 17	0 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			

subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia streptococcal			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinovirus infection			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scedosporium infection			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	4 / 188 (2.13%)	0 / 25 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Respiratory tract infection fungal			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	2 / 188 (1.06%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection pseudomonal			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster virus infection			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 188 (0.53%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 188 (0.00%)	1 / 25 (4.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atypical mycobacterial infection			
subjects affected / exposed	0 / 188 (0.00%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	1 / 188 (0.53%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperphosphataemia			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypervolaemia			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Venetoclax +		

	Rituximab Main Study		
Total subjects affected by serious adverse events			
subjects affected / exposed	101 / 194 (52.06%)		
number of deaths (all causes)	60		
number of deaths resulting from adverse events	4		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma gastric			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Basal cell carcinoma			
subjects affected / exposed	2 / 194 (1.03%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colorectal cancer			
subjects affected / exposed	2 / 194 (1.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Adenocarcinoma of colon			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Lymphoma				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma				
subjects affected / exposed	2 / 194 (1.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Medullary thyroid cancer				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastatic malignant melanoma				
subjects affected / exposed	2 / 194 (1.03%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
Myelodysplastic syndrome				
subjects affected / exposed	2 / 194 (1.03%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Prostate cancer				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostatic adenoma				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transitional cell carcinoma				

subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Squamous cell carcinoma of skin				
subjects affected / exposed	3 / 194 (1.55%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of lung				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastasis				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sebaceous adenoma				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Plasma cell myeloma				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin squamous cell carcinoma recurrent				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Breast cancer				

subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to lung				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colorectal adenocarcinoma				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aortic stenosis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				

Asthenia				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperpyrexia				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	5 / 194 (2.58%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Sudden cardiac death				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Sudden death				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Reproductive system and breast disorders				
Cervical dysplasia				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine haemorrhage				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Bronchiectasis			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Medical observation			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tendon rupture			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Scar			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cardiac failure				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Coronary artery disease				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	2 / 194 (1.03%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Ventricular tachycardia				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pericarditis				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dizziness				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic stroke				

subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lacunar infarction				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Polyneuropathy				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Status epilepticus				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Syncope				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	3 / 194 (1.55%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	3 / 194 (1.55%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	2 / 194 (1.03%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Autoimmune haemolytic anaemia				

subjects affected / exposed	3 / 194 (1.55%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	7 / 194 (3.61%)			
occurrences causally related to treatment / all	7 / 7			
deaths causally related to treatment / all	0 / 0			
Leukocytosis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Disseminated intravascular coagulation				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Immune thrombocytopenia				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Deafness				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vertigo				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				

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

subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal obstruction				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Biliary obstruction				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice cholestatic				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				

Dermatitis allergic				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diabetic foot				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Actinic keratosis				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Nephrolithiasis				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute kidney injury				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic kidney disease				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ureterolithiasis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue				

disorders				
Intervertebral disc protrusion				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal chest pain				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cellulitis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	2 / 194 (1.03%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Atypical pneumonia				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Campylobacter gastroenteritis				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Abscess neck				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemophilus infection				

subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis B				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes simplex otitis externa				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis rotavirus				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	3 / 194 (1.55%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Listeria sepsis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Localised infection				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis				

subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumococcal bacteraemia				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Parainfluenzae virus infection				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritoneal tuberculosis				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Moraxella infection				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	19 / 194 (9.79%)			
occurrences causally related to treatment / all	7 / 23			
deaths causally related to treatment / all	0 / 3			
Pneumonia influenzal				

subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia legionella				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia streptococcal				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	2 / 194 (1.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection viral				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhinovirus infection				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Scedosporium infection				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Respiratory tract infection fungal				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	2 / 194 (1.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tooth abscess				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	4 / 194 (2.06%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection pseudomonal				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				

subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Varicella zoster virus infection				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Viral upper respiratory tract infection				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Atypical mycobacterial infection				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia pseudomonal				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				

subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	4 / 194 (2.06%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	2 / 194 (1.03%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	2 / 194 (1.03%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperphosphataemia			
subjects affected / exposed	2 / 194 (1.03%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypervolaemia			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Bendamustine + Rituximab Main Study	Venetoclax + Rituximab Re-Treatment Substudy	Bendamustine + Rituximab Crossover Substudy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	177 / 188 (94.15%)	9 / 25 (36.00%)	5 / 9 (55.56%)
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 188 (3.72%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	7	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	33 / 188 (17.55%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	44	0	0
Oedema peripheral			
subjects affected / exposed	7 / 188 (3.72%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	11	0	0
Fatigue			
subjects affected / exposed	39 / 188 (20.74%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences (all)	44	1	0
Chills			
subjects affected / exposed	16 / 188 (8.51%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences (all)	20	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	31 / 188 (16.49%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	37	0	0
Dyspnoea			
subjects affected / exposed	14 / 188 (7.45%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	17	0	0
Oropharyngeal pain			
subjects affected / exposed	7 / 188 (3.72%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	7	0	0
Productive cough			
subjects affected / exposed	4 / 188 (2.13%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	5	0	0

Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	12 / 188 (6.38%) 13	0 / 25 (0.00%) 0	0 / 9 (0.00%) 0
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	10 / 188 (5.32%) 11	0 / 25 (0.00%) 0	0 / 9 (0.00%) 0
Neutrophil count decreased subjects affected / exposed occurrences (all)	13 / 188 (6.91%) 27	0 / 25 (0.00%) 0	1 / 9 (11.11%) 1
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 188 (0.53%) 1	0 / 25 (0.00%) 0	1 / 9 (11.11%) 2
White blood cell count decreased subjects affected / exposed occurrences (all)	3 / 188 (1.60%) 4	0 / 25 (0.00%) 0	1 / 9 (11.11%) 1
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	40 / 188 (21.28%) 54	0 / 25 (0.00%) 0	0 / 9 (0.00%) 0
Cardiac disorders Supraventricular tachycardia subjects affected / exposed occurrences (all)	1 / 188 (0.53%) 1	0 / 25 (0.00%) 0	1 / 9 (11.11%) 1
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	11 / 188 (5.85%) 14	0 / 25 (0.00%) 0	0 / 9 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	19 / 188 (10.11%) 21	0 / 25 (0.00%) 0	0 / 9 (0.00%) 0
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	42 / 188 (22.34%) 57	2 / 25 (8.00%) 2	0 / 9 (0.00%) 0
Neutropenia			

subjects affected / exposed	85 / 188 (45.21%)	5 / 25 (20.00%)	3 / 9 (33.33%)
occurrences (all)	182	13	5
Anaemia			
subjects affected / exposed	40 / 188 (21.28%)	1 / 25 (4.00%)	1 / 9 (11.11%)
occurrences (all)	68	1	1
Febrile neutropenia			
subjects affected / exposed	3 / 188 (1.60%)	0 / 25 (0.00%)	1 / 9 (11.11%)
occurrences (all)	3	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	31 / 188 (16.49%)	3 / 25 (12.00%)	0 / 9 (0.00%)
occurrences (all)	43	4	0
Constipation			
subjects affected / exposed	39 / 188 (20.74%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	47	0	0
Abdominal pain			
subjects affected / exposed	6 / 188 (3.19%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	7	0	0
Vomiting			
subjects affected / exposed	22 / 188 (11.70%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	29	0	0
Nausea			
subjects affected / exposed	64 / 188 (34.04%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	82	0	0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	25 / 188 (13.30%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	29	0	0
Pruritus			
subjects affected / exposed	9 / 188 (4.79%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences (all)	9	1	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	11 / 188 (5.85%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	15	0	0
Back pain			
subjects affected / exposed	11 / 188 (5.85%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	11	0	0
Muscle spasms			
subjects affected / exposed	11 / 188 (5.85%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	11	0	0
Infections and infestations			
Oral herpes			
subjects affected / exposed	12 / 188 (6.38%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	12	0	0
Pharyngitis			
subjects affected / exposed	1 / 188 (0.53%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Sinusitis			
subjects affected / exposed	5 / 188 (2.66%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	5	0	0
Upper respiratory tract infection			
subjects affected / exposed	28 / 188 (14.89%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences (all)	42	1	0
Urinary tract infection			
subjects affected / exposed	7 / 188 (3.72%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	9	0	0
Nasopharyngitis			
subjects affected / exposed	11 / 188 (5.85%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	15	0	0
Lower respiratory tract infection			
subjects affected / exposed	4 / 188 (2.13%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	4	0	0
Conjunctivitis			
subjects affected / exposed	5 / 188 (2.66%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	5	0	0
Bronchitis			

subjects affected / exposed	13 / 188 (6.91%)	1 / 25 (4.00%)	0 / 9 (0.00%)
occurrences (all)	14	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	17 / 188 (9.04%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	18	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 188 (0.00%)	0 / 25 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	7 / 188 (3.72%)	0 / 25 (0.00%)	1 / 9 (11.11%)
occurrences (all)	7	0	1

Non-serious adverse events	Venetoclax + Rituximab Main Study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	190 / 194 (97.94%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 194 (7.73%)		
occurrences (all)	15		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	27 / 194 (13.92%)		
occurrences (all)	41		
Oedema peripheral			
subjects affected / exposed	10 / 194 (5.15%)		
occurrences (all)	14		
Fatigue			
subjects affected / exposed	35 / 194 (18.04%)		
occurrences (all)	41		
Chills			
subjects affected / exposed	8 / 194 (4.12%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	36 / 194 (18.56%) 51		
Dyspnoea subjects affected / exposed occurrences (all)	11 / 194 (5.67%) 14		
Oropharyngeal pain subjects affected / exposed occurrences (all)	10 / 194 (5.15%) 12		
Productive cough subjects affected / exposed occurrences (all)	12 / 194 (6.19%) 14		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	21 / 194 (10.82%) 22		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	10 / 194 (5.15%) 17		
Neutrophil count decreased subjects affected / exposed occurrences (all)	11 / 194 (5.67%) 27		
Blood creatinine increased subjects affected / exposed occurrences (all)	5 / 194 (2.58%) 6		
White blood cell count decreased subjects affected / exposed occurrences (all)	1 / 194 (0.52%) 1		
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	16 / 194 (8.25%) 21		
Cardiac disorders Supraventricular tachycardia			

subjects affected / exposed	0 / 194 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 194 (6.19%)		
occurrences (all)	14		
Headache			
subjects affected / exposed	21 / 194 (10.82%)		
occurrences (all)	21		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	23 / 194 (11.86%)		
occurrences (all)	30		
Neutropenia			
subjects affected / exposed	120 / 194 (61.86%)		
occurrences (all)	290		
Anaemia			
subjects affected / exposed	28 / 194 (14.43%)		
occurrences (all)	48		
Febrile neutropenia			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	78 / 194 (40.21%)		
occurrences (all)	120		
Constipation			
subjects affected / exposed	27 / 194 (13.92%)		
occurrences (all)	31		
Abdominal pain			
subjects affected / exposed	13 / 194 (6.70%)		
occurrences (all)	14		
Vomiting			
subjects affected / exposed	15 / 194 (7.73%)		
occurrences (all)	18		
Nausea			

subjects affected / exposed occurrences (all)	42 / 194 (21.65%) 58		
Skin and subcutaneous tissue disorders Dermatitis subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 5 / 194 (2.58%) 5 15 / 194 (7.73%) 19 10 / 194 (5.15%) 11		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all)	 17 / 194 (8.76%) 22 14 / 194 (7.22%) 14 4 / 194 (2.06%) 4		
Infections and infestations Oral herpes subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection	 8 / 194 (4.12%) 11 14 / 194 (7.22%) 17 19 / 194 (9.79%) 26 45 / 194 (23.20%) 81		

subjects affected / exposed occurrences (all)	12 / 194 (6.19%) 22		
Nasopharyngitis subjects affected / exposed occurrences (all)	22 / 194 (11.34%) 29		
Lower respiratory tract infection subjects affected / exposed occurrences (all)	11 / 194 (5.67%) 15		
Conjunctivitis subjects affected / exposed occurrences (all)	10 / 194 (5.15%) 11		
Bronchitis subjects affected / exposed occurrences (all)	20 / 194 (10.31%) 32		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	8 / 194 (4.12%) 11		
Hyperkalaemia subjects affected / exposed occurrences (all)	11 / 194 (5.67%) 16		
Hypokalaemia subjects affected / exposed occurrences (all)	11 / 194 (5.67%) 12		

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.

03 June 2017	The following updates in the protocol were made in Korea. - The description of the fixed sequence testing of the secondary efficacy endpoints in the statistical section of the protocol was streamlined and the details of the testing of secondary endpoints were set out in the statistical analysis plan, in accordance with the international guideline on Statistical Principles for Clinical Trials (ICH E9). This amendment is implemented to allow for a change in the clinical prioritization of the secondary efficacy endpoints to mirror the evolving R/R CLL therapeutic and scientific landscape. - The sample list of prohibited and cautionary medications was updated, incorporating the FDA's updated guidelines.
30 March 2018	- An exploratory objective was added to evaluate best overall response rate (ORR) to next anti-chronic lymphocytic leukemia (CLL) treatment, as assessed by the investigator. - An optional R/C Substudy was added.At the interim analysis (now primary analysis), the study demonstrated that venetoclax and rituximab (venetoclax + R) is superior to bendamustine and rituximab (BR) in participants with relapsed/refractory CLL. The primary endpoint of investigator assessed progression-free survival (PFS) showed significant improvement with venetoclax. - Secondary endpoints, including overall survival (OS), ORR, and complete response rate, also showed consistent clinically meaningful improvements. The Sponsor included an optional R/C Substudy to allow: -- Eligible participants from Arm A (venetoclax + R) who had clinically progressed after finishing treatment, had not received new anti-CLL therapy, and were in need of treatment have the option to receive treatment with venetoclax + R again (re-treatment). This will allow the Sponsor to study the outcomes of participants who are re-treated with venetoclax + R following prior venetoclax + R treatment. -- Eligible participants from Arm B (BR) who had clinically progressed after finishing treatment, have not received new anti-CLL therapy, and are in need of treatment have the option to cross over and receive venetoclax + R given the results of the primary analysis demonstrating superior outcome for venetoclax + R treatment. - The study duration is extended for an additional 45 months to allow for the collection of long-term data including safety, PFS, and OS. At the primary read out, PFS and OS outcomes for participants in the venetoclax + R arm exceed original protocol expectations, thus requiring longer follow-up to enable estimation of a robust efficacy and median PFS.
30 March 2018	- The reporting of secondary malignancies has been extended after the reporting period to capture all events regardless of causality in order to satisfy health authority requirements. The rationale for biomarker assessments has been updated to include next-generation sequencing analysis. These analyses will provide a comprehensive characterization of genomics to enable the understanding of disease pathobiology. - Sample collection for peripheral blood minimal residual disease (MRD) samples has been extended until clinical progression because participants demonstrated persistent MRD negativity and there is a need to better understand the MRD kinetics over longer period of time.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported