Clinical trial results:
A Phase 1/2 Study of Venetoclax in Combination with Low-Dose Cytarabine in Treatment-Naïve Subjects with Acute Myelogenous Leukemia Who Are 60 Years of Age and Who Are Not Eligible for Standard Anthracycline-Based Induction Therapy

Summary

EudraCT number	2014-002610-23
Trial protocol	DE IT
Global end of trial date	10 August 2021

Results information

Result version number	v1 (current)
This version publication date	19 August 2022
First version publication date	19 August 2022

Trial information

Trial identification

Sponsor protocol code	M14-387

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02287233
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	10 August 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the Phase 1 portion are to assess the safety profile, characterize PK, determine the dose schedule, the maximum tolerated dose (MTD), and the recommended Phase 2 dose (RPTD) of venetoclax in combination with low-dose cytarabine (LDAC) in treatment-naïve subjects with AML who are ≥ 65 years of age and who are not eligible for standard induction therapy due to co-morbidity or other factors.
The primary objectives of the initial Phase 2 portion of the study are to evaluate the preliminary estimates of efficacy including the overall response rate (ORR), and to characterize the toxicities of the combination at the RPTD.

Protection of trial subjects:

Subject read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 December 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 26
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	United States: 57
Worldwide total number of subjects	94
EEA total number of subjects	11

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)	2
From 65 to 84 years	86
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Previously untreated adults with acute myeloid leukemia (AML)who were ineligible for intensive chemotherapy were enrolled between December 2014 and May 2017.
The study consisted of a dose escalation phase (Phase 1) and a dose expansion phase (Phase 2).

Pre-assignment

Screening details:

Nine study sites in the United States, Australia, Germany, and Italy screened 116 subjects (most screen failures were due to inclusion/exclusion criteria), and 94 subjects at 9 sites were enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1: 600 mg Venetoclax + LDAC

Arm description:

Venetoclax was administered orally once daily (QD) on Days 2 through 28 of Cycle 1. Dosing started at 50 mg (Day 2) and increased up to 600 mg by Day 6. Beginning with Cycle 2, 600 mg venetoclax was administered Days 1 through 28 of each 28-day cycle. Participants also received low-dose cytarabine (LDAC; 20 mg/m²) administered by subcutaneous injection once daily on Days 1 to 10 of each cycle. Participants could continue receiving treatment until disease progression or until discontinuation criteria were met.

Arm type	Experimental
Investigational medicinal product name	Venetoclax
Investigational medicinal product code	ABT-199 (GDC-0199)
Other name	VENCLEXTA®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets taken orally once a day

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection on Days 1 to 10 of each 28-day cycle

Arm title	Phase 1: 800 mg Venetoclax + LDAC

Arm description:

Venetoclax was administered orally once daily (QD) on Days 2 through 28 of Cycle 1. Dosing started at 100 mg (Day 2) and increased up to 800 mg by Day 6. Beginning with Cycle 2, 800 mg venetoclax was administered Days 1 through 28 of each 28-day cycle. Participants also received LDAC (20 mg/m²) administered by subcutaneous injection once daily on Days 1 to 10 of each cycle.
Participants could continue receiving treatment until disease progression or until discontinuation criteria were met.

Arm type	Experimental

Investigational medicinal product name	Venetoclax
Investigational medicinal product code	ABT-199 (GDC-0199)
Other name	VENCLEXTA®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets taken orally once a day

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection on Days 1 to 10 of each 28-day cycle

Arm title	Phase 2: 600 mg Venetoclax + LDAC

Arm description:

Venetoclax was administered orally once daily (QD) on Days 2 through 28 of Cycle 1. Dosing started at 50 mg, and increased up to 600 mg by Day 6. Beginning with Cycle 2, 600 mg venetoclax was administered Days 1 through 28 of each 28-day cycle. Participants also received LDAC (20 mg/m²) administered by subcutaneous injection once daily on Days 1 to 10 of each cycle.
Participants could continue receiving treatment until disease progression or until discontinuation criteria were met.

Arm type	Experimental
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection on Days 1 to 10 of each 28-day cycle

Investigational medicinal product name	Venetoclax
Investigational medicinal product code	ABT-199 (GDC-0199)
Other name	VENCLEXTA®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets taken orally once a day

Number of subjects in period 1	Phase 1: 600 mg Venetoclax + LDAC	Phase 1: 800 mg Venetoclax + LDAC	Phase 2: 600 mg Venetoclax + LDAC
Started	8	10	76
Treated	8	10	74
Completed	0	0	0
Not completed	8	10	76
Adverse Event Related to Progression	-	2	8
Progressive Disease with Death	-	-	10
Physician decision	1	2	4
Consent withdrawn by subject	1	1	7

Other	3	-	15
Adverse Event Not Related to Progression	1	2	10
Progressive Disease Without Death	2	3	20
Did Not Receive Treatment	-	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1: 600 mg Venetoclax + LDAC

Reporting group description:

Venetoclax was administered orally once daily (QD) on Days 2 through 28 of Cycle 1. Dosing started at 50 mg (Day 2) and increased up to 600 mg by Day 6. Beginning with Cycle 2, 600 mg venetoclax was administered Days 1 through 28 of each 28-day cycle. Participants also received low-dose cytarabine (LDAC; 20 mg/m²) administered by subcutaneous injection once daily on Days 1 to 10 of each cycle. Participants could continue receiving treatment until disease progression or until discontinuation criteria were met.

Reporting group title	Phase 1: 800 mg Venetoclax + LDAC

Reporting group description:

Venetoclax was administered orally once daily (QD) on Days 2 through 28 of Cycle 1. Dosing started at 100 mg (Day 2) and increased up to 800 mg by Day 6. Beginning with Cycle 2, 800 mg venetoclax was administered Days 1 through 28 of each 28-day cycle. Participants also received LDAC (20 mg/m²) administered by subcutaneous injection once daily on Days 1 to 10 of each cycle.
Participants could continue receiving treatment until disease progression or until discontinuation criteria were met.

Reporting group title	Phase 2: 600 mg Venetoclax + LDAC

Reporting group description:

Venetoclax was administered orally once daily (QD) on Days 2 through 28 of Cycle 1. Dosing started at 50 mg, and increased up to 600 mg by Day 6. Beginning with Cycle 2, 600 mg venetoclax was administered Days 1 through 28 of each 28-day cycle. Participants also received LDAC (20 mg/m²) administered by subcutaneous injection once daily on Days 1 to 10 of each cycle.
Participants could continue receiving treatment until disease progression or until discontinuation criteria were met.

Reporting group values	Phase 1: 600 mg Venetoclax + LDAC	Phase 1: 800 mg Venetoclax + LDAC	Phase 2: 600 mg Venetoclax + LDAC
Number of subjects	8	10	76
Age categorical Units: Subjects			
< 65 years	0	0	2
>= 65 years	8	10	74
Age continuous Units: years			
arithmetic mean	75.3	74.4	75.0
standard deviation	± 6.45	± 3.72	± 5.56
Gender categorical Units: Subjects			
Female	3	3	27
Male	5	7	49
Race Units: Subjects			
White	8	10	69
Black or African American	0	0	2
Asian	0	0	2
Missing	0	0	3

Reporting group values	Total		
Number of subjects	94		

Age categorical Units: Subjects			
< 65 years	2		
>= 65 years	92		
Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female	33		
Male	61		
Race Units: Subjects			
White	87		
Black or African American	2		
Asian	2		
Missing	3		

End points

End points reporting groups

Reporting group title	Phase 1: 600 mg Venetoclax + LDAC

Reporting group description:

Venetoclax was administered orally once daily (QD) on Days 2 through 28 of Cycle 1. Dosing started at 50 mg (Day 2) and increased up to 600 mg by Day 6. Beginning with Cycle 2, 600 mg venetoclax was administered Days 1 through 28 of each 28-day cycle. Participants also received low-dose cytarabine (LDAC; 20 mg/m²) administered by subcutaneous injection once daily on Days 1 to 10 of each cycle. Participants could continue receiving treatment until disease progression or until discontinuation criteria were met.

Reporting group title	Phase 1: 800 mg Venetoclax + LDAC

Reporting group description:

Venetoclax was administered orally once daily (QD) on Days 2 through 28 of Cycle 1. Dosing started at 100 mg (Day 2) and increased up to 800 mg by Day 6. Beginning with Cycle 2, 800 mg venetoclax was administered Days 1 through 28 of each 28-day cycle. Participants also received LDAC (20 mg/m²) administered by subcutaneous injection once daily on Days 1 to 10 of each cycle.
Participants could continue receiving treatment until disease progression or until discontinuation criteria were met.

Reporting group title	Phase 2: 600 mg Venetoclax + LDAC

Reporting group description:

Venetoclax was administered orally once daily (QD) on Days 2 through 28 of Cycle 1. Dosing started at 50 mg, and increased up to 600 mg by Day 6. Beginning with Cycle 2, 600 mg venetoclax was administered Days 1 through 28 of each 28-day cycle. Participants also received LDAC (20 mg/m²) administered by subcutaneous injection once daily on Days 1 to 10 of each cycle.
Participants could continue receiving treatment until disease progression or until discontinuation criteria were met.

Subject analysis set title	Phase 1+2: 600 mg Venetoclax + LDAC
Subject analysis set type	Full analysis

Subject analysis set description:

Venetoclax was administered orally once daily (QD) on Days 2 through 28 of Cycle 1. Dosing started at 50 mg, and increased up to 600 mg by Day 6. Beginning with Cycle 2, 600 mg venetoclax was administered Days 1 through 28 of each 28-day cycle. Participants also received LDAC (20 mg/m²) administered by subcutaneous injection once daily on Days 1 to 10 of each cycle.
Participants could continue receiving treatment until disease progression or until discontinuation criteria were met.

Primary: Phase 1: Number of Participants With Dose-limiting Toxicities

End point title	Phase 1: Number of Participants With Dose-limiting

End point description:

Dose-limiting toxicities (DLTs) were determined during cycle 1 of the dose-escalation phase and defined as Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 grade 4 (life threatening requiring urgent intervention) or 5 (resulted in death) toxicity, excluding adverse events commonly caused by AML (eg, neutropenia, fever). Hematologic DLT was defined as failure of platelet recovery to 25 × 10^9/L or greater and absolute neutrophil count (ANC) to 0.5 × 10^9/L or greater within 14 days of the last dose of venetoclax in the absence of residual AML.
The DLT-evaluable population included participants who received at least 80% of planned Cycle 1 doses during the dose-escalation phase (Phase 1)

End point type	Primary

End point timeframe:

Up to 28 days (Cycle 1)

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: No formal statistical testing was conducted.

[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: DLTs were only analyzed in Phase 1.

End point values	Phase 1: 600 mg Venetoclax + LDAC	Phase 1: 800 mg Venetoclax + LDAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	10		
Units: participants	0	1		

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[3][4]

End point description:

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

The pharmacokinetic (PK) population includes participants enrolled in Phase 1 who had at least one dose of venetoclax and had at least one reported PK sample concentration.

End point type	Primary

End point timeframe:

Cycle 1, Day 10 at predose and 2, 4, 6, 8, and 24 hours postdose (venetoclax with LDAC); Cycle 1, Day 18 at predose, 2, 4, 6, 8, and 24 hours postdose (venetoclax alone)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical testing was conducted.

[4] - 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: PK analyses were conducted for Phase 1 only

End point values	Phase 1: 600 mg Venetoclax + LDAC	Phase 1: 800 mg Venetoclax + LDAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	10		
Units: µg/mL				
arithmetic mean (standard deviation)				
Cycle 1, Day 10 (Venetoclax with LDAC)	2.04 (± 1.45)	2.26 (± 0.930)		
Cycle 1, Day 18 (Venetoclax alone)	2.92 (± 2.15)	2.36 (± 1.22)		

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[5][6]

End point description:

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

End point type	Primary

End point timeframe:

Cycle 1, Day 10 at predose and 2, 4, 6, 8, and 24 hours postdose (venetoclax with LDAC); Cycle 1, Day 18 at predose, 2, 4, 6, 8, and 24 hours postdose (venetoclax alone)

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: No formal statistical testing was conducted.

[6] - 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: PK analyses were conducted for Phase 1 only

End point values	Phase 1: 600 mg Venetoclax + LDAC	Phase 1: 800 mg Venetoclax + LDAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	10		
Units: hours				
median (full range (min-max))				
Cycle 1, Day 10 (Venetoclax with LDAC)	4.0 (4.0 to 6.0)	8.0 (4.0 to 8.0)		
Cycle 1, Day 18 (Venetoclax Alone)	7.0 (3.5 to 8.0)	6.6 (4.0 to 8.0)		

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[7][8]

End point description:

End point type	Primary

End point timeframe:

Cycle 1, Day 10 at predose and 2, 4, 6, 8, and 24 hours postdose (venetoclax with LDAC); Cycle 1, Day 18 at predose, 2, 4, 6, 8, and 24 hours postdose (venetoclax alone)

Notes:

[7] - 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: No formal statistical testing was conducted.

[8] - 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: PK analyses were conducted for Phase 1 only

End point values	Phase 1: 600 mg Venetoclax + LDAC	Phase 1: 800 mg Venetoclax + LDAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[9]	10[10]		
Units: µg*h/mL				
arithmetic mean (standard deviation)				
Cycle 1, Day 10 (Venetoclax with LDAC)	33.3 (± 27.5)	33.4 (± 14.1)		
Cycle 1, Day 18 (Venetoclax Alone)	51.8 (± 36.9)	35.4 (± 19.8)		

Notes:

[9] - N=6 on Day 18

[10] - N=9 on Day 18

Statistical analyses

No statistical analyses for this end point

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

End point title	Phase 1: Maximum Observed Plasma Concentration (Cmax) of Cytarabine[11][12]

End point description:

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

End point type	Primary

End point timeframe:

Cycle 1, Day 1 and Day 10 at pre-dose and at 15 and 30 minutes and 1, 3, 6 hours post-dose.

Notes:

[11] - 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: No formal statistical testing was conducted.

[12] - 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: PK analyses were conducted for Phase 1 only

End point values	Phase 1: 600 mg Venetoclax + LDAC	Phase 1: 800 mg Venetoclax + LDAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	10		
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (LDAC Alone)	175 (± 47.0)	174 (± 55.4)		
Cycle 1, Day 10 (LDAC with Venetoclax)	166 (± 32.1)	175 (± 62.3)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Phase 1: Time to Maximum Observed Plasma Concentration (Tmax) of Cytarabine[13][14]

End point description:

End point type	Primary

End point timeframe:

Cycle 1, Day 1 and Day 10 at pre-dose and at 15 and 30 minutes and 1, 3, 6 hours post-dose.

Notes:

[13] - 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: No formal statistical testing was conducted.

[14] - 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: PK analyses were conducted for Phase 1 only

End point values	Phase 1: 600 mg Venetoclax + LDAC	Phase 1: 800 mg Venetoclax + LDAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	10		
Units: hours				
median (full range (min-max))				
Cycle 1, Day 1 (LDAC Alone)	0.3 (0.3 to 0.4)	0.3 (0.2 to 0.5)		
Cycle 1, Day 10 (LDAC with Venetoclax)	0.3 (0.3 to 0.5)	0.3 (0.2 to 0.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Area Under the Plasma Concentration-Time Curve Over Time From 0 to Last Measurable Concentration (AUCt) of Cytarabine

End point title	Phase 1: Area Under the Plasma Concentration-Time Curve Over Time From 0 to Last Measurable Concentration (AUCt) of Cytarabine[15][16]

End point description:

End point type	Primary

End point timeframe:

Cycle 1, Day 1 and Day 10 at pre-dose and at 15 and 30 minutes and 1, 3, 6 hours post-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: No formal statistical testing was conducted.

[16] - 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: PK analyses were conducted for Phase 1 only

End point values	Phase 1: 600 mg Venetoclax + LDAC	Phase 1: 800 mg Venetoclax + LDAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	10		
Units: ng*h/mL				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (LDAC Alone)	194 (± 66.3)	204 (± 62.9)		
Cycle 1, Day 10 (LDAC with Venetoclax)	231 (± 89.0)	202 (± 54.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Overall Response Rate

End point title	Overall Response Rate[17]

End point description:

Overall response rate (ORR) is defined as the percentage of participants who achieved a complete remission (CR), complete remission with incomplete marrow recovery (CRi), or partial remission (PR) per the International Working Group (IWG) for AML response criteria, per investigator assessment.
CR: absolute neutrophil count (ANC) ≥ 10^3 /µL, platelet counts ≥ 10^5 /µL, red blood cell (RBC) transfusion independence (a period of at least 56 days with no RBC transfusion), and bone marrow with < 5% blasts.
CRi: lack of morphologic evidence of leukemia (blasts < 5%), and platelet counts < 10^5 /µL or ANC < 10^3 /µL.
PR: all of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate.

End point type	Primary

End point timeframe:

Response was assessed at Cycle 2, Day 1, Cycle 4, Day 1, and every 3 cycles thereafter; median duration of treatment was 4.2 months.

Notes:

[17] - 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: No formal statistical testing was conducted.

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: percentage of participants				
number (confidence interval 95%)	54.9 (43.5 to 65.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs)[18]

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. Treatment-emergent events are defined as events that began or worsened in severity after the first dose of study drug. The investigator rated the severity of each AE

according to the CTCAE Version 4.0 and the following:
Grade 1: The AE is transient and easily tolerated (mild).
Grade 2: The AE causes discomfort and interrupts usual activities (moderate).
Grade 3: The AE causes considerable interference with usual activities and may be incapacitating (moderate to severe).
Grade 4: The AE is life threatening requiring urgent intervention.
Grade 5: The AE resulted in death.
The investigator assessed each event as either having a reasonable possibility or no reasonable possibility of being related to the use of study drug.

End point type	Primary

End point timeframe:

From first dose of study drug until 30 days after last dose of study drug; median (minimum, maximum) duration of treatment was 4.1 (0.2, 62.8) months overall.

Notes:

[18] - 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: No formal statistical testing was conducted.

End point values	Phase 1: 600 mg Venetoclax + LDAC	Phase 1: 800 mg Venetoclax + LDAC	Phase 2: 600 mg Venetoclax + LDAC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	10	74	
Units: participants				
Any treatment-emergent adverse event (TEAE)	8	10	74	
TEAE with CTCAE Grade 3 or 4	8	10	72	
TEAE with CTCAE Grade 3 or above	8	10	72	
Venetoclax-related TEAE	8	9	66	
LDAC-related TEAE	8	9	71	
TEAE leading to hospitalization	7	8	64	
TEAE leading to venetoclax discontinuation	3	5	24	
TEAE leading to LDAC discontinuation	3	5	26	
TEAE leading to venetoclax interruption	3	4	45	
TEAE leading to LDAC interruption	3	3	38	
TEAE leading to venetoclax reduction	0	1	6	
TEAE leading to LDAC reduction	0	0	1	
TEAE leading to death	1	4	15	

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission Rate

End point title	Complete Remission Rate

End point description:

Complete remission (CR) rate is defined as the percentage of participants who achieved a complete remission at any time point during the study per the modified IWG criteria for AML and investigator assessment.
CR: absolute neutrophil count (ANC) ≥ 10^3 /µL, platelet counts ≥ 10^5 /µL, red blood cell (RBC) transfusion independence (a period of at least 56 days with no RBC transfusion), and bone marrow with < 5% blasts.
Participants who never achieved CR or had no IWG disease assessment were considered to be non-responders in the calculation of CR rate.

End point type	Secondary

End point timeframe:

Response was assessed at Cycle 2, Day 1, Cycle 4, Day 1, and every 3 cycles thereafter; median duration of treatment was 4.2 months.

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: percentage of participants				
number (confidence interval 95%)	25.6 (16.6 to 36.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: CR Plus CR With Incomplete Blood Count Recovery (CRi) Rate

End point title	CR Plus CR With Incomplete Blood Count Recovery (CRi) Rate

End point description:

The percentage of participants who achieved a CR or CRi at any time point during the study per the modified IWG criteria for AML and investigator assessment.
CR: absolute neutrophil count (ANC) ≥ 10^3 /µL, platelet counts ≥ 10^5 /µL, red blood cell (RBC) transfusion independence (a period of at least 56 days with no RBC transfusion), and bone marrow with < 5% blasts.
CRi: lack of morphologic evidence of leukemia (blasts < 5%), and platelet counts < 10^5 /µL or ANC < 10^3 /µL
Participants who never achieved CR or CRi or had no IWG disease assessment were considered to be non-responders in the calculation of CR + CRi rate.

End point type	Secondary

End point timeframe:

Response was assessed at Cycle 2, Day 1, Cycle 4, Day 1, and every 3 cycles thereafter; median duration of treatment was 4.2 months.

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: percentage of participants				
number (confidence interval 95%)	53.7 (42.3 to 64.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: CR Plus CRi Rate by Initiation of Cycle 2

End point title	CR Plus CRi Rate by Initiation of Cycle 2

End point description:

The percentage of participants who achieved a CR or CRi by initiation of Cycle 2 of study treatment per the modified IWG criteria for AML and investigator assessment.
CR: ANC ≥ 10^3 /µL, platelet counts ≥ 10^5 /µL, RBC transfusion independence (a period of at least 56 days with no RBC transfusion), and bone marrow with < 5% blasts.
CRi: Lack of morphologic evidence of leukemia (blasts < 5%), and platelet counts < 10^5 /µL or ANC < 10^3 /µL.
Participants who never achieved CR or CRi or had no IWG disease assessment by initiation of Cycle 2 were considered to be non-responders in the calculation of CR + CRi rate by initiation of Cycle 2.

End point type	Secondary

End point timeframe:

Cycle 2, Day 1

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: percentage of participants				
number (confidence interval 95%)	28.0 (18.7 to 39.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Response of CR + CRi

End point title	Time to First Response of CR + CRi

End point description:

The time to the first response of CR + CRi is defined as the time from the first date of study drug to the first response of CR or CRi.

End point type	Secondary

End point timeframe:

Response was assessed at Cycle 2, Day 1, Cycle 4, Day 1, and every 3 cycles thereafter; median duration of treatment was 4.2 months.

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	44[19]			
Units: months				
median (full range (min-max))	1.4 (0.8 to 14.9)			

Notes:

[19] - Participants with a response of CR or CRi

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Best Response of CR + CRi

End point title	Time to Best Response of CR + CRi

End point description:

The time to the best response of CR + CRi is defined as the time from the first date of study drug to the best response of CR or CRi.

End point type	Secondary

End point timeframe:

Response was assessed at Cycle 2, Day 1, Cycle 4, Day 1, and every 3 cycles thereafter; median duration of treatment was 4.2 months.

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	44[20]			
Units: months				
median (full range (min-max))	2.8 (0.8 to 22.4)			

Notes:

[20] - Participants with a response of CR or CRi

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission With Partial Hematologic Recovery (CRh) Rate

End point title	Complete Remission With Partial Hematologic Recovery (CRh) Rate

End point description:

Complete remission with partial hematologic recovery) is a derived response based on bone marrow blast and hematology laboratory values. CRh rate is defined as the percentage of participants who achieved CRh as the best response at any time point during the study.
A participant achieved a CRh when meeting the following criteria:
- Bone marrow with < 5% blasts and
- Peripheral blood neutrophil count of > 0.5 × 10^3 /µL and
- Peripheral blood platelet count of > 0.5 × 10^5 /µL and

- A 1 week (≥ 7 days) platelet transfusion-free period prior to the hematology lab collection.
Participants who never achieved CRh or did not have disease assessment or hematology data were considered to be non-responders in the calculation of CRh rate.

End point type	Secondary

End point timeframe:

Response was assessed at Cycle 2, Day 1, Cycle 4, Day 1, and every 3 cycles thereafter; median duration of treatment was 4.2 months.

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: percentage of participants				
number (confidence interval 95%)	20.7 (12.6 to 31.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: CR Plus CRh Rate

End point title	CR Plus CRh Rate

End point description:

CR + CRh rate is defined as the percentage of participants who achieved CR or CRh at any time point during the study.
CR: ANC ≥ 10^3 /µL, platelet counts ≥ 10^5 /µL, RBC transfusion independence (a period of at least 56 days with no RBC transfusion), and bone marrow with < 5% blasts.
CRh is a derived response based on bone marrow blast and hematology lab values. A participant achieved a CRh when meeting the following criteria:
- Bone marrow with < 5% blasts and
- Peripheral blood neutrophil count of > 0.5 × 10^3 /µL and
- Peripheral blood platelet count of > 0.5 × 10^5 /µL and
- A 1 week (≥ 7 days) platelet transfusion-free period prior to the hematology lab collection.
Participants who never achieved CR/CRh or did not have disease assessment or hematology data were considered to be non-responders in the calculation of CR + CRh rate.

End point type	Secondary

End point timeframe:

Response was assessed at Cycle 2, Day 1, Cycle 4, Day 1, and every 3 cycles thereafter; median duration of treatment was 4.2 months.

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: percentage of participants				
number (confidence interval 95%)	46.3 (35.3 to			

57.7)

Statistical analyses

No statistical analyses for this end point

Secondary: CR Plus CRh Rate by Initiation of Cycle 2

End point title	CR Plus CRh Rate by Initiation of Cycle 2

End point description:

CR + CRh rate by initiation of Cycle 2 is defined as the percentage of participants who achieved CR or CRh by initiation of Cycle 2 of study treatment.
CR: ANC ≥ 10^3 /µL, platelet counts ≥ 10^5 /µL, RBC transfusion independence (a period of at least 56 days with no RBC transfusion), and bone marrow with < 5% blasts.
CRh is a derived response based on bone marrow blast and hematology lab values. A participant achieved a CRh when meeting the following criteria:
• Bone marrow with < 5% blasts and
• Peripheral blood neutrophil count of > 0.5 × 10^3 /µL and
• Peripheral blood platelet count of > 0.5 × 10^5 /µL and
• A 1 week (≥ 7 days) platelet transfusion-free period prior to the hematology lab collection.

Participants who never achieved CR/CRh or did not have disease assessment by initiation of Cycle 2 were considered to be non-responders in the calculation of CR + CRh rate by initiation of Cycle 2.

End point type	Secondary

End point timeframe:

Cycle 2, Day 1

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: percentage of participants				
number (confidence interval 95%)	30.5 (20.8 to 41.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Response of CR Plus CRh

End point title	Time to First Response of CR Plus CRh

End point description:

The time to the first response of CR + CRh is defined as the time from the first date of study drug to the first response of CR or CRh.

End point type	Secondary

End point timeframe:

Response was assessed at Cycle 2, Day 1, Cycle 4, Day 1, and every 3 cycles thereafter; median duration of treatment was 4.2 months.

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	38[21]			
Units: months				
median (full range (min-max))	1.0 (0.8 to 9.4)			

Notes:

[21] - Participants with a reponse of CR or CRh

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Best Response of CR Plus CRh

End point title	Time to Best Response of CR Plus CRh

End point description:

The time to the best response of CR + CRh is defined as the time from the first date of study drug to the best response of CR or CRh.

End point type	Secondary

End point timeframe:

Response was assessed at Cycle 2, Day 1, Cycle 4, Day 1, and every 3 cycles thereafter; median duration of treatment was 4.2 months.

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	38[22]			
Units: months				
median (full range (min-max))	2.6 (0.8 to 22.4)			

Notes:

[22] - Participants with a response of CR or CRh

Statistical analyses

No statistical analyses for this end point

Secondary: Best Response Based on IWG Criteria

End point title	Best Response Based on IWG Criteria

End point description:

Best response determined using the IWG-AML response criteria during the course of treatment.
-CR: ANC ≥ 10^3 /µL, platelet counts ≥ 10^5 /µL, RBC transfusion independence, and bone marrow with < 5% blasts;
-CRi: lack of morphologic evidence of leukemia (blasts < 5%), and platelet counts < 10^5 /µL or ANC < 10^3 /µL;
-PR: all of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate;
-MLFS: < 5% blasts in an aspirate and/or bone marrow core sample;
-RD: failure to achieve CR, CRi, PR; only including subjects surviving at least 7 days following completion of initial treatment cycle with evidence of persistent leukemia by blood and/or bone marrow examination;
-PD: one or more of the following: ≥ 50% decrement from maximum response levels in neutrophils or platelets; a reduction in hemoglobin by at least 2 g/dL; or transfusion dependence not due to other toxicities and bone marrow blast ≥ 5%.

End point type	Secondary

End point timeframe:

Response was assessed at Cycle 2, Day 1, Cycle 4, Day 1, and every 3 cycles thereafter; median duration of treatment was 4.2 months.

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: participants				
Complete Remission (CR)	21			
Complete Remission with Incomplete Marrow Recovery	23			
Partial Remission (PR)	1			
Morphologically Leukemia Free State (MLFS)	6			
Resistant Disease (RD)	19			
Disease Progression (PD)	4			
Discontinued With No Response Data (DS)	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Complete Response

End point title	Duration of Complete Response

End point description:

Duration of CR is defined as the time from date that a participant achieved CR to the first date of relapse, clinical disease progression or death due to disease progression, whichever occurred earliest. Duration of CR was estimated using Kaplan-Meier methodology. If a participant was still responding at the data cutoff date, then the subject's data was censored at their last disease assessment date. Disease assessment data after the onset of any post-treatment therapy were not included in the duration of CR analysis.
"99999" indicates values that could not be estimated.

End point type	Secondary

End point timeframe:

Median duration of follow-up was 44.5 months (range: 0.3 to 63.7)

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	21[23]			
Units: months				
median (confidence interval 95%)	14.8 (7.2 to 99999)			

Notes:

[23] - Participants with a reponse of CR

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of CR Plus CRi

End point title	Duration of CR Plus CRi

End point description:

Duration of CR + CRi is defined as the time from the date that a participant achieved CR or CRi to the first date of relapse, clinical disease progression or death due to disease progression, whichever occurred earliest. Duration of CR + CRi was estimated using Kaplan-Meier methodology. If a participant was still responding at the data cutoff date, then the participant's data were censored at their last disease assessment date. Disease assessment data after the onset of any post-treatment therapy were not included in the analysis.

End point type	Secondary

End point timeframe:

Median duration of follow-up was 44.5 months (range: 0.3 to 63.7)

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	44[24]			
Units: months				
median (confidence interval 95%)	9.8 (5.3 to 14.9)			

Notes:

[24] - Participants with a response of CR or CRi

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of CRi

End point title	Duration of CRi

End point description:

Duration of CRi is defined as the time from date that a participant achieved CRi to the first date of relapse, clinical disease progression or death due to disease progression, whichever occurred earliest. Duration of CRi was estimated using Kaplan-Meier methodology. If a participant was still responding at the data cutoff date, then the participant's data were censored at their last disease assessment date. Disease assessment data after the onset of any post-treatment therapy were not included in the analysis.

End point type	Secondary

End point timeframe:

Median duration of follow-up was 44.5 months (range: 0.3 to 63.7)

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	23[25]			
Units: months				
median (confidence interval 95%)	4.7 (2.6 to 5.6)			

Notes:

[25] - Participants with a response of CRi

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of CR Plus CRh

End point title	Duration of CR Plus CRh

End point description:

Duration of CR + CRh is defined as the time from date that a participant achieved CR or CRh to the first date of relapse, clinical disease progression or death due to disease progression, whichever occurred earliest. Duration of CR + CRh was estimated using Kaplan-Meier methodology. If a participant was still responding at the data cutoff date, then the participant's data were censored at their last disease assessment date. Disease assessment data after the onset of any post-treatment therapy were not included in the analysis.

End point type	Secondary

End point timeframe:

Median duration of follow-up was 44.5 months (range: 0.3 to 63.7)

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	38[26]			
Units: months				
median (confidence interval 95%)	11.0 (6.1 to 28.2)			

Notes:
[26] - Participants with a response of CR or CRh

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival is defined as the time from the date of first dose to the date of death. All events of death were included, regardless of whether the event occurred while the participant was still taking study drug, or after the participant discontinued study drug. OS was estimated using Kaplan-Meier methodology. Participants who were still alive were censored at the analysis date.

End point type	Secondary

End point timeframe:

Median duration of follow-up was 44.5 months (range: 0.3 to 63.7)

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: months				
median (confidence interval 95%)	9.7 (5.7 to 14.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Post Baseline Transfusion Independence Rate

End point title	Post Baseline Transfusion Independence Rate

End point description:

Post baseline transfusion independence rate was estimated as the percentage of participants who achieved transfusion independence during the evaluation period. Post-baseline transfusion independence is defined as a period of at least 56 days (≥ 56 days) with no RBC or platelet transfusion during the evaluation period. The evaluation period is from the first dose of study drug to the last dose of study drug until the 30 day follow-up visit, disease progression (including clinical progression), or death, whichever was earlier.

End point type	Secondary

End point timeframe:

From the first dose of study drug to the last dose of study drug plus 30 days, disease progression (including clinical progression), or death, whichever was earlier; median duration of treatment was 4.2 months.

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: percentage of participants				
number (confidence interval 95%)				
RBC and platelet	45.1 (34.1 to 56.5)			
RBC	47.6 (36.4 to 58.9)			
Platelet	58.5 (47.1 to 69.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Post Baseline Transfusion Independence Rate Among Participants Transfusion-dependent at Baseline

End point title	Post Baseline Transfusion Independence Rate Among Participants Transfusion-dependent at Baseline

End point description:

Post baseline transfusion independence rate was estimated as the percentage of participants who achieved transfusion independence during the evaluation period. Post-baseline transfusion independence is defined as a period of at least 56 days (≥ 56 days) with no RBC or platelet transfusion during the evaluation period. The evaluation period is from the first dose of study drug to the last dose of study drug until the 30 day follow-up visit, disease progression (including clinical progression), or death, whichever was earlier.

End point type	Secondary

End point timeframe:

From the first dose of study drug to the last dose of study drug plus 30 days, disease progression (including clinical progression), or death, whichever was earlier; median duration of treatment was 4.2 months.

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	60[27]			
Units: percentage of participants				
number (confidence interval 95%)				
RBC and Platelet	45.0 (32.1 to 58.4)			
RBC	45.3 (31.6 to 59.6)			

Platelet	60.9 (38.5 to 80.3)			

Notes:

[27] - Participants who were transfusion-dependent at Baseline; N=53 for RBC and 23 for platelet-dependent

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Post Baseline Transfusion Independence

End point title	Duration of Post Baseline Transfusion Independence

End point description:

The duration of transfusion independence is defined as the first time period that a participant received no RBC/platelet transfusions for at least 56 days during the evaluation period.
Post-baseline transfusion independence is defined as a period of at least 56 days with no RBC or platelet transfusion during the evaluation period. The evaluation period is from the first dose of study drug to the last dose of study drug until the 30 day follow-up visit, disease progression (including clinical progression), or death, whichever was earlier.

End point type	Secondary

End point timeframe:

From the first dose of study drug to the last dose of study drug plus 30 days, disease progression (including clinical progression), or death, whichever was earlier; median duration of treatment was 4.2 months.

End point values	Phase 1+2: 600 mg Venetoclax + LDAC			
Subject group type	Subject analysis set			
Number of subjects analysed	50[28]			
Units: days				
median (full range (min-max))				
RBC and Platelet (N = 37)	150 (56 to 1855)			
RBC (N = 39)	123 (56 to 1881)			
Platelet (N = 48)	155.5 (56 to 1855)			

Notes:

[28] - Participants who were post-baseline RBC or platelet transfusion independent.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until 30 days after last dose of study drug; median (minimum, maximum) duration of treatment was 4.1 (0.2, 62.8) months overall.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Phase 1: 600 mg Venetoclax + LDAC

Reporting group description:

Venetoclax was administered orally once daily (QD) on Days 2 through 28 of Cycle 1. Dosing started at 50 mg (Day 2) and increased up to 600 mg by Day 6. Beginning with Cycle 2, 600 mg venetoclax was administered Days 1 through 28 of each 28-day cycle. Participants also received low-dose cytarabine (LDAC; 20 mg/m²) administered by subcutaneous injection once daily on Days 1 to 10 of each cycle. Participants could continue receiving treatment until disease progression or until discontinuation criteria were met.

Reporting group title	Phase 2: 600 mg Venetoclax + LDAC

Reporting group description:

Venetoclax was administered orally once daily (QD) on Days 2 through 28 of Cycle 1. Dosing started at 50 mg, and increased up to 600 mg by Day 6. Beginning with Cycle 2, 800 mg venetoclax was administered Days 1 through 28 of each 28-day cycle. Participants also received LDAC (20 mg/m²) administered by subcutaneous injection once daily on Days 1 to 10 of each cycle.
Participants could continue receiving treatment until disease progression or until discontinuation criteria were met.

Reporting group title	Phase 1: 800 mg Venetoclax + LDAC

Reporting group description:

Venetoclax was administered orally once daily (QD) on Days 2 through 28 of Cycle 1. Dosing started at 100 mg (Day 2) and increased up to 800 mg by Day 6. Beginning with Cycle 2, 800 mg venetoclax was administered Days 1 through 28 of each 28-day cycle. Participants also received LDAC (20 mg/m²) administered by subcutaneous injection once daily on Days 1 to 10 of each cycle.
Participants could continue receiving treatment until disease progression or until discontinuation criteria were met.

Serious adverse events	Phase 1: 600 mg Venetoclax + LDAC	Phase 2: 600 mg Venetoclax + LDAC	Phase 1: 800 mg Venetoclax + LDAC
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	68 / 74 (91.89%)	9 / 10 (90.00%)
number of deaths (all causes)	6	63	10
number of deaths resulting from adverse events	1	15	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MALIGNANT NEOPLASM PROGRESSION			
subjects affected / exposed	0 / 8 (0.00%)	5 / 74 (6.76%)	2 / 10 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 2
Vascular disorders			

HYPERTENSION			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTENSION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 8 (12.50%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEATH			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
DEVICE RELATED THROMBOSIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
DISEASE PROGRESSION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
GAIT DISTURBANCE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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

HYPERPYREXIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
MUCOSAL INFLAMMATION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
MULTIPLE ORGAN DYSFUNCTION SYNDROME			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (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
PYREXIA			
subjects affected / exposed	1 / 8 (12.50%)	2 / 74 (2.70%)	4 / 10 (40.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUDDEN DEATH			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
DYSPNOEA			
subjects affected / exposed	0 / 8 (0.00%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

EPISTAXIS			
subjects affected / exposed	0 / 8 (0.00%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOXIA			
subjects affected / exposed	1 / 8 (12.50%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG DISORDER			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
PLEURITIC PAIN			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
PNEUMONITIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
PNEUMOTHORAX			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
PULMONARY ALVEOLAR HAEMORRHAGE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
PULMONARY OEDEMA			

subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
Psychiatric disorders			
CONFUSIONAL STATE			
subjects affected / exposed	0 / 8 (0.00%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENTAL STATUS CHANGES			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
PSYCHOTIC DISORDER DUE TO A GENERAL MEDICAL CONDITION			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (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
Investigations			
AMYLASE INCREASED			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
LIPASE INCREASED			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
TROPONIN INCREASED			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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

WHITE BLOOD CELL COUNT INCREASED			
subjects affected / exposed	1 / 8 (12.50%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	1 / 8 (12.50%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
FEMUR FRACTURE			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (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
INTENTIONAL OVERDOSE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
OVERDOSE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
POST-TRAUMATIC PAIN			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (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
SKIN LACERATION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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

SPLENIC RUPTURE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
SUBDURAL HAEMORRHAGE			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 8 (12.50%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 8 (0.00%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIOVENTRICULAR BLOCK FIRST DEGREE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
BRADYCARDIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

SINUS BRADYCARDIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (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
DEMENTIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	0 / 8 (0.00%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
HAEMORRHAGIC STROKE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
HEADACHE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
ISCHAEMIC STROKE			

subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
LACUNAR INFARCTION			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (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
LETHARGY			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
PRESYNCOPE			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBARACHNOID HAEMORRHAGE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
SYNCOPE			
subjects affected / exposed	1 / 8 (12.50%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			

subjects affected / exposed	1 / 8 (12.50%)	22 / 74 (29.73%)	3 / 10 (30.00%)
occurrences causally related to treatment / all	0 / 1	11 / 34	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOLYTIC ANAEMIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
NEUTROPENIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
Eye disorders			
DIPLOPIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 8 (0.00%)	2 / 74 (2.70%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
CONSTIPATION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
DIARRHOEA			

subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
DIVERTICULUM INTESTINAL HAEMORRHAGIC			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL DISORDER			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
HAEMORRHOIDAL HAEMORRHAGE			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTUSSUSCEPTION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
LARGE INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
LARGE INTESTINE PERFORATION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
LARGE INTESTINE POLYP			

subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
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 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
Hepatobiliary disorders			
ACUTE HEPATIC FAILURE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
CHOLECYSTITIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
HEPATIC FAILURE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
DYSURIA			

subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
HAEMATURIA			
subjects affected / exposed	0 / 8 (0.00%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY INCONTINENCE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
URINARY RETENTION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
BONE PAIN			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (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
BURSITIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
OSTEONECROSIS			

subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
Infections and infestations			
BACTERAEMIA			
subjects affected / exposed	0 / 8 (0.00%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACTERIAL SEPSIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
BRONCHOPULMONARY ASPERGILLOSIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CANDIDA PNEUMONIA			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
CELLULITIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
COVID-19			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
CYSTITIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
DEVICE RELATED INFECTION			

subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULITIS			
subjects affected / exposed	0 / 8 (0.00%)	3 / 74 (4.05%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA BACTERAEMIA			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
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	0 / 8 (0.00%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA URINARY TRACT INFECTION			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (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
GASTROENTERITIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
INFECTION			
subjects affected / exposed	0 / 8 (0.00%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTIOUS PLEURAL EFFUSION			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LARGE INTESTINE INFECTION			

subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
NOSOCOMIAL INFECTION			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (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
OSTEOMYELITIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
PARAINFLUENZAE VIRUS INFECTION			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (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
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
PNEUMONIA			
subjects affected / exposed	2 / 8 (25.00%)	11 / 74 (14.86%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 2	4 / 14	0 / 1
deaths causally related to treatment / all	0 / 1	1 / 2	0 / 0
PNEUMONIA KLEBSIELLA			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (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
PULMONARY SEPSIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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 FUNGAL			

subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	0 / 8 (0.00%)	8 / 74 (10.81%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
SEPTIC SHOCK			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
SERRATIA SEPSIS			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL SEPSIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
UPPER RESPIRATORY TRACT INFECTION BACTERIAL			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 8 (0.00%)	2 / 74 (2.70%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UROSEPSIS			

subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
VASCULAR DEVICE INFECTION			
subjects affected / exposed	1 / 8 (12.50%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
FAILURE TO THRIVE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
FLUID OVERLOAD			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	0 / 10 (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
HYPONATRAEMIA			
subjects affected / exposed	2 / 8 (25.00%)	0 / 74 (0.00%)	0 / 10 (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

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

Non-serious adverse events	Phase 1: 600 mg Venetoclax + LDAC	Phase 2: 600 mg Venetoclax + LDAC	Phase 1: 800 mg Venetoclax + LDAC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	74 / 74 (100.00%)	10 / 10 (100.00%)
Vascular disorders			
HAEMATOMA			
subjects affected / exposed	1 / 8 (12.50%)	2 / 74 (2.70%)	1 / 10 (10.00%)
occurrences (all)	1	2	1

HYPERTENSION			
subjects affected / exposed	1 / 8 (12.50%)	14 / 74 (18.92%)	1 / 10 (10.00%)
occurrences (all)	3	19	1
HYPOTENSION			
subjects affected / exposed	2 / 8 (25.00%)	12 / 74 (16.22%)	2 / 10 (20.00%)
occurrences (all)	2	14	3
MACROANGIOPATHY			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
CATHETER SITE INFLAMMATION			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
CATHETER SITE PAIN			
subjects affected / exposed	1 / 8 (12.50%)	2 / 74 (2.70%)	1 / 10 (10.00%)
occurrences (all)	1	3	1
CHEST DISCOMFORT			
subjects affected / exposed	1 / 8 (12.50%)	6 / 74 (8.11%)	0 / 10 (0.00%)
occurrences (all)	1	6	0
CHEST PAIN			
subjects affected / exposed	1 / 8 (12.50%)	3 / 74 (4.05%)	0 / 10 (0.00%)
occurrences (all)	2	3	0
CHILLS			
subjects affected / exposed	1 / 8 (12.50%)	6 / 74 (8.11%)	1 / 10 (10.00%)
occurrences (all)	1	13	1
DEVICE RELATED THROMBOSIS			
subjects affected / exposed	1 / 8 (12.50%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
FATIGUE			
subjects affected / exposed	7 / 8 (87.50%)	28 / 74 (37.84%)	3 / 10 (30.00%)
occurrences (all)	7	52	11
INJECTION SITE HAEMATOMA			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
MALAISE			

subjects affected / exposed	1 / 8 (12.50%)	6 / 74 (8.11%)	0 / 10 (0.00%)
occurrences (all)	1	6	0
MUCOSAL INFLAMMATION			
subjects affected / exposed	1 / 8 (12.50%)	8 / 74 (10.81%)	0 / 10 (0.00%)
occurrences (all)	1	9	0
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 8 (12.50%)	4 / 74 (5.41%)	2 / 10 (20.00%)
occurrences (all)	1	4	2
OEDEMA PERIPHERAL			
subjects affected / exposed	2 / 8 (25.00%)	13 / 74 (17.57%)	2 / 10 (20.00%)
occurrences (all)	5	18	2
PAIN			
subjects affected / exposed	0 / 8 (0.00%)	9 / 74 (12.16%)	0 / 10 (0.00%)
occurrences (all)	0	9	0
PYREXIA			
subjects affected / exposed	1 / 8 (12.50%)	14 / 74 (18.92%)	1 / 10 (10.00%)
occurrences (all)	3	15	1
Respiratory, thoracic and mediastinal disorders			
ATELECTASIS			
subjects affected / exposed	0 / 8 (0.00%)	3 / 74 (4.05%)	1 / 10 (10.00%)
occurrences (all)	0	3	1
COUGH			
subjects affected / exposed	1 / 8 (12.50%)	19 / 74 (25.68%)	1 / 10 (10.00%)
occurrences (all)	1	24	1
DYSPNOEA			
subjects affected / exposed	1 / 8 (12.50%)	20 / 74 (27.03%)	1 / 10 (10.00%)
occurrences (all)	1	33	1
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 8 (12.50%)	3 / 74 (4.05%)	1 / 10 (10.00%)
occurrences (all)	1	3	1
EPISTAXIS			
subjects affected / exposed	1 / 8 (12.50%)	9 / 74 (12.16%)	2 / 10 (20.00%)
occurrences (all)	1	12	2
HYPOXIA			

subjects affected / exposed	1 / 8 (12.50%)	7 / 74 (9.46%)	1 / 10 (10.00%)
occurrences (all)	1	7	1
NASAL CONGESTION			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	1 / 10 (10.00%)
occurrences (all)	0	4	1
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 8 (0.00%)	9 / 74 (12.16%)	1 / 10 (10.00%)
occurrences (all)	0	10	1
PLEURAL EFFUSION			
subjects affected / exposed	2 / 8 (25.00%)	10 / 74 (13.51%)	1 / 10 (10.00%)
occurrences (all)	3	10	2
PLEURITIC PAIN			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
PRODUCTIVE COUGH			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
PULMONARY OEDEMA			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	1 / 10 (10.00%)
occurrences (all)	0	4	1
RESPIRATORY DISTRESS			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
RESPIRATORY TRACT CONGESTION			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 8 (0.00%)	11 / 74 (14.86%)	0 / 10 (0.00%)
occurrences (all)	0	11	0
CONFUSIONAL STATE			
subjects affected / exposed	3 / 8 (37.50%)	7 / 74 (9.46%)	0 / 10 (0.00%)
occurrences (all)	3	7	0
DELIRIUM			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	4	0

DEPRESSION			
subjects affected / exposed	1 / 8 (12.50%)	10 / 74 (13.51%)	0 / 10 (0.00%)
occurrences (all)	2	11	0
FLAT AFFECT			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
HALLUCINATION, VISUAL			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
INSOMNIA			
subjects affected / exposed	1 / 8 (12.50%)	17 / 74 (22.97%)	1 / 10 (10.00%)
occurrences (all)	1	17	1
MOOD ALTERED			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
PROCEDURAL ANXIETY			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
RESTLESSNESS			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
SLEEP DISORDER			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Investigations			
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED			
subjects affected / exposed	1 / 8 (12.50%)	8 / 74 (10.81%)	0 / 10 (0.00%)
occurrences (all)	1	14	0
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 8 (12.50%)	7 / 74 (9.46%)	1 / 10 (10.00%)
occurrences (all)	2	9	5
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 8 (0.00%)	8 / 74 (10.81%)	0 / 10 (0.00%)
occurrences (all)	0	10	0

BLOOD ALBUMIN DECREASED			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	13	0
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	0 / 8 (0.00%)	10 / 74 (13.51%)	0 / 10 (0.00%)
occurrences (all)	0	27	0
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	0 / 8 (0.00%)	19 / 74 (25.68%)	2 / 10 (20.00%)
occurrences (all)	0	33	4
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 8 (0.00%)	8 / 74 (10.81%)	1 / 10 (10.00%)
occurrences (all)	0	18	7
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	1 / 8 (12.50%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
BLOOD URIC ACID INCREASED			
subjects affected / exposed	1 / 8 (12.50%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
HEART RATE IRREGULAR			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
INTERNATIONAL NORMALISED RATIO INCREASED			
subjects affected / exposed	0 / 8 (0.00%)	8 / 74 (10.81%)	0 / 10 (0.00%)
occurrences (all)	0	11	0
LIVER FUNCTION TEST ABNORMAL			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
LIVER FUNCTION TEST INCREASED			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	0 / 8 (0.00%)	15 / 74 (20.27%)	0 / 10 (0.00%)
occurrences (all)	0	116	0
NEUTROPHIL COUNT DECREASED			

subjects affected / exposed	0 / 8 (0.00%)	14 / 74 (18.92%)	0 / 10 (0.00%)
occurrences (all)	0	92	0
PLATELET COUNT DECREASED			
subjects affected / exposed	1 / 8 (12.50%)	20 / 74 (27.03%)	0 / 10 (0.00%)
occurrences (all)	1	152	0
PROTHROMBIN TIME PROLONGED			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
SPECIFIC GRAVITY URINE DECREASED			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
TROPONIN INCREASED			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
WEIGHT DECREASED			
subjects affected / exposed	0 / 8 (0.00%)	6 / 74 (8.11%)	0 / 10 (0.00%)
occurrences (all)	0	6	0
WEIGHT INCREASED			
subjects affected / exposed	1 / 8 (12.50%)	3 / 74 (4.05%)	1 / 10 (10.00%)
occurrences (all)	1	3	1
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	0 / 8 (0.00%)	28 / 74 (37.84%)	2 / 10 (20.00%)
occurrences (all)	0	170	2
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	0 / 8 (0.00%)	2 / 74 (2.70%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
FALL			
subjects affected / exposed	0 / 8 (0.00%)	7 / 74 (9.46%)	1 / 10 (10.00%)
occurrences (all)	0	9	1
HEAD INJURY			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
INFUSION RELATED REACTION			

subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	1 / 10 (10.00%)
occurrences (all)	0	6	1
OVERDOSE			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
PERIORBITAL HAEMATOMA			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
PROCEDURAL PAIN			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	1 / 10 (10.00%)
occurrences (all)	0	4	2
SUNBURN			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
TOOTH FRACTURE			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
WOUND			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Cardiac disorders			
ANGINA PECTORIS			
subjects affected / exposed	1 / 8 (12.50%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 8 (0.00%)	6 / 74 (8.11%)	0 / 10 (0.00%)
occurrences (all)	0	8	0
BRADYCARDIA			
subjects affected / exposed	2 / 8 (25.00%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences (all)	2	3	0
CARDIAC FAILURE			
subjects affected / exposed	1 / 8 (12.50%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
SINUS TACHYCARDIA			
subjects affected / exposed	0 / 8 (0.00%)	6 / 74 (8.11%)	0 / 10 (0.00%)
occurrences (all)	0	9	0

TACHYCARDIA			
subjects affected / exposed	0 / 8 (0.00%)	6 / 74 (8.11%)	1 / 10 (10.00%)
occurrences (all)	0	6	1
Nervous system disorders			
CEREBRAL MICROANGIOPATHY			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
DIZZINESS			
subjects affected / exposed	2 / 8 (25.00%)	11 / 74 (14.86%)	1 / 10 (10.00%)
occurrences (all)	7	18	1
HEADACHE			
subjects affected / exposed	3 / 8 (37.50%)	20 / 74 (27.03%)	2 / 10 (20.00%)
occurrences (all)	4	24	2
LETHARGY			
subjects affected / exposed	1 / 8 (12.50%)	2 / 74 (2.70%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
PARAESTHESIA			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
RESTLESS LEGS SYNDROME			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
SINUS HEADACHE			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
SOMNOLENCE			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
TASTE DISORDER			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
TREMOR			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
Blood and lymphatic system disorders			

ANAEMIA			
subjects affected / exposed	5 / 8 (62.50%)	19 / 74 (25.68%)	2 / 10 (20.00%)
occurrences (all)	6	72	2
FEBRILE NEUTROPENIA			
subjects affected / exposed	1 / 8 (12.50%)	12 / 74 (16.22%)	0 / 10 (0.00%)
occurrences (all)	1	13	0
HYPOFIBRINOGENAEMIA			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
LEUKOPENIA			
subjects affected / exposed	0 / 8 (0.00%)	2 / 74 (2.70%)	1 / 10 (10.00%)
occurrences (all)	0	4	2
NEUTROPENIA			
subjects affected / exposed	4 / 8 (50.00%)	19 / 74 (25.68%)	4 / 10 (40.00%)
occurrences (all)	10	25	5
THROMBOCYTOPENIA			
subjects affected / exposed	4 / 8 (50.00%)	26 / 74 (35.14%)	4 / 10 (40.00%)
occurrences (all)	4	44	11
Eye disorders			
ERYTHEMA OF EYELID			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
EYE PAIN			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
RETINAL HAEMORRHAGE			
subjects affected / exposed	1 / 8 (12.50%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
VISION BLURRED			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	1 / 8 (12.50%)	3 / 74 (4.05%)	1 / 10 (10.00%)
occurrences (all)	1	3	1
ABDOMINAL PAIN			

subjects affected / exposed	1 / 8 (12.50%)	11 / 74 (14.86%)	1 / 10 (10.00%)
occurrences (all)	1	17	2
ABDOMINAL PAIN LOWER			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	1 / 10 (10.00%)
occurrences (all)	0	5	1
CONSTIPATION			
subjects affected / exposed	2 / 8 (25.00%)	27 / 74 (36.49%)	3 / 10 (30.00%)
occurrences (all)	3	30	3
DIARRHOEA			
subjects affected / exposed	6 / 8 (75.00%)	34 / 74 (45.95%)	2 / 10 (20.00%)
occurrences (all)	7	61	4
DRY MOUTH			
subjects affected / exposed	0 / 8 (0.00%)	3 / 74 (4.05%)	1 / 10 (10.00%)
occurrences (all)	0	3	1
DYSPEPSIA			
subjects affected / exposed	1 / 8 (12.50%)	6 / 74 (8.11%)	0 / 10 (0.00%)
occurrences (all)	1	7	0
ERUCTATION			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
FLATULENCE			
subjects affected / exposed	0 / 8 (0.00%)	2 / 74 (2.70%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
GASTROINTESTINAL PAIN			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
HAEMORRHOIDS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1

LIP ULCERATION			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
MOUTH HAEMORRHAGE			
subjects affected / exposed	2 / 8 (25.00%)	6 / 74 (8.11%)	0 / 10 (0.00%)
occurrences (all)	2	8	0
MOUTH ULCERATION			
subjects affected / exposed	0 / 8 (0.00%)	6 / 74 (8.11%)	0 / 10 (0.00%)
occurrences (all)	0	6	0
NAUSEA			
subjects affected / exposed	8 / 8 (100.00%)	48 / 74 (64.86%)	6 / 10 (60.00%)
occurrences (all)	13	67	12
ODYNOPHAGIA			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
PARAESTHESIA ORAL			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
STOMATITIS			
subjects affected / exposed	0 / 8 (0.00%)	6 / 74 (8.11%)	1 / 10 (10.00%)
occurrences (all)	0	7	1
TONGUE HAEMATOMA			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
TOOTHACHE			
subjects affected / exposed	1 / 8 (12.50%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	1	4	0
TRICHOGLOSSIA			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
VOMITING			
subjects affected / exposed	3 / 8 (37.50%)	21 / 74 (28.38%)	3 / 10 (30.00%)
occurrences (all)	4	30	5
Skin and subcutaneous tissue disorders			
ACNE			

subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
DRY SKIN			
subjects affected / exposed	2 / 8 (25.00%)	6 / 74 (8.11%)	0 / 10 (0.00%)
occurrences (all)	2	6	0
ERYTHEMA			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
NAIL DISCOLOURATION			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
PETECHIAE			
subjects affected / exposed	1 / 8 (12.50%)	7 / 74 (9.46%)	1 / 10 (10.00%)
occurrences (all)	1	14	1
PRURITUS			
subjects affected / exposed	0 / 8 (0.00%)	10 / 74 (13.51%)	0 / 10 (0.00%)
occurrences (all)	0	11	0
PURPURA			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
RASH			
subjects affected / exposed	1 / 8 (12.50%)	7 / 74 (9.46%)	0 / 10 (0.00%)
occurrences (all)	1	8	0
RASH ERYTHEMATOUS			
subjects affected / exposed	1 / 8 (12.50%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
RASH MACULAR			
subjects affected / exposed	1 / 8 (12.50%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
RASH MACULO-PAPULAR			
subjects affected / exposed	1 / 8 (12.50%)	5 / 74 (6.76%)	0 / 10 (0.00%)
occurrences (all)	1	5	0
RASH PAPULAR			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
SKIN LESION			

subjects affected / exposed	1 / 8 (12.50%)	2 / 74 (2.70%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
STASIS DERMATITIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	2 / 8 (25.00%)	6 / 74 (8.11%)	3 / 10 (30.00%)
occurrences (all)	3	10	3
HAEMATURIA			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
POLLAKIURIA			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
URINARY INCONTINENCE			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
Endocrine disorders			
HYPERTHYROIDISM			
subjects affected / exposed	1 / 8 (12.50%)	1 / 74 (1.35%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 8 (12.50%)	12 / 74 (16.22%)	3 / 10 (30.00%)
occurrences (all)	1	20	3
BACK PAIN			
subjects affected / exposed	2 / 8 (25.00%)	14 / 74 (18.92%)	2 / 10 (20.00%)
occurrences (all)	2	16	2
BONE PAIN			
subjects affected / exposed	1 / 8 (12.50%)	1 / 74 (1.35%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
CHONDROCALCINOSIS PYROPHOSPHATE			
subjects affected / exposed	1 / 8 (12.50%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
GROIN PAIN			

subjects affected / exposed	1 / 8 (12.50%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
JOINT SWELLING			
subjects affected / exposed	1 / 8 (12.50%)	3 / 74 (4.05%)	2 / 10 (20.00%)
occurrences (all)	1	3	2
LIMB MASS			
subjects affected / exposed	1 / 8 (12.50%)	1 / 74 (1.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
MUSCLE SPASMS			
subjects affected / exposed	0 / 8 (0.00%)	3 / 74 (4.05%)	1 / 10 (10.00%)
occurrences (all)	0	4	1
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	5	0
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	1 / 8 (12.50%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	1	4	0
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
NECK PAIN			
subjects affected / exposed	3 / 8 (37.50%)	4 / 74 (5.41%)	1 / 10 (10.00%)
occurrences (all)	3	4	1
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 8 (12.50%)	11 / 74 (14.86%)	3 / 10 (30.00%)
occurrences (all)	2	13	3
Infections and infestations			
BRONCHOPULMONARY ASPERGILLOSIS ALLERGIC			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
CELLULITIS			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
CLOSTRIDIUM DIFFICILE INFECTION			

subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
DEVICE RELATED INFECTION			
subjects affected / exposed	0 / 8 (0.00%)	5 / 74 (6.76%)	0 / 10 (0.00%)
occurrences (all)	0	5	0
ESCHERICHIA URINARY TRACT INFECTION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
HERPES SIMPLEX			
subjects affected / exposed	0 / 8 (0.00%)	1 / 74 (1.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
HORDEOLUM			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
NASOPHARYNGITIS			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
ORAL CANDIDIASIS			
subjects affected / exposed	0 / 8 (0.00%)	5 / 74 (6.76%)	1 / 10 (10.00%)
occurrences (all)	0	7	1
PARONYCHIA			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
PNEUMONIA			
subjects affected / exposed	0 / 8 (0.00%)	5 / 74 (6.76%)	0 / 10 (0.00%)
occurrences (all)	0	6	0
SIALOADENITIS			
subjects affected / exposed	1 / 8 (12.50%)	0 / 74 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 8 (12.50%)	4 / 74 (5.41%)	1 / 10 (10.00%)
occurrences (all)	1	4	1
URINARY TRACT INFECTION			

subjects affected / exposed	0 / 8 (0.00%)	7 / 74 (9.46%)	0 / 10 (0.00%)
occurrences (all)	0	9	0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	5 / 8 (62.50%)	25 / 74 (33.78%)	2 / 10 (20.00%)
occurrences (all)	7	32	2
FLUID OVERLOAD			
subjects affected / exposed	2 / 8 (25.00%)	3 / 74 (4.05%)	3 / 10 (30.00%)
occurrences (all)	2	4	3
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 8 (12.50%)	9 / 74 (12.16%)	1 / 10 (10.00%)
occurrences (all)	1	12	3
HYPERMAGNESAEMIA			
subjects affected / exposed	0 / 8 (0.00%)	4 / 74 (5.41%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
HYPERPHOSPHATAEMIA			
subjects affected / exposed	0 / 8 (0.00%)	10 / 74 (13.51%)	0 / 10 (0.00%)
occurrences (all)	0	11	0
HYPERURICAEMIA			
subjects affected / exposed	0 / 8 (0.00%)	7 / 74 (9.46%)	1 / 10 (10.00%)
occurrences (all)	0	7	1
HYPOALBUMINAEMIA			
subjects affected / exposed	0 / 8 (0.00%)	10 / 74 (13.51%)	0 / 10 (0.00%)
occurrences (all)	0	28	0
HYPOCALCAEMIA			
subjects affected / exposed	1 / 8 (12.50%)	22 / 74 (29.73%)	1 / 10 (10.00%)
occurrences (all)	1	61	1
HYPOCHLORAEMIA			
subjects affected / exposed	0 / 8 (0.00%)	0 / 74 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
HYPOGLYCAEMIA			
subjects affected / exposed	1 / 8 (12.50%)	2 / 74 (2.70%)	0 / 10 (0.00%)
occurrences (all)	1	4	0
HYPOKALAEMIA			
subjects affected / exposed	4 / 8 (50.00%)	36 / 74 (48.65%)	3 / 10 (30.00%)
occurrences (all)	5	77	5

HYPOMAGNESAEMIA			
subjects affected / exposed	1 / 8 (12.50%)	27 / 74 (36.49%)	3 / 10 (30.00%)
occurrences (all)	2	44	4
HYPONATRAEMIA			
subjects affected / exposed	0 / 8 (0.00%)	16 / 74 (21.62%)	1 / 10 (10.00%)
occurrences (all)	0	48	1
HYPOPHOSPHATAEMIA			
subjects affected / exposed	2 / 8 (25.00%)	22 / 74 (29.73%)	1 / 10 (10.00%)
occurrences (all)	3	41	1
TUMOUR LYSIS SYNDROME			
subjects affected / exposed	0 / 8 (0.00%)	2 / 74 (2.70%)	1 / 10 (10.00%)
occurrences (all)	0	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 November 2015	The purpose of this amendment is to: ● Update ABT-199 throughout protocol with venetoclax (ABT-199/GDC-0199). ● Update Introduction with the most current venetoclax information released in the Investigator's Brochure (IB) Edition 6. ● Update 95% Confidence Intervals for Assumed Observed Rates Based on Sample Size of 50 Subjects; and increase the number of subjects to be enrolled in Phase 2 to approximately 50 to improve accuracy of estimation of the Overall Response Rate (ORR). ● Update Inclusion Criteria to remove the requirement to do 24-hour urine collection for subjects whose BMI is > 25 and alert investigators to consider measuring creatinine clearance in other situations if appropriate. ● Update Exclusion Criteria, Prior and Concomitant Therapy; Excluded and Cautionary Medications and Dietary Restrictions to be consistent with updated PK findings. ● Replace Week 12 with Cycle 3 throughout the protocol. ● Change every 12 weeks to every 3 Cycles. ● Add Bone Marrow Aspirate for Bcl-2 Family Protein Analysis sample to allow investigation of the relationship between pre-treatment potential biomarkers and response to venetoclax treatment and to evaluate for the potential change of potential biomarkers after treatment. ● Add a Cycle 4 Day 1 pharmacogenetic sample. ● Update Tumor Lysis Syndrome Prophylaxis to start 24 hours prior to first dose and Confinement requirements since for some subjects hydration and allopurinol administration can be achieved equally well without hospital admission. ● Clarified sample analysis process information. ● Clarified results to be reported ● Update Deaths to note that deaths due solely to the progression of AML should not be considered an adverse event. ● Addition of AbbVie Medical Escalation Hotline information. ● Clarify definition of dose-limiting toxicity.

28 November 2016	• Updated introduction with new venetoclax preclinical toxicology. • Updated the primary objective and added Cohort C to the study, increasing the sample size by 20 subjects, to evaluate ORR and safety when allowing subjects who potentially require co-treatment with a strong CYP3A inhibitor. • Added the Cohort C study population to add additional objective criteria to help define subjects with AML who are not eligible for anthracycline-based induction therapy. • Added the Cohort C dosing instruction to simplify dosing for subjects to receive both LDC and venetoclax starting on Day 1. • Updated Overall Study Design and Plan, Safety and Efficacy Measurement, Discontinuation of Individual Subjects with Post-treatment follow-up visit and Survival Assessment language to evaluate the disease course and survival of subjects after study treatment has concluded. • Inclusion Criteria updated to clarify subject's age, include subjects with ECOG performance status of 3 for subjects who are 60 – 74 years of age, include subjects with Creatinine Clearance of greater or equal to 30 mL/min, clarify bilirubin requirements for subjects with different age group, and clarify the postmenopausal female population requirement for the study entry. • Exclusion Criteria updated to allow strong and moderate CYP3A inhibitors under cautionary medication with appropriate dose reduction, allow subjects with cardiovascular disability status of New York Heart Association up to Class 2, exclude subjects with history of myeloproliferative neoplasm (MPN) including polycythemia vera, myelofibrosis, essential thrombocythemia, or chronic myelogenous leukemia. • Updated dose modification required if moderate or strong CYP3A inhibitor is taken. • Added Complaints section. • Updated Dose Reduction Guidelines for Management of Persistent Neutropenia or Thrombocytopenia. • Updated Prophylaxis and Management of Tumor Lysis Syndrome (TLS).
31 May 2017	• Updated introduction section with the new venetoclax preclinical toxicology. • Efficacy endpoint was modified to remove Time to Progression (TTP) and Progression Free Survival (PFS) and add Event Free Survival (EFS) throughout the protocol. • Leukemia response rate was updated to include MLFS. • Updated Sample List of Excluded and Cautionary Medications to change the classification of diltiazem from strong to moderate CYP3A inhibitor.
24 January 2018	• Update Efficacy Summaries section to add CRh rates and transfusion independence endpoints. • Updated Excluded and Cautionary Medications and Dietary Restrictions Table to remove weak CYP3A inhibitors, weak CYP3A inducers and OATP1B1/B3 inhibitors as these classes of drugs are no longer considered to be cautionary. • Updated list of Signatories for Protocol Amendment 4. • Update Appendix C, Sample List of Excluded and Cautionary Medications to remove examples of weak CYP3A inhibitors, weak CYP3A inducers and OATP1B1/B3 inhibitors, as these drugs are no longer considered to be cautionary.

22 March 2019	The purpose of this amendment was: ● To extend allowable treatment period from 2 to 3 years from last subject enrolled in the study. ● Update "from last subject enrolled" to "from last subject's last dose" when referring to the point at which post-treatment and survival assessments are conducted from. ● To update the Post-Treatment/Survival follow-up visits to occur every 12 weeks (± 1 week) for 1 year from last subject's last dose. ● To update survival period to occur every 12 weeks up to 1 year from last subject's last dose to reduce burden to subjects who are in long term follow up and no longer receiving study therapy. ● To update Venetoclax Preclinical Toxicology and Clinical Data Rationale to be consistent with the IB v10.0. ● Update Sample List of Excluded and Cautionary Medications to remove examples Azithromycin. The rationale for removal is the results of DDI study of azithromycin evaluating its effect on venetoclax PK, exposures of venetoclax did not change significantly.
17 February 2020	The purpose of this amendment was to: ● To extend allowable treatment period from 3 to 4 years from last subject enrolled in the study. ● To update Venetoclax Clinical Data Rationale to be consistent with the IB v12.0.
22 October 2020	The purpose of this amendment was to: ● Benefits and Risks - included information on the re-evaluation of the benefit and risk with consideration of Coronavirus Disease 2019 present in subject's region. ● Safety and Efficacy Measurements Assessed and Flow Chart - added instructions for necessary changes to activities or procedures in the event of temporary study [drug] interruption/halt. ● Treatments Administered - included instructions that in the event the subject cannot pick up venetoclax onsite, DTP shipment can be done as needed and permitted by local regulations. ● Protocol Deviations - clarified that protocol deviations may include modifications due to COVID-19. ● Ethical Conduct of the Study - noted that AbbVie will modify the study protocol as necessary due to the pandemic. Investigators must also notify AbbVie if any urgent safety measures are taken. ● Source Documents - noted that remote monitoring may be employed as needed. ● Modified the language for survival and post treatment follow up time frames to permit a shorter duration of follow up if all patients have discontinued and most patients have expired.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported