



Clinical trial results:

A Prospective, Open-Label, Multicenter Randomized Phase III Trial to Compare The Efficacy and Safety of A Combined Regimen of Obinutuzumab and Venetoclax (GDC-0199/ABT-199) Versus Obinutuzumab and Chlorambucil in Previously Untreated Patients With CLL and Coexisting Medical Conditions

Summary

EudraCT number	2014-001810-24
Trial protocol	DE DK GB EE AT BG ES HR IT FR PL
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	01 September 2019
First version publication date	01 September 2019

Trial information

Trial identification

Sponsor protocol code	BO25323
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02242942
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	17 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 August 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

This study compared the efficacy and safety of a combined regimen of obinutuzumab and venetoclax versus obinutuzumab + chlorambucil in subjects with previously untreated chronic lymphocytic leukemia (CLL) and coexisting medical conditions. The study had a safety run-in phase and a main randomized phase with two treatment arms.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 December 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 47
Country: Number of subjects enrolled	New Zealand: 20
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Bulgaria: 33
Country: Number of subjects enrolled	Croatia: 12
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Russian Federation: 41
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Brazil: 22
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	United States: 30
Country: Number of subjects enrolled	Denmark: 21
Country: Number of subjects enrolled	France: 39
Country: Number of subjects enrolled	Germany: 58
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	Switzerland: 3

Country: Number of subjects enrolled	United Kingdom: 8
Worldwide total number of subjects	445
EEA total number of subjects	262

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)	74
From 65 to 84 years	356
85 years and over	15

Subject disposition

Recruitment

Recruitment details:

A total of 445 subjects were enrolled in the study in 130 centers in 21 countries. The safety run-in cohort enrolled 13 subjects and the main randomized main part of the trial enrolled 432 subjects.

Pre-assignment

Screening details:

Subjects with previously untreated CLL and coexisting medical conditions were enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Obinutuzumab + Chlorambucil

Arm description:

Subjects received obinutuzumab for 6 cycles and chlorambucil for 12 cycles. Cycles comprised of 28 days.

Arm type	Experimental
Investigational medicinal product name	Chlorambucil
Investigational medicinal product code	RO0059978
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Chlorambucil was administered orally at a dose of 0.5 mg/kg on Day 1 and Day 15 of each 28-day cycle for 12 cycles.

Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	RO5072759
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received obinutuzumab 1000 mg on Days 1, 8 and 15 of Cycle 1 and 1000 mg on Day 1 through Cycles 2-6.

Arm title	Obinutuzumab + Venetoclax
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Arm description:

Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days.

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	RO5072759
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received obinutuzumab 1000 mg on Days 1, 8 and 15 of Cycle 1 and 1000 mg on Day 1 through Cycles 2-6.

Investigational medicinal product name	Venetoclax
Investigational medicinal product code	RO553-7382
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received venetoclax 400 mg daily orally for twelve 28-day cycles.	
Arm title	Safety Run-in Obinutuzumab + Venetoclax

Arm description:

Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days.

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	RO5072759
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received obinutuzumab intravenously for six 28-day cycles.

Investigational medicinal product name	Venetoclax
Investigational medicinal product code	RO553-7382
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received venetoclax 400 mg orally daily for twelve 28-day cycles.

Number of subjects in period 1	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax	Safety Run-in Obinutuzumab + Venetoclax
Started	216	216	13
Treated	214	212	13
Completed	0	0	0
Not completed	216	216	13
Adverse event, serious fatal	17	20	2
Consent withdrawn by subject	8	10	-
Physician decision	1	-	-
On-going in Study	190	186	11

Baseline characteristics

Reporting groups

Reporting group title	Obinutuzumab + Chlorambucil
Reporting group description: Subjects received obinutuzumab for 6 cycles and chlorambucil for 12 cycles. Cycles comprised of 28 days.	
Reporting group title	Obinutuzumab + Venetoclax
Reporting group description: Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days.	
Reporting group title	Safety Run-in Obinutuzumab + Venetoclax
Reporting group description: Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days.	

Reporting group values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax	Safety Run-in Obinutuzumab + Venetoclax
Number of subjects	216	216	13
Age categorical Units: Subjects			
Adults (18-64 years)	37	36	1
Elderly (From 65-84 years)	174	172	10
Elderly 85 years and over	5	8	2
Age Continuous Units: Years			
arithmetic mean	71.1	71.1	75.4
standard deviation	± 8.0	± 8.2	± 7.8
Sex: Female, Male Units: Subjects			
Female	73	70	5
Male	143	146	8

Reporting group values	Total		
Number of subjects	445		
Age categorical Units: Subjects			
Adults (18-64 years)	74		
Elderly (From 65-84 years)	356		
Elderly 85 years and over	15		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	148		
Male	297		

End points

End points reporting groups

Reporting group title	Obinutuzumab + Chlorambucil
Reporting group description:	
Subjects received obinutuzumab for 6 cycles and chlorambucil for 12 cycles. Cycles comprised of 28 days.	
Reporting group title	Obinutuzumab + Venetoclax
Reporting group description:	
Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days.	
Reporting group title	Safety Run-in Obinutuzumab + Venetoclax
Reporting group description:	
Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days.	

Primary: Progression Free Survival (PFS) Based on Investigator Assessment According to IWCLL Criteria

End point title	Progression Free Survival (PFS) Based on Investigator Assessment According to IWCLL Criteria ^[1]
End point description:	
PFS was determined according to IWCLL 2008 criteria and defined as the time from randomisation to the first occurrence of PD or death from any cause. Disease progression was characterized by at least one of the following: 1) $\geq 50\%$ increase in the absolute number of circulating lymphocytes to at least $5 \times 10^9/L$; 2) Appearance of new palpable lymph nodes (> 15 mm in longest diameter) or any new extra-nodal lesion; 3) $\geq 50\%$ increase in the longest diameter of any previous site of lymphadenopathy; 4) $\geq 50\%$ increase in the enlargement of the liver and/or spleen; 5) Transformation to a more aggressive histology. Intent to treat (ITT) population was defined as all randomised subjects. Here, 9999 indicates that the data for the specific time point were not evaluable due to insufficient number of subjects with events.	
End point type	Primary
End point timeframe:	
Baseline until disease progression or death up to approximately 3.75 years	

Notes:

[1] - 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: Efficacy data were analysed only for the randomised arms in the main study.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	216		
Units: months				
median (confidence interval 95%)	9999 (31.1 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	Main study analysis
Comparison groups	Obinutuzumab + Venetoclax v Obinutuzumab + Chlorambucil

Number of subjects included in analysis	432
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.53

Secondary: Progression Free Survival (PFS) Based on Institutional Review Committee (IRC)-Assessments According to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Criteria

End point title	Progression Free Survival (PFS) Based on Institutional Review Committee (IRC)-Assessments According to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Criteria ^[2]
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End point description:

PFS was determined according to IWCLL 2008 criteria and defined as the time from randomisation to the first occurrence of progressive disease (PD) or death from any cause. Disease progression was characterised by at least one of the following: 1) $\geq 50\%$ increase in the absolute number of circulating lymphocytes to at least $5 \times 10^9/L$; 2) Appearance of new palpable lymph nodes (> 15 mm in longest diameter) or any new extra-nodal lesion; 3) $\geq 50\%$ increase in the longest diameter of any previous site of lymphadenopathy; 4) $\geq 50\%$ increase in the enlargement of the liver and/or spleen; 5) Transformation to a more aggressive histology. ITT population was defined as all randomised subjects. Here, 9999 indicates that the data for the specific time point were not evaluable due to insufficient number of subjects with events.

End point type	Secondary
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End point timeframe:

Baseline until disease progression or death up to approximately 3.75 years

Notes:

[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: Efficacy data were analysed only for the randomised arms in the main study.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	216		
Units: months				
median (confidence interval 95%)	9999 (31.1 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With an Overall Response (OR) at Completion of Treatment, as Determined by the Investigator According to IWCLL Criteria

End point title	Percentage of Subjects With an Overall Response (OR) at Completion of Treatment, as Determined by the Investigator According to IWCLL Criteria ^[3]
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End point description:

OR: complete response (CR), CR with incomplete bone marrow recovery (CRi), or partial response (PR) according to IWCLL 2008 criteria. CR requires all of the following: peripheral blood lymphocytes below $4 \times 10^9/L$, absence of lymphadenopathy by physical examination and computed tomography (CT) scan, no hepatomegaly or splenomegaly, absence of disease or constitutional symptoms, blood counts of neutrophils $>1.5 \times 10^9/L$, platelets $>100 \times 10^9/L$ and hemoglobin >110 g/L, bone marrow normocellular for age without clonal infiltrate (except for CRi). PR: two of the following for at least 2 months: $\geq 50\%$ decrease in peripheral blood lymphocyte count from the pretreatment value, $\geq 50\%$ reduction in lymphadenopathy, $\geq 50\%$ reduction of liver and/or spleen enlargement, and at least one of the following counts: neutrophils $>1.5 \times 10^9/L$, platelets $>100 \times 10^9/L$ and hemoglobin >110 g/L. ITT population: all randomised subjects. 9999: data not evaluable due to insufficient number of events.

End point type	Secondary
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End point timeframe:

At the completion of treatment assessment 3 months after treatment completion (at approximately 15 months)

Notes:

[3] - 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: Efficacy data were analysed only for the randomised arms in the main study.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	216		
Units: percentage of subjects				
number (confidence interval 95%)	71.3 (64.77 to 77.23)	84.7 (79.22 to 89.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With a Complete Response Rate (CRR) at the Completion of Treatment Assessment as Determined by the Investigator According to IWCLL Criteria

End point title	Percentage of Subjects With a Complete Response Rate (CRR) at the Completion of Treatment Assessment as Determined by the Investigator According to IWCLL Criteria ^[4]
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End point description:

CRR was defined as the rate of a clinical response of CR or CRi according to IWCLL 2008 criteria. CR requires all of the following: peripheral blood lymphocytes below $4 \times 10^9/L$, absence of lymphadenopathy by physical examination and CT scan, no hepatomegaly or splenomegaly, absence of disease or constitutional symptoms, blood counts of neutrophils $>1.5 \times 10^9/L$, platelets $>100 \times 10^9/L$ and hemoglobin >110 g/L, bone marrow at least normocellular for age without clonal infiltrate (except for CRi). ITT population was defined as all randomised subjects.

End point type	Secondary
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End point timeframe:

At the completion of treatment assessment 3 months after treatment completion (at approximately 15 months)

Notes:

[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: Efficacy data were analysed only for the randomised arms in the main study.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	216		
Units: percentage of subjects				
number (confidence interval 95%)	23.1 (17.70 to 29.35)	49.5 (42.68 to 56.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Minimal Residual Disease (MRD) Negativity in Peripheral Blood as Measured by Allele-Specific Oligonucleotide Polymerase Chain Reaction (ASO-PCR) at Completion of Treatment

End point title	Percentage of Subjects With Minimal Residual Disease (MRD) Negativity in Peripheral Blood as Measured by Allele-Specific Oligonucleotide Polymerase Chain Reaction (ASO-PCR) at Completion of Treatment ^[5]
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End point description:

MRD negativity was defined as having < 1 CLL cell per 10,000 leucocytes in peripheral blood. ITT population was defined as all randomised subjects.

End point type	Secondary
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End point timeframe:

At the completion of treatment assessment 3 months after treatment completion (at approximately 15 months)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Efficacy data were analysed only for the randomised arms in the main study.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	216		
Units: percentage of subjects				
number (confidence interval 95%)	35.2 (28.83 to 41.95)	75.5 (69.17 to 81.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With MRD Negativity in Bone marrow as Measured by ASO-PCR at Completion of Treatment

End point title	Percentage of Subjects With MRD Negativity in Bone marrow as Measured by ASO-PCR at Completion of Treatment ^[6]
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End point description:

MRD negativity was defined as having < 1 CLL cell per 10,000 leucocytes in bone marrow. ITT population was defined as all randomised subjects.

End point type	Secondary
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End point timeframe:

At the completion of treatment assessment 3 months after treatment completion (at approximately 15 months)

Notes:

[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: Efficacy data were analysed only for the randomised arms in the main study.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	216		
Units: percentage of subjects				
number (confidence interval 95%)	17.1 (12.36 to 22.83)	56.9 (50.05 to 63.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS) ^[7]
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End point description:

OS was defined as the time between the date of randomization and the date of death due to any cause.
ITT population was defined as all randomised subjects.

End point type	Secondary
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End point timeframe:

Baseline until death, up to approximately 5.75 years

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data will be analysed only for the randomised arms in the main study once data collection is complete.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[8]	0 ^[9]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[8] - Data to be reported upon study completion.

[9] - Data to be reported upon study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With MRD Negativity in Peripheral Blood as Measured by ASO-PCR at Completion of Combination Treatment Assessment

End point title	Percentage of Subjects With MRD Negativity in Peripheral Blood as Measured by ASO-PCR at Completion of Combination Treatment Assessment ^[10]
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End point description:

MRD negativity was defined as having < 1 CLL cell per 10,000 leucocytes in peripheral blood. ITT population was defined as all randomised subjects.

End point type	Secondary
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End point timeframe:

Day 1 Cycle 9 or 3 months after last IV infusion, approximately 9 months

Notes:

[10] - 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: Efficacy data were analysed only for the randomised arms in the main study.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	216		
Units: percentage of subjects				
number (confidence interval 95%)	38.4 (31.91 to 45.27)	71.3 (64.77 to 77.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With MRD Negativity in Bone Marrow as Measured by ASO-PCR at Completion of Combination Treatment Assessment

End point title	Percentage of Subjects With MRD Negativity in Bone Marrow as Measured by ASO-PCR at Completion of Combination Treatment Assessment ^[11]
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End point description:

MRD negativity was defined as having < 1 CLL cell per 10,000 leucocytes in bone marrow. ITT population was defined as all randomised subjects.

End point type	Secondary
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End point timeframe:

Day 1 Cycle 9 or 3 months after last IV infusion at approximately 9 months

Notes:

[11] - 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: Efficacy data were analysed only for the randomised arms in the main study.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	216		
Units: percentage of subjects				
number (confidence interval 95%)	13.0 (8.79 to 18.19)	51.4 (44.51 to 58.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With OR at Completion of Combination Treatment Response Assessment

End point title	Percentage of Subjects With OR at Completion of Combination Treatment Response Assessment ^[12]
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End point description:

OR was defined as CR, CRi or PR according to IWCLL 2008 criteria. CR required all of the following: peripheral blood lymphocytes below $4 \times 10^9/L$, absence of lymphadenopathy by physical examination, no hepatomegaly or splenomegaly, Absence of disease or constitutional symptoms, blood counts of neutrophils $>1.5 \times 10^9/L$, platelets $>100 \times 10^9/L$ and hemoglobin >110 g/L. PR: two of the following features for at least 2 months: $\geq 50\%$ decrease in peripheral blood lymphocyte count from the pretreatment value, $\geq 50\%$ reduction in lymphadenopathy, $\geq 50\%$ reduction of liver and/or spleen enlargement, and at least one of the following blood counts: neutrophils $>1.5 \times 10^9/L$, platelets $>100 \times 10^9/L$ and hemoglobin >110 g/L. ITT population was defined as all randomised subjects.

End point type	Secondary
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End point timeframe:

Day 1 Cycle 7 or 28 days after last IV infusion, approximately 6 months

Notes:

[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: Efficacy data were analysed only for the randomised arms in the main study.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	216		
Units: percentage of subjects				
number (confidence interval 95%)	86.6 (81.29 to 90.82)	88.4 (83.39 to 92.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response (DOR)

End point title	Duration of Objective Response (DOR) ^[13]
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End point description:

PD was defined as lymphadenopathy, $\geq 50\%$ increase in liver or spleen size, $\geq 50\%$ increase in lymphocyte count, transformation to a more aggressive histology or occurrence of cytopenia. ITT population was defined as all randomised subjects.

End point type	Secondary
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End point timeframe:

Time from the first occurrence of a documented objective response to the time of PD as determined by the investigator or death from any cause, up to approximately 5.75 years

Notes:

[13] - 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: Data will be analysed only for the randomised arms in the main study once data collection is complete.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[14]	0 ^[15]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[14] - Data to be reported upon study completion.

[15] - Data to be reported upon study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects By Best Response Achieved (CR, CRi, PR, Stable Disease (SD), or PD)

End point title	Percentage of Subjects By Best Response Achieved (CR, CRi, PR, Stable Disease (SD), or PD) ^[16]
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End point description:

CR: Peripheral blood lymphocytes below $4 \times 10^9/L$, absence of lymphadenopathy by physical examination and CT scan, no hepatomegaly or splenomegaly, absence of disease or constitutional symptoms, blood counts of neutrophils $>1.5 \times 10^9/L$, platelets $>100 \times 10^9/L$ and hemoglobin >110 g/L, bone marrow normocellular for age without clonal infiltrate (except for CRi). PR: any 2 for at least 2 months: $\geq 50\%$ decrease in peripheral blood lymphocyte count from the pretreatment value, $\geq 50\%$ reduction in lymphadenopathy, $\geq 50\%$ reduction of liver and/or spleen enlargement, and at least one of the following: neutrophils $>1.5 \times 10^9/L$, platelets $>100 \times 10^9/L$ and hemoglobin >110 g/L. PD: lymphadenopathy, $\geq 50\%$ increase in liver or spleen size, $\geq 50\%$ increase in lymphocyte count, transformation to a more aggressive histology or occurrence of cytopenia. SD: non-response used to characterize subjects who did not achieve a CR or a PR, and who have not exhibited PD. ITT population: all randomised subjects.

End point type	Secondary
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End point timeframe:

Baseline up to the completion of treatment assessment 3 months after treatment completion (up to approximately 15 months)

Notes:

[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: Efficacy data were analysed only for the randomised arms in the main study.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	216		
Units: percentage of subjects				
number (not applicable)				
CR	56.0	70.4		
CRi	5.6	7.9		
PR	29.2	13.4		
SD	1.9	0.5		
PD	0.5	0.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival

End point title	Event-Free Survival ^[17]
End point description: ITT population was defined as all randomised subjects.	
End point type	Secondary
End point timeframe: Time between date of randomisation and the date of disease progression/relapse on the basis of investigator-assessment, death, or start of a new anti-leukemic therapy, up to 5.75 years	

Notes:

[17] - 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: Data will be analysed only for the randomised arms in the main study once data collection is complete.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[18]	0 ^[19]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[18] - Data to be reported upon study completion.

[19] - Data to be reported upon study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Next Anti-Leukemic Treatment

End point title	Time to Next Anti-Leukemic Treatment ^[20]
End point description: ITT population was defined as all randomised subjects.	
End point type	Secondary
End point timeframe: Time between the date of randomization and the date of first intake of new anti-leukemic therapy, up to 5.75 years	

Notes:

[20] - 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: Data will be analysed only for the randomised arms in the main study once data collection is complete.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[21]	0 ^[22]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[21] - Data to be reported upon study completion.

[22] - Data to be reported upon study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs)

End point title	Number of Subjects With Adverse Events (AEs) ^[23]
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End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as AEs. Safety population was defined as all subjects who received at least one dose of any study medication (i.e., obinutuzumab, venetoclax, or chlorambucil).

End point type	Secondary
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End point timeframe:

Up to approximately 5.75 years

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data will be analysed only for the randomised arms in the main study once data collection is complete.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[24]	0 ^[25]		
Units: subjects				

Notes:

[24] - Data to be reported upon study completion.

[25] - Data to be reported upon study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With CD19 + /CD5+ B Cells or CD14+ monocytes

End point title	Percentage of Subjects With CD19 + /CD5+ B Cells or CD14+ monocytes
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End point description:

ITT population was defined as all randomised subjects.

End point type	Secondary
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End point timeframe:

Baseline up to approximately 5.75 years

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax	Safety Run-in Obinutuzumab + Venetoclax	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[26]	0 ^[27]	0 ^[28]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[26] - Data to be reported upon study completion.

[27] - Data to be reported upon study completion.

[28] - Data to be reported upon study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Human-Anti-Human Antibodies

End point title	Percentage of Subjects With Human-Anti-Human Antibodies
End point description:	ITT population was defined as all randomised subjects.
End point type	Secondary
End point timeframe:	
Baseline up to approximately 5.75 years	

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax	Safety Run-in Obinutuzumab + Venetoclax	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[29]	0 ^[30]	0 ^[31]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[29] - Data to be reported upon study completion.

[30] - Data to be reported upon study completion.

[31] - Data to be reported upon study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Recorded as Premature Study Withdrawals

End point title	Percentage of Subjects Recorded as Premature Study Withdrawals
End point description:	ITT population was defined as all randomised subjects.
End point type	Secondary
End point timeframe:	
Up to approximately 5.75 years	

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax	Safety Run-in Obinutuzumab + Venetoclax	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[32]	0 ^[33]	0 ^[34]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[32] - Data to be reported upon study completion.

[33] - Data to be reported upon study completion.

[34] - Data to be reported upon study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Venetoclax

End point title	Plasma Concentrations of Venetoclax ^[35]
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End point description:

Analysis population consisted of those subjects from whom one or more plasma samples were collected and who had received at least one dose of venetoclax treatment.

End point type	Secondary
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End point timeframe:

Pre-venetoclax dose (0 hour) and 4 hours post- venetoclax dose on Day 1 Cycle 4

Notes:

[35] - 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: Samples were only collected for the obinutuzumab + venetoclax arm in the study.

End point values	Obinutuzumab + Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	201			
Units: µg/mL				
arithmetic mean (standard deviation)				
Pre-Dose (n=129)	0.578 (± 0.533)			
4 hours Post-Dose (n=142)	1.21 (± 0.765)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentrations of Obinutuzumab

End point title	Serum Concentrations of Obinutuzumab ^[36]
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End point description:

Analysis population consisted of subjects from whom one or more serum samples were collected and

who had received at least one dose of obinutuzumab treatment.

End point type	Secondary
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End point timeframe:

Pre-obinutuzumab infusion (0 hour) and end of obinutuzumab infusion on Day 1 Cycle 4

Notes:

[36] - 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: Samples were only collected for the obinutuzumab + venetoclax arm in the study.

End point values	Obinutuzumab + Venetoclax			
Subject group type	Reporting group			
Number of subjects analysed	201			
Units: µg/mL				
arithmetic mean (standard deviation)				
Pre-Dose (n=133)	258 (± 140)			
4 hours Post-Dose (n=133)	568 (± 187)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in M.D. Anderson Symptom Inventory-CLL (MDASI-CLL) score

End point title	Change From Baseline in M.D. Anderson Symptom Inventory-CLL (MDASI-CLL) score ^[37]
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End point description:

MDASI-CLL: questionnaire of 25 items related to CLL specific symptoms that a subject may have experienced in the past 24 hours. Subjects were asked to rate the severity of 13 symptoms called mean core symptom severity (i.e., pain, fatigue, nausea, disturbed sleep, distressed, shortness of breath, remembering things, lack of appetite, drowsy, dry mouth, sadness, vomiting, numbness or tingling), 6 disease-specific symptoms called mean module symptom severity (night sweats, fevers and chills, lymph node swelling, diarrhea, easy bruising or bleeding, constipation) and 6 mean interference on life questions (i.e., general activity, walking, work, mood, relations with other people, enjoyment of life) on a scale from 0 to 10 with 0 indicating that the symptom is "not present"/"did not interfere" with the subject's activities and 10 indicating "as bad as you can imagine"/"interfered completely". Scores were averaged (range 0 to 10) for each part.

End point type	Secondary
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End point timeframe:

Baseline up to approximately 5.75 years

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data will be analysed only for the randomised arms in the main study once data collection is complete.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[38]	0 ^[39]		
Units: score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[38] - Data to be reported upon study completion.

[39] - Data to be reported upon study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQC30)

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQC30)
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End point description:

The EORTC QLQ-C30 is a validated and reliable self-report measure consisting of 30 questions incorporated into five functional scales (physical, role, cognitive, emotional, and social scales), three symptom scales (fatigue, pain, nausea, and vomiting scales), and a global health status/global quality-of-life scale. The remaining single items (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) assess the additional symptoms experienced by patients with cancer and the perceived financial burden of treatment. The 28 function and symptom items were scored on a 4-point scale that ranged from "not at all" to "very much," and the 2 global health status/global quality-of-life items were scored on a 7-point scale that ranged from "very poor" to "excellent." Raw average scale scores were linearly transformed to range 0-100 with higher scores indicating higher response levels (i.e., higher functioning, higher symptom severity).

End point type	Secondary
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End point timeframe:

Baseline up to approximately 5.75 years

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax	Safety Run-in Obinutuzumab + Venetoclax	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[40]	0 ^[41]	0 ^[42]	
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[40] - Data to be reported upon study completion.

[41] - Data to be reported upon study completion.

[42] - Data to be reported upon study completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQol 5 Dimension Questionnaire (EQ-5D-3L)

End point title	Change From Baseline in EuroQol 5 Dimension Questionnaire (EQ-5D-3L) ^[43]
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End point description:

The EQ-5D-3L questionnaire is a generic, preference based health utility measure that assesses 5 health states (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and is used to build a composite of the patient's health status. The EQ-5D-3L was employed in this study to calculate health utilities for economic modeling, which ranged 0-1. The EQ-5D-3L also contained a visual analog scale (VAS) to assess the participant's overall health, which ranged from 0-100 with a higher score indicating a worse health status.

End point type	Secondary
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End point timeframe:

Baseline up to approximately 5.75 years

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data will be analysed only for the randomised arms in the main study once data collection is complete.

End point values	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[44]	0 ^[45]		
Units: score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[44] - Data to be reported upon study completion.

[45] - Data to be reported upon study completion.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs: up to 1 year, Grade 3-4 AEs: up to 1.5 years, Grade 3-4 major infections: up to 3 years (causality only if subject received leukemic treatment). SAEs: before PD up to 3.75 years, after PD only related SAEs and second primary malignancies.

Adverse event reporting additional description:

Safety population was defined as all subjects who received at least one dose of any study medication (i.e., obinutuzumab, venetoclax, or chlorambucil).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Obinutuzumab + Chlorambucil
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Reporting group description:

Subjects received obinutuzumab for 6 cycles and chlorambucil for 12 cycles. Cycles comprised of 28 days.

Reporting group title	Obinutuzumab + Venetoclax
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Reporting group description:

Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days.

Reporting group title	Safety Run-in Obinutuzumab + Venetoclax
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Reporting group description:

Subjects received obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles comprised of 28 days.

Serious adverse events	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax	Safety Run-in Obinutuzumab + Venetoclax
Total subjects affected by serious adverse events			
subjects affected / exposed	90 / 214 (42.06%)	104 / 212 (49.06%)	10 / 13 (76.92%)
number of deaths (all causes)	9	16	2
number of deaths resulting from adverse events	1	5	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Anal squamous cell carcinoma			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Basal cell carcinoma			

subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Bladder cancer			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Bladder cancer recurrent			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Bladder neoplasm			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive breast carcinoma			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Lung adenocarcinoma			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Lung adenocarcinoma stage IV			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Malignant melanoma			

subjects affected / exposed	1 / 214 (0.47%)	1 / 212 (0.47%)	0 / 13 (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
Metastatic malignant melanoma			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Myelodysplastic syndrome			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Penile cancer			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Prostate cancer			
subjects affected / exposed	0 / 214 (0.00%)	2 / 212 (0.94%)	0 / 13 (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
Prostate cancer metastatic			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Salivary gland adenoma			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Sarcoma of skin			

subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Skin squamous cell carcinoma metastatic			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	3 / 214 (1.40%)	2 / 212 (0.94%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
T-cell lymphoma			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 214 (0.00%)	2 / 212 (0.94%)	0 / 13 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Hypertension			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Hypotension			
subjects affected / exposed	2 / 214 (0.93%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			

subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Thrombophlebitis superficial			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Surgical and medical procedures			
Aortic valve replacement			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Medical device removal			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Asthenia			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Chills			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Device related thrombosis			
subjects affected / exposed	1 / 214 (0.47%)	1 / 212 (0.47%)	0 / 13 (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
Fatigue			
subjects affected / exposed	1 / 214 (0.47%)	1 / 212 (0.47%)	0 / 13 (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
General physical health deterioration			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pyrexia			
subjects affected / exposed	7 / 214 (3.27%)	8 / 212 (3.77%)	2 / 13 (15.38%)
occurrences causally related to treatment / all	5 / 8	3 / 8	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Bronchitis chronic			

subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Bronchopneumopathy			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Bronchospasm			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 214 (0.93%)	3 / 212 (1.42%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 214 (0.47%)	1 / 212 (0.47%)	0 / 13 (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
Dyspnoea			
subjects affected / exposed	0 / 214 (0.00%)	2 / 212 (0.94%)	0 / 13 (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
Hypoxia			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Lung disorder			
subjects affected / exposed	1 / 214 (0.47%)	1 / 212 (0.47%)	0 / 13 (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
Pleural effusion			

subjects affected / exposed	2 / 214 (0.93%)	1 / 212 (0.47%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Pulmonary oedema			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Delirium			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Depression			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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			

Alanine aminotransferase increased			
subjects affected / exposed	3 / 214 (1.40%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 214 (1.87%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood urea increased			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Hepatic enzyme increased			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Prothrombin time prolonged			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Transaminases increased			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Injury, poisoning and procedural complications			
Chillblains			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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

Clavicle fracture			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Femoral neck fracture			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Head injury			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Infusion related reaction			
subjects affected / exposed	13 / 214 (6.07%)	9 / 212 (4.25%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	12 / 13	9 / 9	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	2 / 214 (0.93%)	0 / 212 (0.00%)	0 / 13 (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
Lumbar vertebral fracture			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Pelvic fracture			

subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Subcutaneous haematoma			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Subdural haematoma			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Thoracic vertebral fracture			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Toxicity to various agents			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Transfusion reaction			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Traumatic haemothorax			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Vasoplegia syndrome			

subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound evisceration			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Congenital, familial and genetic disorders			
Gilbert's syndrome			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 214 (0.00%)	2 / 212 (0.94%)	0 / 13 (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
Atrial fibrillation			
subjects affected / exposed	3 / 214 (1.40%)	1 / 212 (0.47%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	2 / 214 (0.93%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 214 (0.47%)	1 / 212 (0.47%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0

Cardiac failure			
subjects affected / exposed	1 / 214 (0.47%)	3 / 212 (1.42%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Myocardial infarction			
subjects affected / exposed	3 / 214 (1.40%)	1 / 212 (0.47%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	2 / 214 (0.93%)	0 / 212 (0.00%)	0 / 13 (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
Tachycardia			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Cerebral infarction			

subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Cerebral ischaemia			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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	0 / 214 (0.00%)	1 / 212 (0.47%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculopathy			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Seizure			

subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 214 (0.93%)	1 / 212 (0.47%)	0 / 13 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 214 (0.47%)	1 / 212 (0.47%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar insufficiency			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 214 (0.47%)	2 / 212 (0.94%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Coombs negative haemolytic anaemia			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Febrile neutropenia			

subjects affected / exposed	8 / 214 (3.74%)	11 / 212 (5.19%)	3 / 13 (23.08%)
occurrences causally related to treatment / all	9 / 10	11 / 12	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 214 (0.47%)	3 / 212 (1.42%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Splenic infarction			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenomegaly			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Thrombocytopenia			
subjects affected / exposed	5 / 214 (2.34%)	2 / 212 (0.94%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	5 / 5	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 214 (0.00%)	2 / 212 (0.94%)	0 / 13 (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
Eye disorders			

Amaurosis fugax			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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 inflammation			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Keratitis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Diarrhoea			
subjects affected / exposed	0 / 214 (0.00%)	2 / 212 (0.94%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Enteritis			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Faecaloma			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Gastric ulcer perforation			

subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Inguinal hernia			
subjects affected / exposed	1 / 214 (0.47%)	2 / 212 (0.94%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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 gastrointestinal haemorrhage			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Cholelithiasis			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Rash			

subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Urticaria			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	2 / 214 (0.93%)	0 / 212 (0.00%)	0 / 13 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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 pain			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Spondylitis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 214 (0.47%)	1 / 212 (0.47%)	0 / 13 (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

Bronchiolitis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 214 (0.93%)	2 / 212 (0.94%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Candida infection			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Cellulitis			
subjects affected / exposed	0 / 214 (0.00%)	3 / 212 (1.42%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Cytomegalovirus infection			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Device related infection			

subjects affected / exposed	0 / 214 (0.00%)	2 / 212 (0.94%)	0 / 13 (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
Eczema infected			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Endocarditis			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Erysipelas			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Gastroenteritis			
subjects affected / exposed	2 / 214 (0.93%)	0 / 212 (0.00%)	0 / 13 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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 infection			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Hepatitis E			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Herpes zoster			

subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	2 / 214 (0.93%)	2 / 212 (0.94%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 2	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Infectious pleural effusion			
subjects affected / exposed	1 / 214 (0.47%)	1 / 212 (0.47%)	0 / 13 (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
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Influenza			
subjects affected / exposed	2 / 214 (0.93%)	1 / 212 (0.47%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Listeriosis			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Lung infection			
subjects affected / exposed	2 / 214 (0.93%)	0 / 212 (0.00%)	0 / 13 (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
Muscle abscess			

subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Neutropenic infection			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 214 (0.47%)	1 / 212 (0.47%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	9 / 214 (4.21%)	10 / 212 (4.72%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	6 / 11	3 / 10	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia fungal			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Pneumonia haemophilus			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomembranous colitis			

subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Pyelonephritis			
subjects affected / exposed	1 / 214 (0.47%)	1 / 212 (0.47%)	0 / 13 (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
Respiratory tract infection			
subjects affected / exposed	1 / 214 (0.47%)	2 / 212 (0.94%)	0 / 13 (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
Sepsis			
subjects affected / exposed	2 / 214 (0.93%)	6 / 212 (2.83%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	1 / 2	3 / 7	0 / 2
deaths causally related to treatment / all	0 / 1	2 / 5	0 / 1
Septic shock			
subjects affected / exposed	2 / 214 (0.93%)	1 / 212 (0.47%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Sinusitis aspergillus			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Soft tissue infection			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Staphylococcal infection			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	1 / 214 (0.47%)	1 / 212 (0.47%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 214 (0.47%)	2 / 212 (0.94%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Varicella zoster virus infection			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Wound infection fungal			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Dehydration			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Hypercalcaemia			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Hyperglycaemia			
subjects affected / exposed	2 / 214 (0.93%)	1 / 212 (0.47%)	0 / 13 (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
Hyperkalaemia			

subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	0 / 13 (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
Hypoglycaemia			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	0 / 13 (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
Hyponatraemia			
subjects affected / exposed	1 / 214 (0.47%)	1 / 212 (0.47%)	0 / 13 (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
Tumour lysis syndrome			
subjects affected / exposed	4 / 214 (1.87%)	1 / 212 (0.47%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	4 / 4	1 / 1	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	Obinutuzumab + Chlorambucil	Obinutuzumab + Venetoclax	Safety Run-in Obinutuzumab + Venetoclax
Total subjects affected by non-serious adverse events			
subjects affected / exposed	205 / 214 (95.79%)	193 / 212 (91.04%)	12 / 13 (92.31%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	5 / 214 (2.34%)	6 / 212 (2.83%)	1 / 13 (7.69%)
occurrences (all)	6	6	1
Benign breast neoplasm			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Seborrhoeic keratosis			
subjects affected / exposed	0 / 214 (0.00%)	2 / 212 (0.94%)	1 / 13 (7.69%)
occurrences (all)	0	2	1
Skin papilloma			

subjects affected / exposed occurrences (all)	0 / 214 (0.00%) 0	1 / 212 (0.47%) 1	1 / 13 (7.69%) 1
Vascular disorders			
Flushing			
subjects affected / exposed	3 / 214 (1.40%)	2 / 212 (0.94%)	2 / 13 (15.38%)
occurrences (all)	3	2	2
Hypertension			
subjects affected / exposed	11 / 214 (5.14%)	12 / 212 (5.66%)	0 / 13 (0.00%)
occurrences (all)	12	17	0
Hypotension			
subjects affected / exposed	8 / 214 (3.74%)	11 / 212 (5.19%)	2 / 13 (15.38%)
occurrences (all)	10	15	2
Thrombophlebitis			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Asthenia			
subjects affected / exposed	17 / 214 (7.94%)	14 / 212 (6.60%)	0 / 13 (0.00%)
occurrences (all)	20	20	0
Chills			
subjects affected / exposed	10 / 214 (4.67%)	12 / 212 (5.66%)	1 / 13 (7.69%)
occurrences (all)	13	14	1
Extravasation			
subjects affected / exposed	2 / 214 (0.93%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
Fatigue			
subjects affected / exposed	29 / 214 (13.55%)	32 / 212 (15.09%)	3 / 13 (23.08%)
occurrences (all)	36	40	6
Influenza like illness			
subjects affected / exposed	3 / 214 (1.40%)	4 / 212 (1.89%)	1 / 13 (7.69%)
occurrences (all)	3	4	1
Oedema			

subjects affected / exposed	7 / 214 (3.27%)	3 / 212 (1.42%)	1 / 13 (7.69%)
occurrences (all)	7	3	1
Oedema peripheral			
subjects affected / exposed	16 / 214 (7.48%)	17 / 212 (8.02%)	1 / 13 (7.69%)
occurrences (all)	18	20	2
Pyrexia			
subjects affected / exposed	26 / 214 (12.15%)	40 / 212 (18.87%)	3 / 13 (23.08%)
occurrences (all)	28	53	4
Sensation of foreign body			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 214 (11.21%)	33 / 212 (15.57%)	6 / 13 (46.15%)
occurrences (all)	27	37	6
Dyspnoea			
subjects affected / exposed	11 / 214 (5.14%)	11 / 212 (5.19%)	1 / 13 (7.69%)
occurrences (all)	12	12	2
Epistaxis			
subjects affected / exposed	4 / 214 (1.87%)	3 / 212 (1.42%)	1 / 13 (7.69%)
occurrences (all)	5	3	1
Pharyngeal paraesthesia			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	3 / 214 (1.40%)	6 / 212 (2.83%)	1 / 13 (7.69%)
occurrences (all)	3	6	2
Rhinorrhoea			
subjects affected / exposed	3 / 214 (1.40%)	3 / 212 (1.42%)	1 / 13 (7.69%)
occurrences (all)	3	3	1
Throat irritation			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Psychiatric disorders			

Depression subjects affected / exposed occurrences (all)	1 / 214 (0.47%) 1	8 / 212 (3.77%) 8	1 / 13 (7.69%) 1
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	13 / 214 (6.07%) 15	11 / 212 (5.19%) 15	0 / 13 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	17 / 214 (7.94%) 20	12 / 212 (5.66%) 14	0 / 13 (0.00%) 0
Blood albumin decreased subjects affected / exposed occurrences (all)	0 / 214 (0.00%) 0	0 / 212 (0.00%) 0	1 / 13 (7.69%) 1
Blood creatinine increased subjects affected / exposed occurrences (all)	6 / 214 (2.80%) 6	7 / 212 (3.30%) 9	1 / 13 (7.69%) 2
Blood glucose increased subjects affected / exposed occurrences (all)	1 / 214 (0.47%) 1	1 / 212 (0.47%) 1	1 / 13 (7.69%) 1
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	2 / 214 (0.93%) 2	2 / 212 (0.94%) 2	2 / 13 (15.38%) 2
Blood magnesium decreased subjects affected / exposed occurrences (all)	0 / 214 (0.00%) 0	1 / 212 (0.47%) 1	1 / 13 (7.69%) 1
Blood phosphorus increased subjects affected / exposed occurrences (all)	1 / 214 (0.47%) 1	2 / 212 (0.94%) 4	1 / 13 (7.69%) 1
C-reactive protein increased subjects affected / exposed occurrences (all)	2 / 214 (0.93%) 2	4 / 212 (1.89%) 4	1 / 13 (7.69%) 1
Neutrophil count decreased subjects affected / exposed occurrences (all)	11 / 214 (5.14%) 32	10 / 212 (4.72%) 27	0 / 13 (0.00%) 0
Procalcitonin increased			

subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Protein total decreased			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Transaminases increased			
subjects affected / exposed	2 / 214 (0.93%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
Weight decreased			
subjects affected / exposed	5 / 214 (2.34%)	5 / 212 (2.36%)	1 / 13 (7.69%)
occurrences (all)	5	5	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Eye contusion			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Fall			
subjects affected / exposed	8 / 214 (3.74%)	5 / 212 (2.36%)	1 / 13 (7.69%)
occurrences (all)	11	7	1
Head injury			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	103 / 214 (48.13%)	89 / 212 (41.98%)	9 / 13 (69.23%)
occurrences (all)	131	122	10
Limb injury			
subjects affected / exposed	4 / 214 (1.87%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	4	0	1
Skin abrasion			
subjects affected / exposed	0 / 214 (0.00%)	2 / 212 (0.94%)	1 / 13 (7.69%)
occurrences (all)	0	2	1
Cardiac disorders			

Coronary artery disease subjects affected / exposed occurrences (all)	0 / 214 (0.00%) 0	0 / 212 (0.00%) 0	1 / 13 (7.69%) 1
Tachycardia subjects affected / exposed occurrences (all)	1 / 214 (0.47%) 1	5 / 212 (2.36%) 5	1 / 13 (7.69%) 1
Ventricular extrasystoles subjects affected / exposed occurrences (all)	1 / 214 (0.47%) 1	1 / 212 (0.47%) 1	1 / 13 (7.69%) 1
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	17 / 214 (7.94%) 20	16 / 212 (7.55%) 18	4 / 13 (30.77%) 5
Headache subjects affected / exposed occurrences (all)	21 / 214 (9.81%) 24	23 / 212 (10.85%) 29	3 / 13 (23.08%) 3
Paraesthesia subjects affected / exposed occurrences (all)	1 / 214 (0.47%) 1	4 / 212 (1.89%) 4	1 / 13 (7.69%) 1
Presyncope subjects affected / exposed occurrences (all)	1 / 214 (0.47%) 1	1 / 212 (0.47%) 1	2 / 13 (15.38%) 3
Somnolence subjects affected / exposed occurrences (all)	0 / 214 (0.00%) 0	1 / 212 (0.47%) 1	1 / 13 (7.69%) 1
Syncope subjects affected / exposed occurrences (all)	4 / 214 (1.87%) 4	5 / 212 (2.36%) 5	2 / 13 (15.38%) 2
Tremor subjects affected / exposed occurrences (all)	3 / 214 (1.40%) 4	6 / 212 (2.83%) 6	1 / 13 (7.69%) 1
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	39 / 214 (18.22%) 55	33 / 212 (15.57%) 53	2 / 13 (15.38%) 2
Leukopenia			

subjects affected / exposed	13 / 214 (6.07%)	12 / 212 (5.66%)	1 / 13 (7.69%)
occurrences (all)	19	23	1
Neutropenia			
subjects affected / exposed	122 / 214 (57.01%)	121 / 212 (57.08%)	8 / 13 (61.54%)
occurrences (all)	294	370	12
Thrombocytopenia			
subjects affected / exposed	49 / 214 (22.90%)	49 / 212 (23.11%)	2 / 13 (15.38%)
occurrences (all)	76	86	5
Ear and labyrinth disorders			
Excessive cerumen production			
subjects affected / exposed	0 / 214 (0.00%)	1 / 212 (0.47%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 214 (4.67%)	11 / 212 (5.19%)	2 / 13 (15.38%)
occurrences (all)	11	15	2
Abdominal pain upper			
subjects affected / exposed	4 / 214 (1.87%)	7 / 212 (3.30%)	1 / 13 (7.69%)
occurrences (all)	4	7	1
Constipation			
subjects affected / exposed	19 / 214 (8.88%)	28 / 212 (13.21%)	5 / 13 (38.46%)
occurrences (all)	23	32	6
Diarrhoea			
subjects affected / exposed	32 / 214 (14.95%)	59 / 212 (27.83%)	5 / 13 (38.46%)
occurrences (all)	42	99	8
Dry mouth			
subjects affected / exposed	4 / 214 (1.87%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	4	0	1
Dyspepsia			
subjects affected / exposed	3 / 214 (1.40%)	7 / 212 (3.30%)	1 / 13 (7.69%)
occurrences (all)	3	7	1
Epigastric discomfort			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Haemorrhoids			

subjects affected / exposed occurrences (all)	0 / 214 (0.00%) 0	2 / 212 (0.94%) 2	1 / 13 (7.69%) 1
Nausea subjects affected / exposed occurrences (all)	46 / 214 (21.50%) 62	40 / 212 (18.87%) 61	4 / 13 (30.77%) 7
Stomatitis subjects affected / exposed occurrences (all)	2 / 214 (0.93%) 2	1 / 212 (0.47%) 1	1 / 13 (7.69%) 2
Vomiting subjects affected / exposed occurrences (all)	18 / 214 (8.41%) 22	21 / 212 (9.91%) 27	3 / 13 (23.08%) 3
Skin and subcutaneous tissue disorders			
Dry skin subjects affected / exposed occurrences (all)	6 / 214 (2.80%) 7	4 / 212 (1.89%) 4	2 / 13 (15.38%) 2
Erythema subjects affected / exposed occurrences (all)	4 / 214 (1.87%) 4	2 / 212 (0.94%) 2	2 / 13 (15.38%) 2
Pruritus subjects affected / exposed occurrences (all)	9 / 214 (4.21%) 9	18 / 212 (8.49%) 20	6 / 13 (46.15%) 6
Rash subjects affected / exposed occurrences (all)	12 / 214 (5.61%) 13	12 / 212 (5.66%) 12	2 / 13 (15.38%) 3
Urticaria subjects affected / exposed occurrences (all)	5 / 214 (2.34%) 5	0 / 212 (0.00%) 0	1 / 13 (7.69%) 1
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	2 / 214 (0.93%) 2	1 / 212 (0.47%) 1	1 / 13 (7.69%) 1
Renal failure subjects affected / exposed occurrences (all)	1 / 214 (0.47%) 1	1 / 212 (0.47%) 1	1 / 13 (7.69%) 3
Renal impairment			

subjects affected / exposed occurrences (all)	0 / 214 (0.00%) 0	2 / 212 (0.94%) 2	1 / 13 (7.69%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	18 / 214 (8.41%)	16 / 212 (7.55%)	1 / 13 (7.69%)
occurrences (all)	23	19	1
Back pain			
subjects affected / exposed	20 / 214 (9.35%)	21 / 212 (9.91%)	2 / 13 (15.38%)
occurrences (all)	21	24	2
Groin pain			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Intervertebral disc protrusion			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	11 / 214 (5.14%)	10 / 212 (4.72%)	1 / 13 (7.69%)
occurrences (all)	11	11	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 214 (0.00%)	2 / 212 (0.94%)	2 / 13 (15.38%)
occurrences (all)	0	4	2
Musculoskeletal pain			
subjects affected / exposed	4 / 214 (1.87%)	7 / 212 (3.30%)	1 / 13 (7.69%)
occurrences (all)	4	8	2
Pain in extremity			
subjects affected / exposed	13 / 214 (6.07%)	10 / 212 (4.72%)	1 / 13 (7.69%)
occurrences (all)	14	11	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 214 (2.34%)	11 / 212 (5.19%)	1 / 13 (7.69%)
occurrences (all)	6	14	2
Cystitis			
subjects affected / exposed	2 / 214 (0.93%)	1 / 212 (0.47%)	1 / 13 (7.69%)
occurrences (all)	2	1	1
Ear infection			

subjects affected / exposed	0 / 214 (0.00%)	2 / 212 (0.94%)	1 / 13 (7.69%)
occurrences (all)	0	2	1
Eye infection			
subjects affected / exposed	1 / 214 (0.47%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	3
Herpes zoster			
subjects affected / exposed	6 / 214 (2.80%)	9 / 212 (4.25%)	1 / 13 (7.69%)
occurrences (all)	7	9	1
Influenza			
subjects affected / exposed	4 / 214 (1.87%)	3 / 212 (1.42%)	1 / 13 (7.69%)
occurrences (all)	4	3	1
Localised infection			
subjects affected / exposed	3 / 214 (1.40%)	1 / 212 (0.47%)	1 / 13 (7.69%)
occurrences (all)	3	1	1
Nasopharyngitis			
subjects affected / exposed	14 / 214 (6.54%)	16 / 212 (7.55%)	0 / 13 (0.00%)
occurrences (all)	16	16	0
Oral herpes			
subjects affected / exposed	4 / 214 (1.87%)	5 / 212 (2.36%)	1 / 13 (7.69%)
occurrences (all)	5	7	4
Paronychia			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	3 / 214 (1.40%)	6 / 212 (2.83%)	1 / 13 (7.69%)
occurrences (all)	3	9	1
Respiratory tract infection			
subjects affected / exposed	6 / 214 (2.80%)	10 / 212 (4.72%)	1 / 13 (7.69%)
occurrences (all)	7	14	3
Rhinitis			
subjects affected / exposed	5 / 214 (2.34%)	2 / 212 (0.94%)	1 / 13 (7.69%)
occurrences (all)	6	3	1
Sinusitis			
subjects affected / exposed	6 / 214 (2.80%)	8 / 212 (3.77%)	1 / 13 (7.69%)
occurrences (all)	6	8	1
Upper respiratory tract infection			

subjects affected / exposed	15 / 214 (7.01%)	16 / 212 (7.55%)	2 / 13 (15.38%)
occurrences (all)	17	19	4
Urinary tract infection			
subjects affected / exposed	9 / 214 (4.21%)	10 / 212 (4.72%)	1 / 13 (7.69%)
occurrences (all)	10	13	1
Viral skin infection			
subjects affected / exposed	0 / 214 (0.00%)	0 / 212 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 214 (2.80%)	10 / 212 (4.72%)	1 / 13 (7.69%)
occurrences (all)	8	10	1
Gout			
subjects affected / exposed	1 / 214 (0.47%)	3 / 212 (1.42%)	1 / 13 (7.69%)
occurrences (all)	2	4	1
Hyperglycaemia			
subjects affected / exposed	7 / 214 (3.27%)	14 / 212 (6.60%)	2 / 13 (15.38%)
occurrences (all)	7	16	4
Hyperkalaemia			
subjects affected / exposed	5 / 214 (2.34%)	4 / 212 (1.89%)	5 / 13 (38.46%)
occurrences (all)	6	13	7
Hyperphosphataemia			
subjects affected / exposed	3 / 214 (1.40%)	4 / 212 (1.89%)	1 / 13 (7.69%)
occurrences (all)	3	5	1
Tumour lysis syndrome			
subjects affected / exposed	1 / 214 (0.47%)	2 / 212 (0.94%)	2 / 13 (15.38%)
occurrences (all)	1	2	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2014	Correction of inclusion criterion and clarification of adverse event (AE) reporting.
07 November 2014	Alignment of contraceptive requirements with product information for obinutuzumab in the inclusion criteria.
21 May 2015	Modification/correction of tumor lysis syndrome (TLS) laboratory assessments. Correction/modification of inclusion and exclusion criteria regarding infection and timing of CYP3A inhibitors/inducers relative to venetoclax dosing. Reporting of AEs and serious adverse events (SAEs) during follow-up period was modified in accordance with German Ethics Committee Chairman recommendation. Contraception and pregnancy testing requirements were updated to comply with International Conference for Harmonization (ICH) and health authority guidance.
02 November 2015	Inclusion of new safety data for obinutuzumab relating to subjects with previous history of gastrointestinal bleeding. Cytogenetic sample moved to screening visit so that results are available prior to randomization of the subject into the trial, allowing investigators to decide whether alternative treatment should be considered, particularly for subjects with 17p deletion and/or TP53 mutation. Clarification of eligibility of subjects with previous infections and timing of CYP3A inhibitors/inducers relative to venetoclax dosing, and clarification that subjects with previous deep vein thrombosis or pulmonary embolism could continue treatment if they did not revert to > Grade 1.
29 March 2017	Modification of timing of the interim analysis for efficacy to introduce a date-based stopping rule for PFS. Amendment of PFS analysis assumptions. Clarification that all response assessments to be made according to iwCLL criteria. In addition, clarification of response criteria for stable disease. Removal of requirement for first meal of day to be a low-fat meal.
12 February 2018	Addition of the option to add an additional earlier interim efficacy analysis to mitigate the potential for an undue delay in delivery of the study read-out. Prolongation of blood sample collection to characterize MRD kinetics in subjects responding longer than originally expected. Addition of complete response as a stand-alone secondary endpoint. Clarification of time windows for assessment of blood sampling for B-cell recovery and removal of an inconsistency in reporting instructions for unrelated SAEs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported