Clinical trial results:
A Phase 2 Open-Label Study of the Efficacy of ABT-199 (GDC-0199) in Subjects with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukemia Harboring the 17p Deletion

Summary

EudraCT number	2012-004027-20
Trial protocol	GB DE PL FR
Global end of trial date	28 October 2020

Results information

Result version number	v1 (current)
This version publication date	22 October 2021
First version publication date	22 October 2021

Trial information

Trial identification

Sponsor protocol code	M13-982

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01889186
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
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	28 October 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was an open-label, multicenter, global study to determine the efficacy of ABT-199 (Venetoclax) monotherapy in participants with relapsed/refractory (R/R) or previously untreated chronic lymphocytic leukemia (CLL) harboring 17p deletion. This study was designed to enroll approximately 150 participants in 2 cohorts: a main cohort of approximately 100 participants, and a safety expansion (SE) cohort of approximately 50 participants. The primary objective of the main cohort was to evaluate the efficacy of ABT-199 monotherapy in participants with R/R CLL harboring the 17p deletion. The primary objective of the safety expansion cohort was to evaluate the safety of ABT-199 in approximately 50 participants with R/R CLL harboring 17p deletion treated per updated tumor lysis syndrome (TLS) prophylaxis and management measures.

Protection of trial subjects:

Subjects must have voluntarily signed and dated an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study specific procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 56
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	158
EEA total number of subjects	72

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)	66
From 65 to 84 years	91
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All treated participants: all participants who received at least one dose of ABT-199 in either the Main Cohort or Safety Expansion Cohort

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	Main Cohort

Arm description:

Participants received ABT-199 tablets once daily (QD) orally for up to 79 months. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg.

Arm type	Experimental
Investigational medicinal product name	ABT-199 (Main Cohort)
Investigational medicinal product code	
Other name	Venetoclax, GDC-0199
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a test dose of ABT-199 of ≤ 20 mg on Week 1 Day 1 of the Lead-In Period. For those with significant electrolyte and/or lymphocyte changes within 24 hours of the first dose, the 20 mg dose was maintained for 7 days with escalation to 50 mg on Week 2 Day 1. If none of the electrolyte and/or lymphocyte changes occurred within 24 hours from ABT-199 20 mg dose administration, the participant was dose-escalated to 50 mg on Week 1 Day 2. After the first dose of 50 mg, if no laboratory abnormalities occurred, the participant remained on the 50 mg dose through Week 1. After receiving the 50 mg dose for approximately 1 week (6 to 7 days), the following dose escalation proceeded with weekly increases in dose: 100 mg 200 mg 400 mg (or additional lead-in steps to designated 400 mg dose), as tolerated.

Arm title	Safety Expansion Cohort

Arm description:

Participants received ABT-199 tablets once daily (QD) orally for up to 68 months. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg.

Arm type	Experimental
Investigational medicinal product name	ABT-199 (Safety Expansion Cohort)
Investigational medicinal product code	
Other name	Venetoclax, GDC-0199
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received an initial dose of ABT-199 of 20 mg on Week 1 Day 1 of the Lead-In Period. If one or more electrolyte changes (from the 0 hr measurement prior to dosing) suggestive of laboratory tumor lysis syndrome (LTLS) or clinical TLS (CTLS) occurred within 24 hours of the 20 mg dose, no additional doses were administered until resolution. Upon resolution of laboratory abnormalities, the 20 mg dose was continued through Week 1. If no significant findings suggestive of clinical or laboratory TLS occurred within 24 hours, the 20 mg dose was continued through Week 1 Day 7, and escalated to a dose of 50 mg on Week 2 Day 1. Those who had drug interruptions may have been allowed to escalate to and be

maintained at 50 mg for 1 week after they had been on a 20 mg dose for at least 1 week (5 – 7 days). After a week at 50 mg, weekly dose escalations were implemented as follows: 100 mg 200 mg 400 mg (or additional lead-in steps to designated 400 mg dose) as tolerated.

Number of subjects in period 1	Main Cohort	Safety Expansion Cohort
Started	107	51
Completed	0	0
Not completed	107	51
Adverse event-- not related to progression	18	5
Progressive disease per protocol	46	17
Other, not specified	18	15
COVID-19 logistical restrictions	1	-
Stem cell transplant	2	1
Progressive disease-- Richter's	12	7
Withdrew consent	2	3
Adverse event-- related to progression	7	2
Investigator request	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Main Cohort
Reporting group description:	
Participants received ABT-199 tablets once daily (QD) orally for up to 79 months. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg.	
Reporting group title	Safety Expansion Cohort
Reporting group description:	
Participants received ABT-199 tablets once daily (QD) orally for up to 68 months. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg.	

Reporting group values	Main Cohort	Safety Expansion Cohort	Total
Number of subjects	107	51	158
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	65.7	65.4	
standard deviation	± 9.87	± 9.97	-
Gender categorical			
Units: Subjects			
Female	37	22	59
Male	70	29	99

End points

End points reporting groups

Reporting group title	Main Cohort

Reporting group description:

Participants received ABT-199 tablets once daily (QD) orally for up to 79 months. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg.

Reporting group title	Safety Expansion Cohort

Reporting group description:

Participants received ABT-199 tablets once daily (QD) orally for up to 68 months. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg.

Subject analysis set title	All Treated Participants
Subject analysis set type	Per protocol

Subject analysis set description:

Participants in the Main Cohort received ABT-199 tablets once daily (QD) orally for up to 79 months,and those in the Safety Expansion Cohort received ABT-199 tablets once daily (QD) orally for up to 68 months. For both groups, the starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg.

Primary: Overall Response Rate (Main Cohort)

End point title	Overall Response Rate (Main Cohort)[1][2]

End point description:

The overall response rate (ORR) is defined as the proportion of participants with an overall response (complete remission [CR] + complete remission with incomplete marrow recovery [CRi] + nodular partial remission [nPR] + partial remission [PR]) per the 2008 Modified International Workshop for Chronic Lymphocytic Leukemia (IWCLL)/National Cancer Institute-Working Group (NCI-CWG) criteria as assessed by the Independent Review Committee (IRC) in the first 70 participants treated in the Main Cohort.

End point type	Primary

End point timeframe:

Up to 36 weeks

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: The ORR for ABT-199 was tested to reject the null hypothesis of ORR = 40%. If the null hypothesis is rejected and the ORR is higher than 40%, then ABT-199 has been shown to have an ORR significantly higher than 40%. The p-value of <0.001 is from the exact binomial distribution comparing ABT-199 ORR to the 40% historical control rate.
[2] - 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 primary endpoint included the Main Cohort group only.

End point values	Main Cohort			
Subject group type	Reporting group			
Number of subjects analysed	70[3]			
Units: percentage of participants				
number (confidence interval 95%)	77.1 (65.6 to 86.3)			

Notes:

[3] - The first 70 participants who were treated with ABT-199 in the Main Cohort

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Adverse Events (Safety Expansion Cohort)

End point title	Number of Participants With Adverse Events (Safety Expansion Cohort)[4][5]

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 the first dose of study drug until 30 days following last dose of study drug (up to 69 months)

Notes:

[4] - 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 data per protocol are presented in the Endpoint Data Table.

[5] - 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 primary endpoint included the Safety Expansion Cohort group only.

End point values	Safety Expansion Cohort			
Subject group type	Reporting group			
Number of subjects analysed	51[6]			
Units: participants	51			

Notes:

[6] - All treated participants in the Safety Expansion Cohort

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) (Safety Expansion Cohort)

End point title	Overall Response Rate (ORR) (Safety Expansion Cohort)[7]

End point description:

The overall response rate (ORR) is defined as the proportion of participants with an overall response (complete remission [CR] + complete remission with incomplete marrow recovery [CRi] + nodular partial remission [nPR] + partial remission [PR]) per the 2008 Modified International Workshop for Chronic Lymphocytic Leukemia (IWCLL)/National Cancer Institute-Working Group (NCI-CWG) criteria.

End point type	Secondary

End point timeframe:

Up to the data cutoff date of 15 June 2017, approximately 4 years of follow-up

Notes:

[7] - 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 secondary endpoint included the Safety Expansion Cohort group only.

End point values	Safety Expansion Cohort			
Subject group type	Reporting group			
Number of subjects analysed	51[8]			
Units: percentage of participants				
number (confidence interval 95%)	82.4 (69.1 to 91.6)			

Notes:

[8] - All treated participants in the Safety Expansion Cohort

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission (CR) Rate

End point title	Complete Remission (CR) Rate

End point description:

Complete remission was defined as the proportion of participants who achieved a CR or Complete Remission with Incomplete Marrow Recovery(CRi) per the 2008 Modified International Workshop for Chronic Lymphocytic Leukemia (IWCLL)/National Cancer Institute-Working Group (NCI-CWG) criteria. Participants who did not achieve a CR or CRi were considered to be non-responders in the calculation of CR rate.

End point type	Secondary

End point timeframe:

Up to the data cutoff date of 15 June 2017, approximately 4 years of follow-up

End point values	Main Cohort	Safety Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107[9]	51[10]		
Units: percentage of participants				
number (confidence interval 95%)	21.5 (14.1 to 30.5)	27.5 (15.9 to 41.7)		

Notes:

[9] - All treated participants in the Main Cohort

[10] - All treated participants in the Safety Expansion Cohort

Statistical analyses

No statistical analyses for this end point

Secondary: Partial Remission (PR) Rate

End point title	Partial Remission (PR) Rate

End point description:

PR rate was defined as the proportion of participants who achieved a nodular partial remission (nPR) or PR per the 2008 Modified International Workshop for Chronic Lymphocytic Leukemia (IWCLL)/National Cancer Institute Working Group (NCI-CWG) criteria. Participants who did not achieve a nPR or PR were considered to be non-responders in the calculation of PR rate.

End point type	Secondary

End point timeframe:

Up to the data cutoff date of 15 June 2017, approximately 4 years of follow-up

End point values	Main Cohort	Safety Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107[11]	51[12]		
Units: percentage of participants				
number (confidence interval 95%)	53.3 (43.4 to 63.0)	54.9 (40.3 to 68.9)		

Notes:

[11] - All treated participants in the Main Cohort

[12] - All treated participants in the Safety Expansion Cohort

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Overall Response

End point title	Duration of Overall Response

End point description:

Duration of overall response (DoR) was defined as the number of days from the date of first response (CR, CRi, nPR, or PR) by either CT scan or physical exam determination to the earliest recurrence (progressive disease; PD) or death. For participants who had a PR before CR, CRi, or nPR in subsequent visits, the DoR was computed from the earliest PR. If a participant was still responding, then their data was censored at the date of their last available disease assessment. To be included in the DoR analysis, participants must have had a response per the 2008 Modified International Workshop for Chronic Lymphocytic Leukemia (IWCLL)/National Cancer Institute-Working Group (NCICWG) criteria (CR, CRi, confirmed nPR, or confirmed PR). For participants who never experienced response, their data was not included in the analysis.

999 and 99999 in the table below = not calculable/estimable due to insufficient number of events

End point type	Secondary

End point timeframe:

Up to the data cutoff date of 15 June 2017, approximately 4 years of follow-up

End point values	Main Cohort	Safety Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80[13]	42[14]		
Units: months				
median (confidence interval 95%)	35.3 (26.5 to 99999)	999 (27.3 to 99999)		

Notes:

[13] - All treated participants in the Main Cohort with a response and available data

[14] - All treated participants in the Safety Expansion Cohort with a response and available data

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Duration of progression-free survival (PFS) was defined as the number of days from the date of first dose to the date of earliest disease progression or death. All disease progression was included regardless of whether the event occurred while the participant was taking ABT-199 or had previously discontinued ABT-199. If the participant does not experience disease progression or death, then the data was censored at the date of last disease assessment. Data for participants without any disease assessments performed after the baseline visit were censored at the date of first dose plus 1 day.

99999 in the table below = not calculable/estimable due to insufficient number of events

End point type	Secondary

End point timeframe:

Up to the data cutoff date of 15 June 2017, approximately 4 years of follow-up

End point values	Main Cohort	Safety Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107[15]	51[16]		
Units: months				
median (confidence interval 95%)	24.7 (21.7 to 35.9)	30.2 (24.7 to 99999)		

Notes:

[15] - All treated participants in the Main Cohort with available data

[16] - All treated participants in the Safety Expansion Cohort with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free Survival

End point title	Event-free Survival

End point description:

Event-free survival (EFS) was defined as the number of days from the date of first dose to the date of

earliest disease progression, death, or start of a new anti-leukemic therapy. If the specified event (disease progression, death, start of a new anti-leukemic treatment) did not occur, participants were censored at the date of last disease assessment. Data for participants without any disease assessments performed after the baseline visit were censored at the date of first dose plus 1 day.

99999 in the table below = not calculable/estimable due to insufficient number of events

End point type	Secondary

End point timeframe:

Up to the data cutoff date of 15 June 2017, approximately 4 years of follow-up

End point values	Main Cohort	Safety Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107[17]	51[18]		
Units: months				
median (confidence interval 95%)	24.7 (19.7 to 35.9)	30.2 (24.7 to 99999)		

Notes:

[17] - All treated participants in the Main Cohort with available data

[18] - All treated participants in the Safety Expansion Cohort with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression

End point title	Time to Progression

End point description:

Time to progression (TTP) was defined as the number of days from the date of first dose to the date of earliest disease progression. All disease progression was included regardless of whether the event occurred while the participant was taking ABT-199 or had previously discontinued ABT-199. If the participant did not experience disease progression, then the data was censored at the date of last available disease assessment. Data for participants without any disease assessments performed after the baseline visit were censored at the date of first dose plus 1 day.

99999 in the table below = not calculable/estimable due to insufficient number of events

End point type	Secondary

End point timeframe:

Up to the data cutoff date of 15 June 2017, approximately 4 years of follow-up

End point values	Main Cohort	Safety Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107[19]	51[20]		
Units: months				
median (confidence interval 95%)	28.2 (21.9 to 39.0)	30.2 (27.0 to 99999)		

Notes:

[19] - All treated participants in the Main Cohort with available data

[20] - All treated participants in the Safety Expansion Cohort with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Response

End point title	Time to First Response

End point description:

Time to first response was defined as the number of days from the date of first dose to the date of the first sign of response (CR, CRi, nPR, or PR) given the participant has had a CR, CRi, confirmed nPR, or confirmed PR per the 2008 Modified International Workshop for Chronic Lymphocytic Leukemia (IWCLL)/National Cancer Institute Working Group (NCI-CWG) criteria. The first response could have been an assessment by physical exam as long as the results were later confirmed per the 2008 Modified IWCLL NCI-WG criteria. For participants who never experienced a response, the participant's data were not included in the analysis.

End point type	Secondary

End point timeframe:

Up to the data cutoff date of 15 June 2017, approximately 4 years of follow-up

End point values	Main Cohort	Safety Expansion Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80[21]	42[22]		
Units: months				
arithmetic mean (confidence interval 95%)	1.1 (1.0 to 1.3)	1.3 (1.1 to 1.5)		

Notes:

[21] - All treated participants in the Main Cohort with a response and available data

[22] - All treated participants in the Safety Expansion Cohort with a response and available data

Statistical analyses

No statistical analyses for this end point

Secondary: Time to 50% Reduction in Absolute Lymphocyte Count

End point title	Time to 50% Reduction in Absolute Lymphocyte Count[23]

End point description:

Time to 50% reduction in absolute lymphocyte count (ALC) was defined as the number of days (hours if applicable) from the date of first dose to the date when the ALC had reduced to 50% of the baseline value. Only participants with a baseline of ALC > 5 × 10^9 /L were included in the analysis. For participants who never achieved a 50% reduction in ALC, the participant's data were not included in the analysis.

End point type	Secondary

End point timeframe:

Up to the data cutoff date of 15 June 2017, approximately 4 years of follow-up

Notes:

[23] - 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: The statistical analysis data per protocol are presented in the Endpoint Data Table.

End point values	Main Cohort	All Treated Participants		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	85[24]	125[25]		
Units: weeks				
arithmetic mean (confidence interval 95%)	1.1 (0.9 to 1.2)	1.2 (1.1 to 1.4)		

Notes:

[24] - Treated participants with a baseline of ALC > 5 × 10^9 /L, 50% reduction in ALC, and available data
[25] - Treated participants with a baseline of ALC > 5 × 10^9 /L, 50% reduction in ALC, and available data

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) was defined as number of days from the date of first dose to the date of death. For participants who did not die, their data was censored at the date of last study visit or the last known date to be alive, whichever was later.

99999 in the table below = not calculable/estimable due to insufficient number of events

End point type	Secondary

End point timeframe:

Up to the data cutoff date of 15 December 2020, approximately 7.5 years of follow-up

End point values	All Treated Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	158[26]			
Units: months				
median (confidence interval 95%)	62.4 (51.6 to 99999)			

Notes:

[26] - All treated participants with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Moved on to Stem Cell Transplant

End point title	Percentage of Participants Who Moved on to Stem Cell Transplant[27]

End point description:

The percentage of participants who moved on to stem cell transplant was summarized.

End point type	Secondary

End point timeframe:

Up to the data cutoff date of 15 June 2017, approximately 4 years of follow-up

Notes:

[27] - 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: The statistical analysis data per protocol are presented in the Endpoint Data Table.

End point values	Main Cohort	All Treated Participants		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	107[28]	158[29]		
Units: percentage of participants				
number (confidence interval 95%)	2.8 (0.6 to 8.0)	2.5 (0.7 to 6.4)		

Notes:

[28] - All treated participants with available data

[29] - All treated participants with available data

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) were collected from first dose of study drug until 30 days after last study drug administration, up to 80 months for Main Cohort and up to 69 months for Safety Expansion Cohort.

Adverse event reporting additional description:

TEAEs and SAEs are defined as any AE or SAE with onset or worsening reported by a participant from the time that the first dose of study drug is administered until 30 days have elapsed following discontinuation of study drug. TEAEs were collected whether elicited or spontaneously reported by the participant.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Main Cohort

Reporting group description:

Participants received ABT-199 tablets once daily (QD) orally for up to 79 months. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg.

Reporting group title	Safety Expansion Cohort

Reporting group description:

Participants received ABT-199 tablets once daily (QD) orally for up to 68 months. The starting dose was 20 mg daily, increasing over a period of 5 weeks up to the daily dose of 400 mg.

Serious adverse events	Main Cohort	Safety Expansion Cohort	
Total subjects affected by serious adverse events			
subjects affected / exposed	78 / 107 (72.90%)	34 / 51 (66.67%)	
number of deaths (all causes)	62	19	
number of deaths resulting from adverse events	19	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACOUSTIC NEUROMA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYELOID LEUKAEMIA			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ADENOCARCINOMA OF COLON			

subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BASAL CELL CARCINOMA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST CANCER			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHIAL CARCINOMA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CENTRAL NERVOUS SYSTEM LYMPHOMA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC LYMPHOCYTIC LEUKAEMIA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLORECTAL CANCER			
subjects affected / exposed	1 / 107 (0.93%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT MELANOMA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT NEOPLASM OF UNKNOWN PRIMARY SITE			

subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT NEOPLASM PROGRESSION			
subjects affected / exposed	18 / 107 (16.82%)	4 / 51 (7.84%)	
occurrences causally related to treatment / all	2 / 18	0 / 4	
deaths causally related to treatment / all	1 / 11	0 / 1	
MYELODYSPLASTIC SYNDROME			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLASMA CELL MYELOMA			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
SKIN PAPILLOMA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UTERINE CANCER			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

CIRCULATORY COLLAPSE				
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
DEEP VEIN THROMBOSIS				
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
HYPERTENSIVE CRISIS				
subjects affected / exposed	1 / 107 (0.93%)	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
HYPOTENSION				
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE				
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
General disorders and administration site conditions				
GAIT DISTURBANCE				
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
GENERAL PHYSICAL HEALTH DETERIORATION				
subjects affected / exposed	4 / 107 (3.74%)	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 4	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
HYPOTHERMIA				

subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPAIRED HEALING			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTIPLE ORGAN DYSFUNCTION SYNDROME			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PAIN			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERFORMANCE STATUS DECREASED			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	8 / 107 (7.48%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	3 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

HYPOGAMMAGLOBULINAEMIA			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
VAGINAL PROLAPSE			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
BRONCHITIS CHRONIC			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			

subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA ASPIRATION			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY MASS			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
CONFUSIONAL STATE			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISORIENTATION			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUICIDAL IDEATION			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD GLUCOSE FLUCTUATION			

subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CANDIDA TEST POSITIVE			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA TEST POSITIVE			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET COUNT DECREASED			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ANASTOMOTIC LEAK			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANKLE FRACTURE			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FOOT FRACTURE			

subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
JOINT DISLOCATION			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCLE STRAIN			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIUS FRACTURE			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
ATRIAL SEPTAL DEFECT			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYDROCELE			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 107 (0.93%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

ANGINA PECTORIS			
subjects affected / exposed	2 / 107 (1.87%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	3 / 107 (2.80%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FLUTTER			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK SECOND DEGREE			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIOGENIC SHOCK			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIOPULMONARY FAILURE			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
CORONARY ARTERY DISEASE			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSIVE HEART DISEASE			

subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 107 (0.93%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYCARDIA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
ATAXIA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL INFARCTION			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISTURBANCE IN ATTENTION			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGIC STROKE			

subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROGRESSIVE SUPRANUCLEAR PALSY			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	3 / 107 (2.80%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	4 / 107 (3.74%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
AUTOIMMUNE HAEMOLYTIC ANAEMIA			
subjects affected / exposed	7 / 107 (6.54%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	5 / 10	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	7 / 107 (6.54%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	7 / 9	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOLYSIS			

subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGIC DIATHESIS			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMMUNE THROMBOCYTOPENIA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHADENOPATHY			
subjects affected / exposed	3 / 107 (2.80%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	2 / 107 (1.87%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	3 / 107 (2.80%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
RETINAL ARTERY OCCLUSION			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VISION BLURRED			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

ABDOMINAL PAIN			
subjects affected / exposed	2 / 107 (1.87%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APHTHOUS ULCER			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASCITES			
subjects affected / exposed	1 / 107 (0.93%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 107 (0.00%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPHAGIA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTERITIS			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER HAEMORRHAGE			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INGUINAL HERNIA			

subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL PSEUDO-OBSTRUCTION			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOOTH LOSS			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UMBILICAL HERNIA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	1 / 107 (0.93%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLANGITIS			

subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLELITHIASIS			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC FUNCTION ABNORMAL			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
DECUBITUS ULCER			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYTHEMA NODOSUM			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN HAEMORRHAGE			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLADDER DISORDER			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS NONINFECTIVE			

subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSURIA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATURIA			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL DISORDER			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NECK PAIN			
subjects affected / exposed	1 / 107 (0.93%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOARTHRITIS			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEONECROSIS			

subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ADENOVIRUS INFECTION			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BETA HAEMOLYTIC STREPTOCOCCAL INFECTION			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHOPULMONARY ASPERGILLOSIS			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CAMPYLOBACTER INFECTION			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE COLITIS			

subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE INFECTION			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMPYEMA			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA INFECTION			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA SEPSIS			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA URINARY TRACT INFECTION			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS SALMONELLA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			

subjects affected / exposed	3 / 107 (2.80%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER CUTANEOUS DISSEMINATED			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPETIGO			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTED SKIN ULCER			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
KLEBSIELLA BACTERAEMIA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
KLEBSIELLA SEPSIS			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 107 (1.87%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	2 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
METAPNEUMOVIRUS INFECTION			

subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NASOPHARYNGITIS			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIC SEPSIS			
subjects affected / exposed	1 / 107 (0.93%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOMYELITIS			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAINFLUENZAE VIRUS INFECTION			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCYSTIS JIROVECII INFECTION			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	14 / 107 (13.08%)	8 / 51 (15.69%)	
occurrences causally related to treatment / all	2 / 15	3 / 9	
deaths causally related to treatment / all	1 / 1	0 / 0	
PNEUMONIA FUNGAL			

subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA RESPIRATORY SYNCYTIAL VIRAL			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL INFECTION			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSEUDOMONAS INFECTION			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY MYCOSIS			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY SEPSIS			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY SYNCYTIAL VIRUS INFECTION			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
RHINOVIRUS INFECTION			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCROTAL ABSCESS			

subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCROTAL INFECTION			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	2 / 107 (1.87%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPTIC SHOCK			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SOFT TISSUE INFECTION			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUSITIS			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	1 / 107 (0.93%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 107 (1.87%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			

subjects affected / exposed	3 / 107 (2.80%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
subjects affected / exposed	2 / 107 (1.87%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR DEVICE INFECTION			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL INFECTION			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
CACHEXIA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERCALCAEMIA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKALAEMIA			
subjects affected / exposed	0 / 107 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERPHOSPHATAEMIA			

subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	1 / 107 (0.93%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR LYSIS SYNDROME			
subjects affected / exposed	2 / 107 (1.87%)	3 / 51 (5.88%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Main Cohort	Safety Expansion Cohort	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 107 (96.26%)	50 / 51 (98.04%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	15 / 107 (14.02%)	4 / 51 (7.84%)	
occurrences (all)	19	4	
General disorders and administration site conditions			
CHILLS			
subjects affected / exposed	9 / 107 (8.41%)	5 / 51 (9.80%)	
occurrences (all)	9	9	
FATIGUE			
subjects affected / exposed	27 / 107 (25.23%)	16 / 51 (31.37%)	
occurrences (all)	32	18	
OEDEMA PERIPHERAL			
subjects affected / exposed	12 / 107 (11.21%)	5 / 51 (9.80%)	
occurrences (all)	15	5	
PAIN			
subjects affected / exposed	9 / 107 (8.41%)	4 / 51 (7.84%)	
occurrences (all)	10	5	
PYREXIA			

subjects affected / exposed	16 / 107 (14.95%)	6 / 51 (11.76%)	
occurrences (all)	22	11	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	16 / 107 (14.95%)	14 / 51 (27.45%)	
occurrences (all)	20	19	
DYSPNOEA			
subjects affected / exposed	7 / 107 (6.54%)	7 / 51 (13.73%)	
occurrences (all)	7	10	
EPISTAXIS			
subjects affected / exposed	6 / 107 (5.61%)	2 / 51 (3.92%)	
occurrences (all)	9	2	
NASAL CONGESTION			
subjects affected / exposed	0 / 107 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	6	
OROPHARYNGEAL PAIN			
subjects affected / exposed	6 / 107 (5.61%)	3 / 51 (5.88%)	
occurrences (all)	7	3	
PRODUCTIVE COUGH			
subjects affected / exposed	2 / 107 (1.87%)	3 / 51 (5.88%)	
occurrences (all)	2	4	
UPPER-AIRWAY COUGH SYNDROME			
subjects affected / exposed	1 / 107 (0.93%)	3 / 51 (5.88%)	
occurrences (all)	1	3	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	4 / 107 (3.74%)	4 / 51 (7.84%)	
occurrences (all)	4	4	
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	8 / 107 (7.48%)	2 / 51 (3.92%)	
occurrences (all)	11	3	
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	6 / 107 (5.61%)	3 / 51 (5.88%)	
occurrences (all)	6	3	
NEUTROPHIL COUNT DECREASED			

subjects affected / exposed	3 / 107 (2.80%)	3 / 51 (5.88%)	
occurrences (all)	6	3	
PLATELET COUNT DECREASED			
subjects affected / exposed	3 / 107 (2.80%)	3 / 51 (5.88%)	
occurrences (all)	3	5	
WEIGHT DECREASED			
subjects affected / exposed	6 / 107 (5.61%)	0 / 51 (0.00%)	
occurrences (all)	10	0	
WEIGHT INCREASED			
subjects affected / exposed	7 / 107 (6.54%)	1 / 51 (1.96%)	
occurrences (all)	9	1	
Injury, poisoning and procedural complications			
ARTHROPOD BITE			
subjects affected / exposed	1 / 107 (0.93%)	4 / 51 (7.84%)	
occurrences (all)	1	4	
FALL			
subjects affected / exposed	7 / 107 (6.54%)	0 / 51 (0.00%)	
occurrences (all)	8	0	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	6 / 107 (5.61%)	7 / 51 (13.73%)	
occurrences (all)	7	8	
HEADACHE			
subjects affected / exposed	16 / 107 (14.95%)	12 / 51 (23.53%)	
occurrences (all)	20	12	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	27 / 107 (25.23%)	11 / 51 (21.57%)	
occurrences (all)	55	16	
AUTOIMMUNE HAEMOLYTIC ANAEMIA			
subjects affected / exposed	1 / 107 (0.93%)	3 / 51 (5.88%)	
occurrences (all)	1	4	
LEUKOPENIA			
subjects affected / exposed	9 / 107 (8.41%)	2 / 51 (3.92%)	
occurrences (all)	14	2	
NEUTROPENIA			

subjects affected / exposed	47 / 107 (43.93%)	22 / 51 (43.14%)	
occurrences (all)	127	49	
THROMBOCYTOPENIA			
subjects affected / exposed	24 / 107 (22.43%)	9 / 51 (17.65%)	
occurrences (all)	55	20	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	8 / 107 (7.48%)	2 / 51 (3.92%)	
occurrences (all)	9	2	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	8 / 107 (7.48%)	8 / 51 (15.69%)	
occurrences (all)	9	9	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	4 / 107 (3.74%)	4 / 51 (7.84%)	
occurrences (all)	5	4	
CONSTIPATION			
subjects affected / exposed	11 / 107 (10.28%)	9 / 51 (17.65%)	
occurrences (all)	15	10	
DIARRHOEA			
subjects affected / exposed	42 / 107 (39.25%)	26 / 51 (50.98%)	
occurrences (all)	60	45	
DYSPEPSIA			
subjects affected / exposed	6 / 107 (5.61%)	3 / 51 (5.88%)	
occurrences (all)	6	3	
FLATULENCE			
subjects affected / exposed	4 / 107 (3.74%)	3 / 51 (5.88%)	
occurrences (all)	4	4	
NAUSEA			
subjects affected / exposed	35 / 107 (32.71%)	24 / 51 (47.06%)	
occurrences (all)	45	32	
VOMITING			
subjects affected / exposed	17 / 107 (15.89%)	2 / 51 (3.92%)	
occurrences (all)	21	2	
Skin and subcutaneous tissue disorders			

ALOPECIA			
subjects affected / exposed	4 / 107 (3.74%)	3 / 51 (5.88%)	
occurrences (all)	4	4	
DRY SKIN			
subjects affected / exposed	7 / 107 (6.54%)	4 / 51 (7.84%)	
occurrences (all)	7	5	
NIGHT SWEATS			
subjects affected / exposed	3 / 107 (2.80%)	3 / 51 (5.88%)	
occurrences (all)	3	3	
PRURITUS			
subjects affected / exposed	7 / 107 (6.54%)	4 / 51 (7.84%)	
occurrences (all)	10	4	
RASH			
subjects affected / exposed	11 / 107 (10.28%)	6 / 51 (11.76%)	
occurrences (all)	13	6	
SKIN LESION			
subjects affected / exposed	2 / 107 (1.87%)	4 / 51 (7.84%)	
occurrences (all)	3	4	
Renal and urinary disorders			
POLLAKIURIA			
subjects affected / exposed	1 / 107 (0.93%)	3 / 51 (5.88%)	
occurrences (all)	1	3	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	10 / 107 (9.35%)	9 / 51 (17.65%)	
occurrences (all)	11	12	
BACK PAIN			
subjects affected / exposed	13 / 107 (12.15%)	7 / 51 (13.73%)	
occurrences (all)	16	8	
MUSCLE SPASMS			
subjects affected / exposed	4 / 107 (3.74%)	5 / 51 (9.80%)	
occurrences (all)	4	5	
MYALGIA			
subjects affected / exposed	2 / 107 (1.87%)	9 / 51 (17.65%)	
occurrences (all)	2	10	
PAIN IN EXTREMITY			

subjects affected / exposed	6 / 107 (5.61%)	4 / 51 (7.84%)	
occurrences (all)	10	5	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	13 / 107 (12.15%)	0 / 51 (0.00%)	
occurrences (all)	17	0	
CONJUNCTIVITIS			
subjects affected / exposed	6 / 107 (5.61%)	3 / 51 (5.88%)	
occurrences (all)	7	5	
HERPES ZOSTER			
subjects affected / exposed	6 / 107 (5.61%)	5 / 51 (9.80%)	
occurrences (all)	7	5	
INFLUENZA			
subjects affected / exposed	6 / 107 (5.61%)	3 / 51 (5.88%)	
occurrences (all)	7	3	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	4 / 107 (3.74%)	4 / 51 (7.84%)	
occurrences (all)	7	6	
NASOPHARYNGITIS			
subjects affected / exposed	19 / 107 (17.76%)	8 / 51 (15.69%)	
occurrences (all)	32	11	
PNEUMONIA			
subjects affected / exposed	7 / 107 (6.54%)	6 / 51 (11.76%)	
occurrences (all)	8	6	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	11 / 107 (10.28%)	0 / 51 (0.00%)	
occurrences (all)	15	0	
SINUSITIS			
subjects affected / exposed	6 / 107 (5.61%)	4 / 51 (7.84%)	
occurrences (all)	7	6	
SKIN INFECTION			
subjects affected / exposed	0 / 107 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	4	
TOOTH INFECTION			

subjects affected / exposed	2 / 107 (1.87%)	3 / 51 (5.88%)	
occurrences (all)	2	3	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	22 / 107 (20.56%)	15 / 51 (29.41%)	
occurrences (all)	36	20	
URINARY TRACT INFECTION			
subjects affected / exposed	12 / 107 (11.21%)	8 / 51 (15.69%)	
occurrences (all)	15	14	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	6 / 107 (5.61%)	1 / 51 (1.96%)	
occurrences (all)	6	1	
HYPERKALAEMIA			
subjects affected / exposed	6 / 107 (5.61%)	6 / 51 (11.76%)	
occurrences (all)	9	9	
HYPERPHOSPHATAEMIA			
subjects affected / exposed	17 / 107 (15.89%)	3 / 51 (5.88%)	
occurrences (all)	20	4	
HYPOKALAEMIA			
subjects affected / exposed	14 / 107 (13.08%)	5 / 51 (9.80%)	
occurrences (all)	25	6	
HYPOMAGNESAEMIA			
subjects affected / exposed	3 / 107 (2.80%)	3 / 51 (5.88%)	
occurrences (all)	3	5	
HYPOPHOSPHATAEMIA			
subjects affected / exposed	4 / 107 (3.74%)	4 / 51 (7.84%)	
occurrences (all)	7	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2013	Protocol Amendment 1 A total of 107 subjects (comprising the main cohort) were enrolled under this amendment. The main purpose of this amendment was to implement more stringent measures (referred to as "Post May 2013" measures) for prophylaxis and management of Tumor Lysis Syndrome (TLS), including modifications to the dosing regimen with a starting dose of 20 mg and a ramp up of 4 – 5 weeks, and to introduce TLS risk assessment with prophylaxis and monitoring according to the risk as well as intensive laboratory monitoring. The implemented measures were instituted in response to TLS events reported in the Venetoclax clinical program, including 2 deaths observed in the setting of TLS in subjects with relapsed or refractory CLL.
25 July 2014	Protocol Amendment 2 A total of 44 subjects (all in the safety expansion cohort) were enrolled under this amendment. The main purpose of the amendment was to introduce revised measures for prophylaxis and management of Tumor Lysis Syndrome (TLS) in response to an extensive analysis among the Chronic Lymphocytic Leukemia (CLL) studies, including 58 subjects that demonstrated a substantial reduction in the frequency and severity of laboratory tumor lysis syndrome (LTLS) and no events of clinical tumor lysis syndrome (CTLS). The revised measures included a starting dose of 20 mg and 5 step ramp-up to 400 mg, less stringent TLS prophylaxis and monitoring (referred to as "Current" measures) depending on the risk category, and the addition of a safety expansion cohort to evaluate these measures.
19 December 2014	Protocol Amendment 3 A total of 7 subjects (all in the safety expansion cohort) were enrolled under this amendment. The main purpose of the amendment was to include subjects in the study with previously untreated Chronic Lymphocytic Leukemia (CLL) harboring 17p deletion in the Safety Expansion Cohort, as there is no standard treatment for these patients. The amendment also clarified, for medium-risk Tumor Lysis Syndrome (TLS) subjects, the meaning of higher tumor burden to include an absolute lymphocyte count (ALC) value > 100 × 10^9 /L or the presence of multiple bulky nodes and added the collection of extra efficacy endpoints to both cohorts.
16 May 2016	Protocol Amendment 4 No subject was enrolled under this amendment; however, the protocol was updated to allow subjects with progressive disease (PD) to continue treatment with Venetoclax when, in the opinion of the investigator, it was in the subject's best interest to stay on drug. The protocol was updated to reflect the approved name, Venetoclax, and to incorporate Germany-specific updates (including the most current version of table for excluded and cautionary medications and food items).
08 September 2016	Protocol Amendment 5 No subject was enrolled under this amendment. The purpose of this amendment was to update the expected duration of treatment to approximately 24 months or greater, and to include collection of data pertaining to Richter's Transformation and second primary malignancies during the Survival period.

28 February 2017	Protocol Amendment 6 No subject was enrolled under this amendment. The purpose of this amendment was to extend access to Venetoclax from up to 2 years to up to 5 years following the last subject's first dose (12 May 2020) for subjects who continue to derive clinical benefit. Additionally, post-treatment visits were discontinued as of 12 May 2017 because there were too few subjects in the Post Treatment period to provide any meaningful statistical analyses. During the Survival Extended Access period, collection of blood for Minimal Residual Disease (MRD) PCR every 12 weeks was added. Subjects with progressive disease (PD) who remained on Venetoclax were allowed to concurrently receive other approved treatments for Chronic Lymphocytic Leukemia (CLL).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27178240