

**Clinical trial results:****A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Combination with Obinutuzumab versus Chlorambucil in Combination with Obinutuzumab in Subjects with Treatment-naïve Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma****Summary**

EudraCT number	2014-002069-31
Trial protocol	SE IT CZ AT BE ES PL
Global end of trial date	03 September 2019

Results information

Result version number	v2 (current)
This version publication date	27 August 2020
First version publication date	12 April 2019
Version creation reason	• New data added to full data set In the current CSR addendum for Study 1130, data are summarized for subjects through the clinical data cut-off date for the final analysis (17 October 2019, with last subject last visit on 03 September 2019), covering approximately 19 months of additional follow-up. At study closure, sites with active subjects without progressive disease who were still receiving ibrutinib treatment were given an option to enroll in an extension study to continue ibrutinib treatment. Information on the subject di

Trial information**Trial identification**

Sponsor protocol code	PCYC-1130-CA
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02264574
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharmacyclics LLC
Sponsor organisation address	995 East Arques Avenue, Sunnyvale, United States, 94085-4521
Public contact	Clinical Trial information, Pharmacyclics LLC, +1 4087740330, info@pcyc.com
Scientific contact	Clinical Trial information, Pharmacyclics LLC, +1 4087740330, info@pcyc.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of ibrutinib in combination with obinutuzumab compared to chlorambucil in combination with obinutuzumab based on the Independent Review Committee (IRC) assessment of progression-free survival (PFS) in subjects with treatment-naïve chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator:

The anti-CD20 antibody obinutuzumab was chosen as the appropriate anti-CD20 antibody partner to ibrutinib in Study 1130 based on results from the Phase 3 CLL11 study demonstrating superior efficacy. In the CLL11 study, obinutuzumab was used with chlorambucil (Clb+Ob; N = 333) in the first-line setting in patients with CLL with comorbidities in a comparison to either chlorambucil alone or to the combination of chlorambucil and rituximab.

Actual start date of recruitment	06 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	Turkey: 28
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 24
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 8

Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	New Zealand: 9
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Russian Federation: 20
Worldwide total number of subjects	229
EEA total number of subjects	110

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)	46
From 65 to 84 years	177
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 71 sites: 8 in the US, 36 in the EU, and 27 sites in 6 additional countries (Canada, Australia, New Zealand, Russia, Israel, Turkey). The first subject consented 06 Oct 2014 and the data base lock for the last visit of the last subjects was 17 Oct 2019.

Pre-assignment

Screening details:

Eligible subjects required to have had a diagnosis of active CLL/SLL conformant to IWCLL 2008 criteria. All subjects were required to have measurable nodal disease. Key exclusion criteria included any previous CLL/SLL treatment; known lymphoma or leukemia of the central nervous system, history/current evidence of Richter's transformation.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	IBR + OB

Arm description:

Ibrutinib given orally at a dose of 420 mg/day until progressive disease or unacceptable toxicity. Intravenous obinutuzumab given on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 1000 mg on Days 8 and 15 of Cycle 1 and 1000 mg on Day 1 of each cycle up to 6 cycles or until progressive disease or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ibrutinib given orally at a dose of 420 mg/day (3 capsules of 140 mg each) until progressive disease or unacceptable toxicity.

Investigational medicinal product name	obinutuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous obinutuzumab given on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 1000 mg on Days 8 and 15 of Cycle 1 and 1000 mg on Day 1 of each cycle up to 6 cycles or until disease progression or unacceptable toxicity.

Arm title	CLB + OB
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Arm description:

Chlorambucil given orally at a dose of 0.5 mg/kg body weight up to a total of 6 cycles on Days 1 and 15 of each cycle or until disease progression or unacceptable toxicity.

Intravenous obinutuzumab given on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 1000 mg on Days 8 and 15 of Cycle 1 and 1000 mg on Day 1 of each cycle up to 6 cycles or until disease progression or unacceptable toxicity.

Arm type	Active comparator
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Investigational medicinal product name	chlorambucil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Chlorambucil given orally at a dose of 0.5 mg/kg body weight on Days 1 and 15 of each cycle plus intravenous obinutuzumab per instructions shown for Arm A up to a total of 6 cycles.

Investigational medicinal product name	obinutuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous obinutuzumab given on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 1000 mg on Days 8 and 15 of Cycle 1 and 1000 mg on Day 1 of each cycle up to 6 cycles or until disease progression or unacceptable toxicity.

Number of subjects in period 1	IBR + OB	CLB + OB
Started	113	116
Completed	107	108
Not completed	6	8
Consent withdrawn by subject	6	5
various other reasons	-	3

Baseline characteristics

Reporting groups

Reporting group title	IBR + OB
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Reporting group description:

Ibrutinib given orally at a dose of 420 mg/day until progressive disease or unacceptable toxicity.
Intravenous obinutuzumab given on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 1000 mg on Days 8 and 15 of Cycle 1 and 1000 mg on Day 1 of each cycle up to 6 cycles or until progressive disease or unacceptable toxicity.

Reporting group title	CLB + OB
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Reporting group description:

Chlorambucil given orally at a dose of 0.5 mg/kg body weight up to a total of 6 cycles on Days 1 and 15 of each cycle or until disease progression or unacceptable toxicity.
Intravenous obinutuzumab given on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 1000 mg on Days 8 and 15 of Cycle 1 and 1000 mg on Day 1 of each cycle up to 6 cycles or until disease progression or unacceptable toxicity.

Reporting group values	IBR + OB	CLB + OB	Total
Number of subjects	113	116	229
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	22	24	46
From 65-84 years	88	89	177
85 years and over	3	3	6
Age continuous			
Units: years			
median	70.0	72.0	
full range (min-max)	47 to 87	40 to 86	-
Gender categorical			
Units: Subjects			
Female	46	37	83
Male	67	79	146

End points

End points reporting groups

Reporting group title	IBR + OB
Reporting group description: Ibrutinib given orally at a dose of 420 mg/day until progressive disease or unacceptable toxicity. Intravenous obinutuzumab given on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 1000 mg on Days 8 and 15 of Cycle 1 and 1000 mg on Day 1 of each cycle up to 6 cycles or until progressive disease or unacceptable toxicity.	
Reporting group title	CLB + OB
Reporting group description: Chlorambucil given orally at a dose of 0.5 mg/kg body weight up to a total of 6 cycles on Days 1 and 15 of each cycle or until disease progression or unacceptable toxicity. Intravenous obinutuzumab given on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 1000 mg on Days 8 and 15 of Cycle 1 and 1000 mg on Day 1 of each cycle up to 6 cycles or until disease progression or unacceptable toxicity.	

Primary: Progression Free Survival (PFS) - Investigator assessed

End point title	Progression Free Survival (PFS) - Investigator assessed
End point description: PFS in this final analysis is defined as time from the date of randomization to the date of first investigator-confirmed disease progression (PD) or date of death due to any cause, whichever occurs first, regardless of the use of subsequent antineoplastic therapy prior to documented PD or death. As the median PFS was not reached in the experimental (Ibr+Ob) arm at time of analysis, Kaplan Meier point estimates of the PFS rate at 48 months are presented. For the final analysis the primary efficacy endpoint was investigator-assessed PFS (primary analysis: IRC-assessed PFS).	
End point type	Primary
End point timeframe: The final analysis was performed after a median follow-up time 44.6 months.	

End point values	IBR + OB	CLB + OB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: percent				
number (confidence interval 95%)	74.0 (64.3 to 81.4)	22.0 (11.0 to 35.4)		

Statistical analyses

Statistical analysis title	Progression free survival (PFS)
Statistical analysis description: The treatment effect was tested with an unstratified log rank test. The hazard ratio and its 95% confidence interval were based on a Cox regression model with treatment as the only covariate.	
Comparison groups	IBR + OB v CLB + OB

Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.251
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.162
upper limit	0.389

Secondary: PFS in high-risk subpopulation - Investigator assessed

End point title	PFS in high-risk subpopulation - Investigator assessed
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End point description:

PFS per investigator assessment as defined in primary endpoint was analyzed within a high-risk subpopulation which defined as randomized subjects with del17p/TP53 mutation or del 11q or unmutated IGHV at baseline.

As the upper 95% CI value was not estimable in the experimental (Ibr+Ob) arm at time of analysis, Kaplan Meier point estimates of the PFS rate at 48 months are presented. Median PFS was 49.0 months in the Ibr+Ob arm and 18.0 months in the CLB+Ob arm.

End point type	Secondary
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End point timeframe:

Results after an overall median follow-up time of 44.6 months.

End point values	IBR + OB	CLB + OB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	75		
Units: percent				
number (confidence interval 95%)	70.3 (57.6 to 79.8)	8.0 (2.3 to 18.6)		

Statistical analyses

Statistical analysis title	PFS in high risk group
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Statistical analysis description:

The treatment effect was tested with an unstratified log rank test. The hazard ratio and its 95% confidence interval were based on an unstratified Cox regression model with treatment as the only covariate.

Comparison groups	IBR + OB v CLB + OB
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Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.169
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.102
upper limit	0.282

Secondary: Rate of Sustained Hemoglobin Improvement

End point title	Rate of Sustained Hemoglobin Improvement
End point description:	Proportion of subjects with hemoglobin increase ≥ 2 g/dL over baseline continuously for ≥ 56 days without blood transfusions or growth factors.
End point type	Secondary
End point timeframe:	Results at an overall median follow-up time of 44.6 months.

End point values	IBR + OB	CLB + OB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: percent				
number (not applicable)	44.2	44.0		

Statistical analyses

Statistical analysis title	Proportion of Sustained Hemoglobin Improvement
Comparison groups	IBR + OB v CLB + OB
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9657
Method	Chi-squared

Secondary: MRD negative response rate

End point title	MRD negative response rate
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End point description:

MRD-negative response in bone marrow and/or peripheral blood samples.

MRD samples collected before initiation of subsequent antineoplastic treatment and the MRD status were reported by central lab within 5 days after sample taken are used in this summary.

Subjects with missing MRD data are considered non-responders.

End point type	Secondary
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End point timeframe:

Results at an overall median follow-up time of 44.6 months.

End point values	IBR + OB	CLB + OB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: percent				
number (not applicable)	38.1	25.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate - Investigator assessed

End point title	Overall Response Rate - Investigator assessed
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End point description:

ORR included subjects with complete response, complete response with incomplete blood count recovery, and partial response.

End point type	Secondary
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End point timeframe:

Results after a median follow-up time of 44.6 months.

End point values	IBR + OB	CLB + OB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: percent				
number (not applicable)	91.2	81.0		

Statistical analyses

Statistical analysis title	Overall response rate
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Comparison groups	IBR + OB v CLB + OB
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Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0273
Method	Chi-squared
Parameter estimate	Rate ratio
Point estimate	1.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.013
upper limit	1.25

Secondary: Overall survival

End point title	Overall survival
End point description:	
As the median OS was not reached in either treatment arm at time of analysis, Kaplan Meier point estimates of the OS rate at 48 months are presented.	
End point type	Secondary
End point timeframe:	
Results are presented after a median follow-up time of 44.6 months.	

End point values	IBR + OB	CLB + OB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: percent				
number (confidence interval 95%)	80.5 (71.6 to 86.9)	81.3 (72.8 to 87.4)		

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	IBR + OB v CLB + OB
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7934
Method	unstratified logrank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.083

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.595
upper limit	1.973

Secondary: Rate of sustained platelet improvement

End point title	Rate of sustained platelet improvement
End point description:	
Sustained platelet improvement was defined as platelet counts increase $\geq 50\%$ over baseline continuously for ≥ 56 days without blood transfusion or growth factors.	
End point type	Secondary
End point timeframe:	
Results are presented after a median follow-up time of 44.6 months.	

End point values	IBR + OB	CLB + OB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: percent				
number (not applicable)	30.1	14.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30 days after the last dose of study drug

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Arm IBR + OB
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Reporting group description: -

Reporting group title	Arm CLB +OB
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Reporting group description: -

Serious adverse events	Arm IBR + OB	Arm CLB +OB	
Total subjects affected by serious adverse events			
subjects affected / exposed	69 / 113 (61.06%)	41 / 115 (35.65%)	
number of deaths (all causes)	22	21	
number of deaths resulting from adverse events	14	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	3 / 113 (2.65%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign renal neoplasm			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colorectal cancer			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer metastatic			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoma			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			

subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Essential thrombocythaemia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kaposi's sarcoma			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Prostate cancer			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 113 (3.54%)	4 / 115 (3.48%)	
occurrences causally related to treatment / all	2 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site haematoma			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 113 (1.77%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Multi-organ disorder			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 113 (0.88%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Completed suicide			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Confusional state			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 113 (1.77%)	8 / 115 (6.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 113 (0.88%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 113 (1.77%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal compression fracture			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	6 / 113 (5.31%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	6 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	3 / 113 (2.65%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 113 (0.88%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 113 (1.77%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 113 (1.77%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis constrictive			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 113 (1.77%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 113 (1.77%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			

subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	5 / 113 (4.42%)	7 / 115 (6.09%)	
occurrences causally related to treatment / all	4 / 5	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 113 (2.65%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	4 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	2 / 113 (1.77%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 113 (0.88%)	2 / 115 (1.74%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplastic anaemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 113 (1.77%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 113 (0.88%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal rupture			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			

subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 113 (0.00%)	2 / 115 (1.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 113 (1.77%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	2 / 113 (1.77%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	1 / 113 (0.88%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 113 (1.77%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compartment syndrome			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inclusion body myositis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteonecrosis of jaw			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 113 (7.08%)	5 / 115 (4.35%)	
occurrences causally related to treatment / all	8 / 14	2 / 5	
deaths causally related to treatment / all	1 / 1	0 / 1	
Gastroenteritis			
subjects affected / exposed	3 / 113 (2.65%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 113 (2.65%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 113 (0.88%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			

subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective staphylococcal			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective aneurysm			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeria sepsis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 113 (1.77%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 113 (1.77%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 113 (0.00%)	2 / 115 (1.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular device infection			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate infection			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis fungal			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 113 (0.00%)	5 / 115 (4.35%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm IBR + OB	Arm CLB +OB	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 113 (99.12%)	112 / 115 (97.39%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 113 (19.47%)	5 / 115 (4.35%)	
occurrences (all)	24	10	
Hypotension			

subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	6 / 115 (5.22%) 6	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	22 / 113 (19.47%)	19 / 115 (16.52%)	
occurrences (all)	27	24	
Pyrexia			
subjects affected / exposed	19 / 113 (16.81%)	28 / 115 (24.35%)	
occurrences (all)	29	37	
Oedema peripheral			
subjects affected / exposed	14 / 113 (12.39%)	8 / 115 (6.96%)	
occurrences (all)	18	9	
Asthenia			
subjects affected / exposed	12 / 113 (10.62%)	17 / 115 (14.78%)	
occurrences (all)	14	18	
Chills			
subjects affected / exposed	7 / 113 (6.19%)	10 / 115 (8.70%)	
occurrences (all)	7	11	
Peripheral swelling			
subjects affected / exposed	7 / 113 (6.19%)	2 / 115 (1.74%)	
occurrences (all)	8	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	33 / 113 (29.20%)	14 / 115 (12.17%)	
occurrences (all)	48	19	
Dyspnoea			
subjects affected / exposed	12 / 113 (10.62%)	15 / 115 (13.04%)	
occurrences (all)	20	20	
Oropharyngeal pain			
subjects affected / exposed	8 / 113 (7.08%)	4 / 115 (3.48%)	
occurrences (all)	11	4	
Productive cough			
subjects affected / exposed	8 / 113 (7.08%)	2 / 115 (1.74%)	
occurrences (all)	9	2	
Epistaxis			

subjects affected / exposed occurrences (all)	7 / 113 (6.19%) 11	9 / 115 (7.83%) 12	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 113 (11.50%)	5 / 115 (4.35%)	
occurrences (all)	14	5	
Anxiety			
subjects affected / exposed	10 / 113 (8.85%)	8 / 115 (6.96%)	
occurrences (all)	12	8	
Depression			
subjects affected / exposed	7 / 113 (6.19%)	1 / 115 (0.87%)	
occurrences (all)	10	1	
Investigations			
Blood creatinine increased			
subjects affected / exposed	8 / 113 (7.08%)	1 / 115 (0.87%)	
occurrences (all)	14	1	
Weight decreased			
subjects affected / exposed	3 / 113 (2.65%)	6 / 115 (5.22%)	
occurrences (all)	3	6	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	26 / 113 (23.01%)	61 / 115 (53.04%)	
occurrences (all)	30	70	
Fall			
subjects affected / exposed	10 / 113 (8.85%)	3 / 115 (2.61%)	
occurrences (all)	10	4	
Contusion			
subjects affected / exposed	6 / 113 (5.31%)	1 / 115 (0.87%)	
occurrences (all)	6	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	16 / 113 (14.16%)	0 / 115 (0.00%)	
occurrences (all)	20	0	
Palpitations			
subjects affected / exposed	7 / 113 (6.19%)	3 / 115 (2.61%)	
occurrences (all)	7	3	

Nervous system disorders	Dizziness			
	subjects affected / exposed	12 / 113 (10.62%)	7 / 115 (6.09%)	
	occurrences (all)	15	9	
	Headache			
	subjects affected / exposed	9 / 113 (7.96%)	13 / 115 (11.30%)	
	occurrences (all)	16	17	
	Tremor			
	subjects affected / exposed	4 / 113 (3.54%)	7 / 115 (6.09%)	
	occurrences (all)	4	7	
Blood and lymphatic system disorders	Neutropenia			
	subjects affected / exposed	50 / 113 (44.25%)	73 / 115 (63.48%)	
	occurrences (all)	153	216	
	Thrombocytopenia			
	subjects affected / exposed	39 / 113 (34.51%)	29 / 115 (25.22%)	
	occurrences (all)	97	58	
	Anaemia			
	subjects affected / exposed	19 / 113 (16.81%)	29 / 115 (25.22%)	
	occurrences (all)	31	47	
	Spontaneous haematoma			
	subjects affected / exposed	10 / 113 (8.85%)	1 / 115 (0.87%)	
	occurrences (all)	12	1	
	Increased tendency to bruise			
	subjects affected / exposed	6 / 113 (5.31%)	0 / 115 (0.00%)	
	occurrences (all)	7	0	
Eye disorders	Cataract			
	subjects affected / exposed	11 / 113 (9.73%)	1 / 115 (0.87%)	
	occurrences (all)	13	1	
	Vision blurred			
	subjects affected / exposed	9 / 113 (7.96%)	7 / 115 (6.09%)	
	occurrences (all)	11	8	
	Lacrimation increased			
	subjects affected / exposed	8 / 113 (7.08%)	5 / 115 (4.35%)	
	occurrences (all)	8	7	
	Dry eye			

subjects affected / exposed occurrences (all)	7 / 113 (6.19%) 7	3 / 115 (2.61%) 3	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	39 / 113 (34.51%)	12 / 115 (10.43%)	
occurrences (all)	61	13	
Constipation			
subjects affected / exposed	19 / 113 (16.81%)	14 / 115 (12.17%)	
occurrences (all)	24	17	
Nausea			
subjects affected / exposed	15 / 113 (13.27%)	34 / 115 (29.57%)	
occurrences (all)	18	44	
Vomiting			
subjects affected / exposed	12 / 113 (10.62%)	14 / 115 (12.17%)	
occurrences (all)	18	17	
Dyspepsia			
subjects affected / exposed	9 / 113 (7.96%)	2 / 115 (1.74%)	
occurrences (all)	10	2	
Abdominal pain			
subjects affected / exposed	9 / 113 (7.96%)	6 / 115 (5.22%)	
occurrences (all)	12	8	
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 113 (7.08%)	3 / 115 (2.61%)	
occurrences (all)	9	3	
Stomatitis			
subjects affected / exposed	7 / 113 (6.19%)	1 / 115 (0.87%)	
occurrences (all)	12	1	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	17 / 113 (15.04%)	2 / 115 (1.74%)	
occurrences (all)	27	2	
Rash			
subjects affected / exposed	10 / 113 (8.85%)	1 / 115 (0.87%)	
occurrences (all)	15	1	
Pruritus			

subjects affected / exposed	9 / 113 (7.96%)	4 / 115 (3.48%)	
occurrences (all)	13	4	
Dry skin			
subjects affected / exposed	7 / 113 (6.19%)	0 / 115 (0.00%)	
occurrences (all)	7	0	
Ecchymosis			
subjects affected / exposed	7 / 113 (6.19%)	0 / 115 (0.00%)	
occurrences (all)	8	0	
Onychoclasia			
subjects affected / exposed	7 / 113 (6.19%)	0 / 115 (0.00%)	
occurrences (all)	7	0	
Petechiae			
subjects affected / exposed	6 / 113 (5.31%)	0 / 115 (0.00%)	
occurrences (all)	8	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	6 / 113 (5.31%)	0 / 115 (0.00%)	
occurrences (all)	7	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	27 / 113 (23.89%)	12 / 115 (10.43%)	
occurrences (all)	33	12	
Back pain			
subjects affected / exposed	21 / 113 (18.58%)	12 / 115 (10.43%)	
occurrences (all)	26	14	
Muscle spasms			
subjects affected / exposed	16 / 113 (14.16%)	7 / 115 (6.09%)	
occurrences (all)	22	8	
Pain in extremity			
subjects affected / exposed	12 / 113 (10.62%)	10 / 115 (8.70%)	
occurrences (all)	13	10	
Myalgia			
subjects affected / exposed	7 / 113 (6.19%)	4 / 115 (3.48%)	
occurrences (all)	10	4	
Musculoskeletal pain			

subjects affected / exposed occurrences (all)	6 / 113 (5.31%) 7	3 / 115 (2.61%) 3	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	18 / 113 (15.93%)	7 / 115 (6.09%)	
occurrences (all)	22	7	
Nasopharyngitis			
subjects affected / exposed	15 / 113 (13.27%)	4 / 115 (3.48%)	
occurrences (all)	29	4	
Urinary tract infection			
subjects affected / exposed	13 / 113 (11.50%)	7 / 115 (6.09%)	
occurrences (all)	22	7	
Conjunctivitis			
subjects affected / exposed	12 / 113 (10.62%)	2 / 115 (1.74%)	
occurrences (all)	20	2	
Pneumonia			
subjects affected / exposed	12 / 113 (10.62%)	5 / 115 (4.35%)	
occurrences (all)	18	5	
Respiratory tract infection			
subjects affected / exposed	8 / 113 (7.08%)	1 / 115 (0.87%)	
occurrences (all)	11	1	
Oral herpes			
subjects affected / exposed	1 / 113 (0.88%)	6 / 115 (5.22%)	
occurrences (all)	1	6	
Bronchitis			
subjects affected / exposed	8 / 113 (7.08%)	2 / 115 (1.74%)	
occurrences (all)	9	2	
Cellulitis			
subjects affected / exposed	6 / 113 (5.31%)	3 / 115 (2.61%)	
occurrences (all)	7	3	
Herpes zoster			
subjects affected / exposed	6 / 113 (5.31%)	3 / 115 (2.61%)	
occurrences (all)	7	3	
Metabolism and nutrition disorders			
Hyperuricaemia			

subjects affected / exposed	15 / 113 (13.27%)	0 / 115 (0.00%)	
occurrences (all)	25	0	
Decreased appetite			
subjects affected / exposed	11 / 113 (9.73%)	5 / 115 (4.35%)	
occurrences (all)	12	5	
Hypokalaemia			
subjects affected / exposed	7 / 113 (6.19%)	2 / 115 (1.74%)	
occurrences (all)	10	2	
Hyperglycaemia			
subjects affected / exposed	6 / 113 (5.31%)	7 / 115 (6.09%)	
occurrences (all)	9	9	
Iron deficiency			
subjects affected / exposed	9 / 113 (7.96%)	0 / 115 (0.00%)	
occurrences (all)	10	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 August 2014	Updated safety information for ibrutinib. • Provided background and safety information for obinutuzumab including guidance for premedication for subjects at risk for tumor lysis syndrome, and dose modification upon development of thrombocytopenia. • Included interim analysis to be conducted at approximately 66 PFS events. • Clarified establishment of independent data monitoring committee to replace safety monitoring committee for monitoring of efficacy and safety data given the added interim efficacy analysis. • Clarified that progressive disease could be assessed based on $\geq 50\%$ increase from nadir rather than baseline count if the ALC is $\geq 30,000/\mu\text{L}$ and lymphocyte doubling time is rapid
10 May 2016	• Aligned language with IB Version 9.0 and clarified certain aspects of the clinical study protocol • To include obinutuzumab-related infusion reactions by treatment arm under secondary safety objectives • Updated response evaluation schedule and number of subject visits. • Updated study evaluations information to expand biomarker analysis and include a peripheral blood and bone marrow aspirate for MRD assessment. • Removed the 36-month timepoint from interim analysis • Aligned pregnancy language with relevant study drug labels
17 February 2017	• Removed the planned interim analysis and updated plans for primary analysis to ensure maturity of PFS outcome data per FDA feedback. • Revised EQ-5D-5L endpoint in secondary efficacy analysis section to clarify that methods will be detailed in SAP. • Revised study design to include potential roll-over to long-term extension study for subjects who choose to continue ibrutinib on a clinical protocol when access to commercial ibrutinib is not feasible. • Updated safety language for alignment with latest version of ibrutinib IB. • Updated MRD information to clarify that peripheral blood or bone marrow would be used for the evaluation of MRD in all responders if available. • Updated criteria for CR to clarify that the confirmatory marrow aspirate and biopsy would be performed by local laboratory

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30522969>