Clinical trial results:
iNNOVATE Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination with Rituximab in Subjects with Waldenstrom's Macroglobulinemia

Summary

EudraCT number	2013-005478-22
Trial protocol	IT DE ES GR GB
Global end of trial date	07 November 2019

Results information

Result version number	v2 (current)
This version publication date	05 November 2020
First version publication date	24 February 2019
Version creation reason	• Changes to summary attachments CSR Addendum

Trial information

Trial identification

Sponsor protocol code	PCYC-1127-CA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02165397
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharmacyclics
Sponsor organisation address	995 East Arques Avenue, Sunnyvale, United States, 94085-4521
Public contact	Medical Monitor, Pharmacyclics, Incorporated Lori Styles 995 East Arques Avenue Sunnyvale CA 94085-4521 US, 001 4082153770, lstyles@pcyc.com
Scientific contact	Medical Monitor, Pharmacyclics, Incorporated Lori Styles 995 East Arques Avenue Sunnyvale CA 94085-4521 US, 001 4082153770, lstyles@pcyc.com

Notes:

Paediatric regulatory details

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

Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of the addition of ibrutinib to rituximab on progression-free survival (PFS) assessed by an independent review committee (IRC) in subjects with Waldenstrom`s Macroglobulinemia WM. Efficacy evaluations will be based on the modified Consensus Response Criteria from the VIth International Workshop for WM (NCCN 2014).

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, with the exception of the issues discussed in Section 4.4 of the CSR. These issues/non-conformances did not have an impact on the overall conclusions of this study

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 July 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: 18
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Greece: 29
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	United States: 26
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Australia: 27
Worldwide total number of subjects	181
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)	72
From 65 to 84 years	99
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

Multi-center, 1:1 randomized Phase 3 comparing ibrutinib and rituximab to placebo and rituximab conducted in 48 sites, (10 in the US, 30 in Europe, 4 in Canada and 4 in Australia). In addition, an open-label substudy was included to further investigate the safety and efficacy of ibrutinib in subjects refractory to treatment with rituximab.

Pre-assignment

Screening details:

Eligible subjects were ≥ 18 years of age with untreated WM or previously treated WM. During the screening phase, the subjects' eligibility was to be determined. Eligible subjects must have had clinicopathological diagnosis of WM confirmed by central pathology review and in accordance with the consensus panel of the Second IWWM.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Double-blind study: subjects, investigators, and the Sponsor's study team members were blinded to treatment assignment. Data that could potentially unblind the treatment assignment (ie, study drug plasma concentrations) was to be handled with special care to ensure that the integrity of the blind was maintained and the potential for bias minimized.
This included making special provisions, such as segregating the data in question from view by the investigators and the team involved in the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ibrutinib and Rituximab

Arm description:

Subjects receiving ibrutinib and rituximab in combination.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Rituximab 375 mg/m^2 IV was administered per package insert instructions weekly for 4 consecutive weeks, followed by a second 4-week rituximab course after a 3-month interval (Day 1 of Weeks 1-4 and Weeks 17-20 (total of 8 infusions of rituximab).

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 was administered daily at a dose of 420 mg (3 capsules of 140 mg) until progression, discontinuation due to toxicity or other reasons to discontinue treatment.

Arm title	Placebo and Rituximab

Arm description:

Subjects receiving placebo and rituximab in combination.

Arm type	Placebo
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Rituximab 375 mg/m^2 IV was administered per package insert instructions weekly for 4 consecutive weeks, followed by a second 4-week rituximab course after a 3-month interval (Day 1 of Weeks 1-4 and Weeks 17-20 (total of 8 infusions of rituximab).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered as capsules identical to ibrutinib until progression, discontinuation due to toxicity or other reasons for discontinuation of treatment.

Arm title	Open-label ritux refractory arm

Arm description:

Subjects (rituximab refractory) in this arm were treated with ibrutinib 420 mg monotherapy in an open-labeled substudy independently of the 2 randomized main treatment arm (R+I and R+P)

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 was administered daily at a dose of 420 mg (3 capsules of 140 mg) until disease progression, discontinuation due to toxicity or other reasons to discontinue treatment.

Number of subjects in period 1	Ibrutinib and Rituximab	Placebo and Rituximab	Open-label ritux refractory arm
Started	75	75	31
Completed	68	66	29
Not completed	7	9	2
Consent withdrawn by subject	6	6	1
Lost to follow-up	1	3	-
Patient relocated to China	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Ibrutinib and Rituximab
Reporting group description:	
Subjects receiving ibrutinib and rituximab in combination.	
Reporting group title	Placebo and Rituximab
Reporting group description:	
Subjects receiving placebo and rituximab in combination.	
Reporting group title	Open-label ritux refractory arm
Reporting group description:	
Subjects (rituximab refractory) in this arm were treated with ibrutinib 420 mg monotherapy in an open-labeled substudy independently of the 2 randomized main treatment arm (R+I and R+P)	

Reporting group values	Ibrutinib and Rituximab	Placebo and Rituximab	Open-label ritux refractory arm
Number of subjects	75	75	31
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)	28	30	14
From 65-84 years	42	43	14
85 years and over	5	2	3
Age continuous			
Mean age of subjects incl. standard deviation			
Units: years			
arithmetic mean	69.2	66.1	66.4
standard deviation	± 10.90	± 11.10	± 10.76
Gender categorical Units: Subjects			
Female	30	21	11
Male	45	54	20

Reporting group values	Total		
Number of subjects	181		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	72		
From 65-84 years	99		
85 years and over	10		
Age continuous			
Mean age of subjects incl. standard deviation			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	62		
Male	119		

End points

End points reporting groups

Reporting group title	Ibrutinib and Rituximab
Reporting group description:	
Subjects receiving ibrutinib and rituximab in combination.	
Reporting group title	Placebo and Rituximab
Reporting group description:	
Subjects receiving placebo and rituximab in combination.	
Reporting group title	Open-label ritux refractory arm
Reporting group description:	
Subjects (rituximab refractory) in this arm were treated with ibrutinib 420 mg monotherapy in an open-labeled substudy independently of the 2 randomized main treatment arm (R+I and R+P)	

Primary: Progression free survival (54 month landmark)

End point title	Progression free survival (54 month landmark)
End point description:	
KM point estimates of the PFS rate per IRC assessment at 54 months. PFS is defined as time from the date of randomization to the date of first IRC-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 Ibr+R arm (38.7 months in the open-label ritux refractory arm, 20.3 months in the Pbo+R arm), PFS rates at 54 months are presented.	
End point type	Primary
End point timeframe:	
Results at a median time on study of 49.7 months for Ibr+R and Pbo+R and 57.9 months for the open-label ritux refractory arm.	

End point values	Ibrutinib and Rituximab	Placebo and Rituximab	Open-label ritux refractory arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	75	31	
Units: percentage				
number (confidence interval 95%)	68.0 (54.8 to 78.1)	25.3 (15.3 to 36.6)	39.7 (22.3 to 56.7)	

Statistical analyses

Statistical analysis title	Progression free survival (PFS)
Statistical analysis description:	
The treatment effect was tested with a stratified log rank test. The hazard ratio and its 95% confidence interval were based on a Cox regression model stratified by the randomization stratification factors.	
Comparison groups	Placebo and Rituximab v Ibrutinib and Rituximab

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.148
upper limit	0.42

Secondary: Response rate (CR, VGPR, PR)

End point title	Response rate (CR, VGPR, PR)

End point description:

Response rate is defined as proportion of subjects achieving a best overall response of confirmed CR, VGPR, or PR per the IRC assessment at or prior to initiation of subsequent antineoplastic therapy

End point type	Secondary

End point timeframe:

Response rate at a median time on study of 49.7 months for Ibr+R and Pbo+R and 57.9 months for the open-label ritux refractory arm.

End point values	Ibrutinib and Rituximab	Placebo and Rituximab	Open-label ritux refractory arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	75	31	
Units: percentage				
number (not applicable)	76.0	30.7	77.4	

Statistical analyses

Statistical analysis title	Response Rate

Statistical analysis description:

Response rate was compared using Cochran-Mantel-Haenszel (CMH) chi-square test.

Comparison groups	Ibrutinib and Rituximab v Placebo and Rituximab
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate ratio
Point estimate	2.526

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.753
upper limit	3.639

Secondary: Time to next treatment (54 month landmark)

End point title	Time to next treatment (54 month landmark)

End point description:

TTnT is defined as time from the date of randomization to the start date of any subsequent WM treatment. As the median TTnT was not reached in the Ibr+R and the open-label ritux refractory arm (18.1 months in the Pbo+R arm), TTnT rates at 54 months are presented.

End point type	Secondary

End point timeframe:

Results at a median time on study of 49.7 months for Ibr+R and Pbo+R and 57.9 months for the open-label ritux refractory arm.

End point values	Ibrutinib and Rituximab	Placebo and Rituximab	Open-label ritux refractory arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	75	31	
Units: percentage				
number (confidence interval 95%)	87.4 (77.2 to 93.3)	29.4 (18.2 to 41.6)	64.6 (44.1 to 79.2)	

Statistical analyses

Statistical analysis title	Time to next treatment (TTnT)
Comparison groups	Ibrutinib and Rituximab v Placebo and Rituximab
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.102
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.049
upper limit	0.212

Secondary: Rate of sustained improvement in hemoglobin

End point title	Rate of sustained improvement in hemoglobin

End point description:

Proportion of subjects achieving a sustained improvement in hemoglobin (Hgb) at or prior to initiation of subsequent antineoplastic therapy. Hgb improvement is defined as an increase of ≥ 2 g/dL over baseline regardless of baseline value, or an increase to >11 g/dL with a ≥0.5 g/dL improvement if baseline is ≤ 11 g/dL. Sustained Hgb improvement is defined as improvement that is sustained continuously for ≥ 56 days (8 weeks) without blood transfusion or growth factors.

End point type	Secondary

End point timeframe:

Sustained improvement in hemoglobin at a median time on study of 49.7 months for Ibr+R and Pbo+R and 57.9 months for the open-label ritux refractory arm.

End point values	Ibrutinib and Rituximab	Placebo and Rituximab	Open-label ritux refractory arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	75	31	
Units: percent				
number (not applicable)	77.3	42.7	71.0	

Statistical analyses

Statistical analysis title	Rate of sustained improvement in hemoglobin
Comparison groups	Ibrutinib and Rituximab v Placebo and Rituximab
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Rate ratio
Point estimate	1.813
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.357
upper limit	2.421

Secondary: FACIT-Fatigue Subscale Score

End point title	FACIT-Fatigue Subscale Score

End point description:

Proportion of subjects with ≥ 3 points increase from baseline by Week 25 in fatigue experience score.

End point type	Secondary

End point timeframe:

Results for 25 weeks of treatment.

End point values	Ibrutinib and Rituximab	Placebo and Rituximab	Open-label ritux refractory arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	75	31	
Units: percent				
number (not applicable)	68.0	54.7	87.1	

Statistical analyses

Statistical analysis title	FACIT-Fatigue Subscale Score
Comparison groups	Ibrutinib and Rituximab v Placebo and Rituximab
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1059
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate Ratio
Point estimate	1.238
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.955
upper limit	1.603

Secondary: Overall Survival (54 months landmark)

End point title	Overall Survival (54 months landmark)

End point description:

As the median overall survival has not been reached in none of the arms, the Kaplan-Meier estimates at 54 months are presented.

End point type	Secondary

End point timeframe:

Results at a median time on study of 49.7 months for Ibr+R and Pbo+R and 57.9 months for the open-label ritux refractory arm.

End point values	Ibrutinib and Rituximab	Placebo and Rituximab	Open-label ritux refractory arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	75	31	
Units: percent				
number (confidence interval 95%)	86.4 (73.7 to 93.3)	84.2 (71.3 to 91.6)	73.4 (53.7 to 85.7)	

Statistical analyses

Statistical analysis title	Overall survival (54 months landmark analysis)
Comparison groups	Ibrutinib and Rituximab v Placebo and Rituximab
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.643 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.808
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.328
upper limit	1.99

Notes:

[1] - p-value is from unstratified logrank test.

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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	ibrutinib and rituximab
Reporting group description:	
Subjects who received ibrutinib and rituximab in combination	
Reporting group title	Placebo and Rituximab
Reporting group description:	
subjects who received placebo and rituximab in combination	
Reporting group title	Open-label ritux refractory arm
Reporting group description:	
Subject in this arm were treated with ibrutinib 420 mg monotherapy in an open-labeled substudy independently of the 2 randomized main treatment arm (R+I and R+P)	

Serious adverse events	ibrutinib and rituximab	Placebo and Rituximab	Open-label ritux refractory arm
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 75 (53.33%)	25 / 75 (33.33%)	16 / 31 (51.61%)
number of deaths (all causes)	9	10	8
number of deaths resulting from adverse events	1	3	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign pancreatic neoplasm			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 75 (1.33%)	1 / 75 (1.33%)	0 / 31 (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

Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer metastatic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bing-Neel syndrome			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 75 (1.33%)	1 / 75 (1.33%)	0 / 31 (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
Circulatory collapse			

subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (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
Fatigue			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (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
General physical health deterioration			
subjects affected / exposed	1 / 75 (1.33%)	1 / 75 (1.33%)	0 / 31 (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
Asthenia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchopneumopathy			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 75 (1.33%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (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			
Fall			
subjects affected / exposed	3 / 75 (4.00%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 75 (0.00%)	5 / 75 (6.67%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon injury			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal fracture			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	8 / 75 (10.67%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	7 / 8	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Prinzmetal angina			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (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
Left ventricular failure			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Syncope			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphasia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (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
Neutropenia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			

subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Ulcerative keratitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 75 (1.33%)	1 / 75 (1.33%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (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
Abdominal pain upper			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecalith			

subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 75 (1.33%)	1 / 75 (1.33%)	0 / 31 (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
Cholecystitis acute			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eczema			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dysuria			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (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			
Arthralgia			
subjects affected / exposed	3 / 75 (4.00%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint swelling			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue necrosis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (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
Synovial cyst			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture pain			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tendonitis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mobility decreased			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 75 (10.67%)	2 / 75 (2.67%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	5 / 9	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	4 / 75 (5.33%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	1 / 4	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal sepsis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orchitis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic abscess			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			

subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemianopia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			

subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	ibrutinib and rituximab	Placebo and Rituximab	Open-label ritux refractory arm
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 75 (100.00%)	75 / 75 (100.00%)	30 / 31 (96.77%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour flare			
subjects affected / exposed	6 / 75 (8.00%)	35 / 75 (46.67%)	0 / 31 (0.00%)
occurrences (all)	7	54	0
Basal cell carcinoma			
subjects affected / exposed	4 / 75 (5.33%)	4 / 75 (5.33%)	0 / 31 (0.00%)
occurrences (all)	4	6	0
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 75 (24.00%)	3 / 75 (4.00%)	8 / 31 (25.81%)
occurrences (all)	29	4	16
Hypotension			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	5
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	17 / 75 (22.67%)	9 / 75 (12.00%)	5 / 31 (16.13%)
occurrences (all)	25	12	8
Asthenia			
subjects affected / exposed	12 / 75 (16.00%)	19 / 75 (25.33%)	4 / 31 (12.90%)
occurrences (all)	15	26	5
Fatigue			

subjects affected / exposed	13 / 75 (17.33%)	18 / 75 (24.00%)	5 / 31 (16.13%)
occurrences (all)	27	23	8
Pyrexia			
subjects affected / exposed	12 / 75 (16.00%)	12 / 75 (16.00%)	11 / 31 (35.48%)
occurrences (all)	15	18	14
Chills			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Influenza like illness			
subjects affected / exposed	4 / 75 (5.33%)	4 / 75 (5.33%)	0 / 31 (0.00%)
occurrences (all)	4	4	0
Chest pain			
subjects affected / exposed	4 / 75 (5.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences (all)	4	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 75 (21.33%)	8 / 75 (10.67%)	9 / 31 (29.03%)
occurrences (all)	24	9	9
Dyspnoea			
subjects affected / exposed	8 / 75 (10.67%)	10 / 75 (13.33%)	3 / 31 (9.68%)
occurrences (all)	9	13	5
Epistaxis			
subjects affected / exposed	8 / 75 (10.67%)	7 / 75 (9.33%)	4 / 31 (12.90%)
occurrences (all)	10	8	5
Rhinorrhoea			
subjects affected / exposed	5 / 75 (6.67%)	5 / 75 (6.67%)	2 / 31 (6.45%)
occurrences (all)	5	5	2
Productive cough			
subjects affected / exposed	3 / 75 (4.00%)	4 / 75 (5.33%)	0 / 31 (0.00%)
occurrences (all)	3	7	0
Oropharyngeal pain			
subjects affected / exposed	4 / 75 (5.33%)	2 / 75 (2.67%)	3 / 31 (9.68%)
occurrences (all)	4	2	3
Psychiatric disorders			

Insomnia			
subjects affected / exposed	12 / 75 (16.00%)	3 / 75 (4.00%)	2 / 31 (6.45%)
occurrences (all)	15	3	2
Depression			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	3
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	32 / 75 (42.67%)	43 / 75 (57.33%)	0 / 31 (0.00%)
occurrences (all)	59	122	0
Contusion			
subjects affected / exposed	7 / 75 (9.33%)	1 / 75 (1.33%)	2 / 31 (6.45%)
occurrences (all)	10	2	2
Traumatic haematoma			
subjects affected / exposed	5 / 75 (6.67%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences (all)	5	0	0
Fall			
subjects affected / exposed	7 / 75 (9.33%)	3 / 75 (4.00%)	3 / 31 (9.68%)
occurrences (all)	8	4	4
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	11 / 75 (14.67%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences (all)	18	1	0
Palpitations			
subjects affected / exposed	4 / 75 (5.33%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	5	0	3
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 75 (17.33%)	17 / 75 (22.67%)	7 / 31 (22.58%)
occurrences (all)	19	18	8
Dizziness			
subjects affected / exposed	10 / 75 (13.33%)	6 / 75 (8.00%)	4 / 31 (12.90%)
occurrences (all)	13	6	5
Paraesthesia			
subjects affected / exposed	4 / 75 (5.33%)	4 / 75 (5.33%)	2 / 31 (6.45%)
occurrences (all)	4	4	2

Peripheral sensory neuropathy			
subjects affected / exposed	5 / 75 (6.67%)	4 / 75 (5.33%)	2 / 31 (6.45%)
occurrences (all)	6	5	2
Sciatica			
subjects affected / exposed	6 / 75 (8.00%)	0 / 75 (0.00%)	3 / 31 (9.68%)
occurrences (all)	6	0	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 75 (22.67%)	21 / 75 (28.00%)	5 / 31 (16.13%)
occurrences (all)	22	37	7
Neutropenia			
subjects affected / exposed	12 / 75 (16.00%)	7 / 75 (9.33%)	9 / 31 (29.03%)
occurrences (all)	20	7	14
Increased tendency to bruise			
subjects affected / exposed	9 / 75 (12.00%)	2 / 75 (2.67%)	8 / 31 (25.81%)
occurrences (all)	9	2	9
Thrombocytopenia			
subjects affected / exposed	5 / 75 (6.67%)	8 / 75 (10.67%)	6 / 31 (19.35%)
occurrences (all)	6	18	12
Spontaneous haematoma			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Lymphadenopathy			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	3
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	4 / 31 (12.90%)
occurrences (all)	0	0	5
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	9 / 75 (12.00%)	3 / 75 (4.00%)	0 / 31 (0.00%)
occurrences (all)	12	3	0
Cataract			
subjects affected / exposed	7 / 75 (9.33%)	1 / 75 (1.33%)	4 / 31 (12.90%)
occurrences (all)	7	1	5
Eye irritation			

subjects affected / exposed	6 / 75 (8.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences (all)	8	1	0
Dry eye			
subjects affected / exposed	5 / 75 (6.67%)	5 / 75 (6.67%)	3 / 31 (9.68%)
occurrences (all)	9	7	3
Lacrimation increased			
subjects affected / exposed	9 / 75 (12.00%)	3 / 75 (4.00%)	0 / 31 (0.00%)
occurrences (all)	9	4	0
Photophobia			
subjects affected / exposed	6 / 75 (8.00%)	2 / 75 (2.67%)	0 / 31 (0.00%)
occurrences (all)	7	2	0
Vision blurred			
subjects affected / exposed	7 / 75 (9.33%)	2 / 75 (2.67%)	4 / 31 (12.90%)
occurrences (all)	8	3	4
Diplopia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Vitreous detachment			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Vitreous floaters			
subjects affected / exposed	4 / 75 (5.33%)	2 / 75 (2.67%)	2 / 31 (6.45%)
occurrences (all)	8	2	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	23 / 75 (30.67%)	11 / 75 (14.67%)	14 / 31 (45.16%)
occurrences (all)	35	13	22
Nausea			
subjects affected / exposed	17 / 75 (22.67%)	9 / 75 (12.00%)	7 / 31 (22.58%)
occurrences (all)	24	14	8
Dyspepsia			
subjects affected / exposed	13 / 75 (17.33%)	1 / 75 (1.33%)	2 / 31 (6.45%)
occurrences (all)	14	1	2
Constipation			
subjects affected / exposed	9 / 75 (12.00%)	9 / 75 (12.00%)	5 / 31 (16.13%)
occurrences (all)	13	12	10

Abdominal pain upper			
subjects affected / exposed	4 / 75 (5.33%)	2 / 75 (2.67%)	2 / 31 (6.45%)
occurrences (all)	9	2	2
Dry mouth			
subjects affected / exposed	4 / 75 (5.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences (all)	4	0	0
Vomiting			
subjects affected / exposed	5 / 75 (6.67%)	8 / 75 (10.67%)	0 / 31 (0.00%)
occurrences (all)	9	10	0
Abdominal pain			
subjects affected / exposed	4 / 75 (5.33%)	2 / 75 (2.67%)	4 / 31 (12.90%)
occurrences (all)	5	2	6
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 75 (9.33%)	1 / 75 (1.33%)	3 / 31 (9.68%)
occurrences (all)	7	1	4
Abdominal discomfort			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	4
Abdominal distension			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Gingival bleeding			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Stomatitis			
subjects affected / exposed	4 / 75 (5.33%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences (all)	4	1	0
Gastritis			
subjects affected / exposed	4 / 75 (5.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences (all)	4	0	0
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	9 / 75 (12.00%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences (all)	11	0	0
Petechiae			

subjects affected / exposed	7 / 75 (9.33%)	0 / 75 (0.00%)	4 / 31 (12.90%)
occurrences (all)	8	0	5
Pruritus			
subjects affected / exposed	6 / 75 (8.00%)	4 / 75 (5.33%)	2 / 31 (6.45%)
occurrences (all)	8	4	2
Rash erythematous			
subjects affected / exposed	7 / 75 (9.33%)	2 / 75 (2.67%)	0 / 31 (0.00%)
occurrences (all)	8	4	0
Rash maculo-papular			
subjects affected / exposed	5 / 75 (6.67%)	3 / 75 (4.00%)	3 / 31 (9.68%)
occurrences (all)	7	4	7
Dry skin			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	6 / 31 (19.35%)
occurrences (all)	0	0	6
Actinic keratosis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	4
Onycholysis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Onychoclasis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	4 / 31 (12.90%)
occurrences (all)	0	0	4
Psoriasis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Dermatitis contact			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	4
Skin lesion			
subjects affected / exposed	4 / 75 (5.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences (all)	5	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 75 (25.33%)	9 / 75 (12.00%)	7 / 31 (22.58%)
occurrences (all)	30	10	11
Pain in extremity			
subjects affected / exposed	10 / 75 (13.33%)	6 / 75 (8.00%)	5 / 31 (16.13%)
occurrences (all)	11	6	5
Back pain			
subjects affected / exposed	13 / 75 (17.33%)	7 / 75 (9.33%)	9 / 31 (29.03%)
occurrences (all)	16	7	14
Myalgia			
subjects affected / exposed	5 / 75 (6.67%)	3 / 75 (4.00%)	2 / 31 (6.45%)
occurrences (all)	8	8	2
Osteoarthritis			
subjects affected / exposed	4 / 75 (5.33%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences (all)	4	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Muscular weakness			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Muscle spasms			
subjects affected / exposed	16 / 75 (21.33%)	9 / 75 (12.00%)	5 / 31 (16.13%)
occurrences (all)	25	10	7
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	11 / 75 (14.67%)	0 / 75 (0.00%)	3 / 31 (9.68%)
occurrences (all)	17	0	7
Bronchitis			
subjects affected / exposed	11 / 75 (14.67%)	5 / 75 (6.67%)	3 / 31 (9.68%)
occurrences (all)	17	7	4
Influenza			
subjects affected / exposed	10 / 75 (13.33%)	5 / 75 (6.67%)	2 / 31 (6.45%)
occurrences (all)	10	5	2
Upper respiratory tract infection			

subjects affected / exposed	10 / 75 (13.33%)	3 / 75 (4.00%)	6 / 31 (19.35%)
occurrences (all)	23	6	22
Herpes zoster			
subjects affected / exposed	6 / 75 (8.00%)	1 / 75 (1.33%)	2 / 31 (6.45%)
occurrences (all)	7	1	2
Oral herpes			
subjects affected / exposed	6 / 75 (8.00%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences (all)	8	0	0
Pneumonia			
subjects affected / exposed	5 / 75 (6.67%)	2 / 75 (2.67%)	2 / 31 (6.45%)
occurrences (all)	9	2	3
Rhinitis			
subjects affected / exposed	4 / 75 (5.33%)	1 / 75 (1.33%)	2 / 31 (6.45%)
occurrences (all)	4	3	2
Respiratory tract infection			
subjects affected / exposed	6 / 75 (8.00%)	2 / 75 (2.67%)	5 / 31 (16.13%)
occurrences (all)	7	3	7
Cellulitis			
subjects affected / exposed	4 / 75 (5.33%)	1 / 75 (1.33%)	3 / 31 (9.68%)
occurrences (all)	7	1	3
Conjunctivitis			
subjects affected / exposed	4 / 75 (5.33%)	3 / 75 (4.00%)	4 / 31 (12.90%)
occurrences (all)	5	4	5
Paronychia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Sinusitis			
subjects affected / exposed	4 / 75 (5.33%)	2 / 75 (2.67%)	4 / 31 (12.90%)
occurrences (all)	5	3	7
Nasopharyngitis			
subjects affected / exposed	12 / 75 (16.00%)	7 / 75 (9.33%)	3 / 31 (9.68%)
occurrences (all)	17	8	3
Localised infection			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Respiratory tract infection viral			

subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Folliculitis			
subjects affected / exposed	4 / 75 (5.33%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences (all)	5	1	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	9 / 75 (12.00%)	1 / 75 (1.33%)	2 / 31 (6.45%)
occurrences (all)	12	2	2
Gout			
subjects affected / exposed	4 / 75 (5.33%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences (all)	5	1	0
Hyperuricaemia			
subjects affected / exposed	4 / 75 (5.33%)	4 / 75 (5.33%)	2 / 31 (6.45%)
occurrences (all)	5	4	2
Decreased appetite			
subjects affected / exposed	3 / 75 (4.00%)	7 / 75 (9.33%)	3 / 31 (9.68%)
occurrences (all)	3	7	3
Iron deficiency			
subjects affected / exposed	4 / 75 (5.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences (all)	4	0	0
Hyponatraemia			
subjects affected / exposed	5 / 75 (6.67%)	2 / 75 (2.67%)	0 / 31 (0.00%)
occurrences (all)	8	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2014	Added open-label substudy treatment arm for subjects refractory to the last prior rituximab-containing therapy in alignment with the scientific advice received from the European Medicines Agency (subjects not suitable for Ibr+R or Pbo+R treatment in the randomized study may be enrolled into the substudy to received single-agent ibrutinib), with efficacy and safety to be descriptively summarized and analyzed separately from the randomized treatment arms. • Revised inclusion criteria to allow ECOG PS status of 2. • Changed a randomization factor from prior rituximab exposure (yes vs. no) to ECOG PS (0-1 vs. 2) to ensure treatment balance for subjects with ECOG PS of 2. • Changed FACT-An from a secondary to an exploratory objective.
09 February 2015	• Allowed inclusion of subjects with untreated WM. • Updated the number of prior systemic treatment regimens for stratification from 1-2 vs. ≥3 to 0 vs. 1-2 vs. ≥3 to maintain balance between the 2 randomized treatment arms with regard to the addition of previously untreated subjects. • Revised the O'Brien-Fleming boundary from 60% (~42 PFS events) to 70% (~50 PFS events) for the interim analysis for the randomized arms. • Added new or additional guidance or information on the use of anticoagulants, antiplatelets, prednisone or equivalent, P-glycoprotein substrates, dose modifications for subjects with hepatic impairment, and major hemorrhage.
09 October 2015	• Updated enrollment criteria to allow for the inclusion of subjects with abnormal coagulation results unrelated to coagulopathy or bleeding disorders due to interfering substances. • Clarified enrollment criteria abstinence language. • Updated enrollment criteria for next-line ibrutinib therapy to allow involvement of CNS by WM. • Added planned subgroup analyses to be conducted for the PFS primary efficacy endpoint. • Updated risk sections and CYP3A section to align with current version of IB.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported