Clinical trial results:
Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Efficacy of Venetoclax (ABT 199) in Relapsed/Refractory Subjects With Chronic Lymphocytic Leukemia (CLL)

Summary

EudraCT number	2015-003667-11
Trial protocol	GR SE BE NL DE AT IE PT FI DK ES FR IT
Global end of trial date	17 March 2022

Results information

Result version number	v1
This version publication date	09 March 2023
First version publication date	09 March 2023

Trial information

Trial identification

Sponsor protocol code	M15-550

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02756611
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy of venetoclax monotherapy in participants with relapsed/refractory CLL with or without the 17p deletion or TP53 mutation, including those who have received prior treatment with a B-cell receptor inhibitor (BCRi).

Protection of trial subjects:

All subjects entering the study had to sign an informed consent that was explained to them and questions encouraged.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 June 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Greece: 29
Country: Number of subjects enrolled	Ireland: 13
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Puerto Rico: 5
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	Switzerland: 9
Country: Number of subjects enrolled	Turkey: 50

Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	258
EEA total number of subjects	136

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)	94
From 65 to 84 years	157
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 59 sites in 19 countries. The primary analysis of results occurred after all participants completed the Week 48 disease assessment, with a data cut-off date of 30 June 2019.

Pre-assignment

Screening details:

Overall, 287 subjects were screened for this study, and 258 subjects were enrolled (29 subjects were screening failures due to inclusion/exclusion criteria, withdrawal of consent, or other reason), including 191 subjects who were B-cell receptor inhibitor (BCRi) naïve and 67 subjects who had been previously exposed to BCRi.

Period 1

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

Arms

Arm title	Venetoclax

Arm description:

Participants received venetoclax on a once daily (QD) dosing schedule for up to 108 weeks. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg.
In countries where venetoclax was not commercially available, participants who continued to derive benefit after 2 years of treatment could extend their treatment for up to two additional years plus one additional year until the venetoclax extension study was open.

Arm type	Experimental
Investigational medicinal product name	Venetoclax
Investigational medicinal product code	ABT-199
Other name	Venclexta®, Venclyxto®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets for oral administration

Number of subjects in period 1	Venetoclax
Started	258
Completed	124
Not completed	134
Consent withdrawn by subject	2
Transitioned to long-term extension study M19-388	49
Other	10
Death	70
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	Venetoclax
Reporting group description:	
Participants received venetoclax on a once daily (QD) dosing schedule for up to 108 weeks. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg. In countries where venetoclax was not commercially available, participants who continued to derive benefit after 2 years of treatment could extend their treatment for up to two additional years plus one additional year until the venetoclax extension study was open.	

Reporting group values	Venetoclax	Total	
Number of subjects	258	258	
Age categorical Units: Subjects			
< 65 years	94	94	
>= 65 years	164	164	
Age continuous Units: years			
arithmetic mean	67.7		
standard deviation	± 9.04	-	
Gender categorical Units: Subjects			
Female	78	78	
Male	180	180	
Race Units: Subjects			
White	252	252	
Black or African American	3	3	
Asian	2	2	
Missing	1	1	
Ethnicity Units: Subjects			
Hispanic or Latino	9	9	
Not Hispanic or Latino	248	248	
Missing	1	1	
Geographic Region Units: Subjects			
Europe	161	161	
North America	28	28	
Rest of the World	69	69	
Prior Treatment With B-cell Receptor Inhibitor (BCRi) Units: Subjects			
BCRi-naive	191	191	
BCRi-exposed	67	67	

End points

End points reporting groups

Reporting group title	Venetoclax

Reporting group description:

Participants received venetoclax on a once daily (QD) dosing schedule for up to 108 weeks. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg.
In countries where venetoclax was not commercially available, participants who continued to derive benefit after 2 years of treatment could extend their treatment for up to two additional years plus one additional year until the venetoclax extension study was open.

Primary: Complete Remission Rate in Participants Not Previously Treated With BCRi Therapy - Primary Analysis

End point title	Complete Remission Rate in Participants Not Previously Treated With BCRi Therapy - Primary Analysis[1]

End point description:

Complete remission rate is defined as the percentage of participants achieving a best response of complete remission (CR) or complete remission with incomplete marrow recovery (CRi) assessed by the investigator based on 2008 Modified International Workshop for Chronic Lymphocytic Leukemia National Cancer Institute-Working Group (IWCLL NCI-WG) criteria.
CR required all of the following:
•Peripheral blood lymphocytes < 4000/µL;
•Absence of lymphadenopathy by physical examination and computed tomography scan;
•No hepatomegaly or splenomegaly by physical examination;
•Absence of disease or constitutional symptoms (unexplained fevers > 38°C, drenching night sweats, > 10% weight loss in last 6 months);
•Blood counts above the following: Neutrophils > 1500/µL, platelets > 100,000/µL, and hemoglobin > 110 g/L;
•Bone marrow at least normocellular for age, < 30% lymphocytes.
CRi was defined as for CR but with persistent cytopenia apparently unrelated to CLL but related to drug toxicity.

End point type	Primary

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 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: Statistical analyses cannot be entered for single-arm studies. Please see attachment.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	191[2]			
Units: percentage of participants				
number (confidence interval 95%)	35.1 (28.3 to 42.3)			

Notes:

[2] - All treated participants who were BCRi treatment naive.

Attachments (see zip file)	Complete Remission Rate in BCRi-naive Subjects/Complete

Statistical analyses

No statistical analyses for this end point

Primary: Complete Remission Rate in Participants Not Previously Treated With BCRi Therapy - Final Analysis

End point title	Complete Remission Rate in Participants Not Previously Treated With BCRi Therapy - Final Analysis[3]

End point description:

Complete remission rate is defined as the percentage of participants achieving a best response of complete remission (CR) or complete remission with incomplete marrow recovery (CRi) assessed by the investigator based on 2008 modified IWCLL NCI-WG criteria.
CR required all of the following:
• Peripheral blood lymphocytes < 4000/µL;
• Absence of lymphadenopathy by physical examination and computed tomography scan;
• No hepatomegaly or splenomegaly by physical examination;
• Absence of disease or constitutional symptoms (unexplained fevers > 38°C, drenching night sweats, > 10% weight loss in last 6 months);
• Blood counts above the following: Neutrophils > 1500/µL, platelets > 100,000/µL, and hemoglobin > 110 g/L;
• Bone marrow at least normocellular for age, < 30% lymphocytes.
CRi was defined as for CR but with persistent cytopenia apparently unrelated to CLL but related to drug toxicity.

End point type	Primary

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

Notes:

[3] - 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: Statistical analyses cannot be entered for single-arm studies. Please see attachment.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	191[4]			
Units: percentage of participants				
number (confidence interval 95%)	34.6 (27.8 to 41.8)			

Notes:

[4] - All treated participants who were BCRi treatment naive.

Attachments (see zip file)	Complete Remission Rate in BCRi-naive Subjects/Complete

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission Rate in Participants Previously Treated With BCRi Therapy - Primary Analysis

End point title	Complete Remission Rate in Participants Previously Treated With BCRi Therapy - Primary Analysis

End point description:

Complete remission rate is defined as the percentage of participants achieving a best response of complete remission (CR) or complete remission with incomplete marrow recovery (CRi) assessed by the investigator based on 2008 Modified IWCLL NCI-WG criteria.
CR required all of the following:
• Peripheral blood lymphocytes < 4000/µL;
• Absence of lymphadenopathy by physical examination and computed tomography scan;
• No hepatomegaly or splenomegaly by physical examination;

• Absence of disease or constitutional symptoms (unexplained fevers > 38°C, drenching night sweats, > 10% weight loss in last 6 months);
• Blood counts above the following: Neutrophils > 1500/µL, platelets > 100,000/µL, and hemoglobin > 110 g/L;
• Bone marrow at least normocellular for age, < 30% lymphocytes.
CRi was defined as for CR but with persistent cytopenia apparently unrelated to CLL but related to drug toxicity.

End point type	Secondary

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 months.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	67[5]			
Units: percentage of participants				
number (confidence interval 95%)	25.4 (15.5 to 37.5)			

Notes:

[5] - All treated participants who were previously treated with BCRi

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) - Primary Analysis

End point title	Overall Response Rate (ORR) - Primary Analysis

End point description:

Overall response rate was defined as the percentage of participants with an overall best response of CR, CRi, nodular partial remission (nPR), or confirmed partial remission (PR) based on the 2008 modified IWCLL NCI-WG criteria assessed by the investigator.
CR and CRi are defined above.
nPR is defined as for CR but bone marrow nodules could be identified histologically.
For PR at least 2 of the following must be met:
•≥ 50% decrease in peripheral blood lymphocyte count from the Baseline value;
•≥ 50% reduction in lymphadenopathy;
•≥ 50% reduction in the size of the liver and/or spleen (if abnormal prior to therapy);
In addition at least 1 of the following criteria must be met:
•Neutrophils > 1,500/µL or ≥ 50% improvement over Baseline;
•Platelets > 100,000/µL or ≥ 50% improvement over Baseline;
•Hemoglobin > 11.0 g/dL or ≥ 50% improvement over Baseline without transfusions or exogenous growth factors.
PR must have been confirmed at least 7 weeks later.

End point type	Secondary

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 months.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	258[6]			
Units: percentage of participants				
number (confidence interval 95%)	79.8 (74.4 to 84.6)			

Notes:

[6] - All treated participants

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Overall Response (DOR) - Primary Analysis

End point title	Duration of Overall Response (DOR) - Primary Analysis

End point description:

Duration of response was defined as the time from the date of first response (CR, CRi, nPR, or PR) to the earliest date that progressive disease (PD) was objectively documented (radiographic or clinical) or death. Duration of response was analyzed by Kaplan-Meier (K-M) methodology. If a participant was still responding the data were censored at the date of the last available disease assessment prior to the data cutoff date.

End point type	Secondary

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 months.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	205[7]			
Units: months				
median (confidence interval 95%)	25.2 (23.0 to 25.2)			

Notes:

[7] - Participants who had an overall response of CR, CRi, nPR, or confirmed PR.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP) - Primary Analysis

End point title	Time to Progression (TTP) - Primary Analysis

End point description:

Time to progression was defined as the time from the date of first dose of venetoclax to the date of earliest PD (radiographic or clinical). Participants who did not experience disease progression were censored at the date of the last available disease assessment prior to the data cutoff date; participants with no post-baseline disease assessments were censored at the first dose date plus 1 day. Time to progression was estimated using Kaplan-Meier methodology.

End point type	Secondary

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 months.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	258[8]			
Units: months				
median (confidence interval 95%)	30.5 (29.6 to 30.5)			

Notes:

[8] - All treated participants

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) - Primary Analysis

End point title	Progression-Free Survival (PFS) - Primary Analysis

End point description:

Progression-free survival (PFS) was defined as the time from the date of first dose of venetoclax to the date of earliest PD (radiographic or clinical) or death. Participants who did not experience disease progression or death were censored at the date of the last available disease assessment prior to the data cutoff date; participants with no post-baseline tumor assessment or clinical assessment for progression were censored at the date of first dose plus 1 day. Progression-free survival was analyzed by Kaplan-Meier methodology.

End point type	Secondary

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 months.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	258[9]			
Units: months				
number (confidence interval 95%)	30.5 (28.6 to 30.5)			

Notes:

[9] - All treated participants

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Primary Analysis

End point title	Overall Survival (OS) - Primary Analysis

End point description:

Overall survival (time to death) was defined as the number of days from the first dose date of venetoclax to the date of death. If a participant had not died the data were censored at the date when they were last known to be alive prior to the cutoff date. Overall survival was analyzed using Kaplan-

Meier methodology.
"99999" indicates data that could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 months.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	258[10]			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Notes:

[10] - All treated participants

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Cancer Therapy – Leukemia Questionnaire (FACT-Leu)

End point title	Change From Baseline in Functional Assessment of Cancer Therapy – Leukemia Questionnaire (FACT-Leu)

End point description:

The FACT-Leu is a 44-item, leukemia-specific questionnaire designed to assess health-related quality of life (HRQoL) and leukemia-specific symptoms using a core set of questions (Functional Assessment of Cancer Therapy-General; FACT-G), and a leukemia-specific subscale. Questions are scored on a scale from 0 (not at all) to 4 (very much).
FACT-G consists of 27 general items divided into 4 primary HRQoL domains: Physical Well-being (PWB; 7 items; score range 0-28), Social/Family Well-being (SWB; 7 items; score range 0-28), Emotional Well-being (EWB; 6 items; score range 0-24), Functional Well-being (FWB; 7 items; score range 0-28). The leukemia subscale consists of 17 items (score range 0-68) that assess patient concerns relating to leukemia. Three summary scales were calculated: FACT-Trial Outcome Index (TOI) composed of the PWB, FWB, and leukemia subscale (score range 0-124); FACT-G (score range 0-108) and the FACT-Leu Total (range 0-176). Higher scores reflect better HRQoL.

End point type	Secondary

End point timeframe:

Baseline and Weeks 48 and 108

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	205[11]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Physical well-being - Week 48 (N=205)	1.2 (± 4.07)			
Physical well-being - Week 108 (N=153)	0.9 (± 4.20)			
Social/family well-being - Week 48 (N=203)	0.2 (± 5.14)			

Social/family well-being - Week 108 (N=151)	-0.4 (± 4.86)			
Emotional well-being - Week 48 (N=202)	2.1 (± 3.52)			
Emotional well-being - Week 108 (N=154)	1.7 (± 3.94)			
Functional well-being - Week 48 (N=202)	1.8 (± 5.63)			
Functional well-being - Week 108 (N=153)	1.4 (± 5.67)			
Leukemia subscale - Week 48 (N=202)	6.8 (± 7.99)			
Leukemia subscale - Week 108 (N=153)	6.0 (± 9.08)			
FACT-G total score - Week 48 (N=200)	5.5 (± 12.34)			
FACT-G total score - Week 108 (N=148)	3.6 (± 13.56)			
FACT-leukemia TOI - Week 48 (N=201)	9.8 (± 14.23)			
FACT-leukemia TOI - Week 108 (N=150)	8.2 (± 15.61)			
FACT-leukemia total score - Week 48 (N=199)	12.3 (± 18.18)			
FACT-leukemia total score - Week 108 (N=147)	9.5 (± 20.62)			

Notes:

[11] - All treated participants with available data for each scale at each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue)

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue)

End point description:

The FACIT-Fatigue questionnaire measures fatigue and its effect on functioning and daily activities. The FACIT-Fatigue includes 13 items answered on a 5-point rating scale based on a 7-day recall period. Scores range from 0 to 52, with lower scores reflecting greater fatigue.

End point type	Secondary

End point timeframe:

Baseline and Weeks 48 and 108

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	205[12]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 48	4.9 (± 9.43)			
Week 108	3.3 (± 9.96)			

Notes:

[12] - Treated participants with available data at each timepoint. N=154 at Week 108.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQoL 5 Dimension 5 Level Questionnaire (EQ-5D-5L) Health Index Score

End point title	Change From Baseline in EuroQoL 5 Dimension 5 Level Questionnaire (EQ-5D-5L) Health Index Score

End point description:

The EQ-5D-5L is a generic measure of health status consisting of two parts: a descriptive system consisting of 5 items and a visual analog scale (VAS).
The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The participant is asked to rate each dimension on 5 levels of severity (1: no problems, 2: slight problems, 3: moderate problems, 4: severe problems, 5: extreme problems).
The scores for the 5 dimensions are used to compute a single health utility index score representing the general health status of the individual. The health index score ranges from zero (defined as a health state equivalent to being dead) to 1 (full health).

End point type	Secondary

End point timeframe:

Baseline and Weeks 48 and 108

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	204[13]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 48	0.0 (± 0.14)			
Week 108	0.0 (± 0.15)			

Notes:

[13] - All treated participants with available data at each time point. N=152 at Week 108.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQoL 5 Dimension 5 Level Questionnaire (EQ-5D-5L) Visual Analog Scale Score

End point title	Change From Baseline in EuroQoL 5 Dimension 5 Level Questionnaire (EQ-5D-5L) Visual Analog Scale Score

End point description:

The EQ-5D-5L is a generic measure of health status consisting of two parts, a descriptive system consisting of 5 items and a visual analog scale (VAS).
The VAS assesses the participant's self-rated overall health on a scale from 0 (worst health imaginable) to 100 (best health imaginable).

End point type	Secondary

End point timeframe:

Baseline and Weeks 48 and 108

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	204[14]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 48	8.5 (± 14.43)			
Week 108	7.1 (± 14.61)			

Notes:

[14] - All treated participants with available data at each time point; N=156 at Week 108.

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission Rate in Participants Previously Treated With BCRi Therapy - Final Analysis

End point title	Complete Remission Rate in Participants Previously Treated With BCRi Therapy - Final Analysis

End point description:

Complete remission rate is defined as the percentage of participants achieving a best response of complete remission (CR) or complete remission with incomplete marrow recovery (CRi) assessed by the investigator based on 2008 modified IWCLL NCI-WG criteria.
CR required all of the following:
• Peripheral blood lymphocytes < 4000/µL;
• Absence of lymphadenopathy by physical examination and computed tomography scan;
• No hepatomegaly or splenomegaly by physical examination;
• Absence of disease or constitutional symptoms (unexplained fevers > 38°C, drenching night sweats, > 10% weight loss in last 6 months);
• Blood counts above the following: Neutrophils > 1500/µL, platelets > 100,000/µL, and hemoglobin > 110 g/L;
• Bone marrow at least normocellular for age, < 30% lymphocytes;
CRi was defined as for CR but with persistent cytopenia apparently unrelated to CLL but related to drug toxicity.

End point type	Secondary

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	67[15]			
Units: percentage of participants				
number (confidence interval 95%)	26.9 (16.8 to 39.1)			

Notes:

[15] - All treated participants who were previously treated with BCRi

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) - Final Analysis

End point title	Overall Response Rate (ORR) - Final Analysis

End point description:

Overall response rate was defined as the percentage of participants with an overall best response of CR, CRi, nodular partial remission (nPR), or confirmed partial remission (PR) based on the 2008 modified IWCLL NCI-WG criteria assessed by the investigator.
CR and CRi are defined above. nPR is defined as for CR but bone marrow nodules could be identified histologically.
For PR at least 2 of the following must be met:
• 50% decrease in peripheral blood lymphocyte count from the Baseline value;
• 50% reduction in lymphadenopathy;
• 50% reduction in the size of the liver and/or spleen (if abnormal prior to therapy);
In addition at least 1 of the following criteria must be met:
• Neutrophils > 1,500/µL or ≥ 50% improvement over Baseline;
• Platelets > 100,000/µL or ≥ 50% improvement over Baseline;
• Hemoglobin > 11.0 g/dL or ≥ 50% improvement over Baseline without transfusions or exogenous growth factors.
PR must have been confirmed at least 7 weeks later.

End point type	Secondary

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	258[16]			
Units: percentage of participants				
number (confidence interval 95%)	79.8 (74.4 to 84.6)			

Notes:

[16] - All treated participants

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Overall Response (DOR) - Final Analysis

End point title	Duration of Overall Response (DOR) - Final Analysis

End point description:

Duration of response was defined as the time from the date of first response (CR, CRi, nPR, or PR) to the earliest date that progressive disease (PD) was objectively documented (radiographic or clinical) or death. Duration of response was analyzed by Kaplan-Meier (K-M) methodology. If a participant was still responding the data were censored at the date of the last available disease assessment prior to the data cutoff date.

End point type	Secondary

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	205[17]			
Units: months				
median (confidence interval 95%)	25.1 (19.4 to 28.6)			

Notes:

[17] - Participants who had an overall response of CR, CRi, nPR, or confirmed PR.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP) - Final Analysis

End point title	Time to Progression (TTP) - Final Analysis

End point description:

Time to progression was defined as the time from the date of first dose of venetoclax to the date of earliest PD (radiographic or clinical). Participants who did not experience disease progression were censored at the date of the last available disease assessment prior to the data cutoff date; participants with no post-baseline disease assessments were censored at the first dose date plus 1 day. Time to progression was estimated using Kaplan-Meier methodology.

End point type	Secondary

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	258[18]			
Units: months				
median (confidence interval 95%)	28.3 (23.4 to 32.6)			

Notes:

[18] - All treated participants

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) - Final Analysis

End point title	Progression-Free Survival (PFS) - Final Analysis

End point description:

Progression-free survival (PFS) was defined as the time from the date of first dose of venetoclax to the date of earliest PD (radiographic or clinical) or death. Participants who did not experience disease progression or death were censored at the date of the last available disease assessment prior to the data cutoff date; participants with no post-baseline tumor assessment or clinical assessment for progression were censored at the date of first dose plus 1 day. Progression-free survival was analyzed by Kaplan-Meier methodology.

End point type	Secondary

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	258[19]			
Units: months				
median (confidence interval 95%)	28.3 (22.2 to 30.5)			

Notes:

[19] - All treated participants

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Final Analysis

End point title	Overall Survival (OS) - Final Analysis

End point description:

Overall survival (time to death) was defined as the time from the first dose date of venetoclax to the date of death. If a participant had not died the data were censored at the date when they were last known to be alive prior to the cutoff date. Overall survival was analyzed using Kaplan-Meier methodology. "99999" indicates data that could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	258[20]			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Notes:

[20] - All treated participants

Statistical analyses

No statistical analyses for this end point

Post-hoc: Minimal Residual Disease (MRD) Negativity Rate - Primary Analysis

End point title	Minimal Residual Disease (MRD) Negativity Rate - Primary Analysis

End point description:

The MRD negativity rate is defined as the percentage of participants who had MRD negative status with less than one CLL cell per 10,000 leukocytes ($< 10^4$) in peripheral blood and bone marrow. MRD was

evaluated using next-generation sequencing. Per protocol, peripheral blood MRD assessments were to be collected from all participants at Week 24 and Week 48 and at the time the bone marrow assessment for confirmation of CR/CRi, and bone marrow (BM) MRD assessments were to be collected for participants undergoing a bone marrow procedure for confirmation of CR/CRi. Participants with no blood or BM MRD assessments were included in the calculation of MRD negativity rate as not having MRD negative status.

End point type	Post-hoc

End point timeframe:

From first dose of study drug until the last participant completed Week 48 assessments (data cut-off date 30 June 2019); overall median time on follow-up was 23.2 months.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	258[21]			
Units: percentage of participants				
number (confidence interval 95%)				
Peripheral blood	39.9 (33.9 to 46.2)			
Bone marrow	9.7 (6.4 to 14.0)			

Notes:

[21] - All treated participants

Statistical analyses

No statistical analyses for this end point

Post-hoc: Minimal Residual Disease (MRD) Negativity Rate - Final Analysis

End point title	Minimal Residual Disease (MRD) Negativity Rate - Final Analysis

End point description:

The MRD negativity rate is defined as the percentage of participants who had MRD negative status with less than one CLL cell per 10,000 leukocytes ($< 10^4$) in peripheral blood and bone marrow. MRD was evaluated using next-generation sequencing. Per protocol, peripheral blood MRD assessments were to be collected from all participants at Week 24 and Week 48 and at the time the bone marrow assessment for confirmation of CR/CRi, and bone marrow MRD assessments were to be collected for participants undergoing a bone marrow procedure for confirmation of CR/CRi. Participants with no blood or BM MRD assessments were included in the calculation of MRD negativity rate as not having MRD negative status.

End point type	Post-hoc

End point timeframe:

From first dose of study drug until the end of study; overall median time on follow-up was 49.5 months.

End point values	Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	258[22]			
Units: percentage of participants				
number (confidence interval 95%)				
Peripheral blood	40.3 (34.3 to 46.6)			

Bone marrow	10.5 (7.0 to 14.9)			

Notes:

[22] - All treated participants

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality is reported up to the end of the study; median time on study was 210 weeks. Adverse events are reported from the first dose of venetoclax up to 30 days after last dose; median (min, max) duration of treatment was 108 (0.1, 255) weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Venetoclax

Reporting group description:

Participants received venetoclax on a once daily dosing schedule for up to 108 weeks. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg. Participants who continued to derive benefit after 2 years of treatment may have continued venetoclax therapy for up to 3 additional years.

Serious adverse events	Venetoclax		
Total subjects affected by serious adverse events			
subjects affected / exposed	136 / 258 (52.71%)		
number of deaths (all causes)	70		
number of deaths resulting from adverse events	13		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CENTRAL NERVOUS SYSTEM LYMPHOMA			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BREAST CANCER			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BLADDER CANCER			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ADRENAL ADENOMA			

subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ADENOMA BENIGN				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
INFECTED NEOPLASM				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
DIFFUSE LARGE B-CELL LYMPHOMA				
subjects affected / exposed	2 / 258 (0.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
CHRONIC LYMPHOCYTIC LEUKAEMIA TRANSFORMATION				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
LUNG ADENOCARCINOMA				
subjects affected / exposed	2 / 258 (0.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
MYELODYSPLASTIC SYNDROME				
subjects affected / exposed	4 / 258 (1.55%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
PROSTATE CANCER				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SQUAMOUS CELL CARCINOMA				

subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SKIN NEOPLASM BLEEDING				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
RECTAL ADENOCARCINOMA				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SQUAMOUS CELL CARCINOMA OF SKIN				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
DEEP VEIN THROMBOSIS				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
AORTIC INTRAMURAL HAEMATOMA				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ANEURYSM				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HYPERTENSIVE CRISIS				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				

CHEST PAIN				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FATIGUE				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PYREXIA				
subjects affected / exposed	11 / 258 (4.26%)			
occurrences causally related to treatment / all	6 / 12			
deaths causally related to treatment / all	0 / 0			
MULTIPLE ORGAN DYSFUNCTION SYNDROME				
subjects affected / exposed	2 / 258 (0.78%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
MUCOSAL HAEMORRHAGE				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MALAISE				
subjects affected / exposed	2 / 258 (0.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
GENERAL PHYSICAL HEALTH DETERIORATION				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
DRUG HYPERSENSITIVITY				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

HYPERSENSITIVITY			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	3 / 258 (1.16%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
PROSTATIC PAIN			
subjects affected / exposed	1 / 258 (0.39%)		
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	2 / 258 (0.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
ASTHMA			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ATELECTASIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BRONCHIECTASIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			

subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
DYSPNOEA				
subjects affected / exposed	5 / 258 (1.94%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
COUGH				
subjects affected / exposed	3 / 258 (1.16%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
DYSPNOEA EXERTIONAL				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PHARYNGEAL DISORDER				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
OROPHARYNGEAL PAIN				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
LUNG DISORDER				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HAEMOPTYSIS				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
EPISTAXIS				

subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PHARYNGEAL SWELLING				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PLEURAL EFFUSION				
subjects affected / exposed	3 / 258 (1.16%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
PNEUMONITIS				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PULMONARY EMBOLISM				
subjects affected / exposed	2 / 258 (0.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
PULMONARY HYPERTENSION				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
CONFUSIONAL STATE				
subjects affected / exposed	2 / 258 (0.78%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
DEPRESSION				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MENTAL STATUS CHANGES				

subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
READING DISORDER				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
ASPARTATE AMINOTRANSFERASE INCREASED				
subjects affected / exposed	3 / 258 (1.16%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
BLOOD BILIRUBIN INCREASED				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
WEIGHT DECREASED				
subjects affected / exposed	2 / 258 (0.78%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
BLOOD POTASSIUM INCREASED				
subjects affected / exposed	3 / 258 (1.16%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
GENERAL PHYSICAL CONDITION ABNORMAL				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PLATELET COUNT DECREASED				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
BLOOD LACTATE DEHYDROGENASE				

INCREASED				
subjects affected / exposed	4 / 258 (1.55%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
BLOOD CREATININE INCREASED				
subjects affected / exposed	2 / 258 (0.78%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
BLOOD PHOSPHORUS INCREASED				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
CLAVICLE FRACTURE				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CONTUSION				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FALL				
subjects affected / exposed	2 / 258 (0.78%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
FEMORAL NECK FRACTURE				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FRACTURE				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

HIP FRACTURE				
subjects affected / exposed	2 / 258 (0.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
HEAD INJURY				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HUMERUS FRACTURE				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
INFUSION RELATED REACTION				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PELVIC FRACTURE				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
HYDROCELE				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
AORTIC VALVE STENOSIS				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ATRIAL FIBRILLATION				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

ATRIOVENTRICULAR BLOCK			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BRADYCARDIA			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BIFASCICULAR BLOCK			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CARDIAC ARREST			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CARDIAC FAILURE			
subjects affected / exposed	2 / 258 (0.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	2 / 258 (0.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
CORONARY ARTERY DISEASE			
subjects affected / exposed	2 / 258 (0.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			

ATAXIA			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DIZZINESS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DYSARTHRIA			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SCIATICA			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
METABOLIC ENCEPHALOPATHY			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ISCHAEMIC STROKE			
subjects affected / exposed	2 / 258 (0.78%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
FACIAL PARALYSIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SEIZURE			

subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SUBARACHNOID HAEMORRHAGE				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SOMNOLENCE				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SYNCOPE				
subjects affected / exposed	2 / 258 (0.78%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
ANAEMIA				
subjects affected / exposed	5 / 258 (1.94%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
AUTOIMMUNE HAEMOLYTIC ANAEMIA				
subjects affected / exposed	3 / 258 (1.16%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	1 / 1			
APLASIA PURE RED CELL				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
FEBRILE NEUTROPENIA				
subjects affected / exposed	15 / 258 (5.81%)			
occurrences causally related to treatment / all	13 / 18			
deaths causally related to treatment / all	0 / 0			
GRANULOMATOUS LYMPHADENITIS				

subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
LEUKOCYTOSIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
INTRAVASCULAR HAEMOLYSIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
HAEMOLYSIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
NEUTROPENIA			
subjects affected / exposed	4 / 258 (1.55%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
THROMBOCYTOPENIA			
subjects affected / exposed	3 / 258 (1.16%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
PANCYTOPENIA			
subjects affected / exposed	2 / 258 (0.78%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
DEAFNESS NEUROSENSORY			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

DIARRHOEA				
subjects affected / exposed	5 / 258 (1.94%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
ASCITES				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ABDOMINAL PAIN				
subjects affected / exposed	3 / 258 (1.16%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
DIVERTICULUM INTESTINAL HAEMORRHAGIC				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
INGUINAL HERNIA				
subjects affected / exposed	2 / 258 (0.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
INTESTINAL OBSTRUCTION				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
RECTAL PERFORATION				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
VOMITING				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				

BILE DUCT STONE			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BILIARY COLIC			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CHOLELITHIASIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CHOLANGITIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
GALLBLADDER NECROSIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
HEPATIC CIRRHOSIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
PARANEOPLASTIC PEMPHIGUS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
SKIN ULCER			
subjects affected / exposed	2 / 258 (0.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
RASH			

subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
BLADDER MASS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
ARTHRITIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
BACK PAIN			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
OSTEOPOROSIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
OSTEOARTHRITIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
HAEMATOMA MUSCLE			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BONE PAIN			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

PAIN IN EXTREMITY			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SPINAL PAIN			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
ABSCESS LIMB			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
ARTHRITIS BACTERIAL			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BRONCHITIS			
subjects affected / exposed	2 / 258 (0.78%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
BRONCHIOLITIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
CELLULITIS			
subjects affected / exposed	2 / 258 (0.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
ESCHERICHIA INFECTION			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
EPIDIDYMITIS			

subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ENDOPHTHALMITIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DIVERTICULITIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	2 / 258 (0.78%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
INFLUENZA			
subjects affected / exposed	3 / 258 (1.16%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
HERPES ZOSTER			
subjects affected / exposed	2 / 258 (0.78%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
GASTROENTERITIS			
subjects affected / exposed	2 / 258 (0.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
LOCALISED INFECTION			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
LOWER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	4 / 258 (1.55%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
NEUTROPENIC SEPSIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 258 (0.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
RESPIRATORY SYNCYTIAL VIRUS INFECTION			
subjects affected / exposed	2 / 258 (0.78%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
PYELONEPHRITIS			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA BACTERIAL			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			
subjects affected / exposed	21 / 258 (8.14%)		
occurrences causally related to treatment / all	7 / 30		
deaths causally related to treatment / all	0 / 0		
OSTEOMYELITIS			

subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
UROSEPSIS				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
UPPER RESPIRATORY TRACT INFECTION				
subjects affected / exposed	2 / 258 (0.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
TONSILLITIS BACTERIAL				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
STAPHYLOCOCCAL INFECTION				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SKIN INFECTION				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SEPTIC SHOCK				
subjects affected / exposed	2 / 258 (0.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
SEPSIS				
subjects affected / exposed	1 / 258 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
DIABETES MELLITUS				

subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CACHEXIA			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
FLUID RETENTION			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HYPOGLYCAEMIA			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HYPERPHOSPHATAEMIA			
subjects affected / exposed	3 / 258 (1.16%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
HYPERKALAEMIA			
subjects affected / exposed	4 / 258 (1.55%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 258 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
TUMOUR LYSIS SYNDROME			
subjects affected / exposed	2 / 258 (0.78%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Venetoclax		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	246 / 258 (95.35%)		
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	29 / 258 (11.24%)		
occurrences (all)	34		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	32 / 258 (12.40%)		
occurrences (all)	41		
PYREXIA			
subjects affected / exposed	43 / 258 (16.67%)		
occurrences (all)	56		
OEDEMA PERIPHERAL			
subjects affected / exposed	13 / 258 (5.04%)		
occurrences (all)	17		
FATIGUE			
subjects affected / exposed	45 / 258 (17.44%)		
occurrences (all)	56		
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	23 / 258 (8.91%)		
occurrences (all)	26		
OROPHARYNGEAL PAIN			
subjects affected / exposed	14 / 258 (5.43%)		
occurrences (all)	15		
COUGH			
subjects affected / exposed	52 / 258 (20.16%)		
occurrences (all)	63		
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	25 / 258 (9.69%)		
occurrences (all)	27		

Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	13 / 258 (5.04%)		
occurrences (all)	15		
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	28 / 258 (10.85%)		
occurrences (all)	47		
WEIGHT DECREASED			
subjects affected / exposed	22 / 258 (8.53%)		
occurrences (all)	25		
PLATELET COUNT DECREASED			
subjects affected / exposed	21 / 258 (8.14%)		
occurrences (all)	27		
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	13 / 258 (5.04%)		
occurrences (all)	13		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	27 / 258 (10.47%)		
occurrences (all)	29		
DIZZINESS			
subjects affected / exposed	20 / 258 (7.75%)		
occurrences (all)	26		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	57 / 258 (22.09%)		
occurrences (all)	84		
NEUTROPENIA			
subjects affected / exposed	108 / 258 (41.86%)		
occurrences (all)	251		
THROMBOCYTOPENIA			
subjects affected / exposed	53 / 258 (20.54%)		
occurrences (all)	88		
Gastrointestinal disorders			

ABDOMINAL PAIN subjects affected / exposed occurrences (all)	21 / 258 (8.14%) 23		
ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all)	13 / 258 (5.04%) 17		
CONSTIPATION subjects affected / exposed occurrences (all)	34 / 258 (13.18%) 42		
DIARRHOEA subjects affected / exposed occurrences (all)	95 / 258 (36.82%) 170		
VOMITING subjects affected / exposed occurrences (all)	20 / 258 (7.75%) 24		
NAUSEA subjects affected / exposed occurrences (all)	69 / 258 (26.74%) 98		
DYSPEPSIA subjects affected / exposed occurrences (all)	13 / 258 (5.04%) 13		
Skin and subcutaneous tissue disorders DRY SKIN subjects affected / exposed occurrences (all)	17 / 258 (6.59%) 22		
PRURITUS subjects affected / exposed occurrences (all)	25 / 258 (9.69%) 29		
RASH subjects affected / exposed occurrences (all)	20 / 258 (7.75%) 33		
Musculoskeletal and connective tissue disorders PAIN IN EXTREMITY subjects affected / exposed occurrences (all)	14 / 258 (5.43%) 17		
MUSCLE SPASMS			

subjects affected / exposed	17 / 258 (6.59%)		
occurrences (all)	20		
BACK PAIN			
subjects affected / exposed	34 / 258 (13.18%)		
occurrences (all)	36		
ARTHRALGIA			
subjects affected / exposed	37 / 258 (14.34%)		
occurrences (all)	48		
Infections and infestations			
INFLUENZA			
subjects affected / exposed	14 / 258 (5.43%)		
occurrences (all)	14		
HERPES ZOSTER			
subjects affected / exposed	14 / 258 (5.43%)		
occurrences (all)	17		
URINARY TRACT INFECTION			
subjects affected / exposed	25 / 258 (9.69%)		
occurrences (all)	39		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	47 / 258 (18.22%)		
occurrences (all)	68		
PNEUMONIA			
subjects affected / exposed	16 / 258 (6.20%)		
occurrences (all)	19		
NASOPHARYNGITIS			
subjects affected / exposed	39 / 258 (15.12%)		
occurrences (all)	62		
Metabolism and nutrition disorders			
HYPERURICAEMIA			
subjects affected / exposed	17 / 258 (6.59%)		
occurrences (all)	17		
HYPERPHOSPHATAEMIA			
subjects affected / exposed	20 / 258 (7.75%)		
occurrences (all)	23		
HYPERKALAEMIA			

subjects affected / exposed	21 / 258 (8.14%)		
occurrences (all)	31		
DECREASED APPETITE			
subjects affected / exposed	24 / 258 (9.30%)		
occurrences (all)	29		
HYPOCALCAEMIA			
subjects affected / exposed	15 / 258 (5.81%)		
occurrences (all)	19		
HYPOKALAEMIA			
subjects affected / exposed	15 / 258 (5.81%)		
occurrences (all)	20		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2016	Updates included: ● Revised Inclusion Criteria to remove the double-barrier method as an acceptable form of contraception. ● Updated Safety Variables to include details about the safety monitoring to be performed throughout the study. ● Revised Suitability of Subject Population to remove the sentence related to treatment naïve subjects being included in this study population.
22 May 2017	Updates included: ● Revised the protocol title. Added the study name 'Venice I.' Added that the protocol will be conducted in compliance with the Declaration of Helsinki. ● Simplified language around the patient population included in the study. ● Updated the primary endpoint to exclude subjects previously treated with BCRi therapy in order to analyze BCRi treated subjects separately in the secondary endpoints. ● Added 6 sites to the study. ● Clarified that relapsed/refractory subjects with or without the 17p deletion or TP53 mutation status, including subjects with an unknown status, can be enrolled, as well as subjects who have been previously treated with BCRi therapy. ● Added INR as a reportable lab result for coagulation parameters. ● Updated contraception requirements. ● Updated Prior and Concomitant Therapy section. ● Updated Tumor Lysis Syndrome (TLS) prophylaxis and management, including pre-and post-dose laboratory requirements. ● Included a 30-day safety follow up visit after last dose of venetoclax. ● Implemented a Data Monitoring Committee. ● Clarified that any subject who has not experienced progressive disease at the time of study drug discontinuation will be followed up with phone calls until death, discontinuation from the study or upon study completion. ● Clarified that MRI should only be used in case a CT scan with contrast is medically contraindicated. ● Updated use of diaries from Week 20 to Week 24. ● Corrected details of 2008 Modified IWCLL NCI-WG Criteria for Tumor Response. ● Updated the relationship to study drug definitions used to assess adverse events. ● Updated Dose Modifications Based on Toxicities section. ● Specified that immunizations with live virus vaccines should not be administered prior to, during, or after treatment with venetoclax until B-cell recovery occurs. ● Updated NCI CTCAE version. ● Updates and corrections made to align with standard AbbVie template and Investigator’s brochure.

23 July 2018	Updates included: ● Updated the Venetoclax Clinical Data section to align with the most recent Investigator's Brochure. ● Changed MRD level and the rate of MRD negativity from secondary endpoints to exploratory endpoints; clarified that MRD will be assessed in the peripheral blood and bone marrow (BM) by flow cytometry and PCR. ● Updated the number of sites to the study. ● Add a ± 2 day visit window as of Week 8. ● Clarified that BM examinations at screening are not required. BM samples will be collected for subjects with CR to confirm response. Subjects with PR at Week 48 may have a BM examination between Weeks 48-108 to confirm CR based on laboratory tests and physical exam. ● Removed requirement to evaluate lymph nodes except for screening and Weeks 24, 36 and 48. ● Clarified that subjects with ongoing AEs or unresolved clinically significant laboratory results 30 days after last dose of study drug will be followed-up until the AE has resolved to ≤ Grade 1 or baseline or the investigator judges that the event is unlikely to resolve. ● Added Extended Access Phase section to explain that in countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years. ● Clarified that subjects have the right to withdraw from the study and/or study treatment at any time. ● Updated pregnancy verbiage in line with AbbVie's latest standard language. ● Clarified that subjects will be followed for survival every 6 months even if they had an event of progression, required alternate therapy, etc. ● Added reference to DMC separate charter and details of DMC review. ● Added that Adverse Event/Concomitant medication assessment is to be done also at the following visits: within 72 hours of Week (W)2 Day (D)1, W3 D1, W4 D1 and W5 D1. ● Separated the study activities list for Extended Access Visits from the main study activities list.
12 October 2020	Updates included: Updated to indicate that if a subject in the extended access phase of this study continues to derive benefit from Venetoclax after the 2-year extension, then per PI's assessment, subjects who are transferring to the venetoclax extension study, Study M19-388, may remain in Extended Access for up to additional 1 year or until the extension study is approved and initiated at the site, whichever is sooner.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported