



Clinical trial results:

A Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors BGB-3111 and Ibrutinib in Subjects with Waldenström's Macroglobulinemia (WM)

Summary

EudraCT number	2016-002980-33
Trial protocol	DE BE SE ES NL PL GR GB CZ FR IT
Global end of trial date	21 June 2022

Results information

Result version number	v1
This version publication date	14 April 2023
First version publication date	14 April 2023

Trial information

Trial identification

Sponsor protocol code	BGB-3111-302
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03053440
WHO universal trial number (UTN)	U1111-1285-6790

Notes:

Sponsors

Sponsor organisation name	BeiGene
Sponsor organisation address	1840 Gateway Drive, San Mateo, CA , United States, 94404
Public contact	BeiGene Clinical Support, BeiGene USA, Inc., +1 877-828-5568, clinicaltrials@beigene.com
Scientific contact	BeiGene Clinical Support, BeiGene USA, Inc., +1 877-828-5568, clinicaltrials@beigene.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	29 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of zanubrutinib (BGB-3111) vs ibrutinib in subjects with MYD88MUT WM

Protection of trial subjects:

This study was conducted in accordance with sponsor procedures, which comply with the principles of GCP, International Council on Harmonisation Guidelines, the Declaration of Helsinki, and applicable local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 62
Country: Number of subjects enrolled	United States: 19
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	Czechia: 7
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Italy: 23
Worldwide total number of subjects	201
EEA total number of subjects	90

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	58
From 65 to 84 years	134
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

A total of 229 participants were randomized to Arms A and B in 12 countries in European Union, United Kingdom and United States.

Pre-assignment

Screening details:

The screening period consisted of Days -35 to -1.

Period 1

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

Arms

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

Arm description:

Participants diagnosed with WM with mutated MYD88 gene received 420 mg ibrutinib once daily orally until progressive disease, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor

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

Dosage and administration details:

Ibrutinib 420 milligrams (mg) once a day

Arm title	Arm B: Zanubrutinib
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Arm description:

Participants diagnosed with WM with mutated MYD88 gene received 160 mg zanubrutinib twice daily orally until progressive disease, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor

Arm type	Experimental
Investigational medicinal product name	Zanubrutinib
Investigational medicinal product code	
Other name	Brukinsa, BGB-3111
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Zanubrutinib 160 mg twice a day

Number of subjects in period 1	Arm A: Ibrutinib	Arm B: Zanubrutinib
Started	99	102
Completed	0	0
Not completed	99	102
Adverse event, serious fatal	19	14
Consent withdrawn by subject	9	8
Physician decision	2	1
Sponsor's decision to end study	20	13
Lost to follow-up	1	-
Enrolled in Long-term extension study	48	66

Baseline characteristics

Reporting groups

Reporting group title	Arm A: Ibrutinib
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Reporting group description:

Participants diagnosed with WM with mutated MYD88 gene received 420 mg ibrutinib once daily orally until progressive disease, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor

Reporting group title	Arm B: Zanubrutinib
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Reporting group description:

Participants diagnosed with WM with mutated MYD88 gene received 160 mg zanubrutinib twice daily orally until progressive disease, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor

Reporting group values	Arm A: Ibrutinib	Arm B: Zanubrutinib	Total
Number of subjects	99	102	201
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	69.9 ± 8.58	69.2 ± 10.26	-
Gender categorical Units: Subjects			
Female	34	33	67
Male	65	69	134
Ethnicity Units: Subjects			
Hispanic or Latino	4	4	8
Not Hispanic or Latino	91	82	173
Unknown or Not Reported	4	16	20
Race Units: Subjects			
Asian	0	4	4
White	94	88	182
Unknown or Not Reported	5	10	15

End points

End points reporting groups

Reporting group title	Arm A: Ibrutinib
Reporting group description: Participants diagnosed with WM with mutated MYD88 gene received 420 mg ibrutinib once daily orally until progressive disease, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor	
Reporting group title	Arm B: Zanubrutinib
Reporting group description: Participants diagnosed with WM with mutated MYD88 gene received 160 mg zanubrutinib twice daily orally until progressive disease, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor	

Primary: Percentage of participants achieving either a complete response (CR) or very good partial response (VGPR) using an adaptation of the response criteria updated at the Sixth IWWM as assessed by an independent review committee (IRC)

End point title	Percentage of participants achieving either a complete response (CR) or very good partial response (VGPR) using an adaptation of the response criteria updated at the Sixth IWWM as assessed by an independent review committee (IRC)
End point description: Percentage of participants with CR, defined as normal serum immunoglobulin M (IgM) levels, disappearance of monoclonal protein by immunofixation, and negative cryoglobulinemia if cryoglobulinemia was positive at baseline, or VGPR, defined as $\geq 90\%$ reduction in serum IgM level from baseline or normal serum IgM values. Intent to Treat (ITT) Analysis Set: Includes all randomized participants assigned to an arm.	
End point type	Primary
End point timeframe: Up to approximately 2 years and 7 months	

End point values	Arm A: Ibrutinib	Arm B: Zanubrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: Percentage of Participants				
number (confidence interval 95%)	19.2 (12.0 to 28.3)	28.4 (19.9 to 38.2)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Arm A: Ibrutinib v Arm B: Zanubrutinib

Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0921 ^[1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	10.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	22

Notes:

[1] - Based on Cochran-Mantel-Haenszel test stratified by the stratification factors per IRT. p Value is 2-sided

Secondary: Percentage of Participants Achieving Major Response Rate (MRR) as assessed by IRC

End point title	Percentage of Participants Achieving Major Response Rate (MRR) as assessed by IRC
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End point description:

MRR defined as the proportion of participants achieving a best response of response of CR, VGPR, or partial response (PR). MRR defined as the proportion of participants achieving a best response of response of CR, VGPR, or partial response (PR). ITT Analysis Set

End point type	Secondary
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End point timeframe:

Up to approximately 2 years and 7 months

End point values	Arm A: Ibrutinib	Arm B: Zanubrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	100		
Units: Percentage of Participants				
number (confidence interval 95%)	77.8 (68.3 to 85.5)	77.5 (68.1 to 85.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as assessed by IRC

End point title	Duration of Response (DOR) as assessed by IRC
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End point description:

DOR defined as the time from first determination of response (CR, VGPR or PR) until first documentation of progression or death, whichever comes first. ITT Analysis set

End point type	Secondary
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End point timeframe:

Up to approximately 2 years and 7 months

End point values	Arm A: Ibrutinib	Arm B: Zanubrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99 ^[2]	102 ^[3]		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[2] - 9999 = Not Estimable due to insufficient number of events

[3] - 9999 = Not Estimable due to insufficient number of events

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving either CR or VGPR in as assessed by the investigator

End point title	Percentage of participants achieving either CR or VGPR in as assessed by the investigator
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End point description:

Percentage of participants with CR, defined as normal serum immunoglobulin M (IgM) levels, disappearance of monoclonal protein by immunofixation, and negative cryoglobulinemia if cryoglobulinemia was positive at Baseline, or VGPR, defined as $\geq 90\%$ reduction in serum IgM level from baseline or normal serum IgM values. ITT Analysis set

End point type	Secondary
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End point timeframe:

Up to approximately 5 years and 5 months

End point values	Arm A: Ibrutinib	Arm B: Zanubrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	101		
Units: Percentage of Participants				
number (confidence interval 95%)	25.3 (17.1 to 35.0)	38.2 (28.8 to 48.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR in as assessed by the Investigator

End point title	DOR in as assessed by the Investigator
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End point description:

DOR is defined as the time from first determination of response (CR, VGPR or PR) until first documentation of progression or death, whichever comes first. ITT Analysis Set

End point type	Secondary
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End point timeframe:

Up to approximately 5 years and 5 months

End point values	Arm A: Ibrutinib	Arm B: Zanubrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99 ^[4]	102 ^[5]		
Units: Months				
median (confidence interval 95%)	9999 (53.5 to 9999)	9999 (9999 to 9999)		

Notes:

[4] - 9999 = Not Estimable due to insufficient number of events

[5] - 9999 = Not Estimable due to insufficient number of events

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) as assessed by the Investigator

End point title	Progression Free Survival (PFS) as assessed by the Investigator
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End point description:

PFS as assessed by the Investigator, defined as time from randomization to the first documentation of progression (per modified IWWM criteria) or death, whichever occurs first. ITT Analysis Set

End point type	Secondary
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End point timeframe:

Up to approximately 5 years and 5 months

End point values	Arm A: Ibrutinib	Arm B: Zanubrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99 ^[6]	102 ^[7]		
Units: Months				
median (confidence interval 95%)	9999 (54.4 to 9999)	9999 (9999 to 9999)		

Notes:

[6] - 9999 = Not Estimable due to insufficient number of events

[7] - 9999 = Not Estimable due to insufficient number of events

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) as assessed by the IRC

End point title	Progression Free Survival (PFS) as assessed by the IRC
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End point description:

PFS as assessed by the IRC, defined as time from randomization to the first documentation of progression (per modified IWWM criteria) or death, whichever occurs first. ITT Analysis Set

End point type	Secondary
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End point timeframe:
Up to approximately 2 years and 7 months

End point values	Arm A: Ibrutinib	Arm B: Zanubrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99 ^[8]	102 ^[9]		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[8] - 9999 = Not Estimable due to insufficient number of events

[9] - 9999 = Not Estimable due to insufficient number of events

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Resolution of all Treatment-precipitating Symptoms

End point title	Percentage of participants with Resolution of all Treatment-precipitating Symptoms
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End point description:

End point type	Secondary
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End point timeframe:

Up to approximately 5 years and 5 months

End point values	Arm A: Ibrutinib	Arm B: Zanubrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: Percentage of Participants				
number (not applicable)	78.6	79.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with an anti-Lymphoma effect

End point title	Percentage of participants with an anti-Lymphoma effect
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End point description:

ITT Analysis Set

End point type	Secondary
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End point timeframe:
Up to approximately 5 years and 5 months

End point values	Arm A: Ibrutinib	Arm B: Zanubrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: Percentage of Participants				
number (not applicable)	84.2	78.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-Emergent adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants with Treatment-Emergent adverse Events (TEAEs) and Serious Adverse Events (SAEs)
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End point description:

Safety Analysis Set includes all participants who received any dose of zanubrutinib or ibrutinib

End point type	Secondary
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End point timeframe:

Up to approximately 5 years and 5 months

End point values	Arm A: Ibrutinib	Arm B: Zanubrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	101		
Units: Percentage of Participants				
number (not applicable)				
Participants with At Least 1 TEAE	98	101		
Participants with SAEs	50	59		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR as Assessed by IRC: Event -Free Rate

End point title	DOR as Assessed by IRC: Event -Free Rate
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End point description:

Estimated percentage of participants who were event-free based on Kaplan-Meier method.

End point type	Secondary
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End point timeframe:

12 and 18 months from the date of randomization (up to approximately 2 years and 7 months)

End point values	Arm A: Ibrutinib	Arm B: Zanubrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: Percentage of Participants				
number (confidence interval 95%)				
12 Months	87.9 (77.0 to 93.8)	94.4 (85.8 to 97.9)		
18 Months	87.9 (77.0 to 93.8)	85.2 (71.7 to 92.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR as Assessed by the Investigator: Event-Free Rate

End point title DOR as Assessed by the Investigator: Event-Free Rate

End point description:

Estimated percentage of participants who were event-free based on Kaplan-Meier method.

End point type Secondary

End point timeframe:

24, 36 and 48 months from the date of randomization (up to approximately 5 years and 5 months)

End point values	Arm A: Ibrutinib	Arm B: Zanubrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: Percentage of Participants				
number (confidence interval 95%)				
24 Months	87.7 (77.8 to 93.4)	89.7 (80.4 to 94.7)		
36 Months	77.5 (65.9 to 85.6)	81.1 (70.1 to 88.4)		
48 Months	73.9 (61.6 to 82.8)	81.1 (70.1 to 88.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Assessed by IRC: Event-Free Rate

End point title	PFS as Assessed by IRC: Event-Free Rate
End point description:	
Estimated percentage of participants who were event-free based on Kaplan-Meier method	
End point type	Secondary
End point timeframe:	
12 and 18 months from the date of randomization (up to approximately 2 years and 7 months)	

End point values	Arm A: Ibrutinib	Arm B: Zanubrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: Percentage of Participants				
number (confidence interval 95%)				
12 Months	87.2 (78.6 to 92.5)	89.7 (81.7 to 94.3)		
18 Months	83.8 (74.5 to 89.9)	85.0 (75.2 to 91.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Assessed by the Investigator: Event-Free Rate

End point title	PFS as Assessed by the Investigator: Event-Free Rate
End point description:	
Percentage of participants who were event-free based on Kaplan-Meier method.	
End point type	Secondary
End point timeframe:	
24, 36 and 48 months from the date of randomization (up to approximately 5 years and 5 months)	

End point values	Arm A: Ibrutinib	Arm B: Zanubrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: Percentage of Participants				
number (confidence interval 95%)				
24 Months	80.6 (70.9 to 87.3)	88.5 (80.2 to 93.5)		
36 Months	74.8 (64.5 to 82.5)	78.3 (68.4 to 85.5)		
48 Months	67.3 (56.3 to 76.1)	78.3 (68.4 to 85.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Approximately 5 years 5 months

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22
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Reporting groups

Reporting group title	Ibrutinib
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Reporting group description:

Ibrutinib

Reporting group title	Zanubrutinib
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Reporting group description:

Zanubrutinib

Serious adverse events	Ibrutinib	Zanubrutinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 98 (51.02%)	59 / 101 (58.42%)	
number of deaths (all causes)	18	14	
number of deaths resulting from adverse events	7	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 98 (0.00%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	3 / 98 (3.06%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			

subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma transformation			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodular melanoma			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral vascular disorder			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Death			
subjects affected / exposed	2 / 98 (2.04%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 98 (3.06%)	4 / 101 (3.96%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug withdrawal syndrome			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Amyloidosis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal prolapse			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			

subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 98 (0.00%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 98 (2.04%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	1 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
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 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			

subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Interferon gamma release assay positive			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 98 (1.02%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

subjects affected / exposed	1 / 98 (1.02%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 98 (1.02%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital haematoma			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress fracture			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			

subjects affected / exposed	1 / 98 (1.02%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	3 / 98 (3.06%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	5 / 98 (5.10%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	4 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			

subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
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	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 98 (2.04%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomegaly			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac tamponade			

subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial haemorrhage			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	3 / 98 (3.06%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 98 (1.02%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			

subjects affected / exposed	2 / 98 (2.04%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 98 (3.06%)	3 / 101 (2.97%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 98 (1.02%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic disorder			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			

subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 98 (0.00%)	3 / 101 (2.97%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 98 (0.00%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 98 (0.00%)	3 / 101 (2.97%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperviscosity syndrome			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal inflammation			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			

subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral blood blister			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic disorder			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	2 / 98 (2.04%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 98 (1.02%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 98 (1.02%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 98 (1.02%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 98 (2.04%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal stenosis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain abscess			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	2 / 98 (2.04%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 98 (2.04%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 98 (2.04%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cryptococcal fungaemia			

subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 98 (1.02%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 98 (1.02%)	3 / 101 (2.97%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 98 (0.00%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurocryptococcosis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	14 / 98 (14.29%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	6 / 15	0 / 4	
deaths causally related to treatment / all	1 / 2	0 / 0	
Paronychia			
subjects affected / exposed	1 / 98 (1.02%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis			

subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-acute COVID-19 syndrome			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	4 / 98 (4.08%)	3 / 101 (2.97%)	
occurrences causally related to treatment / all	1 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Streptococcal endocarditis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
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	1 / 98 (1.02%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 98 (2.04%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 98 (2.04%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	1 / 98 (1.02%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 101 (0.99%)	
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: 3 %

Non-serious adverse events	Ibrutinib	Zanubrutinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 98 (97.96%)	99 / 101 (98.02%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	5 / 98 (5.10%)	4 / 101 (3.96%)	
occurrences (all)	5	4	
Squamous cell carcinoma of skin			
subjects affected / exposed	5 / 98 (5.10%)	3 / 101 (2.97%)	
occurrences (all)	6	3	
Seborrhoeic keratosis			
subjects affected / exposed	3 / 98 (3.06%)	0 / 101 (0.00%)	
occurrences (all)	3	0	
Bladder transitional cell carcinoma			

subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 4	0 / 101 (0.00%) 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	24 / 98 (24.49%)	16 / 101 (15.84%)	
occurrences (all)	46	20	
Haematoma			
subjects affected / exposed	9 / 98 (9.18%)	5 / 101 (4.95%)	
occurrences (all)	11	7	
Hypotension			
subjects affected / exposed	2 / 98 (2.04%)	4 / 101 (3.96%)	
occurrences (all)	3	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 98 (6.12%)	9 / 101 (8.91%)	
occurrences (all)	9	14	
Chest pain			
subjects affected / exposed	5 / 98 (5.10%)	4 / 101 (3.96%)	
occurrences (all)	5	4	
Chills			
subjects affected / exposed	4 / 98 (4.08%)	3 / 101 (2.97%)	
occurrences (all)	5	3	
Drug withdrawal syndrome			
subjects affected / exposed	2 / 98 (2.04%)	4 / 101 (3.96%)	
occurrences (all)	3	4	
Fatigue			
subjects affected / exposed	19 / 98 (19.39%)	26 / 101 (25.74%)	
occurrences (all)	25	49	
Gait disturbance			
subjects affected / exposed	0 / 98 (0.00%)	4 / 101 (3.96%)	
occurrences (all)	0	4	
Influenza like illness			
subjects affected / exposed	5 / 98 (5.10%)	6 / 101 (5.94%)	
occurrences (all)	7	9	
Pyrexia			

subjects affected / exposed occurrences (all)	12 / 98 (12.24%) 21	16 / 101 (15.84%) 30	
Peripheral swelling subjects affected / exposed occurrences (all)	12 / 98 (12.24%) 12	5 / 101 (4.95%) 6	
Oedema peripheral subjects affected / exposed occurrences (all)	22 / 98 (22.45%) 38	19 / 101 (18.81%) 29	
Malaise subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	1 / 101 (0.99%) 1	
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	2 / 98 (2.04%) 2	4 / 101 (3.96%) 4	
Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	1 / 101 (0.99%) 1	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	20 / 98 (20.41%) 29	20 / 101 (19.80%) 36	
Epistaxis subjects affected / exposed occurrences (all)	21 / 98 (21.43%) 35	18 / 101 (17.82%) 21	
Nasal congestion subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 6	2 / 101 (1.98%) 2	
Oropharyngeal pain subjects affected / exposed occurrences (all)	10 / 98 (10.20%) 11	4 / 101 (3.96%) 5	
Dyspnoea subjects affected / exposed occurrences (all)	9 / 98 (9.18%) 11	17 / 101 (16.83%) 22	
Dyspnoea exertional			

subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	2 / 101 (1.98%) 2	
Pneumonitis subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	1 / 101 (0.99%) 1	
Productive cough subjects affected / exposed occurrences (all)	4 / 98 (4.08%) 4	6 / 101 (5.94%) 7	
Rhinorrhoea subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 5	2 / 101 (1.98%) 2	
Wheezing subjects affected / exposed occurrences (all)	1 / 98 (1.02%) 1	4 / 101 (3.96%) 4	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	9 / 98 (9.18%) 10	3 / 101 (2.97%) 4	
Depression subjects affected / exposed occurrences (all)	4 / 98 (4.08%) 4	3 / 101 (2.97%) 4	
Anxiety subjects affected / exposed occurrences (all)	7 / 98 (7.14%) 7	5 / 101 (4.95%) 5	
Investigations Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	4 / 98 (4.08%) 4	0 / 101 (0.00%) 0	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 5	2 / 101 (1.98%) 2	
Neutrophil count decreased subjects affected / exposed occurrences (all)	4 / 98 (4.08%) 9	8 / 101 (7.92%) 33	
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 6	2 / 101 (1.98%) 2	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	27 / 98 (27.55%)	19 / 101 (18.81%)	
occurrences (all)	59	38	
Joint injury			
subjects affected / exposed	4 / 98 (4.08%)	1 / 101 (0.99%)	
occurrences (all)	5	1	
Fall			
subjects affected / exposed	10 / 98 (10.20%)	9 / 101 (8.91%)	
occurrences (all)	12	17	
Limb injury			
subjects affected / exposed	5 / 98 (5.10%)	5 / 101 (4.95%)	
occurrences (all)	7	5	
Procedural pain			
subjects affected / exposed	0 / 98 (0.00%)	4 / 101 (3.96%)	
occurrences (all)	0	5	
Skin laceration			
subjects affected / exposed	8 / 98 (8.16%)	5 / 101 (4.95%)	
occurrences (all)	13	5	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	4 / 98 (4.08%)	4 / 101 (3.96%)	
occurrences (all)	4	4	
Atrial fibrillation			
subjects affected / exposed	18 / 98 (18.37%)	7 / 101 (6.93%)	
occurrences (all)	24	8	
Sinus bradycardia			
subjects affected / exposed	3 / 98 (3.06%)	6 / 101 (5.94%)	
occurrences (all)	3	6	
Palpitations			
subjects affected / exposed	10 / 98 (10.20%)	6 / 101 (5.94%)	
occurrences (all)	15	8	
Bradycardia			

subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 4	1 / 101 (0.99%) 1	
Atrial flutter subjects affected / exposed occurrences (all)	4 / 98 (4.08%) 4	1 / 101 (0.99%) 1	
Nervous system disorders			
Neuralgia subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	0 / 101 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	15 / 98 (15.31%) 20	17 / 101 (16.83%) 20	
Dizziness subjects affected / exposed occurrences (all)	14 / 98 (14.29%) 16	15 / 101 (14.85%) 29	
Paraesthesia subjects affected / exposed occurrences (all)	8 / 98 (8.16%) 10	4 / 101 (3.96%) 6	
Syncope subjects affected / exposed occurrences (all)	6 / 98 (6.12%) 7	3 / 101 (2.97%) 5	
Sciatica subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 4	1 / 101 (0.99%) 1	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 6	8 / 101 (7.92%) 10	
Blood and lymphatic system disorders			
Thrombocytopenia subjects affected / exposed occurrences (all)	16 / 98 (16.33%) 47	15 / 101 (14.85%) 61	
Neutropenia subjects affected / exposed occurrences (all)	16 / 98 (16.33%) 51	29 / 101 (28.71%) 87	
Lymphadenopathy			

subjects affected / exposed occurrences (all)	1 / 98 (1.02%) 1	4 / 101 (3.96%) 4	
Anaemia subjects affected / exposed occurrences (all)	22 / 98 (22.45%) 48	18 / 101 (17.82%) 57	
Increased tendency to bruise subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 6	3 / 101 (2.97%) 3	
Ear and labyrinth disorders			
Tinnitus subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 4	6 / 101 (5.94%) 6	
Vertigo subjects affected / exposed occurrences (all)	4 / 98 (4.08%) 4	3 / 101 (2.97%) 3	
Eye disorders			
Cataract subjects affected / exposed occurrences (all)	6 / 98 (6.12%) 7	3 / 101 (2.97%) 4	
Conjunctival haemorrhage subjects affected / exposed occurrences (all)	6 / 98 (6.12%) 10	5 / 101 (4.95%) 9	
Dry eye subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	2 / 101 (1.98%) 2	
Ocular hyperaemia subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	1 / 101 (0.99%) 1	
Retinal haemorrhage subjects affected / exposed occurrences (all)	4 / 98 (4.08%) 8	0 / 101 (0.00%) 0	
Vision blurred subjects affected / exposed occurrences (all)	6 / 98 (6.12%) 7	3 / 101 (2.97%) 3	
Gastrointestinal disorders			

Abdominal discomfort subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 5	1 / 101 (0.99%) 1
Abdominal distension subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	2 / 101 (1.98%) 2
Abdominal pain subjects affected / exposed occurrences (all)	6 / 98 (6.12%) 9	4 / 101 (3.96%) 5
Abdominal pain upper subjects affected / exposed occurrences (all)	6 / 98 (6.12%) 7	4 / 101 (3.96%) 4
Constipation subjects affected / exposed occurrences (all)	12 / 98 (12.24%) 18	20 / 101 (19.80%) 25
Diarrhoea subjects affected / exposed occurrences (all)	36 / 98 (36.73%) 62	23 / 101 (22.77%) 38
Dyspepsia subjects affected / exposed occurrences (all)	7 / 98 (7.14%) 7	6 / 101 (5.94%) 7
Dry mouth subjects affected / exposed occurrences (all)	4 / 98 (4.08%) 4	5 / 101 (4.95%) 5
Dysphagia subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 4	3 / 101 (2.97%) 4
Inguinal hernia subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	1 / 101 (0.99%) 1
Haemorrhoids subjects affected / exposed occurrences (all)	4 / 98 (4.08%) 5	2 / 101 (1.98%) 2
Gingival bleeding subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 6	2 / 101 (1.98%) 2

Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 5	4 / 101 (3.96%) 4	
Mouth ulceration subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 9	2 / 101 (1.98%) 2	
Nausea subjects affected / exposed occurrences (all)	15 / 98 (15.31%) 22	19 / 101 (18.81%) 25	
Rectal haemorrhage subjects affected / exposed occurrences (all)	2 / 98 (2.04%) 3	5 / 101 (4.95%) 5	
Stomatitis subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 7	4 / 101 (3.96%) 4	
Vomiting subjects affected / exposed occurrences (all)	15 / 98 (15.31%) 20	14 / 101 (13.86%) 27	
Skin and subcutaneous tissue disorders			
Actinic keratosis subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 6	3 / 101 (2.97%) 3	
Dermatitis subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 6	1 / 101 (0.99%) 1	
Dry skin subjects affected / exposed occurrences (all)	7 / 98 (7.14%) 12	2 / 101 (1.98%) 5	
Ecchymosis subjects affected / exposed occurrences (all)	4 / 98 (4.08%) 6	1 / 101 (0.99%) 1	
Erythema subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	5 / 101 (4.95%) 5	
Nail disorder			

subjects affected / exposed	3 / 98 (3.06%)	1 / 101 (0.99%)
occurrences (all)	3	1
Onychoclasia		
subjects affected / exposed	10 / 98 (10.20%)	1 / 101 (0.99%)
occurrences (all)	10	1
Petechiae		
subjects affected / exposed	5 / 98 (5.10%)	7 / 101 (6.93%)
occurrences (all)	6	8
Pruritus		
subjects affected / exposed	6 / 98 (6.12%)	15 / 101 (14.85%)
occurrences (all)	10	20
Rash maculo-papular		
subjects affected / exposed	2 / 98 (2.04%)	4 / 101 (3.96%)
occurrences (all)	2	6
Rash erythematous		
subjects affected / exposed	1 / 98 (1.02%)	5 / 101 (4.95%)
occurrences (all)	1	6
Rash		
subjects affected / exposed	19 / 98 (19.39%)	19 / 101 (18.81%)
occurrences (all)	25	25
Purpura		
subjects affected / exposed	6 / 98 (6.12%)	4 / 101 (3.96%)
occurrences (all)	9	4
Psoriasis		
subjects affected / exposed	3 / 98 (3.06%)	0 / 101 (0.00%)
occurrences (all)	3	0
Rosacea		
subjects affected / exposed	5 / 98 (5.10%)	2 / 101 (1.98%)
occurrences (all)	5	2
Skin fissures		
subjects affected / exposed	3 / 98 (3.06%)	1 / 101 (0.99%)
occurrences (all)	4	2
Skin ulcer		
subjects affected / exposed	4 / 98 (4.08%)	3 / 101 (2.97%)
occurrences (all)	4	3
Skin toxicity		

subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	1 / 101 (0.99%) 1	
Skin lesion subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	6 / 101 (5.94%) 9	
Renal and urinary disorders			
Haematuria subjects affected / exposed occurrences (all)	13 / 98 (13.27%) 17	11 / 101 (10.89%) 13	
Pollakiuria subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	1 / 101 (0.99%) 1	
Urinary retention subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0	4 / 101 (3.96%) 6	
Dysuria subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	0 / 101 (0.00%) 0	
Acute kidney injury subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 4	1 / 101 (0.99%) 1	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	24 / 98 (24.49%) 50	24 / 101 (23.76%) 42	
Back pain subjects affected / exposed occurrences (all)	18 / 98 (18.37%) 23	18 / 101 (17.82%) 31	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 4	3 / 101 (2.97%) 4	
Muscular weakness subjects affected / exposed occurrences (all)	1 / 98 (1.02%) 1	4 / 101 (3.96%) 4	
Muscle spasms			

subjects affected / exposed	28 / 98 (28.57%)	12 / 101 (11.88%)	
occurrences (all)	43	15	
Joint swelling			
subjects affected / exposed	4 / 98 (4.08%)	4 / 101 (3.96%)	
occurrences (all)	5	5	
Rotator cuff syndrome			
subjects affected / exposed	3 / 98 (3.06%)	3 / 101 (2.97%)	
occurrences (all)	3	3	
Pain in extremity			
subjects affected / exposed	10 / 98 (10.20%)	15 / 101 (14.85%)	
occurrences (all)	12	21	
Osteoporosis			
subjects affected / exposed	3 / 98 (3.06%)	1 / 101 (0.99%)	
occurrences (all)	3	1	
Osteoarthritis			
subjects affected / exposed	3 / 98 (3.06%)	2 / 101 (1.98%)	
occurrences (all)	3	2	
Neck pain			
subjects affected / exposed	6 / 98 (6.12%)	3 / 101 (2.97%)	
occurrences (all)	6	3	
Myalgia			
subjects affected / exposed	3 / 98 (3.06%)	7 / 101 (6.93%)	
occurrences (all)	4	9	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 98 (4.08%)	4 / 101 (3.96%)	
occurrences (all)	4	4	
COVID-19			
subjects affected / exposed	5 / 98 (5.10%)	9 / 101 (8.91%)	
occurrences (all)	5	10	
Cellulitis			
subjects affected / exposed	7 / 98 (7.14%)	6 / 101 (5.94%)	
occurrences (all)	18	10	
Conjunctivitis			
subjects affected / exposed	7 / 98 (7.14%)	2 / 101 (1.98%)	
occurrences (all)	7	3	

Cystitis		
subjects affected / exposed	3 / 98 (3.06%)	0 / 101 (0.00%)
occurrences (all)	3	0
Ear infection		
subjects affected / exposed	3 / 98 (3.06%)	2 / 101 (1.98%)
occurrences (all)	3	2
Folliculitis		
subjects affected / exposed	5 / 98 (5.10%)	2 / 101 (1.98%)
occurrences (all)	6	2
Gastroenteritis		
subjects affected / exposed	5 / 98 (5.10%)	6 / 101 (5.94%)
occurrences (all)	6	7
Herpes zoster		
subjects affected / exposed	4 / 98 (4.08%)	5 / 101 (4.95%)
occurrences (all)	4	5
Laryngitis		
subjects affected / exposed	3 / 98 (3.06%)	0 / 101 (0.00%)
occurrences (all)	3	0
Localised infection		
subjects affected / exposed	11 / 98 (11.22%)	2 / 101 (1.98%)
occurrences (all)	15	2
Furuncle		
subjects affected / exposed	4 / 98 (4.08%)	0 / 101 (0.00%)
occurrences (all)	7	0
Lower respiratory tract infection		
subjects affected / exposed	10 / 98 (10.20%)	8 / 101 (7.92%)
occurrences (all)	15	13
Nail infection		
subjects affected / exposed	6 / 98 (6.12%)	0 / 101 (0.00%)
occurrences (all)	11	0
Nasopharyngitis		
subjects affected / exposed	9 / 98 (9.18%)	14 / 101 (13.86%)
occurrences (all)	10	21
Onychomycosis		
subjects affected / exposed	5 / 98 (5.10%)	1 / 101 (0.99%)
occurrences (all)	5	1

Oral herpes			
subjects affected / exposed	5 / 98 (5.10%)	1 / 101 (0.99%)	
occurrences (all)	7	1	
Paronychia			
subjects affected / exposed	3 / 98 (3.06%)	2 / 101 (1.98%)	
occurrences (all)	4	2	
Pneumonia			
subjects affected / exposed	9 / 98 (9.18%)	3 / 101 (2.97%)	
occurrences (all)	9	3	
Respiratory tract infection			
subjects affected / exposed	3 / 98 (3.06%)	8 / 101 (7.92%)	
occurrences (all)	4	10	
Rhinitis			
subjects affected / exposed	7 / 98 (7.14%)	7 / 101 (6.93%)	
occurrences (all)	8	12	
Sinusitis			
subjects affected / exposed	10 / 98 (10.20%)	6 / 101 (5.94%)	
occurrences (all)	11	9	
Skin infection			
subjects affected / exposed	7 / 98 (7.14%)	3 / 101 (2.97%)	
occurrences (all)	16	4	
Tooth infection			
subjects affected / exposed	5 / 98 (5.10%)	3 / 101 (2.97%)	
occurrences (all)	9	3	
Urinary tract infection			
subjects affected / exposed	17 / 98 (17.35%)	16 / 101 (15.84%)	
occurrences (all)	38	25	
Upper respiratory tract infection			
subjects affected / exposed	31 / 98 (31.63%)	33 / 101 (32.67%)	
occurrences (all)	55	49	
Wound infection			
subjects affected / exposed	3 / 98 (3.06%)	0 / 101 (0.00%)	
occurrences (all)	3	0	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	4 / 98 (4.08%)	3 / 101 (2.97%)
occurrences (all)	10	4
Gout		
subjects affected / exposed	5 / 98 (5.10%)	3 / 101 (2.97%)
occurrences (all)	6	3
Decreased appetite		
subjects affected / exposed	4 / 98 (4.08%)	4 / 101 (3.96%)
occurrences (all)	6	4
Hypokalaemia		
subjects affected / exposed	6 / 98 (6.12%)	3 / 101 (2.97%)
occurrences (all)	6	14
Hyponatraemia		
subjects affected / exposed	1 / 98 (1.02%)	4 / 101 (3.96%)
occurrences (all)	1	4
Iron deficiency		
subjects affected / exposed	7 / 98 (7.14%)	7 / 101 (6.93%)
occurrences (all)	7	8
Hypoalbuminaemia		
subjects affected / exposed	3 / 98 (3.06%)	1 / 101 (0.99%)
occurrences (all)	5	1
Vitamin D deficiency		
subjects affected / exposed	2 / 98 (2.04%)	5 / 101 (4.95%)
occurrences (all)	2	5
Hyperuricaemia		
subjects affected / exposed	9 / 98 (9.18%)	4 / 101 (3.96%)
occurrences (all)	14	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 November 2016	<ul style="list-style-type: none">• Updated background with new zanubrutinib trial results and data on role of MYD88 mutation in responsiveness of WM to BTK inhibitors• Changed the primary objective to the proportion of patients who achieved CR/VGPR, based on the clarification of the primary study hypothesis that stemmed from the updated zanubrutinib data• Added major response rate and VGPR/CR (by investigator assessment) as secondary endpoints• Added antitumor activity and safety of zanubrutinib in MYD88WT WM patients as an exploratory endpoint• Added quality of life and medical resource utilization as exploratory endpoints• Identified patients with MYD88MUT WM as the primary population for randomization and study analyses (Cohort 1)• Revised sample size consideration• Added language describing sequential analysis approach to the primary and secondary endpoints• Identified treatment cohorts based on MYD88 mutational status: Cohort 1 (MYD88MUT) and newly added Cohort 2 (MYD88WT)• Added the inclusion criterion to clarify that treatment-naïve patients were considered inappropriate candidates for intensive therapy• Added the inclusion criterion to require measurable disease, in accordance with the response rate primary objective• Added clarification for efficacy assessments in the occasion of study drug holding and plasmapheresis
08 May 2017	<ul style="list-style-type: none">• study rationale, benefit/risk assessment, and dose justification• Updated the timing of response assessments to every 4 weeks (each cycle)Increased the screening phase to up to 35 days before randomization• Added EQ-5D to quality-of-life assessments• Updated the timing of bone marrow assessment for the presence of WM• Clarified the study population by providing definitions for relapsed/refractory• Clarified that up to 20% of patients may have been treatment naïve• Updated the eligibility criteria to clarify that patients may have had relapsed/refractory or treatment-naïve WM considered by their treating physician to be inappropriate for standard chemoimmunotherapy regimens• Clarified blinding of the Independent Review Committee and DMC• Clarified dose modification to allow for study drug to be held for up to 2 consecutive cycles and that more than 1 drug hold was allowed over the course of the study• Removed the ECHO/MUGA from screening and exclusion criteria• Added the requirement for confirmation of disease transformation by biopsy• Added adverse events of special interest• Updated pregnancy and contraception language

02 February 2018	<ul style="list-style-type: none"> • Updated the total number of patients to approximately 210. Cohort 1 included approximately 150 patients with relapsed/refractory disease and 38 treatment-naïve MYD88MUT patients. Cohort 2 included approximately 22 MYD88WT patients. • Revised the statistical analysis methods for analyzing relapsed/refractory MYD88MUT patients • Changed the timing of the interim analysis to 6 months after the first 50 patients with relapsed/refractory disease were randomized to Cohort 1 • Updated the sample size considerations to have the power to test the primary endpoint in the Cohort 1 Relapsed/Refractory Analysis Set • Changed the timing of the primary analysis from 9 months to 12 months • Added an assessment of impact of plasmapheresis on zanubrutinib PK as a new exploratory objective and endpoint • Revised the zanubrutinib and ibrutinib guidelines for dose modification, reduction, and discontinuation • Added ventricular arrhythmia as an adverse event of special interest <p>Revised the definition of treatment-emergent adverse event to be consistent with other protocols</p> <ul style="list-style-type: none"> • Clarified that evaluation of extramedullary disease included evaluation of splenomegaly rather than organomegaly • Clarified that infection prophylaxis was per institutional standards • Clarified when corticosteroid usage was prohibited • Added that all treatment-related serious adverse events were to be followed until resolution or stabilization • Revised the efficacy follow-up to continue even though a patient may have started a new anticancer therapy after the last dose of study drug • Added that patients who continued to benefit from zanubrutinib after disease progression may have remained on study upon discussion with the medical monitor or designee • Added back ECHO/MUGA assessments at screening and when clinically indicated
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21 September 2018	<ul style="list-style-type: none"> • Clarified for patients with mild hepatic impairment (Child-Pugh Class A) and moderate hepatic impairment (Child-Pugh Class B) to refer to the local prescribing guidelines for specific instructions on ibrutinib dose modifications • Removed the QT/QTc prolonging drug guidance • Removed the adverse events of special interest list, including protocol definitions and associated expedited reporting requirements • Updated Phase 1 first-in-human study data • Clarified the maximum number of repetitions of a failed screening test to be 1 time • Updated the overdose reporting guidance • Added guidance about the potential for opportunistic infections in patients with hematologic malignancies, particularly for those having received prior lymphodepleting chemotherapy or prolonged corticosteroid exposure • Added that patients who remained on the study after disease progression continued to follow the required assessments during the treatment phase • Clarified that the serum IgM value at Cycle 1 Day 1 served as the baseline for all assessments except for patients who had undergone plasmapheresis • Clarified that assessments were performed in the same laboratory using the same methodology throughout the study • Clarified that patients with new disease symptoms documented objective evidence of disease progression according to the disease-specific response criteria • Clarified that as part of the tumor assessment, the physical examination was also to be included the evaluation of the presence and degree of enlarged lymph nodes and splenomegaly • Clarified that ECGs were to be performed in triplicate at each timepoint assessment • Clarified the sample collection practices for cryoglobulin, serum immunoglobulins, and immunofixation for patients with cryoglobulinemia at screening • Clarified that the clinical significance of a laboratory test abnormality was at the judgment of the investigator
26 August 2019	<ul style="list-style-type: none"> • Clarified that capsules or other dose forms and strengths were allowed for ibrutinib • Clarified that a barrier method of contraception must have also been used if hormonal contraceptives were used • Added section on dose modifications for zanubrutinib when coadministered with strong/moderate CYP3A inhibitors/inducers • Clarified medications to be used with caution • Clarified use of efficacy criteria with and without consideration of extramedullary disease • Clarified instructions for post-baseline CT scans • Updated lists of moderate and strong CYP3A inhibitors and inducers

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported