Clinical trial results:
A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Rituximab versus Placebo in Combination with Rituximab in Treatment Naïve Subjects with Follicular Lymphoma (PERSPECTIVE)

Summary

EudraCT number	2016-003202-14
Trial protocol	GB ES CZ HU PT BE GR NL AT FR IT
Global end of trial date	09 June 2025

Results information

Result version number	v1 (current)
This version publication date	01 April 2026
First version publication date	01 April 2026

Trial information

Trial identification

Sponsor protocol code	PCYC-1141-CA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03112174
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB
Public contact	AbbVie, Global Medical Services, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	AbbVie, Global Medical Services, 001 8006339110, abbvieclinicaltrials@abbvie.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 June 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 June 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a randomized, double-blind, placebo-controlled, multicenter Phase 3 study to evaluate the efficacy and safety of ibrutinib in combination with rituximab versus placebo in combination with rituximab in treatment naïve participants with follicular lymphoma (FL)

Protection of trial subjects:

Subject and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Czechia: 17
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Italy: 39
Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Russian Federation: 28
Country: Number of subjects enrolled	Spain: 65
Country: Number of subjects enrolled	Taiwan: 22
Country: Number of subjects enrolled	Türkiye: 23
Country: Number of subjects enrolled	United States: 93
Country: Number of subjects enrolled	United Kingdom: 10

Worldwide total number of subjects	445
EEA total number of subjects	230

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)	44
From 65 to 84 years	383
85 years and over	18

Subject disposition

Recruitment

Recruitment details:

In total, 445 participants were enrolled at 128 sites in 19 countries.

Pre-assignment

Screening details:

Participants were randomly assigned in a 3:1 ratio to the Ibrutinib + Rituximab arm (Arm A; n=334) or the Placebo + Rituximab arm (Arm B; n=111). Randomization was stratified based on: (a) age (60-69 vs. ≥70 yrs), (b) Follicular Lymphoma-specific International Prognostic Index (FLIPI)-1 score (low vs. intermediate/high) and (c) ECOG PS (0/1 vs. 2).

Period 1

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

Blinding implementation details:

The interactive voice or web response system (IXRS) assigned a unique treatment code, which dictated the treatment assignment and matching study treatment kit for the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Ibrutinib + Rituximab

Arm description:

Subjects were randomized to receive ibrutinib 560mg orally (PO) once daily (QD) until disease progression or unacceptable toxicity and rituximab 375mg/m^2 weekly (QW) for the first 4 weeks of study treatment (Cycle 1: Days 1, 8, 15, and 22). Beginning with Cycle 3, Day 1, rituximab maintenance therapy was administered as a single dose of 375 mg/m^2 IV every 8 weeks for up to 12 additional doses (approximately 2 years) or until disease progression, unacceptable toxicity, or withdrawal of consent.

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

Dosage and administration details:

Ibrutinib 560mg administered orally daily

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Rituxan
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab 375mg/m^2 intravenously (IV) weekly

Arm title	Arm B: Placebo + Rituximab

Arm description:

Subjects were randomized to receive placebo PO (4 capsules) daily until disease progression or unacceptable toxicity and rituximab 375mg/m^2 weekly for the first 4 weeks of study treatment (Cycle 1: Days 1, 8, 15, and 22). Beginning with Cycle 3, Day 1, rituximab maintenance therapy was administered as a single dose of 375 mg/m^2 IV every 8 weeks for up to 12 additional doses (approximately 2 years) or until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Rituxan
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab 375mg/m^2 intravenously (IV) weekly

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

Dosage and administration details:

Placebo capsules to match ibrutinib administered orally daily

Number of subjects in period 1	Arm A: Ibrutinib + Rituximab	Arm B: Placebo + Rituximab
Started	334	111
Completed	158	55
Not completed	176	56
Withdrawal of Consent	50	14
Death	109	35
Not Specified	10	3
Lost to follow-up	7	4

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Ibrutinib + Rituximab
Reporting group description:	
Subjects were randomized to receive ibrutinib 560mg orally (PO) once daily (QD) until disease progression or unacceptable toxicity and rituximab 375mg/m^2 weekly (QW) for the first 4 weeks of study treatment (Cycle 1: Days 1, 8, 15, and 22). Beginning with Cycle 3, Day 1, rituximab maintenance therapy was administered as a single dose of 375 mg/m^2 IV every 8 weeks for up to 12 additional doses (approximately 2 years) or until disease progression, unacceptable toxicity, or withdrawal of consent.	
Reporting group title	Arm B: Placebo + Rituximab
Reporting group description:	
Subjects were randomized to receive placebo PO (4 capsules) daily until disease progression or unacceptable toxicity and rituximab 375mg/m^2 weekly for the first 4 weeks of study treatment (Cycle 1: Days 1, 8, 15, and 22). Beginning with Cycle 3, Day 1, rituximab maintenance therapy was administered as a single dose of 375 mg/m^2 IV every 8 weeks for up to 12 additional doses (approximately 2 years) or until disease progression, unacceptable toxicity, or withdrawal of consent.	

Reporting group values	Arm A: Ibrutinib + Rituximab	Arm B: Placebo + Rituximab	Total
Number of subjects	334	111	445
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	73.7	74.2	
standard deviation	± 6.38	± 5.96	-
Gender categorical Units: Subjects			
Female	183	53	236
Male	151	58	209

End points

End points reporting groups

Reporting group title	Arm A: Ibrutinib + Rituximab

Reporting group description:

Subjects were randomized to receive ibrutinib 560mg orally (PO) once daily (QD) until disease progression or unacceptable toxicity and rituximab 375mg/m^2 weekly (QW) for the first 4 weeks of study treatment (Cycle 1: Days 1, 8, 15, and 22). Beginning with Cycle 3, Day 1, rituximab maintenance therapy was administered as a single dose of 375 mg/m^2 IV every 8 weeks for up to 12 additional doses (approximately 2 years) or until disease progression, unacceptable toxicity, or withdrawal of consent.

Reporting group title	Arm B: Placebo + Rituximab

Reporting group description:

Subjects were randomized to receive placebo PO (4 capsules) daily until disease progression or unacceptable toxicity and rituximab 375mg/m^2 weekly for the first 4 weeks of study treatment (Cycle 1: Days 1, 8, 15, and 22). Beginning with Cycle 3, Day 1, rituximab maintenance therapy was administered as a single dose of 375 mg/m^2 IV every 8 weeks for up to 12 additional doses (approximately 2 years) or until disease progression, unacceptable toxicity, or withdrawal of consent.

Primary: Progression-Free Survival (PFS) as Assessed by Investigator

End point title	Progression-Free Survival (PFS) as Assessed by Investigator

End point description:

PFS is the time from the date of randomization to the date of the first documented evidence of disease progression (based on the Revised Response Criteria for Malignant Lymphoma [Cheson 2014, Lugano Classification]) or death from any cause, whichever occurs first. Subjects who initiated subsequent anticancer therapy or missed two or more consecutive overall disease assessments were censored as described in the SAP. Estimated by Kaplan-Meier method.

End point type	Primary

End point timeframe:

Primary Analysis cut-off; median overall follow-up of 53.75 months

End point values	Arm A: Ibrutinib + Rituximab	Arm B: Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334[1]	111[2]		
Units: months				
median (confidence interval 95%)	42.02 (33.31 to 50.83)	32.76 (22.05 to 38.67)		

Notes:

[1] - ITT Population.

[2] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm A: Ibrutinib + Rituximab v Arm B: Placebo + Rituximab

Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0231 [4]
Method	Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.713
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.532
upper limit	0.955

Notes:

[3] - A stratified log-rank test was used to compare PFS between the two arms.

[4] - Stratification was based on FLIPI-1 and ECOG reported at randomization combined into a 3 strata variable: FLIPI-1 score=low; FLIPI-1 score=intermediate/high and ECOG PS score =0/1; FLIPI-1 score=intermediate/high and ECOG PS score=2.

Secondary: Overall Response Rate (ORR) as Assessed by Investigator

End point title	Overall Response Rate (ORR) as Assessed by Investigator

End point description:

ORR is the proportion of subjects who achieved a best overall response of complete response (CR) or partial response (PR) as determined by the investigator according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2014, Lugano Classification). ORR was assessed from the date of randomization through the date of first documented disease progression or initiation of subsequent anti-cancer therapy, whichever occurred first. Subjects who did not have any post-baseline disease assessments or who initiated subsequent anti-cancer therapy prior to a documented response are considered non-responders.

End point type	Secondary

End point timeframe:

Primary Analysis; median overall follow-up of 53.75 months

End point values	Arm A: Ibrutinib + Rituximab	Arm B: Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	111		
Units: Percentage of subjects				
number (confidence interval 95%)	81.4 (76.8 to 85.5)	68.5 (59.0 to 77.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm A: Ibrutinib + Rituximab v Arm B: Placebo + Rituximab

Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Ratio
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.039
upper limit	1.364

Notes:

[5] - Adjustment based on FLIPI-1 and ECOG at randomization combined into a 3 strata variable: FLIPI-1 score=low; FLIPI-1 score=intermediate/high and ECOG performance status score=0/1; FLIPI-1 score=intermediate/high and ECOG performance status score=2.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival is defined as the interval between the date of randomization and the date of the participant's death from any cause. If a participant is not known to have died (this includes participants with unknown death date), OS will be censored at the date the participant was last known to have been alive. Estimated by Kaplan-Meier method.
99999 Explanation: Not reached/ not estimable

End point type	Secondary

End point timeframe:

Final Analysis; median overall follow-up of 58.97 months

End point values	Arm A: Ibrutinib + Rituximab	Arm B: Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334[6]	111[7]		
Units: months				
median (confidence interval 95%)	99999 (69.72 to 99999)	78.98 (57.36 to 99999)		

Notes:

[6] - ITT Population

[7] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm A: Ibrutinib + Rituximab v Arm B: Placebo + Rituximab

Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.6608
Method	Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.758
upper limit	1.548

Notes:

[8] - Hazard ratio is estimated using stratified Cox regression model.

Secondary: Infusion-related Reaction Rate Assessed by Investigator

End point title	Infusion-related Reaction Rate Assessed by Investigator

End point description:

The infusion-related reactions (IRR) rate is the proportion of subjects experiencing infusion related reactions that start on the day of a rituximab infusion and are assessed as related or possibly related to rituximab.

End point type	Secondary

End point timeframe:

Primary Analysis; median overall follow-up of 53.75 months

End point values	Arm A: Ibrutinib + Rituximab	Arm B: Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334[9]	111[10]		
Units: percentage of subjects				
number (confidence interval 95%)	21.3 (17.0 to 26.0)	27.0 (19.0 to 36.3)		

Notes:

[9] - ITT Population

[10] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm B: Placebo + Rituximab v Arm A: Ibrutinib + Rituximab
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2087 [11]
Method	Chi-squared
Parameter estimate	Rate Ratio
Point estimate	0.787

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.544
upper limit	1.137

Notes:

[11] - P-value for rate ratio is based on Chi-Square test.

Secondary: Duration of Response (DOR) as Assessed by Investigator

End point title	Duration of Response (DOR) as Assessed by Investigator

End point description:

DOR is defined as the time from initial complete response (CR) or partial response (PR) to progressive disease (PD) or death due to any cause, whichever is first reported, regardless of discontinuation of study treatment. If such event did not occur, then participants were to be censored at the last adequate disease assessment as required for PFS censoring. Estimated by Kaplan-Meier method.
99999 Explanation: Not reached/ not estimable

End point type	Secondary

End point timeframe:

Primary Analysis; median overall follow-up of 53.75 months

End point values	Arm A: Ibrutinib + Rituximab	Arm B: Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272[12]	76[13]		
Units: months				
median (confidence interval 95%)	44.25 (36.63 to 99999)	34.56 (29.21 to 47.31)		

Notes:

[12] - ITT Population. Subjects achieving a response (partial response or better) are included in analysis.

[13] - ITT Population. Subjects achieving a response (partial response or better) are included in analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. The treatment-emergent period is defined as the period from the date of the first dose of study treatment up to 30 days after the date of the last dose of study treatment or the day before initiation of subsequent anti-cancer therapy, whichever comes first. The treatment-emergent adverse events (TEAEs) are those events that occur or worsen during the treatment-emergent period or that are related to the study treatment.

End point type	Secondary

End point timeframe:

Overall median treatment duration of 22.11 months

End point values	Arm A: Ibrutinib + Rituximab	Arm B: Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330[14]	111[15]		
Units: count of subjects				
number (not applicable)				
Any Treatment-Emergent Adverse Event (TEAE)	324	106		
Grade ≥3 TEAEs	259	63		
Serious Adverse Events (SAEs)	204	45		
Fatal TEAEs	48	6		
Discontinued study drug due to AE	144	16		
Most frequent Grade ≥3 TEAE (neutropenia)	52	8		

Notes:

[14] - Safety Population

[15] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality and adverse event tables include events reported from the time of informed consent/enrollment to end of study. Median time on follow-up was 58.2 months for Arm A (Ibrutinib + Rituximab) and 60.0 months for Arm B (Placebo + Rituximab).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Placebo_Rituximab
Reporting group description: -	
Reporting group title	Ibrutinib_Rituximab

Reporting group description: -

Serious adverse events	Placebo_Rituximab	Ibrutinib_Rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 111 (43.24%)	214 / 334 (64.07%)	
number of deaths (all causes)	40	123	
number of deaths resulting from adverse events	9	53	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BREAST CANCER RECURRENT			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST CANCER			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BOWEN'S DISEASE			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BASAL CELL CARCINOMA			

subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ADENOCARCINOMA OF COLON			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ADENOCARCINOMA GASTRIC			
subjects affected / exposed	2 / 111 (1.80%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
ACUTE MYELOID LEUKAEMIA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CANCER FATIGUE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROSTATE CANCER			
subjects affected / exposed	0 / 111 (0.00%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
OROPHARYNGEAL NEOPLASM BENIGN			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NASAL CAVITY CANCER			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTATIC RENAL CELL CARCINOMA			

subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTASES TO PERITONEUM			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
LUNG CARCINOMA CELL TYPE UNSPECIFIED STAGE IV			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
LUNG CANCER METASTATIC			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INVASIVE LOBULAR BREAST CARCINOMA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
INVASIVE DUCTAL BREAST CARCINOMA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FOLLICULAR LYMPHOMA			
subjects affected / exposed	1 / 111 (0.90%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
CANCER PAIN			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROSTATE CANCER RECURRENT			

subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SIGNET-RING CELL CARCINOMA			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (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 OF SKIN			
subjects affected / exposed	1 / 111 (0.90%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSITIONAL CELL CANCER OF THE RENAL PELVIS AND URETER			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR NECROSIS			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL CELL CARCINOMA RECURRENT			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
HYPERTENSIVE CRISIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOSIS			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

EMBOLISM			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTERIOSCLEROSIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
AORTIC ANEURYSM			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL VENOUS DISEASE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL VASCULAR DISORDER			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROGENIC SHOCK			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

ASTHENIA			
subjects affected / exposed	0 / 111 (0.00%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST PAIN			
subjects affected / exposed	1 / 111 (0.90%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHILLS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEATH			
subjects affected / exposed	2 / 111 (1.80%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 111 (0.90%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	0 / 111 (0.00%)	6 / 334 (1.80%)	
occurrences causally related to treatment / all	0 / 0	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

ANAPHYLACTIC REACTION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
PROSTATITIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UTERINE MASS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VAGINAL HAEMORRHAGE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
RHINORRHOEA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 111 (0.00%)	4 / 334 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 3	
RESPIRATORY ACIDOSIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY OEDEMA			

subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
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	1 / 111 (0.90%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	3 / 111 (2.70%)	5 / 334 (1.50%)	
occurrences causally related to treatment / all	1 / 3	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORGANISING PNEUMONIA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFILTRATION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOXIA			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
HAEMOTHORAX			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			

subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	0 / 111 (0.00%)	4 / 334 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHYLOTHORAX			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	2 / 111 (1.80%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE RESPIRATORY DISTRESS SYNDROME			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	2 / 111 (1.80%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHIAL OBSTRUCTION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
CONFUSIONAL STATE			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DELIRIUM			

subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEPRESSION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENTAL STATUS CHANGES			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSYCHOTIC DISORDER			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
SUICIDAL IDEATION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
OCCULT BLOOD POSITIVE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CRANIOFACIAL FRACTURE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

EXTRA-AXIAL HAEMORRHAGE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			
subjects affected / exposed	0 / 111 (0.00%)	4 / 334 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	1 / 111 (0.90%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
FRACTURE DISPLACEMENT			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEAD INJURY			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	1 / 111 (0.90%)	4 / 334 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
subjects affected / exposed	2 / 111 (1.80%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFUSION RELATED REACTION			

subjects affected / exposed	2 / 111 (1.80%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC FRACTURE			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIB FRACTURE			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL FRACTURE			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETERIC INJURY			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRAUMATIC HAEMATOMA			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBDURAL HAEMATOMA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIOVENTRICULAR BLOCK SECOND DEGREE			

subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANGINA PECTORIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANGINA UNSTABLE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	2 / 111 (1.80%)	21 / 334 (6.29%)	
occurrences causally related to treatment / all	0 / 2	17 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FLUTTER			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK COMPLETE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRADYCARDIA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			

subjects affected / exposed	1 / 111 (0.90%)	4 / 334 (1.20%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 1	1 / 3	
CARDIAC ASTHMA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE			
subjects affected / exposed	1 / 111 (0.90%)	5 / 334 (1.50%)	
occurrences causally related to treatment / all	0 / 1	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE ACUTE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	1 / 111 (0.90%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	0 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC CORONARY SYNDROME			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY OCCLUSION			

subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY STENOSIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PERICARDIAL EFFUSION			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERICARDITIS			
subjects affected / exposed	0 / 111 (0.00%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYCARDIA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
STIFF PERSON SYNDROME			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BASAL GANGLIA HAEMORRHAGE			

subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN OEDEMA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCIATICA			
subjects affected / exposed	1 / 111 (0.90%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC STROKE			
subjects affected / exposed	1 / 111 (0.90%)	6 / 334 (1.80%)	
occurrences causally related to treatment / all	0 / 1	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTRACRANIAL HAEMATOMA			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
HAEMORRHAGIC TRANSFORMATION STROKE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGIC STROKE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COGNITIVE DISORDER			

subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL ISCHAEMIA			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	0 / 111 (0.00%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL HAEMATOMA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	2 / 111 (1.80%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBARACHNOID HAEMORRHAGE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	0 / 111 (0.00%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			

subjects affected / exposed	0 / 111 (0.00%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IRON DEFICIENCY ANAEMIA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	0 / 111 (0.00%)	4 / 334 (1.20%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
LABYRINTHINE FISTULA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VERTIGO			
subjects affected / exposed	1 / 111 (0.90%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
EPIRETINAL MEMBRANE			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETINAL HAEMORRHAGE			

subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VITREOUS HAEMORRHAGE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEOVASCULAR AGE-RELATED MACULAR DEGENERATION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
COLITIS			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	1 / 111 (0.90%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASCITES			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OBSTRUCTIVE PANCREATITIS			

subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER HAEMORRHAGE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTERITIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL POLYP HAEMORRHAGE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHOIDAL HAEMORRHAGE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILEUS PARALYTIC			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INCARCERATED INGUINAL HERNIA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL PERFORATION			

subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE POLYP			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALLORY-WEISS SYNDROME			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MOUTH ULCERATION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	1 / 111 (0.90%)	6 / 334 (1.80%)	
occurrences causally related to treatment / all	1 / 1	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 111 (0.00%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMATOSIS INTESTINALIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			

subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 111 (0.90%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	0 / 111 (0.00%)	5 / 334 (1.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATOLITHIASIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
BILIARY COLIC			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BILIARY OBSTRUCTION			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLELITHIASIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLESTASIS			

subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC CYTOLYSIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC FAILURE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (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 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
DECUBITUS ULCER			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLISTER			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXIC SKIN ERUPTION			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN DISCHARGE			

subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH MACULAR			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH ERYTHEMATOUS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PETECHIAE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC SKIN ULCER			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ECCHYMOSIS			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETIC FOOT			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 111 (0.00%)	6 / 334 (1.80%)	
occurrences causally related to treatment / all	0 / 0	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
CYSTITIS HAEMORRHAGIC			

subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSURIA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL HAEMATOMA			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL HAEMORRHAGE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL IMPAIRMENT			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL TUBULAR NECROSIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUBULOINTERSTITIAL NEPHRITIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY RETENTION			

subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT OBSTRUCTION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
OSTEOARTHRITIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTHRALGIA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTHRITIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
subjects affected / exposed	1 / 111 (0.90%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE PAIN			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FLANK PAIN			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
JOINT EFFUSION			

subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCLE SPASMS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL OSTEOARTHRITIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RHEUMATOID ARTHRITIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
BRONCHITIS BACTERIAL			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL INFECTION			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABSCESS LIMB			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			

subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERAEMIA			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERIAL INFECTION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	1 / 111 (0.90%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHOPULMONARY ASPERGILLOSIS			
subjects affected / exposed	1 / 111 (0.90%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CAMPYLOBACTER GASTROENTERITIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CAMPYLOBACTER INFECTION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CANDIDA SEPSIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARBUNCLE			

subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	0 / 111 (0.00%)	6 / 334 (1.80%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOCARDITIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM COLITIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 111 (0.90%)	25 / 334 (7.49%)	
occurrences causally related to treatment / all	0 / 1	6 / 31	
deaths causally related to treatment / all	0 / 0	1 / 6	
COVID-19 PNEUMONIA			
subjects affected / exposed	5 / 111 (4.50%)	21 / 334 (6.29%)	
occurrences causally related to treatment / all	1 / 6	9 / 35	
deaths causally related to treatment / all	0 / 0	3 / 12	
CYCLOSPORIDIUM INFECTION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETIC FOOT INFECTION			

subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CENTRAL NERVOUS SYSTEM FUNGAL INFECTION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
ENTEROCOLITIS INFECTIOUS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA URINARY TRACT INFECTION			
subjects affected / exposed	1 / 111 (0.90%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GANGRENE			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	2 / 111 (1.80%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS ROTAVIRUS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS B REACTIVATION			

subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTED SKIN ULCER			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
INFECTION			
subjects affected / exposed	1 / 111 (0.90%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIOUS PLEURAL EFFUSION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	2 / 111 (1.80%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
MENINGITIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
NEUTROPENIC SEPSIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL CANDIDIASIS			

subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHARYNGITIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	5 / 111 (4.50%)	36 / 334 (10.78%)	
occurrences causally related to treatment / all	1 / 5	18 / 45	
deaths causally related to treatment / all	0 / 0	1 / 3	
ERYSIPELAS			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA BACTERIAL			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	4 / 111 (3.60%)	11 / 334 (3.29%)	
occurrences causally related to treatment / all	1 / 4	5 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA VIRAL			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROSTATITIS ESCHERICHIA COLI			

subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROTEUS INFECTION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS ACUTE			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 111 (0.00%)	5 / 334 (1.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	1 / 111 (0.90%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	1 / 1	
SEPSIS PASTEURELLA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
SEPTIC SHOCK			
subjects affected / exposed	0 / 111 (0.00%)	4 / 334 (1.20%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	3 / 4	
SPLENIC ABSCESS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPONTANEOUS BACTERIAL PERITONITIS			

subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL BACTERAEMIA			
subjects affected / exposed	0 / 111 (0.00%)	3 / 334 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
STENOTROPHOMONAS INFECTION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STREPTOCOCCAL SEPSIS			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
SUPERINFECTION BACTERIAL			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TONSILLITIS			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 111 (0.90%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT CANDIDIASIS			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA STREPTOCOCCAL			

subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION ENTEROCOCCAL			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION PSEUDOMONAL			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
subjects affected / exposed	0 / 111 (0.00%)	2 / 334 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
HYPOKALAEMIA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKALAEMIA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

HYPERGLYCAEMIA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS INADEQUATE CONTROL			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR LYSIS SYNDROME			
subjects affected / exposed	1 / 111 (0.90%)	0 / 334 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERURICAEMIA			
subjects affected / exposed	0 / 111 (0.00%)	1 / 334 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo_Rituximab	Ibrutinib_Rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	101 / 111 (90.99%)	310 / 334 (92.81%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	10 / 111 (9.01%)	48 / 334 (14.37%)	
occurrences (all)	14	76	

HYPOTENSION			
subjects affected / exposed	6 / 111 (5.41%)	9 / 334 (2.69%)	
occurrences (all)	7	11	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	7 / 111 (6.31%)	35 / 334 (10.48%)	
occurrences (all)	7	44	
CHILLS			
subjects affected / exposed	8 / 111 (7.21%)	12 / 334 (3.59%)	
occurrences (all)	9	15	
FATIGUE			
subjects affected / exposed	16 / 111 (14.41%)	72 / 334 (21.56%)	
occurrences (all)	25	120	
OEDEMA PERIPHERAL			
subjects affected / exposed	18 / 111 (16.22%)	63 / 334 (18.86%)	
occurrences (all)	22	95	
PYREXIA			
subjects affected / exposed	15 / 111 (13.51%)	35 / 334 (10.48%)	
occurrences (all)	21	42	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	17 / 111 (15.32%)	57 / 334 (17.07%)	
occurrences (all)	22	72	
DYSPNOEA			
subjects affected / exposed	20 / 111 (18.02%)	38 / 334 (11.38%)	
occurrences (all)	29	45	
EPISTAXIS			
subjects affected / exposed	3 / 111 (2.70%)	24 / 334 (7.19%)	
occurrences (all)	3	31	
RHINORRHOEA			
subjects affected / exposed	6 / 111 (5.41%)	4 / 334 (1.20%)	
occurrences (all)	7	4	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	12 / 111 (10.81%)	27 / 334 (8.08%)	
occurrences (all)	13	28	

Investigations			
WEIGHT DECREASED			
subjects affected / exposed	4 / 111 (3.60%)	17 / 334 (5.09%)	
occurrences (all)	5	21	
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
subjects affected / exposed	16 / 111 (14.41%)	27 / 334 (8.08%)	
occurrences (all)	18	31	
FALL			
subjects affected / exposed	11 / 111 (9.91%)	33 / 334 (9.88%)	
occurrences (all)	12	36	
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 111 (0.90%)	36 / 334 (10.78%)	
occurrences (all)	1	39	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	5 / 111 (4.50%)	32 / 334 (9.58%)	
occurrences (all)	5	37	
HEADACHE			
subjects affected / exposed	5 / 111 (4.50%)	45 / 334 (13.47%)	
occurrences (all)	6	71	
Blood and lymphatic system disorders			
INCREASED TENDENCY TO BRUISE			
subjects affected / exposed	0 / 111 (0.00%)	31 / 334 (9.28%)	
occurrences (all)	0	40	
ANAEMIA			
subjects affected / exposed	9 / 111 (8.11%)	49 / 334 (14.67%)	
occurrences (all)	13	83	
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 111 (0.90%)	31 / 334 (9.28%)	
occurrences (all)	1	72	
NEUTROPENIA			
subjects affected / exposed	12 / 111 (10.81%)	67 / 334 (20.06%)	
occurrences (all)	15	118	
Eye disorders			

DRY EYE			
subjects affected / exposed	17 / 111 (15.32%)	60 / 334 (17.96%)	
occurrences (all)	26	84	
CATARACT			
subjects affected / exposed	6 / 111 (5.41%)	26 / 334 (7.78%)	
occurrences (all)	8	30	
VITREOUS FLOATERS			
subjects affected / exposed	12 / 111 (10.81%)	26 / 334 (7.78%)	
occurrences (all)	17	34	
VISUAL ACUITY REDUCED			
subjects affected / exposed	17 / 111 (15.32%)	39 / 334 (11.68%)	
occurrences (all)	27	55	
VISION BLURRED			
subjects affected / exposed	10 / 111 (9.01%)	53 / 334 (15.87%)	
occurrences (all)	19	74	
PHOTOPSIA			
subjects affected / exposed	7 / 111 (6.31%)	13 / 334 (3.89%)	
occurrences (all)	13	18	
PHOTOPHOBIA			
subjects affected / exposed	7 / 111 (6.31%)	32 / 334 (9.58%)	
occurrences (all)	13	41	
LACRIMATION INCREASED			
subjects affected / exposed	13 / 111 (11.71%)	40 / 334 (11.98%)	
occurrences (all)	22	58	
EYE PAIN			
subjects affected / exposed	7 / 111 (6.31%)	23 / 334 (6.89%)	
occurrences (all)	11	27	
EYE IRRITATION			
subjects affected / exposed	18 / 111 (16.22%)	41 / 334 (12.28%)	
occurrences (all)	26	56	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	6 / 111 (5.41%)	32 / 334 (9.58%)	
occurrences (all)	7	42	
ABDOMINAL PAIN UPPER			

subjects affected / exposed	9 / 111 (8.11%)	27 / 334 (8.08%)	
occurrences (all)	9	31	
CONSTIPATION			
subjects affected / exposed	16 / 111 (14.41%)	53 / 334 (15.87%)	
occurrences (all)	18	65	
DIARRHOEA			
subjects affected / exposed	15 / 111 (13.51%)	116 / 334 (34.73%)	
occurrences (all)	19	205	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	7 / 111 (6.31%)	16 / 334 (4.79%)	
occurrences (all)	9	19	
NAUSEA			
subjects affected / exposed	12 / 111 (10.81%)	69 / 334 (20.66%)	
occurrences (all)	18	92	
STOMATITIS			
subjects affected / exposed	2 / 111 (1.80%)	26 / 334 (7.78%)	
occurrences (all)	2	41	
VOMITING			
subjects affected / exposed	5 / 111 (4.50%)	41 / 334 (12.28%)	
occurrences (all)	5	62	
Skin and subcutaneous tissue disorders			
ERYTHEMA			
subjects affected / exposed	2 / 111 (1.80%)	17 / 334 (5.09%)	
occurrences (all)	3	18	
DRY SKIN			
subjects affected / exposed	3 / 111 (2.70%)	20 / 334 (5.99%)	
occurrences (all)	3	20	
RASH MACULO-PAPULAR			
subjects affected / exposed	4 / 111 (3.60%)	31 / 334 (9.28%)	
occurrences (all)	5	45	
RASH ERYTHEMATOUS			
subjects affected / exposed	1 / 111 (0.90%)	22 / 334 (6.59%)	
occurrences (all)	2	31	
PRURITUS			

subjects affected / exposed	13 / 111 (11.71%)	26 / 334 (7.78%)	
occurrences (all)	14	36	
ONYCHOCLASIS			
subjects affected / exposed	0 / 111 (0.00%)	17 / 334 (5.09%)	
occurrences (all)	0	18	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	16 / 111 (14.41%)	63 / 334 (18.86%)	
occurrences (all)	24	83	
BACK PAIN			
subjects affected / exposed	15 / 111 (13.51%)	45 / 334 (13.47%)	
occurrences (all)	15	54	
MUSCLE SPASMS			
subjects affected / exposed	8 / 111 (7.21%)	39 / 334 (11.68%)	
occurrences (all)	10	52	
MYALGIA			
subjects affected / exposed	6 / 111 (5.41%)	22 / 334 (6.59%)	
occurrences (all)	7	26	
PAIN IN EXTREMITY			
subjects affected / exposed	6 / 111 (5.41%)	30 / 334 (8.98%)	
occurrences (all)	9	33	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	4 / 111 (3.60%)	23 / 334 (6.89%)	
occurrences (all)	4	27	
CONJUNCTIVITIS			
subjects affected / exposed	5 / 111 (4.50%)	21 / 334 (6.29%)	
occurrences (all)	5	25	
COVID-19			
subjects affected / exposed	22 / 111 (19.82%)	62 / 334 (18.56%)	
occurrences (all)	26	74	
URINARY TRACT INFECTION			
subjects affected / exposed	10 / 111 (9.01%)	60 / 334 (17.96%)	
occurrences (all)	13	122	
UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	6 / 111 (5.41%)	27 / 334 (8.08%)	
occurrences (all)	10	41	
PNEUMONIA			
subjects affected / exposed	4 / 111 (3.60%)	20 / 334 (5.99%)	
occurrences (all)	5	24	
NASOPHARYNGITIS			
subjects affected / exposed	6 / 111 (5.41%)	14 / 334 (4.19%)	
occurrences (all)	7	18	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	4 / 111 (3.60%)	34 / 334 (10.18%)	
occurrences (all)	4	36	
HYPERURICAEMIA			
subjects affected / exposed	6 / 111 (5.41%)	27 / 334 (8.08%)	
occurrences (all)	6	35	
HYPOKALAEMIA			
subjects affected / exposed	3 / 111 (2.70%)	35 / 334 (10.48%)	
occurrences (all)	5	54	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2018	Protocol Amendment 1 Key Changes: - Revised GELF criteria to avoid excluding potential eligible subjects. - Added infusion-related reactions (IRR) as a secondary objective. - Updated rituximab dosing instructions and directed sites to follow regional prescribing information. - Provided guidance on rituximab induction dosing during Cycle 1 if a scheduled dose is missed for reasons not related to rituximab tolerability.
10 March 2021	Protocol Amendment 2 Key Changes: - Responded to an extended enrollment delay by revising the analysis plan for Part 1 (PFS). - Increased the target event count for the final analysis to maintain robustness of the primary endpoint. - Introduced interim analyses, including a pre-specified futility assessment, to allow earlier evaluation and safeguard trial integrity.
10 October 2022	Protocol Amendment 3 Key Changes: -Updated the dose modification guidance for adverse reactions to align with the sponsor’s core product information for ibrutinib, aiming to reduce serious adverse events and improve tolerability for continued treatment.
07 February 2023	Protocol Amendment 4 Key Changes: - Removed Part 2 (Discontinuation Analysis Study) to enable extended overall survival (OS) follow-up. - Added an interim OS analysis timed with the Primary PFS Analysis. - Specified a final OS analysis to occur after accrual of additional OS events.
10 May 2024	Protocol Amendment 5 Key Changes: - Added definitions for serious adverse reactions (SAR) and suspected unexpected serious adverse reactions (SUSAR), including how the sponsor will report them. - Introduced/updated language on protection of subject-specific information (privacy/data protection). - Added or revised wording to ensure compliance with Good Clinical Practice (GCP), the EU Clinical Trials Regulation (EUCTR), and applicable local and global regulatory requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported