Clinical trial results:
A Phase 1/2 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects with Relapsed or Refractory Multiple Myeloma

Summary

EudraCT number	2012-000589-38
Trial protocol	BE
Global end of trial date	08 November 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	M13-367

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01794520
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	08 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The phase 1 primary objectives of this study were to assess the safety profile, characterize pharmacokinetics (PK) and determine the dosing schedule, maximum tolerated dose (MTD), and recommended phase 2 dose (RPTD) of ABT-199 (venetoclax) when administered in participants with relapsed or refractory multiple myeloma. This study also assessed the safety profile and PK of venetoclax in combination with dexamethasone in participants with t(11;14)-positive multiple myeloma.

The phase 2 primary objective was to further evaluate the objective response rate (ORR) and very good partial response or better rate (VGPR+) in participants with t(11;14)-positive multiple myeloma.

Protection of trial subjects:

The Investigator or his/her representative explained the nature of the study to the subject and answered all questions regarding this study. Prior to any study-related screening procedure being performed on the subject the informed consent statement was reviewed, signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	United States: 90
Worldwide total number of subjects	117
EEA total number of subjects	27

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)	60
From 65 to 84 years	57
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects underwent screening procedures within approximately 21 days prior to initial study drug administration, with the exception of the skeletal survey which was to be completed within approximately 30 days prior to planned study drug administration.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1: Venetoclax Dose Escalation/Safety Expansion Cohorts

Arm description:

Participants in the dose-escalation cohort received daily venetoclax at a designated dose (i.e., 300, 600, 900, or 1200 mg) on Days 1 -21 of each cycle after a 2-week lead-in period, in which venetoclax doses were increased weekly. Those with progressive disease (PD) may also have received oral dexamethasone starting at 40 mg (20 mg for those aged ≥75 years) on Days 1, 8, and 15 of each 21-day cycle. Those who completed at least 2 cycles at their designated cohort dose (or current dose) may have progressively escalated their dose to the highest cleared venetoclax dose level or any dose below. Participants in the safety expansion cohort received daily venetoclax at the maximum administered dose (i.e., 1200 mg) on Days 1 - 21 of each cycle after a 2-week lead-in period, in which venetoclax doses were increased weekly. Those with PD may also have received oral dexamethasone starting at 40 mg (20 mg for those aged ≥ 75 years) on Days 1, 8, and 15 of each 21-day cycle.

Arm type	Experimental
Investigational medicinal product name	Venetoclax
Investigational medicinal product code	
Other name	ABT-199, VENCLEXTA®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Each dose of venetoclax was to be taken with approximately 240 mL of water. On days that pre-dose pharmacokinetic (PK) sampling was required, dosing was to occur in the morning at the clinic at approximately 0900 (± 1 hour) to facilitate PK sampling. Dose Escalation cohort participants were to take venetoclax within 30 minutes after the completion of a standard low-fat breakfast with approximately 240 mL of water on Cycle 2 Day 1. On all other dosing days, participants were instructed to take venetoclax orally QD within 30 minutes after the completion of a low-fat breakfast. Tablets were to be swallowed whole and must not have been broken, chewed, or crushed.

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

Dosage and administration details:

Tablets were administered by mouth per the dexamethasone prescribing information.

Arm title	Phase 1: Venetoclax-Dexamethasone Combination

Arm description:

Participants with t(11;14) translocation multiple myeloma received daily venetoclax at a dose of 800 mg (no lead-in period) on Days 1- 21 of each cycle concomitant with weekly dexamethasone at a dose of 40

mg (20 mg for those aged ≥ 75 years).

Arm type	Experimental
Investigational medicinal product name	Venetoclax
Investigational medicinal product code	
Other name	ABT-199, VENCLEXTA®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Each dose of venetoclax was to be taken with approximately 240 mL of water. On days that pre-dose pharmacokinetic (PK) sampling was required, dosing was to occur in the morning at the clinic at approximately 0900 (± 1 hour) to facilitate PK sampling. Dose Escalation cohort participants were to take venetoclax within 30 minutes after the completion of a standard low-fat breakfast with approximately 240 mL of water on Cycle 2 Day 1. On all other dosing days, participants were instructed to take venetoclax orally QD within 30 minutes after the completion of a low-fat breakfast. Tablets were to be swallowed whole and must not have been broken, chewed, or crushed.

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

Dosage and administration details:

Tablets were administered by mouth per the dexamethasone prescribing information.

Arm title	Phase 2: Venetoclax-Dexamethasone Combination Expansion

Arm description:

The Phase 2 cohort further explored the efficacy of venetoclax in combination with dexamethasone in relapsed or refractory participants with t(11;14) translocation multiple myeloma. Participants received daily venetoclax at a dose of 800 mg (no lead-in period) on Days 1- 21 of each cycle concomitant with weekly dexamethasone at a dose of 40 mg (20 mg for those aged ≥ 75 years).

Arm type	Experimental
Investigational medicinal product name	Venetoclax
Investigational medicinal product code	
Other name	ABT-199, VENCLEXTA®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Each dose of venetoclax was to be taken with approximately 240 mL of water. On days that pre-dose pharmacokinetic (PK) sampling was required, dosing was to occur in the morning at the clinic at approximately 0900 (± 1 hour) to facilitate PK sampling. Dose Escalation cohort participants were to take venetoclax within 30 minutes after the completion of a standard low-fat breakfast with approximately 240 mL of water on Cycle 2 Day 1. On all other dosing days, participants were instructed to take venetoclax orally QD within 30 minutes after the completion of a low-fat breakfast. Tablets were to be swallowed whole and must not have been broken, chewed, or crushed.

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

Dosage and administration details:

Tablets were administered by mouth per the dexamethasone prescribing information.

Number of subjects in period 1	Phase 1: Venetoclax Dose Escalation/Safety Expansion Cohorts	Phase 1: Venetoclax-Dexamethasone Combination	Phase 2: Venetoclax-Dexamethasone Combination Expansion
Started	66	20	31
Completed	0	0	0
Not completed	66	20	31
Adverse event- related to progression	3	1	-
Adverse event- not related to progression	4	-	-
Toxicity	2	-	-
Death	1	-	22
Other, not specified	6	1	2
Study terminated by sponsor	2	-	7
Progressive disease	45	18	-
Withdrew consent	2	-	-
Lost to follow-up	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Phase 1: Venetoclax Dose Escalation/Safety Expansion Cohorts

Reporting group description:

Participants in the dose-escalation cohort received daily venetoclax at a designated dose (i.e., 300, 600, 900, or 1200 mg) on Days 1 -21 of each cycle after a 2-week lead-in period, in which venetoclax doses were increased weekly. Those with progressive disease (PD) may also have received oral dexamethasone starting at 40 mg (20 mg for those aged ≥75 years) on Days 1, 8, and 15 of each 21-day cycle. Those who completed at least 2 cycles at their designated cohort dose (or current dose) may have progressively escalated their dose to the highest cleared venetoclax dose level or any dose below. Participants in the safety expansion cohort received daily venetoclax at the maximum administered dose (i.e., 1200 mg) on Days 1 - 21 of each cycle after a 2-week lead-in period, in which venetoclax doses were increased weekly. Those with PD may also have received oral dexamethasone starting at 40 mg (20 mg for those aged ≥ 75 years) on Days 1, 8, and 15 of each 21-day cycle.

Reporting group title	Phase 1: Venetoclax-Dexamethasone Combination

Reporting group description:

Participants with t(11;14) translocation multiple myeloma received daily venetoclax at a dose of 800 mg (no lead-in period) on Days 1- 21 of each cycle concomitant with weekly dexamethasone at a dose of 40 mg (20 mg for those aged ≥ 75 years).

Reporting group title	Phase 2: Venetoclax-Dexamethasone Combination Expansion

Reporting group description:

The Phase 2 cohort further explored the efficacy of venetoclax in combination with dexamethasone in relapsed or refractory participants with t(11;14) translocation multiple myeloma. Participants received daily venetoclax at a dose of 800 mg (no lead-in period) on Days 1- 21 of each cycle concomitant with weekly dexamethasone at a dose of 40 mg (20 mg for those aged ≥ 75 years).

Reporting group values	Phase 1: Venetoclax Dose Escalation/Safety Expansion Cohorts	Phase 1: Venetoclax-Dexamethasone Combination	Phase 2: Venetoclax-Dexamethasone Combination Expansion
Number of subjects	66	20	31
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62.2	63.4	64.9
standard deviation	± 9.95	± 8.13	± 8.31
Gender categorical Units: Subjects			
Female	36	3	13
Male	30	17	18
Race/Ethnicity Units: Subjects			
White	59	17	24
Black	4	2	5
Asian	0	0	1
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Multi Race	0	0	0
Other	0	0	0

Missing	3	1	1

Reporting group values	Total		
Number of subjects	117		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	52		
Male	65		
Race/Ethnicity Units: Subjects			
White	100		
Black	11		
Asian	1		
American Indian or Alaska Native	0		
Native Hawaiian or other Pacific Islander	0		
Multi Race	0		
Other	0		
Missing	5		

End points

End points reporting groups

Reporting group title	Phase 1: Venetoclax Dose Escalation/Safety Expansion Cohorts

Reporting group description:

Participants in the dose-escalation cohort received daily venetoclax at a designated dose (i.e., 300, 600, 900, or 1200 mg) on Days 1 -21 of each cycle after a 2-week lead-in period, in which venetoclax doses were increased weekly. Those with progressive disease (PD) may also have received oral dexamethasone starting at 40 mg (20 mg for those aged ≥75 years) on Days 1, 8, and 15 of each 21-day cycle. Those who completed at least 2 cycles at their designated cohort dose (or current dose) may have progressively escalated their dose to the highest cleared venetoclax dose level or any dose below. Participants in the safety expansion cohort received daily venetoclax at the maximum administered dose (i.e., 1200 mg) on Days 1 - 21 of each cycle after a 2-week lead-in period, in which venetoclax doses were increased weekly. Those with PD may also have received oral dexamethasone starting at 40 mg (20 mg for those aged ≥ 75 years) on Days 1, 8, and 15 of each 21-day cycle.

Reporting group title	Phase 1: Venetoclax-Dexamethasone Combination

Reporting group description:

Participants with t(11;14) translocation multiple myeloma received daily venetoclax at a dose of 800 mg (no lead-in period) on Days 1- 21 of each cycle concomitant with weekly dexamethasone at a dose of 40 mg (20 mg for those aged ≥ 75 years).

Reporting group title	Phase 2: Venetoclax-Dexamethasone Combination Expansion

Reporting group description:

The Phase 2 cohort further explored the efficacy of venetoclax in combination with dexamethasone in relapsed or refractory participants with t(11;14) translocation multiple myeloma. Participants received daily venetoclax at a dose of 800 mg (no lead-in period) on Days 1- 21 of each cycle concomitant with weekly dexamethasone at a dose of 40 mg (20 mg for those aged ≥ 75 years).

Subject analysis set title	300 mg Venetoclax
Subject analysis set type	Per protocol

Subject analysis set description:

Participants who received a 300 mg dose of venetoclax administered on the intensive pharmacokinetic sampling day

Subject analysis set title	600 mg Venetoclax
Subject analysis set type	Per protocol

Subject analysis set description:

Participants who received a 600 mg dose of venetoclax administered on the intensive pharmacokinetic sampling day

Subject analysis set title	900 mg Venetoclax
Subject analysis set type	Per protocol

Subject analysis set description:

Participants who received a 900 mg dose of venetoclax administered on the intensive pharmacokinetic sampling day

Subject analysis set title	1200 mg Venetoclax
Subject analysis set type	Per protocol

Subject analysis set description:

Participants who received a 1200 mg dose of venetoclax administered on the intensive pharmacokinetic sampling day

Primary: Number of Participants With Adverse Events

End point title	Number of Participants With Adverse Events[1]

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. The investigator assesses the relationship of each event to the

use of study drug. A serious adverse event (SAE) is an event that results in death, is life-threatening, requires or prolongs hospitalization, results in a congenital anomaly, persistent or significant disability/incapacity or is an important medical event that, based on medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent any of the outcomes listed above. Treatment emergent adverse events/treatment-emergent serious adverse events (TEAEs/TESAEs) are defined as any event that
began or worsened in severity on or after the first dose of study drug.

End point type	Primary

End point timeframe:

From first dose of study drug until 30 days following last dose of study drug (up to 2482 days)

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: Descriptive data are summarized for this end point per protocol.

End point values	Phase 1: Venetoclax Dose Escalation/Safety Expansion Cohorts	Phase 1: Venetoclax-Dexamethasone Combination	Phase 2: Venetoclax-Dexamethasone Combination Expansion	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66[2]	20[3]	31[4]	
Units: participants				
Any TEAE	66	19	30	
TESAE	26	6	16	

Notes:

[2] - Safety population: all participants who received at least one dose of study drug

[3] - Safety population: all participants who received at least one dose of study drug

[4] - Safety population: all participants who received at least one dose of study drug

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Maximum Observed Plasma Concentration (Cmax) of Venetoclax

End point title	Phase 1: Maximum Observed Plasma Concentration (Cmax) of Venetoclax[5]

End point description:

Cmax is the highest concentration that a drug achieves in the blood after administration in a dosing interval.

End point type	Primary

End point timeframe:

Cycle 2, Day 1 at predose, 2, 4, 6, 8, and 24 hours postdose

Notes:

[5] - 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: The statistical analysis results are presented in the endpoint data table, per protocol.

End point values	300 mg Venetoclax	600 mg Venetoclax	900 mg Venetoclax	1200 mg Venetoclax
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[6]	5[7]	4[8]	12[9]
Units: µg/mL				
arithmetic mean (standard deviation)	0.897 (± 0.593)	2.56 (± 1.77)	1.85 (± 1.30)	4.16 (± 1.52)

Notes:

[6] - Phase 1 dose escalation and safety expansion participants with available data

[7] - Phase 1 dose escalation and safety expansion participants with available data

[8] - Phase 1 dose escalation and safety expansion participants with available data

[9] - Phase 1 dose escalation and safety expansion participants with available data

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Time to Maximum Observed Plasma Concentration (Tmax) of Venetoclax

End point title	Phase 1: Time to Maximum Observed Plasma Concentration (Tmax) of Venetoclax[10]

End point description:

Tmax is the the time at which the maximum plasma concentration (Cmax) is observed.

End point type	Primary

End point timeframe:

Cycle 2, Day 1 at predose, 2, 4, 6, 8, and 24 hours postdose

Notes:

[10] - 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: The statistical analysis results are presented in the endpoint data table, per protocol.

End point values	300 mg Venetoclax	600 mg Venetoclax	900 mg Venetoclax	1200 mg Venetoclax
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[11]	5[12]	4[13]	12[14]
Units: hours				
median (full range (min-max))	5.0 (2.0 to 8.0)	8.0 (2.7 to 8.0)	6.0 (4.0 to 8.0)	6.1 (4.0 to 8.0)

Notes:

[11] - Phase 1 dose escalation and safety expansion participants with available data

[12] - Phase 1 dose escalation and safety expansion participants with available data

[13] - Phase 1 dose escalation and safety expansion participants with available data

[14] - Phase 1 dose escalation and safety expansion participants with available data

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Area Under the Plasma Concentration-Time Curve Over Time From 0 to 24 Hours (AUC0-24) of Venetoclax

End point title	Phase 1: Area Under the Plasma Concentration-Time Curve Over Time From 0 to 24 Hours (AUC0-24) of Venetoclax[15]

End point description:

AUC is a measure of how long and how much drug is present in the body after dosing.

End point type	Primary

End point timeframe:

Cycle 2, Day 1 at predose, 2, 4, 6, 8, and 24 hours postdose (dose escalation cohort); (1200 mg dose): Cycle 2, Day 1 at predose (safety expansion cohort, 1200 mg dose)

Notes:

[15] - 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: The statistical analysis results are presented in the endpoint data table, per protocol.

End point values	300 mg Venetoclax	600 mg Venetoclax	900 mg Venetoclax	1200 mg Venetoclax
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[16]	5[17]	3[18]	9[19]
Units: µg•h/mL				
arithmetic mean (standard deviation)	13.0 (± 8.31)	38.2 (± 25.1)	26.3 (± 20.1)	71.5 (± 35.8)

Notes:

[16] - Phase 1 dose escalation and safety expansion participants with available data

[17] - Phase 1 dose escalation and safety expansion participants with available data

[18] - Phase 1 dose escalation and safety expansion participants with available data

[19] - Phase 1 dose escalation and safety expansion participants with available data

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Overall Response Rate

End point title	Phase 2: Overall Response Rate[20][21]

End point description:

Overall response rate is defined as the percentage of participants with documented best overall response of Partial Response (PR) or better (PR, Very good partial response [VGPR], Complete response [CR], or Stringent complete response [sCR]) per 2016 standard International Myeloma Working Group (IMWG) criteria.

End point type	Primary

End point timeframe:

Response was assessed at Cycle 2, Day 1, and on Day 1 of every cycle thereafter; estimated median time on follow-up was 31.7 months

Notes:

[20] - 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: The statistical analysis results are presented in the endpoint data table, per protocol.

[21] - 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: Primary efficacy endpoints were pre-specified for Phase 2 only.

End point values	Phase 2: Venetoclax-Dexamethasone Combination Expansion			
Subject group type	Reporting group			
Number of subjects analysed	31[22]			
Units: percentage of participants				
number (confidence interval 95%)	48.4 (30.2 to 66.9)			

Notes:

[22] - Phase 2 participants who received venetoclax and had active disease at baseline and available data

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Very Good Partial Response Rate or Better

End point title	Phase 2: Very Good Partial Response Rate or Better[23][24]

End point description:

The percentage of participants with documented best overall response of Very Good Partial Response (VGPR) or better (VGPR, Complete response [CR], or Stringent complete response [sCR]) per 2016 standard International Myeloma Working Group (IMWG) criteria was computed.

End point type	Primary

End point timeframe:

Response was assessed at Cycle 2, Day 1, and on Day 1 of every cycle thereafter; estimated median time on follow-up was 31.7 months

Notes:

[23] - 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: The statistical analysis results are presented in the endpoint data table, per protocol.

[24] - 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: Primary efficacy endpoints were pre-specified for Phase 2 only.

End point values	Phase 2: Venetoclax-Dexamethasone Combination Expansion			
Subject group type	Reporting group			
Number of subjects analysed	31[25]			
Units: percentage of participants				
number (confidence interval 95%)	35.5 (19.2 to 54.6)			

Notes:

[25] - Phase 2 participants who received venetoclax and had active disease at baseline and available data

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Overall Response Rate

End point title	Phase 1: Overall Response Rate[26]

End point description:

Overall response rate is defined as the percentage of participants with documented best overall response of Partial Response (PR) or better (PR, Very good partial response [VGPR], Complete response [CR], or Stringent complete response [sCR]) per 2011 International Myeloma Working Group (IMWG) criteria.

End point type	Secondary

End point timeframe:

Response was assessed at Cycle 2, Day 1, and on Day 1 of every cycle thereafter; estimated median time on follow-up was 8.1 months

Notes:

[26] - 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: This efficacy endpoint was pre-specified as secondary for Phase 1

End point values	Phase 1: Venetoclax Dose Escalation/Safety Expansion Cohorts	Phase 1: Venetoclax-Dexamethasone Combination		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[27]	20[28]		
Units: percentage of participants				
arithmetic mean (confidence interval 95%)	22.7 (13.3 to 34.7)	65.0 (40.8 to 84.6)		

Notes:

[27] - All enrolled Phase 1 participants who had active disease at baseline and received venetoclax

[28] - All enrolled Phase 1 participants who had active disease at baseline and received venetoclax

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)

End point description:

TTR is defined as the number of days from the date of first dose of study drug until the date of their first favorable response of Partial Response (PR) or better (PR, Very good partial response [VGPR], Complete response [CR], or Stringent complete response [sCR]) per 2011 International Myeloma Working Group (IMWG) criteria (Phase 1) or 2016 IMWG criteria (Phase 2). If a participant did not experience a favorable response, they were to be censored at the date of last adequate assessment. TTR was analyzed by Kaplan- Meier (K-M)\ methodology. 99999 in the table below denotes a value that is not estimable/calculable due to low number of participants with events.

End point type	Secondary

End point timeframe:

Response was assessed at Cycle 2, Day 1, and on Day 1 of every cycle thereafter; Estimated median time on follow-up was 8.1 months for Phase 1 and 31.7 months for Phase 2

End point values	Phase 1: Venetoclax Dose Escalation/Safety Expansion Cohorts	Phase 1: Venetoclax-Dexamethasone Combination	Phase 2: Venetoclax-Dexamethasone Combination Expansion	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66[29]	20[30]	31[31]	
Units: months				
median (confidence interval 95%)	56.2 (9.0 to 99999)	2.6 (1.4 to 99999)	0.8 (0.7 to 99999)	

Notes:

[29] - Subjects who rcvd venetoclax, had active disease at baseline, and achieved a response (PR or better)
[30] - Subjects who rcvd venetoclax, had active disease at baseline, and achieved a response (PR or better)
[31] - Subjects who rcvd venetoclax, had active disease at baseline, and achieved a response (PR or better)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

TTP is defined as the number of days from the date of first dose of study drug to the date of first documented disease progression or death due to multiple myeloma, whichever occurs first. TTP was analyzed by Kaplan- Meier (K-M) methodology.

End point type	Secondary

End point timeframe:

Estimated median duration of follow-up was 8.1 months for Phase 1 and 31.7 months for Phase 2

End point values	Phase 1: Venetoclax Dose Escalation/Safety Expansion Cohorts	Phase 1: Venetoclax-Dexamethasone Combination	Phase 2: Venetoclax-Dexamethasone Combination Expansion	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66[32]	20[33]	31	
Units: months				
median (confidence interval 95%)	3.7 (1.9 to 5.3)	12.2 (4.2 to 20.9)	11.2 (5.2 to 18.4)	

Notes:

[32] - All enrolled participants who received venetoclax

[33] - All enrolled participants who received venetoclax

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

DOR is defined as the number of days from the date of first response of Partial Response (PR) or better to the date of first documented disease progression or death due to multiple myeloma, whichever occurs first. DOR was analyzed by Kaplan- Meier (K-M) methodology.

End point type	Secondary

End point timeframe:

Assessed at Cycle 2, Day 1, and on Day 1 of every cycle thereafter; estimated median duration of follow-up was 8.1 months for Phase 1 and 31.7 months for Phase 2

End point values	Phase 1: Venetoclax Dose Escalation/Safety Expansion Cohorts	Phase 1: Venetoclax-Dexamethasone Combination	Phase 2: Venetoclax-Dexamethasone Combination Expansion	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15[34]	13[35]	15[36]	
Units: months				
median (confidence interval 95%)	17.3 (7.8 to 32.2)	13.1 (5.7 to 21.9)	17.5 (7.6 to 28.8)	

Notes:

[34] - Subjects who rcvd venetoclax, had active disease at baseline, and achieved a response (PR or better)
[35] - Subjects who rcvd venetoclax, had active disease at baseline, and achieved a response (PR or better)
[36] - Subjects who rcvd venetoclax, had active disease at baseline, and achieved a response (PR or better)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Progression-Free Survival (PFS)

End point title	Phase 2: Progression-Free Survival (PFS)[37]

End point description:

PFS is defined as the number of days from the date of the first dose of study treatment to the date of first documented disease progression or death due to any cause, whichever occurs first. PFS was analyzed by Kaplan-Meier methodology.

End point type	Secondary

End point timeframe:

Estimated median duration of follow-up was 31.7 months

Notes:

[37] - 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: This endpoint was pre-specified for Phase 2 only.

End point values	Phase 2: Venetoclax-Dexamethasone Combination Expansion			
Subject group type	Reporting group			
Number of subjects analysed	31[38]			
Units: months				
median (confidence interval 95%)	11.2 (5.2 to 18.4)			

Notes:

[38] - Phase 2 participants who received venetoclax and had active disease at baseline and available data

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall Survival (OS)

End point title	Phase 2: Overall Survival (OS)[39]

End point description:

OS is defined as the number of days from the date of the first dose of study drug to the date of death due to any cause. If a participant was not known to have died, OS was censored at the last known alive date. The distribution of OS was estimated using Kaplan-Meier methodology.

End point type	Secondary

End point timeframe:

Estimated median duration of follow-up was 31.7 months

Notes:

[39] - 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: This endpoint was pre-specified for Phase 2 only

End point values	Phase 2: Venetoclax-Dexamethasone Combination Expansion			
Subject group type	Reporting group			
Number of subjects analysed	31[40]			
Units: months				
median (confidence interval 95%)	18.4 (8.2 to 24.3)			

Notes:

[40] - Phase 2 participants who received venetoclax and had active disease at baseline and available data

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Mean Change From Baseline in Brief Pain Inventory - Short Form (BPI-SF) Worst Pain

End point title	Phase 2: Mean Change From Baseline in Brief Pain Inventory - Short Form (BPI-SF) Worst Pain[41]

End point description:

The BPI-SF is a pain-specific measure developed to assess patient-reported severity (or intensity) of pain (4 items) and the impact of pain on daily functioning (7 items) in patients with cancer pain. The four pain severity items assess pain at its "worst in last 24 hours," "least in last 24 hours," "average," and "now" (current pain). For these items, participants are asked to rate their pain on an 11-point numeric rating scale with anchors of 0 (no pain) and 10 (pain as bad as you can imagine). The Worst Pain scores range from 0 to 10, with higher scores indicating severe pain. Negative changes from baseline indicate improvement.

In the table below, 99999 indicates standard deviation not calculable/estimable due to n=1 subject at Cycle 25, Day 1.

End point type	Secondary

End point timeframe:

Baseline; Cycle 3, Day 1; Cycle 5, Day 1; Cycle 7, Day 1; Cycle 9, Day 1; Cycle 11, Day 1; Cycle 13, Day 1; Cycle 15, Day 1; Cycle 17, Day 1; Cycle 19, Day 1; Cycle 21, Day 1; Cycle 23, Day 1; Cycle 25, Day 1; Final visit

Notes:

[41] - 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: This endpoint was pre-specified for Phase 2 only.

End point values	Phase 2: Venetoclax-Dexamethasone Combination Expansion			
Subject group type	Reporting group			
Number of subjects analysed	23[42]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 3, Day 1 (n=16)	0.2 (± 2.47)			
Cycle 5, Day 1 (n=10)	-0.9 (± 1.43)			
Cycle 7, Day 1 (n=8)	-0.9 (± 1.20)			
Cycle 9, Day 1 (n=8)	-0.9 (± 1.46)			
Cycle 11, Day 1 (n=7)	-1.1 (± 1.62)			
Cycle 13, Day 1 (n=7)	0.5 (± 3.84)			
Cycle 15, Day 1 (n=7)	-0.6 (± 1.27)			
Cycle 17, Day 1 (n=6)	-1.6 (± 1.29)			
Cycle 19, Day 1 (n=3)	-1.8 (± 2.00)			
Cycle 21, Day 1 (n=2)	-1.6 (± 2.30)			
Cycle 23, Day 1 (n=2)	-1.6 (± 2.30)			
Cycle 25, Day 1 (n=1)	-3.8 (± 99999)			
Final visit (n=16)	-0.3 (± 1.86)			

Notes:

[42] - Subjects who rcvd ≥ 1 dose of study drug; and have baseline and post-baseline values

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Mean Change From Baseline in Physical Functioning Scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

End point title	Phase 2: Mean Change From Baseline in Physical Functioning Scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)[43]

End point description:

The QLQ-C30 is a 30-item subject self-report questionnaire composed of both multi-item and single scales, including five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). For the Physical Functioning scale, participants rate five items on a four-point scale, with 1 as "not at all" and 4 as "very much." The Physical Functioning Scale scores range from 0 to 100 and were calculated per the EORTC QLQ-C30 Scoring Manual (3rd edition), version 3.0. A high scale score represents high/healthy level of functioning. Positive changes from baseline indicate improvement.

In the table below, 99999 indicates standard deviation not calculable/estimable due to n=1 subject at Cycle 25, Day 1.

End point type	Secondary

End point timeframe:

Baseline; Cycle 3, Day 1; Cycle 5, Day 1; Cycle 7, Day 1; Cycle 9, Day 1; Cycle 11, Day 1; Cycle 13, Day 1; Cycle 15, Day 1; Cycle 17, Day 1; Cycle 19, Day 1; Cycle 21, Day 1; Cycle 23, Day 1; Cycle 25, Day 1; Final visit

Notes:

[43] - 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: This endpoint was pre-specified for Phase 2 only.

End point values	Phase 2: Venetoclax-Dexamethasone Combination Expansion			
Subject group type	Reporting group			
Number of subjects analysed	23[44]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 3, Day 1 (n=16)	-3.7 (± 21.90)			
Cycle 5, Day 1 (n=10)	4.0 (± 15.78)			
Cycle 7, Day 1 (n=8)	8.3 (± 11.13)			
Cycle 9, Day 1 (n=8)	8.3 (± 11.13)			
Cycle 11, Day 1 (n=7)	15.2 (± 9.97)			
Cycle 13, Day 1 (n=7)	11.4 (± 14.76)			
Cycle 15, Day 1 (n=7)	14.3 (± 11.17)			
Cycle 17, Day 1 (n=6)	8.9 (± 13.11)			
Cycle 19, Day 1 (n=3)	-0.0 (± 11.55)			
Cycle 21, Day 1 (n=2)	-13.3 (± 28.28)			
Cycle 23, Day 1 (n=2)	-3.3 (± 14.14)			
Cycle 25, Day 1 (n=1)	6.7 (± 99999)			
Final visit (n=16)	-5.0 (± 19.40)			

Notes:

[44] - Subjects who rcvd ≥ 1 dose of study drug; and have baseline and post-baseline values

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Mean Change From Baseline in Global Health Status/Quality of Life Scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

End point title	Phase 2: Mean Change From Baseline in Global Health Status/Quality of Life Scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)[45]

End point description:

The QLQ-C30 is a 30-item subject self-report questionnaire composed of both multi-item and single scales, including five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). For the Global Health Status/Quality of Life scale, participants rate two items on a seven point scale, with 1 as "very poor" and 7 as "excellent." The Global Health Status/Quality of Life scale ranges from 0 to 100 and was calculated per the EORTC QLQ-C30 Scoring Manual (3rd edition), version 3.0. A high score for the global health status/QoL represents a high QoL. Positive changes from baseline indicate improvement.

In the table below, 99999 indicates standard deviation not calculable/estimable due to n=1 subject at

Cycle 25, Day 1.

End point type	Secondary

End point timeframe:

Baseline; Cycle 3, Day 1; Cycle 5, Day 1; Cycle 7, Day 1; Cycle 9, Day 1; Cycle 11, Day 1; Cycle 13, Day 1; Cycle 15, Day 1; Cycle 17, Day 1; Cycle 19, Day 1; Cycle 21, Day 1; Cycle 23, Day 1; Cycle 25, Day 1; Final visit

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 2 only.

End point values	Phase 2: Venetoclax-Dexamethasone Combination Expansion			
Subject group type	Reporting group			
Number of subjects analysed	23[46]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 3, Day 1 (n=16)	-5.2 (± 25.44)			
Cycle 5, Day 1 (n=10)	6.7 (± 5.27)			
Cycle 7, Day 1 (n=8)	3.1 (± 7.63)			
Cycle 9, Day 1 (n=8)	8.3 (± 11.79)			
Cycle 11, Day 1 (n=7)	0.0 (± 11.79)			
Cycle 13, Day 1 (n=7)	-6.0 (± 6.30)			
Cycle 15, Day 1 (n=7)	4.8 (± 8.13)			
Cycle 17, Day 1 (n=6)	-1.4 (± 12.27)			
Cycle 19, Day 1 (n=3)	-19.4 (± 4.81)			
Cycle 21, Day 1 (n=2)	-33.3 (± 23.57)			
Cycle 23, Day 1 (n=2)	-8.3 (± 0.00)			
Cycle 25, Day 1 (n=1)	-8.3 (± 99999)			
Final visit (n=16)	-11.5 (± 23.55)			

Notes:

[46] - Subjects who rcvd ≥ 1 dose of study drug; and have baseline and post-baseline values

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Mean Change From Baseline in Patient Reported Outcomes Measurement Information System [PROMIS] Cancer Fatigue Short Form [SF] Score

End point title	Phase 2: Mean Change From Baseline in Patient Reported Outcomes Measurement Information System [PROMIS] Cancer Fatigue Short Form [SF] Score[47]

End point description:

PROMIS Cancer Fatigue SF is a seven item questionnaire that assesses the impact and experience of fatigue over the past 7 days. All questions employ the following five response options: 1 = Not at all, 2 = A little bit, 3 = Somewhat, 4 = Quite a bit, and 5 = Very much. The [PROMIS] Cancer Fatigue Short Form [SF] 7a T-Scores range from 29.4 to 83.2, with higher scores indicating more fatigue. Negative changes from baseline indicate improvement.

In the table below, 99999 indicates standard deviation not calculable/estimable due to n=1 subject at

Cycle 25, Day 1.

End point type	Secondary

End point timeframe:

Baseline; Cycle 3, Day 1; Cycle 5, Day 1; Cycle 7, Day 1; Cycle 9, Day 1; Cycle 11, Day 1; Cycle 13, Day 1; Cycle 15, Day 1; Cycle 17, Day 1; Cycle 19, Day 1; Cycle 21, Day 1; Cycle 23, Day 1; Cycle 25, Day 1; Final visit

Notes:

[47] - 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: This endpoint was pre-specified for Phase 2 only.

End point values	Phase 2: Venetoclax-Dexamethasone Combination Expansion			
Subject group type	Reporting group			
Number of subjects analysed	23[48]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 3, Day 1 (n=16)	0.6 (± 5.88)			
Cycle 5, Day 1 (n=10)	-2.9 (± 5.30)			
Cycle 7, Day 1 (n=8)	-1.8 (± 4.21)			
Cycle 9, Day 1 (n=8)	-1.6 (± 4.85)			
Cycle 11, Day 1 (n=7)	0.1 (± 7.24)			
Cycle 13, Day 1 (n=7)	1.0 (± 4.54)			
Cycle 15, Day 1 (n=7)	-3.4 (± 5.69)			
Cycle 17, Day 1 (n=6)	0.6 (± 7.36)			
Cycle 19, Day 1 (n=3)	6.6 (± 2.25)			
Cycle 21, Day 1 (n=2)	11.6 (± 6.51)			
Cycle 23, Day 1 (n=2)	6.0 (± 0.57)			
Cycle 25, Day 1 (n=1)	5.6 (± 99999)			
Final visit (n=16)	1.4 (± 6.51)			

Notes:

[48] - Subjects who rcvd ≥ 1 dose of study drug; and have baseline and post-baseline values

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality is reported from enrollment to 30 days after the last dose of study drug; the median time on follow up was 8.1 months for Phase 1 and 31.7 months for Phase 2.

Adverse event reporting additional description:

TEAEs and SAEs were collected from first dose of study drug until 30 days after last dose of study drug; mean duration on study drug was 279.8 days (MonoVen) and 400.0 days (VenDex) in Phase 1 and 240.3 days in Phase 2 (VenDex).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Phase 1: Venetoclax Dose Escalation/Safety Expansion Cohorts

Reporting group description:

Participants in the dose-escalation cohort received daily venetoclax at a designated dose (i.e., 300, 600, 900, or 1200 mg) on Days 1 -21 of each cycle after a 2-week lead-in period, in which venetoclax doses were increased weekly. Those with progressive disease (PD) may also have received oral dexamethasone starting at 40 mg (20 mg for those aged ≥75 years) on Days 1, 8, and 15 of each 21-day cycle. Those who completed at least 2 cycles at their designated cohort dose (or current dose) may have progressively escalated their dose to the highest cleared venetoclax dose level or any dose below. Participants in the safety expansion cohort received daily venetoclax at the maximum administered dose (i.e., 1200 mg) on Days 1 - 21 of each cycle after a 2-week lead-in period, in which venetoclax doses were increased weekly. Those with PD may also have received oral dexamethasone starting at 40 mg (20 mg for those aged ≥ 75 years) on Days 1, 8, and 15 of each 21-day cycle.

Reporting group title	Phase 1: Venetoclax-Dexamethasone Combination

Reporting group description:

Participants with t(11;14) translocation multiple myeloma received daily venetoclax at a dose of 800 mg (no lead-in period) on Days 1- 21 of each cycle concomitant with weekly dexamethasone at a dose of 40 mg (20 mg for those aged ≥ 75 years).

Reporting group title	Phase 2: Venetoclax-Dexamethasone Combination Expansion

Reporting group description:

The Phase 2 cohort further explored the efficacy of venetoclax in combination with dexamethasone in relapsed or refractory participants with t(11;14) translocation multiple myeloma. Participants received daily venetoclax at a dose of 800 mg (no lead-in period) on Days 1- 21 of each cycle concomitant with weekly dexamethasone at a dose of 40 mg (20 mg for those aged ≥ 75 years).

Serious adverse events	Phase 1: Venetoclax Dose Escalation/Safety Expansion Cohorts	Phase 1: Venetoclax-Dexamethasone Combination	Phase 2: Venetoclax-Dexamethasone Combination Expansion
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 66 (39.39%)	6 / 20 (30.00%)	16 / 31 (51.61%)
number of deaths (all causes)	9	1	22
number of deaths resulting from adverse events	9	1	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CHRONIC MYELOMONOCYTIC LEUKAEMIA			

subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
MALIGNANT NEOPLASM PROGRESSION			
subjects affected / exposed	6 / 66 (9.09%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 6	0 / 0	0 / 1
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTENSION			
subjects affected / exposed	2 / 66 (3.03%)	0 / 20 (0.00%)	0 / 31 (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
THROMBOSIS			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
General disorders and administration site conditions			
CHEST DISCOMFORT			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
CHEST PAIN			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

PAIN			
subjects affected / exposed	2 / 66 (3.03%)	0 / 20 (0.00%)	0 / 31 (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
PYREXIA			
subjects affected / exposed	2 / 66 (3.03%)	0 / 20 (0.00%)	0 / 31 (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
Immune system disorders			
ANAPHYLACTIC REACTION			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	2 / 66 (3.03%)	0 / 20 (0.00%)	0 / 31 (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
Psychiatric disorders			
CONFUSIONAL STATE			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
PLATELET COUNT DECREASED			

subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (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
Injury, poisoning and procedural complications			
CLAVICLE FRACTURE			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FALL			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
RIB FRACTURE			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
Nervous system disorders			
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
SCIATICA			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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

SYNCOPE			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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	1 / 66 (1.52%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERVISCOSITY SYNDROME			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
NEUTROPENIA			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
DYSPEPSIA			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

NAUSEA			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (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
OESOPHAGITIS			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
STOMATITIS			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	1 / 66 (1.52%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
URINARY RETENTION			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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 and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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

BACK PAIN			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
LUMBAR SPINAL STENOSIS			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (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
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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			
ABSCESS BACTERIAL			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
ABSCESS INTESTINAL			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CANDIDA INFECTION			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CELLULITIS			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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 / 66 (1.52%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLOSTRIDIUM DIFFICILE INFECTION			

subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULITIS			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROBACTER SEPSIS			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
ENTEROCOCCAL SEPSIS			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
ENTEROVIRUS INFECTION			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA SEPSIS			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
INFLUENZA			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LISTERIA SEPSIS			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOCALISED INFECTION			

subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
PARAINFLUENZAE VIRUS INFECTION			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	7 / 66 (10.61%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	1 / 9	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA INFLUENZAL			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
PNEUMONIA KLEBSIELLA			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA STREPTOCOCCAL			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
RHINOVIRUS INFECTION			

subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	3 / 66 (4.55%)	1 / 20 (5.00%)	3 / 31 (9.68%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STREPTOCOCCAL SEPSIS			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL INFECTION			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
HYPERCALCAEMIA			

subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
HYPOKALAEMIA			
subjects affected / exposed	2 / 66 (3.03%)	0 / 20 (0.00%)	0 / 31 (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
HYPOPHOSPHATAEMIA			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	0 / 31 (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
TUMOUR LYSIS SYNDROME			
subjects affected / exposed	0 / 66 (0.00%)	2 / 20 (10.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Phase 1: Venetoclax Dose Escalation/Safety Expansion Cohorts	Phase 1: Venetoclax-Dexamethasone Combination	Phase 2: Venetoclax-Dexamethasone Combination Expansion
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 66 (96.97%)	19 / 20 (95.00%)	27 / 31 (87.10%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MALIGNANT MELANOMA			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
PANCREATIC NEUROENDOCRINE TUMOUR			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			

EMBOLISM			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
HOT FLUSH			
subjects affected / exposed	2 / 66 (3.03%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	2	1	0
HYPERTENSION			
subjects affected / exposed	4 / 66 (6.06%)	3 / 20 (15.00%)	2 / 31 (6.45%)
occurrences (all)	4	3	2
HYPOTENSION			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences (all)	1	0	5
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	8 / 66 (12.12%)	0 / 20 (0.00%)	0 / 31 (0.00%)
occurrences (all)	8	0	0
CHILLS			
subjects affected / exposed	2 / 66 (3.03%)	2 / 20 (10.00%)	0 / 31 (0.00%)
occurrences (all)	3	2	0
FACE OEDEMA			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
FATIGUE			
subjects affected / exposed	20 / 66 (30.30%)	2 / 20 (10.00%)	9 / 31 (29.03%)
occurrences (all)	22	2	14
GAIT DISTURBANCE			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	2 / 31 (6.45%)
occurrences (all)	0	1	3
MALAISE			
subjects affected / exposed	1 / 66 (1.52%)	2 / 20 (10.00%)	1 / 31 (3.23%)
occurrences (all)	1	2	1
OEDEMA			

subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
OEDEMA PERIPHERAL			
subjects affected / exposed	2 / 66 (3.03%)	4 / 20 (20.00%)	4 / 31 (12.90%)
occurrences (all)	3	5	4
PAIN			
subjects affected / exposed	3 / 66 (4.55%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences (all)	3	1	1
PYREXIA			
subjects affected / exposed	4 / 66 (6.06%)	4 / 20 (20.00%)	0 / 31 (0.00%)
occurrences (all)	4	4	0
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	11 / 66 (16.67%)	5 / 20 (25.00%)	5 / 31 (16.13%)
occurrences (all)	13	6	7
DYSPHONIA			
subjects affected / exposed	2 / 66 (3.03%)	2 / 20 (10.00%)	1 / 31 (3.23%)
occurrences (all)	2	3	1
DYSPNOEA			
subjects affected / exposed	10 / 66 (15.15%)	1 / 20 (5.00%)	5 / 31 (16.13%)
occurrences (all)	15	1	6
EPISTAXIS			
subjects affected / exposed	2 / 66 (3.03%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences (all)	3	0	3
HICCUPS			
subjects affected / exposed	1 / 66 (1.52%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences (all)	1	1	1
NASAL CONGESTION			
subjects affected / exposed	4 / 66 (6.06%)	5 / 20 (25.00%)	2 / 31 (6.45%)
occurrences (all)	5	7	3
OROPHARYNGEAL PAIN			
subjects affected / exposed	4 / 66 (6.06%)	5 / 20 (25.00%)	3 / 31 (9.68%)
occurrences (all)	4	5	3
PRODUCTIVE COUGH			

subjects affected / exposed	3 / 66 (4.55%)	3 / 20 (15.00%)	3 / 31 (9.68%)
occurrences (all)	4	4	3
UPPER-AIRWAY COUGH SYNDROME			
subjects affected / exposed	1 / 66 (1.52%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
AGITATION			
subjects affected / exposed	0 / 66 (0.00%)	2 / 20 (10.00%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
INSOMNIA			
subjects affected / exposed	6 / 66 (9.09%)	8 / 20 (40.00%)	6 / 31 (19.35%)
occurrences (all)	6	10	6
MOOD ALTERED			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Investigations			
ACTIVATED PARTIAL THROMBOPLASTIN TIME ABNORMAL			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED			
subjects affected / exposed	1 / 66 (1.52%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	5 / 66 (7.58%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	7	4	0
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	4 / 66 (6.06%)	3 / 20 (15.00%)	2 / 31 (6.45%)
occurrences (all)	6	4	3
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	5 / 66 (7.58%)	2 / 20 (10.00%)	0 / 31 (0.00%)
occurrences (all)	5	2	0
BLOOD CREATININE INCREASED			

subjects affected / exposed	7 / 66 (10.61%)	4 / 20 (20.00%)	4 / 31 (12.90%)
occurrences (all)	9	4	4
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	3 / 66 (4.55%)	4 / 20 (20.00%)	4 / 31 (12.90%)
occurrences (all)	4	5	6
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	15 / 66 (22.73%)	3 / 20 (15.00%)	3 / 31 (9.68%)
occurrences (all)	23	5	7
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	11 / 66 (16.67%)	4 / 20 (20.00%)	10 / 31 (32.26%)
occurrences (all)	16	7	11
PLATELET COUNT DECREASED			
subjects affected / exposed	15 / 66 (22.73%)	3 / 20 (15.00%)	2 / 31 (6.45%)
occurrences (all)	25	5	2
WEIGHT DECREASED			
subjects affected / exposed	3 / 66 (4.55%)	1 / 20 (5.00%)	2 / 31 (6.45%)
occurrences (all)	3	1	2
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	14 / 66 (21.21%)	5 / 20 (25.00%)	1 / 31 (3.23%)
occurrences (all)	22	7	3
Injury, poisoning and procedural complications			
ANKLE FRACTURE			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
DENTAL RESTORATION FAILURE			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
FALL			
subjects affected / exposed	2 / 66 (3.03%)	1 / 20 (5.00%)	2 / 31 (6.45%)
occurrences (all)	2	1	2
FEMUR FRACTURE			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
HEAD INJURY			

subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
SKIN LACERATION			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
Cardiac disorders			
SINUS TACHYCARDIA			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	8 / 66 (12.12%)	1 / 20 (5.00%)	4 / 31 (12.90%)
occurrences (all)	11	1	4
HEAD DISCOMFORT			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
HEADACHE			
subjects affected / exposed	12 / 66 (18.18%)	3 / 20 (15.00%)	1 / 31 (3.23%)
occurrences (all)	15	5	1
HYPERSOMNIA			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences (all)	0	2	1
PARAESTHESIA			
subjects affected / exposed	0 / 66 (0.00%)	2 / 20 (10.00%)	4 / 31 (12.90%)
occurrences (all)	0	2	5
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	4 / 66 (6.06%)	2 / 20 (10.00%)	1 / 31 (3.23%)
occurrences (all)	4	2	1
PRESYNCOPE			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
SEIZURE			

subjects affected / exposed	1 / 66 (1.52%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
SYNCOPE			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	13 / 66 (19.70%)	2 / 20 (10.00%)	7 / 31 (22.58%)
occurrences (all)	14	2	9
LEUKOCYTOSIS			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
LEUKOPENIA			
subjects affected / exposed	2 / 66 (3.03%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences (all)	2	0	5
LYMPHOPENIA			
subjects affected / exposed	2 / 66 (3.03%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences (all)	2	0	3
NEUTROPENIA			
subjects affected / exposed	6 / 66 (9.09%)	0 / 20 (0.00%)	3 / 31 (9.68%)
occurrences (all)	7	0	7
THROMBOCYTOPENIA			
subjects affected / exposed	9 / 66 (13.64%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences (all)	13	1	4
Ear and labyrinth disorders			
EAR PAIN			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences (all)	1	0	2
VERTIGO			
subjects affected / exposed	1 / 66 (1.52%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	2	1	0
Eye disorders			
EYE DISCHARGE			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
EYE PAIN			

subjects affected / exposed	1 / 66 (1.52%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences (all)	1	1	1
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	1 / 66 (1.52%)	3 / 20 (15.00%)	1 / 31 (3.23%)
occurrences (all)	1	4	1
ABDOMINAL PAIN			
subjects affected / exposed	5 / 66 (7.58%)	3 / 20 (15.00%)	1 / 31 (3.23%)
occurrences (all)	5	3	1
CONSTIPATION			
subjects affected / exposed	8 / 66 (12.12%)	1 / 20 (5.00%)	4 / 31 (12.90%)
occurrences (all)	9	1	4
DENTAL CARIES			
subjects affected / exposed	2 / 66 (3.03%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	2	2	0
DIARRHOEA			
subjects affected / exposed	26 / 66 (39.39%)	7 / 20 (35.00%)	12 / 31 (38.71%)
occurrences (all)	33	8	16
DYSPEPSIA			
subjects affected / exposed	1 / 66 (1.52%)	2 / 20 (10.00%)	2 / 31 (6.45%)
occurrences (all)	1	2	2
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	1 / 66 (1.52%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
NAUSEA			
subjects affected / exposed	33 / 66 (50.00%)	5 / 20 (25.00%)	10 / 31 (32.26%)
occurrences (all)	39	5	13
STOMATITIS			
subjects affected / exposed	1 / 66 (1.52%)	2 / 20 (10.00%)	0 / 31 (0.00%)
occurrences (all)	1	2	0
TRICHOGLOSSIA			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
UMBILICAL HERNIA			

subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
VOMITING			
subjects affected / exposed	13 / 66 (19.70%)	2 / 20 (10.00%)	5 / 31 (16.13%)
occurrences (all)	16	3	7
Skin and subcutaneous tissue disorders			
ACTINIC KERATOSIS			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
HYPERHIDROSIS			
subjects affected / exposed	0 / 66 (0.00%)	2 / 20 (10.00%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
HYPERKERATOSIS			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
PAPULE			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
PRURITUS			
subjects affected / exposed	5 / 66 (7.58%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	5	1	0
PURPURA			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
RASH			
subjects affected / exposed	6 / 66 (9.09%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences (all)	8	1	2
RASH MACULO-PAPULAR			
subjects affected / exposed	0 / 66 (0.00%)	2 / 20 (10.00%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
SKIN ATROPHY			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
SKIN LESION			
subjects affected / exposed	0 / 66 (0.00%)	2 / 20 (10.00%)	1 / 31 (3.23%)
occurrences (all)	0	2	1

Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
POLLAKIURIA			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	3 / 31 (9.68%)
occurrences (all)	0	1	3
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	12 / 66 (18.18%)	5 / 20 (25.00%)	4 / 31 (12.90%)
occurrences (all)	16	7	5
BACK PAIN			
subjects affected / exposed	11 / 66 (16.67%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	11	1	0
BONE PAIN			
subjects affected / exposed	7 / 66 (10.61%)	1 / 20 (5.00%)	2 / 31 (6.45%)
occurrences (all)	7	1	2
EXOSTOSIS			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
FLANK PAIN			
subjects affected / exposed	5 / 66 (7.58%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences (all)	6	1	1
MUSCLE SPASMS			
subjects affected / exposed	3 / 66 (4.55%)	2 / 20 (10.00%)	1 / 31 (3.23%)
occurrences (all)	5	2	1
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 66 (1.52%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences (all)	1	0	3
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	5 / 66 (7.58%)	2 / 20 (10.00%)	3 / 31 (9.68%)
occurrences (all)	6	2	3
MYALGIA			
subjects affected / exposed	3 / 66 (4.55%)	3 / 20 (15.00%)	1 / 31 (3.23%)
occurrences (all)	4	3	1
NECK PAIN			

subjects affected / exposed	2 / 66 (3.03%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	2	1	0
OSTEONECROSIS OF JAW			
subjects affected / exposed	1 / 66 (1.52%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
PAIN IN EXTREMITY			
subjects affected / exposed	3 / 66 (4.55%)	2 / 20 (10.00%)	3 / 31 (9.68%)
occurrences (all)	3	3	4
SPINAL PAIN			
subjects affected / exposed	1 / 66 (1.52%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	4 / 66 (6.06%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences (all)	5	1	1
CELLULITIS			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
CONJUNCTIVITIS			
subjects affected / exposed	2 / 66 (3.03%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences (all)	2	1	1
CYSTITIS			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
FUNGAL SKIN INFECTION			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
LOCALISED INFECTION			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
NASOPHARYNGITIS			
subjects affected / exposed	4 / 66 (6.06%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences (all)	6	2	1

ORAL CANDIDIASIS			
subjects affected / exposed	1 / 66 (1.52%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences (all)	2	1	1
OTITIS MEDIA			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
PARAINFLUENZAE VIRUS INFECTION			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	3
PNEUMONIA			
subjects affected / exposed	1 / 66 (1.52%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences (all)	1	2	1
RHINOVIRUS INFECTION			
subjects affected / exposed	0 / 66 (0.00%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
SINUSITIS			
subjects affected / exposed	1 / 66 (1.52%)	1 / 20 (5.00%)	2 / 31 (6.45%)
occurrences (all)	1	1	2
SKIN INFECTION			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
TOOTH INFECTION			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	11 / 66 (16.67%)	6 / 20 (30.00%)	3 / 31 (9.68%)
occurrences (all)	17	11	4
URINARY TRACT INFECTION			
subjects affected / exposed	6 / 66 (9.09%)	0 / 20 (0.00%)	1 / 31 (3.23%)
occurrences (all)	7	0	1
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	6 / 66 (9.09%)	2 / 20 (10.00%)	3 / 31 (9.68%)
occurrences (all)	10	2	3
DEHYDRATION			

subjects affected / exposed	2 / 66 (3.03%)	1 / 20 (5.00%)	1 / 31 (3.23%)
occurrences (all)	2	1	1
HYPERCALCAEMIA			
subjects affected / exposed	6 / 66 (9.09%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences (all)	6	0	2
HYPERGLYCAEMIA			
subjects affected / exposed	7 / 66 (10.61%)	6 / 20 (30.00%)	6 / 31 (19.35%)
occurrences (all)	7	9	6
HYPERMAGNESAEMIA			
subjects affected / exposed	1 / 66 (1.52%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
HYPERNATRAEMIA			
subjects affected / exposed	1 / 66 (1.52%)	1 / 20 (5.00%)	2 / 31 (6.45%)
occurrences (all)	1	1	2
HYPERPHOSPHATAEMIA			
subjects affected / exposed	2 / 66 (3.03%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences (all)	2	0	2
HYPERURICAEMIA			
subjects affected / exposed	3 / 66 (4.55%)	3 / 20 (15.00%)	3 / 31 (9.68%)
occurrences (all)	3	4	3
HYPOALBUMINAEMIA			
subjects affected / exposed	1 / 66 (1.52%)	2 / 20 (10.00%)	1 / 31 (3.23%)
occurrences (all)	1	2	2
HYPOCALCAEMIA			
subjects affected / exposed	7 / 66 (10.61%)	3 / 20 (15.00%)	4 / 31 (12.90%)
occurrences (all)	7	4	4
HYPOGLYCAEMIA			
subjects affected / exposed	2 / 66 (3.03%)	0 / 20 (0.00%)	2 / 31 (6.45%)
occurrences (all)	2	0	2
HYPOKALAEMIA			
subjects affected / exposed	11 / 66 (16.67%)	4 / 20 (20.00%)	4 / 31 (12.90%)
occurrences (all)	13	6	7
HYPOMAGNESAEMIA			
subjects affected / exposed	6 / 66 (9.09%)	1 / 20 (5.00%)	3 / 31 (9.68%)
occurrences (all)	7	1	5
HYPONATRAEMIA			

subjects affected / exposed	5 / 66 (7.58%)	1 / 20 (5.00%)	3 / 31 (9.68%)
occurrences (all)	5	1	3
HYPOPHOSPHATAEMIA			
subjects affected / exposed	8 / 66 (12.12%)	8 / 20 (40.00%)	3 / 31 (9.68%)
occurrences (all)	13	14	4
MALNUTRITION			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
STEROID DIABETES			
subjects affected / exposed	0 / 66 (0.00%)	1 / 20 (5.00%)	0 / 31 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2012	Protocol Amendment 1 ● Changed Sponsor from Abbott Laboratories to AbbVie ● Increased maximum dose of ABT-199 from 600 mg/day to 1200 mg/day ● Clarified that if at least 1 subject in a dose escalation cohort experiences a DLT, that cohort may enroll up to 6 subjects and cohort size may be expanded beyond 6 at discretion of AbbVie medical monitor ● Extended option for subjects receiving clinical benefit from dosing with ABT-199 for treatment for up to 2 yrs following enrollment of last subject into study ● Exclusion Criterion 5 changed to only reflect exclusion of HIV-positive subjects ● Allowed subjects with serologic evidence of prior vaccination to hepatitis B (HBV) and without evidence of chronic hepatitis B infection to enroll in the study ● Excluded potent CYP3A inducers ● Excluded subjects from receiving live vaccines within 60 days of study entry ● Added lymphocyte enumerations; updated timeframe for completion of all Screening procedures except Skeletal Survey to within 21 days of first dose of ABT-199; clarified expectations for chemistry and hematology sampling for TLS prophylaxis and monitoring; updated assays included as part of Viral Serologies and Viral Polymerase Chain Reaction (PCR) testing; added long bones (i.e., tibiae, fibulae, tibiae, ulnae, radii) to skeletal survey; removed Cytogenetics/FISH sample collection at confirmation of CR/sCR timepoint; added requirement for ABT-199 pharmacokinetic samples to be drawn at time of TLS event and 24 hours TLS event ● Clarified that worsening of an adverse event is to be recorded as a new adverse event ● Added allowance for implementation of a drug interruption for up to 72 hours for transient (< 48 hrs) chemical changes and laboratory TLS ● Changed size of Safety Expansion Cohort to approximately 12 ● Added Cairo-Bishop Tumor Lysis Syndrome Definition and Grading for definition of laboratory and clinical TLS

22 March 2013	Protocol Amendment 2 ● Updated protocol with the most current information released in Investigator's Brochure Edition 4 ● Inclusion Criteria: added requirement for AbbVie medical monitor approval for subjects at high TLS risk ● Exclusion Criteria: clarified time frame for significant medical history; updated time frame for prior use of monoclonal antibodies for anti-neoplastic intent from 30 days to 8 weeks prior to the first dose of study drug ● Clarified TLS management time points; adjusted pharmacokinetic blood collection time points ● Updated vital signs, chemistry and hematology to align with new TLS prophylaxis and management; replaced use of central laboratory with local laboratory for all testing except IMWG, viral PCR and viral serologies; reduced time points for reticulocyte counts ● Removed hepatitis B, C, and D testing from viral PCR assay ● Updated sample collection for ABT-199 Assay to reflect additional 8 hour post-dose timepoints at Lead-in Days 1 and 8, Cycle 1 Day 1 and optional collections for Intrasubject Dose Escalation ● Updated Adverse Events to include reporting laboratory abnormalities that meet one criterion within the Cairo-Bishop criteria for TLS (after a first dose or escalation dose) as an AE (or SAE) and instructions for documenting these laboratory abnormalities on the appropriate ● Updated expectations for subjects regarding contraceptive use and requested data collection for partners of study subjects that become pregnant during the study ● Clarified requirements for dose reductions following TLS; updated Management of Tumor Lysis Syndrome to reflect more stringent procedures for high-risk subjects, and revise procedures for other subjects to further mitigate the risk of TLS ● Added Appendix G, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS) in Multiple Myeloma Subjects ● Revised Appendix F Cairo-Bishop Tumor Lysis Syndrome Definition and Grading
03 March 2014	Protocol Amendment 3 ● Allowed for use of low-dose (20 mg) weekly dexamethasone in the presence of progressive disease while on ABT-199 monotherapy ● Revised number of subjects to be enrolled in the safety expansion cohort to 36, and increased number of sites to approximately 11 ● Inclusion Criteria: allowed for enrollment of subjects with a history of allogenic stem cell transplant; removed explicit percentage of disease infiltrate in the bone marrow; revised platelet count down to 30,000/mm3 for entry ● Exclusion Criterion 3: Added statement that, for subjects who have required an intervention for a condition within the significant history items noted within the previous 6 months, a discussion between the investigator and AbbVie medical monitor must occur. ● Added detailed uric acid analysis procedure for subjects taking rasburicase ● Updated windows for Screening procedures to reflect "approximately" 3 months for skeletal survey and "approximately" 21 days or 3 weeks for all other procedures ● Updated window for completion of testing for IMWG assessments to approximately 1 week prior to the scheduled assessment to facilitate result availability during the subject's scheduled visit ● Added allowance for consideration of direct thrombin inhibitors in lieu of warfarin to allow for use of newer anticoagulation therapies within this subject population ● Revised pharmacodynamic testing: added minimal residual disease (MRD) testing for all subjects at Screening, confirmation of CR or sCR, and relapse time points to determine residual disease present in the bone marrow ● Clarified that AbbVie does not allow intentional/prospective protocol deviations

01 December 2014	Protocol Amendment 4 ● Updated the tumor lysis syndrome (TLS) prophylaxis guidelines in recognition that no clinical or laboratory incidences of TLS had been observed in this study ● Revised number of subjects to be enrolled in the dose escalation phase to account for increased subject enrollment in earlier cohorts ● Clarified that subjects enrolled in the safety expansion cohort will receive the recommended Phase 2 dose and added information to state how the RPTD was determined ● Removed requirement for "< 4 separate lines of therapy" during safety expansion phase enrollment; clarified that subjects may receive blood transfusions to meet hemoglobin eligibility; clarified collection period for subject's medical history, reporting of serious adverse events relative to the time the informed consent is signed; and criteria when a laboratory test value should be considered an adverse event ● Clarified criteria for Grade 3 and Grade 4 adverse events; clarified expected adverse events due to disease; and clarified adverse event collection period ● Updated statistical rationale for number of subjects expected to be enrolled in the safety expansion cohort ● Added the Howard definition of laboratory tumor lysis syndrome to further clarify criteria for defining TLS as provided by the Cairo-Bishop definition
23 April 2016	Protocol Amendment 5 ● Added venetoclax-dexamethasone combination portion to investigate venetoclax with dexamethasone treatment in 18 subjects with t(11;14)-positive multiple myeloma ● Updated dexamethasone dose from 20 mg to 40 mg and classification of dexamethasone as Investigational Product for subjects who enroll in venetoclax-dexamethasone combination portion ● Updated pharmacodynamic and pharmacogenetic terminology with standardized biomarker and exploratory language ● Added minimal residual disease (MRD) collection at Cycle 5, Day 1 and updated sampling collection volume ● Updated drug-drug interaction (DDI) information for venetoclax and provide additional guidance for concomitant medications and allowed treatments ● Updated guidance for dose modifications based on updated DDI information for venetoclax and for general treatment ● Clarified hepatitis eligibility and eliminate redundancy ● Clarified that intrasubject dose escalation only applies to subjects enrolled to the dose escalation portion ● Clarified bone marrow biopsy collection to confirm complete response or stringent complete response ● Clarified assessments that are not sufficient to determine progressive disease

05 October 2017	Protocol Amendment 6 ● Updated protocol to reflect expansion of the study based on preliminary efficacy data from the VenDex combination cohort for a Phase 2 portion to investigate overall response rate and very good partial response or better rate of venetoclax with dexamethasone treatment in approximately 80 subjects with t(11;14)-positive multiple myeloma ● Revised Inclusion and Exclusion Criteria to align with venetoclax MM program ● Clarified timing of prior and concomitant medication use ● Updated drug-drug interaction (DDI) information for venetoclax and guidance for concomitant medications and allowed treatments ● Clarified sample collection based on subject cohort ● Included IMWG 2016 response criteria for Phase 2 cohort subjects to be assessed based on the most recent response criteria available ● Clarified IMWG response assessments are to be based on central laboratory results and specify an independent review committee will be utilized for Phase 2 subjects ● Specified dosing instructions and investigational product for the Phase 2 cohort. ● Specified subject population for VenDex combination and Phase 2 cohorts ● Provided rationale for the 800 mg selected venetoclax dose ● Specified hospitalizations after study discontinuation for subsequent line of therapy will not be recorded as a serious adverse event, and reporting of cytopenias as adverse events ● Specified medical outcome for either mother or infant, meeting any serious criteria is considered a serious adverse event ● Revised dosing information sections to be consistent with venetoclax MM program guidance ● Updated Appendix F to remove Cairo-Bishop Criteria for Tumor Lysis Syndrome ● Corrected error in Appendix G, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS) in Multiple Myeloma Subjects
11 January 2018	Protocol Amendment 7 ● Added patient reported outcomes (PRO) to the Phase 2 portion to measure quality indicators throughout study ● Revised Inclusion Criteria 3, noting that Phase 2 subjects must have been treated with prior daratumumab combination therapies ● Increased bone marrow aspirate volume collection and prioritization for BCL-2 analysis ● Provided additional guidance for TLS management for subjects considered high risk ● Updated TLS management guidelines in accordance with current venetoclax and therapeutic specific guidelines ● Specified Phase 2 subgroup analysis and clarified Phase 1 portion of the study is dose escalation

30 May 2018	Protocol Amendment 8 ● Clarified that the study is sponsored by AbbVie in collaboration with Roche/Genentech ● Updated to reflect an increase number of Phase 2 subjects from 80 to approximately 80 to 100, and total number of subjects from 166 to approximately 166 to 186 ● Clarified inclusion criteria to allow subjects with two prior lines of therapy and to allow non US subjects who have been treated with Daratumumab monotherapy to be eligible and to require central laboratory confirming t11;14 status to be eligible ● Revised priority sampling of bone marrow aspirate sample ● Added informed consent as a study activity and allowed for subject visits to be scheduled within 4 days due to operational or logistical reasons ● Updated the information in the most current investigator brochure ● Clarified benefit and risk associated with venetoclax and dexamethasone ● Corrected sample volume to align with standardized tube size available for collection ● Clarified skeletal survey results must be obtained within < 30 days prior to planned first dose, to remove reference to legally acceptable representative, and to remove secondary malignancies as part of overall survival information ● Clarified that dexamethasone should be protected from moisture ● Removed limitation of 48 months for treatment duration based on updated information ● Clarified that events with an outcome of death will be included in progression-free survival ● Ensured consistent use of statistical terms and to clarified determination of sample size effect on primary efficacy Phase 2 endpoints ● Revised Appendix G to correct an error
15 March 2019	Protocol Amendment 9 ● Provided guidance to reduce the risk of serious infections in patients treated with venetoclax, to align with similar recommendations made due to findings on a recent Phase III combination study (Study M14-031) ● Updated Exclusion Criterion 1 to exclude subjects with acute infection, regardless of therapy required, within 14 days of first dose ● Updated clinical and safety data per the most recent investigator brochure ● Clarified that the tympanic method for body temperature is acceptable ● Updated guidance in cases of vomiting with current venetoclax safety risk language ● Clarified that the number of deaths summarized was to include all deaths in this study regardless of the number of days after the last dose of study drug ● Corrected timing of screening skeletal survey in line with schedule of assessments
24 September 2019	Protocol Amendment 10 ● Modified guidance to study procedures to reflect Sponsor decision to stop enrolling subjects in the study ● Added information about the use of and the timing for prophylactic antibiotics and recommendations for the administration of intravenous immunoglobulin (IVIG) ● Added the requirement of pneumococcal and influenza vaccinations ● Added text clarifying allowable corticosteroid use while on study treatment ● Clarified IMWG assessments, bone marrow collections, and overall survival assessments ● Updated Adverse Event Collection Period to include any additional relevant clinical information leading to a death in survival is to be reported on the appropriate eCRF for Phase 2 subjects during the follow up period and to specify TLS as an adverse event of special interest. ● Added information about the new Safety Review Committee

03 November 2020	Protocol Amendment 11 • Updated Pretreatment Guidance for required pneumococcal and influenza vaccinations • Updated Excluded and Cautionary Medications to add excluded food • Updated to Overall Survival assessments to provide a ± 2-week window time frame for the 12 week Overall Survival Follow Up assessment intervals • Update to Pregnancy testing to define classification of not of childbearing potential female subjects • Added Non-Treatment Emergent Death Collection details • Updated to Study Procedures-Pro Assessments to discontinue further PRO assessment collections with Amendment 10 • Updated Discontinuation of Individual Subjects to explain that study staff may still use available public records to obtain information about survival status only, as appropriate per local regulations • Updated Subject Information and Consent to reflect expected informed consent process to collect pharmacogenetic testing's and updated proceedings if subject withdraws consent • Update to Source Documents to reflect Investigator responsibilities and conduct of clinical monitoring. • Discontinued further Cytogenetics/FISH, Immunophenotyping and Translational Research collection at Final Visit • Added SARS-CoV-2 test at any timepoint if clinically indicated per Investigator's discretion. • Incorporated protocol modifications due to the COVID-19 pandemic to incorporate interruption/discontinuation of study drug due to confirmed or suspected COVID-19 Infection guidance • Noted that remote monitoring may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site
17 February 2021	Protocol Amendment 12 • Updated to clarify subjects will continue on treatment until the end of study provided they continue to tolerate venetoclax, have no evidence of disease progression, and do not meet any criteria for subject discontinuation • Updated to clarify that the end of study is defined as the date of the last subject's last visit, including Safety Follow Up

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported