



Clinical trial results:

A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Summary

EudraCT number	2018-001366-42
Trial protocol	FR ES BE CZ GB SE NL IT
Global end of trial date	28 February 2024

Results information

Result version number	v1 (current)
This version publication date	16 March 2025
First version publication date	16 March 2025

Trial information

Trial identification

Sponsor protocol code	BGB-3111-305
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03734016
WHO universal trial number (UTN)	-
Other trial identifiers	ChinaDrugTrials.org: CTR20190098

Notes:

Sponsors

Sponsor organisation name	BeiGene, Ltd., c/o BeiGene USA, Inc.
Sponsor organisation address	1840 Gateway Drive, San Mateo, CA , United States, 94404
Public contact	BeiGene Clinical Support, BeiGene, Ltd., 1 877-828-5568, clinicaltrials@beigene.com
Scientific contact	BeiGene Clinical Support, BeiGene, Ltd., 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	28 February 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study is designed to compare the overall response rate of zanubrutinib versus ibrutinib in participants with relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Protection of trial subjects:

This study was conducted in accordance with sponsor procedures, which comply with the principles of Good Clinical Practice (GCP), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guidelines, the Declaration of Helsinki, and applicable local regulatory requirements.

The protocol, any amendments, and informed consent forms were reviewed and approved by the Independent Ethics Committee/Institutional Review Board in conformance with GCP and applicable regulatory requirements.

Before a patient was enrolled in the study, he or she was provided with a written informed consent form that complied with GCP. The investigator (or designee) explained to each patient the nature of the study, its purpose, procedures, expected duration, and the benefits and risks involved with study participation. Patients were given the opportunity to ask questions and were informed of their right to withdraw from the study at any time without prejudice. After this explanation and before enrolling in the study, patients or their legal representatives signed 2 copies of the informed consent form (one copy for the patient and the other for filing with the patient's study records). Informed consent was obtained before any screening or study-specific procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2018
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: 16
Country: Number of subjects enrolled	China: 90
Country: Number of subjects enrolled	New Zealand: 42
Country: Number of subjects enrolled	Türkiye: 4
Country: Number of subjects enrolled	United States: 111
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Poland: 216
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	Belgium: 1

Country: Number of subjects enrolled	Czechia: 58
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 17
Worldwide total number of subjects	652
EEA total number of subjects	357

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)	251
From 65 to 84 years	387
85 years and over	14

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 113 study centers in 15 countries (Australia, Belgium, China, the Czech Republic, France, Germany, Italy, the Netherlands, New Zealand, Poland, Spain, Sweden, Turkey, the United Kingdom, and the United States).

Pre-assignment

Screening details:

Participants were randomly assigned to one of two treatment groups. Randomization was stratified according to age (< 65 versus ≥ 65 years), geographic region (China vs non-China), refractory status (yes or no), and chromosome 17p deletion or TP53 mutation status (present or absent).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Zanubrutinib

Arm description:

Participants received 160 mg zanubrutinib orally twice daily until disease progression, intolerable toxicity, initiation of alternative anticancer therapy, investigator/Sponsor decision, need for prohibited medication, study withdrawal, or pregnancy.

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

Dosage and administration details:

Administered orally twice a day

Arm title	Ibrutinib
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Arm description:

Participants received ibrutinib 420 mg orally once daily until disease progression, intolerable toxicity, initiation of alternative anticancer therapy, investigator/Sponsor decision, need for prohibited medication, study withdrawal, or pregnancy.

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

Dosage and administration details:

Administered orally once a day

Number of subjects in period 1	Zanubrutinib	Ibrutinib
Started	327	325
Received Study Drug	324	324
Completed	0	0
Not completed	327	325
Consent withdrawn by subject	21	27
Physician decision	1	12
Sponsor Ended Study	225	200
Death	69	83
Miscellaneous	5	1
Lost to follow-up	6	2

Baseline characteristics

Reporting groups

Reporting group title	Zanubrutinib
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Reporting group description:

Participants received 160 mg zanubrutinib orally twice daily until disease progression, intolerable toxicity, initiation of alternative anticancer therapy, investigator/Sponsor decision, need for prohibited medication, study withdrawal, or pregnancy.

Reporting group title	Ibrutinib
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Reporting group description:

Participants received ibrutinib 420 mg orally once daily until disease progression, intolerable toxicity, initiation of alternative anticancer therapy, investigator/Sponsor decision, need for prohibited medication, study withdrawal, or pregnancy.

Reporting group values	Zanubrutinib	Ibrutinib	Total
Number of subjects	327	325	652
Age categorical Units: Subjects			
< 65 years	126	125	251
≥ 65 years	201	200	401
Age continuous Units: years			
median	67.0	68.0	
full range (min-max)	35 to 90	35 to 89	-
Gender categorical Units: Subjects			
Female	114	93	207
Male	213	232	445
Race Units: Subjects			
Asian	47	44	91
Native Hawaiian or Other Pacific Islander	3	0	3
Black or African American	4	2	6
White	261	265	526
Other	2	2	4
Multiple	1	0	1
Unknown/Not Reported	9	12	21
Ethnicity Units: Subjects			
Hispanic or Latino	7	13	20
Not Hispanic or Latino	309	298	607
Unknown or Not Reported	11	14	25
Geographic Region Units: Subjects			
Asia	49	45	94
Australia/New Zealand	28	30	58
Europe	198	191	389
North America	52	59	111
Chromosome 17p Deletion (del[17p])			

and TP53 Mutation Status			
Deletion 17p is a chromosomal abnormality that occurs when part or all of the short arm of chromosome 17 is lost. The TP53 gene provides instructions for making a protein called tumor protein p53 (or p53) which acts as a tumor suppressor.			
Units: Subjects			
Del(17p) and/or TP53 mutation	75	75	150
Neither Del(17p) nor TP53 mutation	251	250	501
Missing	1	0	1

End points

End points reporting groups

Reporting group title	Zanubrutinib
Reporting group description: Participants received 160 mg zanubrutinib orally twice daily until disease progression, intolerable toxicity, initiation of alternative anticancer therapy, investigator/Sponsor decision, need for prohibited medication, study withdrawal, or pregnancy.	
Reporting group title	Ibrutinib
Reporting group description: Participants received ibrutinib 420 mg orally once daily until disease progression, intolerable toxicity, initiation of alternative anticancer therapy, investigator/Sponsor decision, need for prohibited medication, study withdrawal, or pregnancy.	

Primary: Overall Response Rate (ORR) Assessed by the Investigator

End point title	Overall Response Rate (ORR) Assessed by the Investigator
End point description: ORR is defined as the percentage of participants with a complete response (CR) / complete response with incomplete bone marrow recovery (CRi), nodular partial response (nPR) or partial response (PR) per investigator assessment. Disease response was assessed in accordance with the 2008 criteria of the International Workshop on CLL (IWCLL), with modification for treatment-related lymphocytosis in participants with CLL and in accordance with the Lugano classification in participants with SLL. ORR was analyzed in the Intent to Treat (ITT) Analysis Set which includes all randomized participants.	
End point type	Primary
End point timeframe: From randomization to the final efficacy analysis cutoff date of 08 August 2022, median time on follow-up was 29.6 months (maximum of 45.2 months).	

End point values	Zanubrutinib	Ibrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327	325		
Units: percentage of participants				
number (confidence interval 95%)	83.5 (79.0 to 87.3)	74.2 (69.0 to 78.8)		

Statistical analyses

Statistical analysis title	Non-inferiority Analysis of ORR
Comparison groups	Zanubrutinib v Ibrutinib

Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	< 0.0001
Method	Stratified Wald test
Parameter estimate	Response ratio
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	1.22

Notes:

[1] - Non-inferiority testing for ORR was performed using a stratified Wald test based on the stratified Mantel-Haenszel response ratio estimate against the non-inferiority margin of 0.8558 on the log scale. Stratification was based on the randomization stratification factors (age, geographic region, refractory status, and 17p deletion and TP53 mutation status).

Statistical analysis title	Superiority Analysis of ORR
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.0035
Method	Cochran-Mantel-Haenszel

Notes:

[2] - Superiority testing was performed using a 2-sided stratified Cochran-Mantel-Haenszel test stratified by the randomization stratification factors (age, geographic region, refractory status, and 17p deletion and TP53 mutation status).

Secondary: ORR Assessed by the Independent Review Committee (IRC)

End point title	ORR Assessed by the Independent Review Committee (IRC)
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End point description:

ORR is defined as the percentage of participants with a complete response (CR) / complete response with incomplete bone marrow recovery (CRI), nodular partial response (nPR) or partial response (PR) assessed by a blinded independent review committee. Overall response was assessed by the IRC for the purpose of regulatory filing with the Food and Drug Administration (FDA).

Disease response was assessed in accordance with the 2008 criteria of the International Workshop on CLL (IWCLL), with modification for treatment-related lymphocytosis in participants with CLL and in accordance with the Lugano classification in participants with SLL.

ORR was analyzed using the ITT Analysis Set.

End point type	Secondary
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End point timeframe:

From randomization to the final efficacy analysis cutoff date of 08 August 2022, median time on follow-up was 29.6 months (maximum of 45.2 months).

End point values	Zanubrutinib	Ibrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327	325		
Units: percentage of participants				
number (confidence interval 95%)	86.2 (82.0 to 89.8)	75.7 (70.7 to 80.3)		

Statistical analyses

Statistical analysis title	Non-inferiority Analysis of ORR
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
P-value	< 0.0001
Method	Stratified Wald test
Parameter estimate	Response ratio
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	1.22

Notes:

[3] - Non-inferiority testing for ORR was performed using a stratified Wald test based on the stratified Mantel-Haenszel response ratio estimate against the non-inferiority margin of 0.8558 on the log scale. Stratification was based on the randomization stratification factors (age, geographic region, refractory status, and 17p deletion and TP53 mutation status).

Statistical analysis title	Superiority Analysis of ORR
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	= 0.0007
Method	Cochran-Mantel-Haenszel

Notes:

[4] - Superiority testing was performed using a 2-sided stratified Cochran-Mantel-Haenszel test stratified by the randomization stratification factors (age, geographic region, refractory status, and 17p deletion and TP53 mutation status).

Secondary: Progression-free Survival (PFS) Assessed by the Investigator

End point title	Progression-free Survival (PFS) Assessed by the Investigator
End point description:	
PFS is defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurred first. Median PFS was estimated using the Kaplan-Meier method. PFS was analyzed using the ITT Analysis Set. "99999" indicates values that could not be estimated due to an insufficient number of participants with events.	
End point type	Secondary

End point timeframe:

From randomization to the final efficacy analysis cutoff date of 08 August 2022, median time on follow-up was 29.6 months (maximum of 45.2 months).

End point values	Zanubrutinib	Ibrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327	325		
Units: months				
median (confidence interval 95%)	99999 (34.3 to 99999)	34.2 (33.3 to 99999)		

Statistical analyses

Statistical analysis title	Non-inferiority Analysis of PFS
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[5]
P-value	< 0.0001
Method	Stratified Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.86

Notes:

[5] - Non-inferiority was tested with a non-inferiority margin (hazard ratio) of 1.33 with the use of a stratified Wald test based on the four randomization stratification factors (age, geographic region, refractory status, and 17p deletion and TP53 mutation status).

Statistical analysis title	Superiority Analysis of PFS
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0024 ^[6]
Method	Stratified Log-rank test

Notes:

[6] - Log-rank test stratified by the randomization stratification factors (age, geographic region, refractory status, and 17p deletion and TP53 mutation status)

Secondary: Progression-free Survival Assessed by the Independent Review Committee

End point title	Progression-free Survival Assessed by the Independent Review Committee
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End point description:

PFS is defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurred first. Median PFS was estimated using the Kaplan-Meier method. PFS was analyzed using the ITT Analysis Set. "99999" indicates values that could not be estimated due to an insufficient number of participants with events.

End point type	Secondary
End point timeframe:	
From randomization to the final efficacy analysis cutoff date of 08 August 2022, median time on follow-up was 29.6 months (maximum of 45.2 months).	

End point values	Zanubrutinib	Ibrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327	325		
Units: months				
median (confidence interval 95%)	99999 (34.3 to 99999)	35.0 (33.2 to 44.3)		

Statistical analyses

Statistical analysis title	Non-inferiority Analysis of PFS per IRC
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[7]
P-value	< 0.0001
Method	Stratified Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.86

Notes:

[7] - Non-inferiority was tested with a non-inferiority margin (hazard ratio) of 1.33 with the use of a stratified Wald test based on the four randomization stratification factors (age, geographic region, refractory status, and 17p deletion and TP53 mutation status).

Statistical analysis title	Superiority Analysis of PFS per IRC
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.0024
Method	Stratified Log-rank test

Notes:

[8] - Log-rank test stratified by the randomization stratification factors (age, geographic region, refractory status, and 17p deletion and TP53 mutation status)

Secondary: Percentage of Participants With Atrial Fibrillation or Atrial Flutter

End point title	Percentage of Participants With Atrial Fibrillation or Atrial Flutter
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End point description:

Participants were considered as having an atrial fibrillation/flutter event if they had a treatment-emergent AE of either "atrial fibrillation" or "atrial flutter".
The analysis was conducted using the Safety Analysis Set which includes all participants who received any dose of study drug.

End point type	Secondary
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End point timeframe:

From randomization to the final efficacy analysis cutoff date of 08 August 2022, median time on follow-up was 29.6 months (maximum of 45.2 months).

End point values	Zanubrutinib	Ibrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	324	324		
Units: percentage of participants				
number (confidence interval 95%)	5.2 (3.1 to 8.3)	13.3 (9.8 to 17.5)		

Statistical analyses

Statistical analysis title	Analysis of Atrial Fibrillation/Flutter
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	648
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Chi-squared
Parameter estimate	Rate Difference
Point estimate	-8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.4
upper limit	-3.6

Secondary: Duration of Response Assessed by the Independent Review Committee

End point title	Duration of Response Assessed by the Independent Review Committee
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End point description:

DOR is defined as the time from the date that response criteria were first met to the date that disease progression was objectively documented or death, whichever occurred first, determined by independent central review. Median DOR was estimated using the Kaplan-Meier method.
The analysis was conducted in participants in the ITT Analysis Set with an objective response per the IRC. "99999" indicates values that could not be estimated due to an insufficient number of participants with an event.

End point type	Secondary
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End point timeframe:

From randomization to the final efficacy analysis cutoff date of 08 August 2022, median time on follow-

up was 29.6 months (maximum of 45.2 months).

End point values	Zanubrutinib	Ibrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282 ^[9]	246 ^[10]		
Units: months				
median (confidence interval 95%)	99999 (31.3 to 99999)	33.9 (32.2 to 41.4)		

Notes:

[9] - Participants with an objective response per IRC

[10] - Participants with an objective response per IRC

Statistical analyses

No statistical analyses for this end point

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

End point title	Duration of Response (DOR) Assessed by the Investigator
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End point description:

DOR is defined as the time from the date that response criteria were first met to the date that disease progression was objectively documented or death, whichever occurred first, determined by investigator assessment. Median DOR was estimated using the Kaplan-Meier method.

The analysis was conducted in participants in the ITT Analysis Set with an objective response per the Investigator. "99999" indicates values that could not be estimated due to an insufficient number of participants with an event.

End point type	Secondary
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End point timeframe:

From randomization to the final efficacy analysis cutoff date of 08 August 2022, median time on follow-up was 29.6 months (maximum of 45.2 months).

End point values	Zanubrutinib	Ibrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273 ^[11]	241 ^[12]		
Units: months				
median (confidence interval 95%)	99999 (31.3 to 99999)	33.9 (33.9 to 99999)		

Notes:

[11] - Participants with an objective response per the investigator

[12] - Participants with an objective response per the investigator

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure

End point title	Time to Treatment Failure
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End point description:

Time to treatment failure is defined as the time from randomization to discontinuation of study drug due

to any reason. Median time to treatment failure was estimated by the Kaplan-Meier method.

End point type	Secondary
End point timeframe:	
From randomization to the final efficacy analysis cutoff date of 08 August 2022, median time on follow-up was 29.6 months (maximum of 45.2 months).	

End point values	Zanubrutinib	Ibrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327	325		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (34.4 to 99999)		

Statistical analyses

Statistical analysis title	Analysis of Time to Treatment Failure
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.72

Secondary: Rate of Partial Response With Lymphocytosis (PR-L) or Higher Assessed by the Independent Review Committee

End point title	Rate of Partial Response With Lymphocytosis (PR-L) or Higher Assessed by the Independent Review Committee
End point description:	
The rate of partial response with lymphocytosis or better is defined as the percentage of participants who achieved a complete response or a complete response with incomplete bone marrow recovery (CR/CRi), nodular partial response, partial response, or partial response with lymphocytosis assessed by the blinded IRC.	
Disease response was assessed per iwCLL 2008 criteria, with modification for treatment-related lymphocytosis for participants with CLL and per Lugano classification for participants with SLL.	
End point type	Secondary
End point timeframe:	
From randomization to the final efficacy analysis cutoff date of 08 August 2022, median time on follow-up was 29.6 months (maximum of 45.2 months).	

End point values	Zanubrutinib	Ibrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327	325		
Units: percentage of participants				
number (confidence interval 95%)	91.7 (88.2 to 94.5)	83.1 (78.5 to 87.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Partial Response With Lymphocytosis (PR-L) or Higher Assessed by the Investigator

End point title	Rate of Partial Response With Lymphocytosis (PR-L) or Higher Assessed by the Investigator
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End point description:

The rate of partial response with lymphocytosis or better is defined as the percentage of participants who achieved a complete response or complete response with incomplete bone marrow recovery (CR/CRi), nodular partial response, partial response, or partial response with lymphocytosis as assessed by the investigator.

Disease response was assessed according to the iwCLL 2008 criteria, with modification for treatment-related lymphocytosis for participants with CLL and in accordance with Lugano classification for participants with SLL.

Partial response with lymphocytosis: blood lymphocytes decreased < 50% or increased from baseline, and otherwise meeting criteria for PR.

End point type	Secondary
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End point timeframe:

From randomization to the final efficacy analysis cutoff date of 08 August 2022, median time on follow-up was 29.6 months (maximum of 45.2 months).

End point values	Zanubrutinib	Ibrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327	325		
Units: percentage of participants				
number (confidence interval 95%)	89.9 (86.1 to 93.0)	82.5 (77.9 to 86.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

Overall survival is defined as the time from randomization to the date of death due to any cause. Median OS was estimated using the Kaplan-Meier method. The analysis was conducted in the ITT Analysis Set. "99999" indicates values that could not be estimated due to an insufficient number of participants with events.

End point type	Secondary
End point timeframe:	
From randomization to the final efficacy analysis cutoff date of 08 August 2022, median time on follow-up was 29.6 months (maximum of 45.2 months).	

End point values	Zanubrutinib	Ibrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327	325		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Analysis of OS
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.11

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status (GHS)/Quality of Life (QOL), Physical Functioning and Role Functioning Scores

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status (GHS)/Quality of Life (QOL), Physical Functioning and Role Functioning Scores
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End point description:

The EORTC QLQ-30 contains 30 questions that incorporate 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The participant answers questions about their health during the past week. There are 28 questions answered on a 4-point scale where 1 = Not at all (best) and 4 = Very Much (worst) and 2 global health quality of life (QOL) questions answered on a 7-point scale where 1 = Very poor and 7 = Excellent. Raw scores are transformed into a 0 to 100 scale via linear transformation. Higher scores in GHS and functional scales indicate better quality of life.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 24 and 48

End point values	Zanubrutinib	Ibrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315 ^[13]	313 ^[14]		
Units: score on a scale				
least squares mean (confidence interval 95%)				
GHS/QoL Scale at Week 24	8.18 (6.25 to 10.12)	5.18 (3.20 to 7.17)		
GHS/QoL Scale at Week 48	7.28 (5.41 to 9.15)	5.93 (3.97 to 7.89)		
Physical Functioning Scale at Week 24	6.55 (4.96 to 8.15)	4.73 (3.08 to 6.38)		
Physical Functioning Scale at Week 48	5.46 (3.87 to 7.04)	4.31 (2.65 to 5.97)		
Role Functioning Scale at Week 24	6.95 (4.85 to 9.06)	6.32 (4.14 to 8.50)		
Role Functioning Scale at Week 48	6.81 (4.61 to 9.02)	5.01 (2.69 to 7.33)		

Notes:

[13] - Participants in the ITT Analysis Set who completed the EORTC QLQ-C30 at Baseline

[14] - Participants in the ITT Analysis Set who completed the EORTC QLQ-C30 at Baseline

Statistical analyses

Statistical analysis title	Analysis of Change in GHS/QOL at Week 24
Statistical analysis description: A linear mixed model for repeated measures (MMRM) includes the repeated measurement of the change from baseline as the dependent variable, and the treatment arm by assessment timepoint interaction, and baseline score as a covariate with an unstructured covariance matrix.	
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0338
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	5.77

Statistical analysis title	Analysis of Change in GHS/QOL at Week 48
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Statistical analysis description:

A linear mixed model for repeated measures (MMRM) includes the repeated measurement of the change

from baseline as the dependent variable, and the treatment arm by assessment timepoint interaction, and baseline score as a covariate with an unstructured covariance matrix.

Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3304
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.37
upper limit	4.06

Statistical analysis title	Analysis of Physical Functioning at Week 24
Statistical analysis description:	
A linear mixed model for repeated measures (MMRM) includes the repeated measurement of the change from baseline as the dependent variable, and the treatment arm by assessment timepoint interaction, and baseline score as a covariate with an unstructured covariance matrix.	
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1189
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	4.12

Statistical analysis title	Analysis of Physical Functioning at Week 48
Statistical analysis description:	
A linear mixed model for repeated measures (MMRM) includes the repeated measurement of the change from baseline as the dependent variable, and the treatment arm by assessment timepoint interaction, and baseline score as a covariate with an unstructured covariance matrix.	
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3274
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	1.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	3.44

Statistical analysis title	Analysis of Role Functioning at Week 24
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Statistical analysis description:

A linear mixed model for repeated measures (MMRM) includes the repeated measurement of the change from baseline as the dependent variable, and the treatment arm by assessment timepoint interaction, and baseline score as a covariate with an unstructured covariance matrix.

Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6821
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	3.66

Statistical analysis title	Analysis of Role Functioning at Week 48
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Statistical analysis description:

A linear mixed model for repeated measures (MMRM) includes the repeated measurement of the change from baseline as the dependent variable, and the treatment arm by assessment timepoint interaction, and baseline score as a covariate with an unstructured covariance matrix.

Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2701
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	5

Secondary: Change From Baseline in EORTC QLQ-C30 Symptom Scales of Fatigue,

Nausea and Vomiting, Pain, and Diarrhoea

End point title	Change From Baseline in EORTC QLQ-C30 Symptom Scales of Fatigue, Nausea and Vomiting, Pain, and Diarrhoea
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End point description:

The EORTC QLQ-30 contains 30 questions that incorporate 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The participant answers questions about their health during the past week. There are 28 questions answered on a 4-point scale where 1 = Not at all (best) and 4 = Very Much (worst) and 2 global health quality of life (QOL) questions answered on a 7-point scale where 1 = Very poor and 7 = Excellent. Raw scores are transformed into a 0 to 100 scale via linear transformation. Lower scores in symptom scales indicate better quality of life.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 24 and 48

End point values	Zanubrutinib	Ibrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315 ^[15]	313 ^[16]		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Fatigue Symptom Scale at Week 24	-12.54 (-14.47 to -10.60)	-10.63 (-12.63 to -8.62)		
Fatigue Symptom Scale at Week 48	-11.13 (-13.19 to -9.08)	-10.78 (-12.93 to -8.63)		
Nausea and Vomiting Symptom Scale at Week 24	-1.21 (-2.03 to -0.38)	-0.92 (-1.77 to -0.07)		
Nausea and Vomiting Symptom Scale at Week 48	-0.92 (-1.94 to 0.10)	-0.40 (-1.47 to 0.66)		
Pain Symptom Scale at Week 24	-5.06 (-7.21 to -2.91)	-3.63 (-5.85 to -1.42)		
Pain Symptom Scale at Week 48	-5.18 (-7.38 to -2.97)	-2.75 (-5.06 to -0.44)		
Diarrhoea Symptom Scale at Week 24	-2.11 (-3.80 to -0.42)	-0.52 (-2.27 to 1.22)		
Diarrhoea Symptom Scale at Week 48	-3.23 (-4.79 to -1.66)	-1.38 (-3.03 to 0.27)		

Notes:

[15] - Participants in the ITT Analysis Set who completed the EORTC QLQ-C30 at Baseline

[16] - Participants in the ITT Analysis Set who completed the EORTC QLQ-C30 at Baseline

Statistical analyses

Statistical analysis title	Analysis of Change in Fatigue Symptoms at Week 24
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1778
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.91

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	0.87

Statistical analysis title	Analysis of Change in Fatigue Symptoms at Week 48
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8174
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.32
upper limit	2.62

Statistical analysis title	Analysis of Nausea and Vomiting Symptom at Week 24
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6294
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.48
upper limit	0.89

Statistical analysis title	Analysis of Nausea and Vomiting Symptom at Week 48
Comparison groups	Zanubrutinib v Ibrutinib

Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4933
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.99
upper limit	0.96

Statistical analysis title	Analysis of Pain Symptoms at Week 24
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3643
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.51
upper limit	1.66

Statistical analysis title	Analysis of Pain Symptoms at Week 48
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1363
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-2.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.62
upper limit	0.77

Statistical analysis title	Analysis of Diarrhoea Symptoms at Week 24
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Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2001
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.01
upper limit	0.84

Statistical analysis title	Analysis of Diarrhoea Symptoms at Week 48
Comparison groups	Zanubrutinib v Ibrutinib
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1121
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.12
upper limit	0.43

Secondary: Change From Baseline in European Quality of Life 5-dimensions 5-levels Health Questionnaire (EQ-5D-5L) Visual Analog Scale (VAS)

End point title	Change From Baseline in European Quality of Life 5-dimensions 5-levels Health Questionnaire (EQ-5D-5L) Visual Analog Scale (VAS)
End point description:	The EQ-5D-5L VAS measures a participant's self-rated health on a scale from 0 to 100, where 100 is 'the best health you can imagine' and 0 is 'the worst health you can imagine.' A higher score indicates better health outcomes.
End point type	Secondary
End point timeframe:	Baseline and Weeks 24 and 48

End point values	Zanubrutinib	Ibrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315 ^[17]	315 ^[18]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 24	7.92 (± 18.245)	3.44 (± 16.972)		
Week 48	7.75 (± 18.806)	3.92 (± 16.778)		

Notes:

[17] - Participants with available data at Baseline and each time point.

Week 24: N=278;

Week 48: N=276

[18] - Participants with available data at Baseline and each time point.

Week 24: N=260;

Week 48: N=254

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)
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End point description:

An adverse event is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drug or not.

A serious adverse event (SAE) is any untoward medical occurrence that, at any dose:

- Resulted in death.
- Was life-threatening.
- Required hospitalization or prolongation of existing hospitalization.
- Resulted in disability/incapacity.
- Resulted in a congenital anomaly/birth defect.
- Was considered a significant medical AE by the investigator based on medical judgment.

The Safety Analysis Set includes all participants who received any dose of study drug.

End point type	Secondary
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End point timeframe:

From first dose of study drug up to 30 days after last dose, up to the end of study data cutoff (28 February 2024); median (range) time on treatment was 41.2 (0.4-59.1) months in the zanubrutinib arm and 37.8 (0.1-60.4) months in the ibrutinib arm.

End point values	Zanubrutinib	Ibrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	324	324		
Units: participants				
Any TEAE	322	323		
Serious adverse events	172	196		

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30 days after last dose, up to the end of study data cutoff (28 February 2024); median (range) time on treatment was 41.2 (0.4-59.1) months in the zanubrutinib arm and 37.8 (0.1-60.4) months in the ibrutinib arm.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26
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Reporting groups

Reporting group title	Zanubrutinib
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Reporting group description:

Participants received 160 mg zanubrutinib orally twice daily until disease progression, intolerable toxicity, initiation of alternative anticancer therapy, investigator/Sponsor decision, need for prohibited medication, study withdrawal, or pregnancy.

Reporting group title	Ibrutinib
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Reporting group description:

Participants received ibrutinib 420 mg orally once daily until disease progression, intolerable toxicity, initiation of alternative anticancer therapy, investigator/Sponsor decision, need for prohibited medication, study withdrawal, or pregnancy.

Serious adverse events	Zanubrutinib	Ibrutinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	172 / 324 (53.09%)	196 / 324 (60.49%)	
number of deaths (all causes)	69	83	
number of deaths resulting from adverse events	43	41	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer metastatic			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma gastric			
subjects affected / exposed	2 / 324 (0.62%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	

Atypical fibroxanthoma			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	3 / 324 (0.93%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign lung neoplasm			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm malignant			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast cancer			
subjects affected / exposed	0 / 324 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choroid melanoma			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chromophobe renal cell carcinoma			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin squamous cell carcinoma metastatic			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	2 / 324 (0.62%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer recurrent			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip squamous cell carcinoma			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoma			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 324 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mantle cell lymphoma			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucoepidermoid carcinoma of salivary gland			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neuroendocrine carcinoma of the cervix			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oral haemangioma			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer			
subjects affected / exposed	4 / 324 (1.23%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer metastatic			

subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (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	3 / 324 (0.93%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	0 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superficial spreading melanoma stage II			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thymoma malignant recurrent			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell cancer of the renal pelvis and ureter			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Varicose vein			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Haematoma			

subjects affected / exposed	0 / 324 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 324 (0.62%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter site haematoma			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			

subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	4 / 324 (1.23%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 4	0 / 3	
Drug withdrawal syndrome			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 324 (0.62%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 324 (0.62%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 324 (0.62%)	5 / 324 (1.54%)	
occurrences causally related to treatment / all	1 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			

subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic organ prolapse			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulva cyst			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (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			
Pleural effusion			
subjects affected / exposed	3 / 324 (0.93%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 324 (0.62%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (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 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			

subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal obstruction			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary necrosis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
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	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 324 (0.31%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary embolism			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood bilirubin increased			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
False positive investigation result			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	2 / 324 (0.62%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	5 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Traumatic haematoma			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Fall			
subjects affected / exposed	2 / 324 (0.62%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scapula fracture			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (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	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
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	0 / 324 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Traumatic liver injury			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic ulcer			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Bronchogenic cyst			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 324 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 324 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 324 (0.62%)	11 / 324 (3.40%)	
occurrences causally related to treatment / all	1 / 3	8 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 324 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial tachycardia			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 324 (0.00%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiac failure			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure chronic			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 324 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dilated cardiomyopathy			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myocardial infarction			
subjects affected / exposed	2 / 324 (0.62%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Myocardial ischaemia			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 324 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			

subjects affected / exposed	2 / 324 (0.62%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 324 (0.31%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery occlusion			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhage			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral haemorrhage			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 324 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cerebrovascular accident			
subjects affected / exposed	3 / 324 (0.93%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dysarthria			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 324 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Post herpetic neuralgia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 324 (1.54%)	4 / 324 (1.23%)	
occurrences causally related to treatment / all	3 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 324 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglobulinaemia			

subjects affected / exposed	1 / 324 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 324 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocytosis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 324 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic haematoma			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic haemorrhage			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 324 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tinnitus			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract nuclear			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryostenosis acquired			

subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratitis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic ischaemic neuropathy			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital oedema			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 324 (0.62%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Constipation			

subjects affected / exposed	0 / 324 (0.00%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 324 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated umbilical hernia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 324 (0.31%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric panniculitis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Noninfective sialoadenitis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal food impaction			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (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	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			

subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 324 (0.31%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bladder dysplasia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 324 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
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			
Chondrocalcinosis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	2 / 324 (0.62%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc compression			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma muscle			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acinetobacter bacteraemia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 324 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 324 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
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 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 324 (0.31%)	3 / 324 (0.93%)	
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 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
COVID-19			
subjects affected / exposed	28 / 324 (8.64%)	20 / 324 (6.17%)	
occurrences causally related to treatment / all	5 / 35	1 / 27	
deaths causally related to treatment / all	0 / 7	0 / 7	
COVID-19 pneumonia			
subjects affected / exposed	33 / 324 (10.19%)	22 / 324 (6.79%)	
occurrences causally related to treatment / all	7 / 44	11 / 35	
deaths causally related to treatment / all	2 / 8	3 / 8	
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 324 (0.93%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryocystitis			

subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalomyelitis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis viral			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal abscess central nervous system			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			

subjects affected / exposed	0 / 324 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus infection			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratitis fungal			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratitis bacterial			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 324 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Infective tenosynovitis			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 324 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 324 (0.31%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	2 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			

subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	0 / 324 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis bacterial			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 324 (0.93%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia cryptococcal			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 324 (0.62%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	3 / 4	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	24 / 324 (7.41%)	33 / 324 (10.19%)	
occurrences causally related to treatment / all	12 / 39	28 / 47	
deaths causally related to treatment / all	2 / 5	2 / 4	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 324 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia parainfluenzae viral			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	2 / 324 (0.62%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 324 (0.31%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory tract infection			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	4 / 324 (1.23%)	3 / 324 (0.93%)	
occurrences causally related to treatment / all	3 / 6	0 / 4	
deaths causally related to treatment / all	1 / 2	0 / 1	
Septic shock			
subjects affected / exposed	1 / 324 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sinusitis			
subjects affected / exposed	2 / 324 (0.62%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin bacterial infection			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	2 / 324 (0.62%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sporotrichosis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 324 (0.31%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tick-borne viral encephalitis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
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	2 / 324 (0.62%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	7 / 324 (2.16%)	10 / 324 (3.09%)	
occurrences causally related to treatment / all	5 / 8	2 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 324 (0.62%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			

subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 324 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 324 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperglycaemia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (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 / 324 (0.00%)	1 / 324 (0.31%)	
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 / 324 (0.00%)	2 / 324 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Water intoxication			
subjects affected / exposed	1 / 324 (0.31%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Zanubrutinib	Ibrutinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	310 / 324 (95.68%)	314 / 324 (96.91%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	14 / 324 (4.32%)	15 / 324 (4.63%)	
occurrences (all)	21	23	
Basal cell carcinoma			
subjects affected / exposed	11 / 324 (3.40%)	17 / 324 (5.25%)	
occurrences (all)	18	40	
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 324 (0.93%)	11 / 324 (3.40%)	
occurrences (all)	3	11	
Hypertension			
subjects affected / exposed	82 / 324 (25.31%)	74 / 324 (22.84%)	
occurrences (all)	154	155	
Haematoma			
subjects affected / exposed	17 / 324 (5.25%)	14 / 324 (4.32%)	
occurrences (all)	23	17	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	21 / 324 (6.48%)	13 / 324 (4.01%)	
occurrences (all)	30	16	
Chest pain			
subjects affected / exposed	2 / 324 (0.62%)	10 / 324 (3.09%)	
occurrences (all)	2	10	
Fatigue			
subjects affected / exposed	36 / 324 (11.11%)	49 / 324 (15.12%)	
occurrences (all)	43	57	
Influenza like illness			
subjects affected / exposed	10 / 324 (3.09%)	7 / 324 (2.16%)	
occurrences (all)	28	10	
Oedema peripheral			

subjects affected / exposed occurrences (all)	24 / 324 (7.41%) 27	24 / 324 (7.41%) 31	
Peripheral swelling subjects affected / exposed occurrences (all)	14 / 324 (4.32%) 15	26 / 324 (8.02%) 30	
Pyrexia subjects affected / exposed occurrences (all)	35 / 324 (10.80%) 44	37 / 324 (11.42%) 50	
Immune system disorders Hypogammaglobulinaemia subjects affected / exposed occurrences (all)	12 / 324 (3.70%) 13	12 / 324 (3.70%) 13	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	46 / 324 (14.20%) 59	43 / 324 (13.27%) 55	
Oropharyngeal pain subjects affected / exposed occurrences (all)	12 / 324 (3.70%) 14	10 / 324 (3.09%) 10	
Dyspnoea subjects affected / exposed occurrences (all)	16 / 324 (4.94%) 19	13 / 324 (4.01%) 16	
Productive cough subjects affected / exposed occurrences (all)	17 / 324 (5.25%) 18	11 / 324 (3.40%) 12	
Epistaxis subjects affected / exposed occurrences (all)	27 / 324 (8.33%) 46	24 / 324 (7.41%) 45	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	25 / 324 (7.72%) 27	26 / 324 (8.02%) 28	
Anxiety subjects affected / exposed occurrences (all)	11 / 324 (3.40%) 11	14 / 324 (4.32%) 22	
Investigations			

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	12 / 324 (3.70%) 20	20 / 324 (6.17%) 29	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	7 / 324 (2.16%) 12	16 / 324 (4.94%) 23	
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	5 / 324 (1.54%) 8	10 / 324 (3.09%) 15	
Blood bilirubin increased subjects affected / exposed occurrences (all)	8 / 324 (2.47%) 14	11 / 324 (3.40%) 20	
Blood creatinine increased subjects affected / exposed occurrences (all)	18 / 324 (5.56%) 36	12 / 324 (3.70%) 21	
Blood pressure increased subjects affected / exposed occurrences (all)	6 / 324 (1.85%) 19	12 / 324 (3.70%) 27	
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	10 / 324 (3.09%) 14	11 / 324 (3.40%) 16	
Neutrophil count decreased subjects affected / exposed occurrences (all)	26 / 324 (8.02%) 75	24 / 324 (7.41%) 69	
Platelet count decreased subjects affected / exposed occurrences (all)	11 / 324 (3.40%) 40	20 / 324 (6.17%) 47	
Weight decreased subjects affected / exposed occurrences (all)	22 / 324 (6.79%) 27	14 / 324 (4.32%) 20	
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) Fall	 49 / 324 (15.12%) 62	 38 / 324 (11.73%) 44	

subjects affected / exposed occurrences (all)	16 / 324 (4.94%) 19	23 / 324 (7.10%) 27	
Skin laceration subjects affected / exposed occurrences (all)	12 / 324 (3.70%) 12	6 / 324 (1.85%) 6	
Cardiac disorders			
Atrial fibrillation subjects affected / exposed occurrences (all)	22 / 324 (6.79%) 27	45 / 324 (13.89%) 69	
Sinus bradycardia subjects affected / exposed occurrences (all)	8 / 324 (2.47%) 10	12 / 324 (3.70%) 15	
Palpitations subjects affected / exposed occurrences (all)	13 / 324 (4.01%) 19	14 / 324 (4.32%) 16	
Cardiac failure subjects affected / exposed occurrences (all)	6 / 324 (1.85%) 7	10 / 324 (3.09%) 10	
Nervous system disorders			
Syncope subjects affected / exposed occurrences (all)	11 / 324 (3.40%) 14	8 / 324 (2.47%) 9	
Paraesthesia subjects affected / exposed occurrences (all)	3 / 324 (0.93%) 3	10 / 324 (3.09%) 12	
Headache subjects affected / exposed occurrences (all)	29 / 324 (8.95%) 36	35 / 324 (10.80%) 46	
Dizziness subjects affected / exposed occurrences (all)	32 / 324 (9.88%) 39	26 / 324 (8.02%) 28	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	53 / 324 (16.36%) 82	56 / 324 (17.28%) 122	
Thrombocytopenia			

subjects affected / exposed occurrences (all)	34 / 324 (10.49%) 90	35 / 324 (10.80%) 92	
Neutropenia subjects affected / exposed occurrences (all)	81 / 324 (25.00%) 195	73 / 324 (22.53%) 162	
Iron deficiency anaemia subjects affected / exposed occurrences (all)	6 / 324 (1.85%) 10	11 / 324 (3.40%) 13	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	11 / 324 (3.40%) 11	6 / 324 (1.85%) 6	
Eye disorders Cataract subjects affected / exposed occurrences (all)	18 / 324 (5.56%) 22	10 / 324 (3.09%) 10	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	20 / 324 (6.17%) 32	21 / 324 (6.48%) 23	
Abdominal pain upper subjects affected / exposed occurrences (all)	14 / 324 (4.32%) 18	7 / 324 (2.16%) 7	
Constipation subjects affected / exposed occurrences (all)	24 / 324 (7.41%) 30	27 / 324 (8.33%) 31	
Diarrhoea subjects affected / exposed occurrences (all)	61 / 324 (18.83%) 106	83 / 324 (25.62%) 158	
Dyspepsia subjects affected / exposed occurrences (all)	25 / 324 (7.72%) 27	23 / 324 (7.10%) 32	
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	15 / 324 (4.63%) 22	17 / 324 (5.25%) 19	
Nausea			

subjects affected / exposed	29 / 324 (8.95%)	32 / 324 (9.88%)	
occurrences (all)	47	38	
Stomatitis			
subjects affected / exposed	11 / 324 (3.40%)	11 / 324 (3.40%)	
occurrences (all)	17	18	
Toothache			
subjects affected / exposed	10 / 324 (3.09%)	6 / 324 (1.85%)	
occurrences (all)	11	9	
Vomiting			
subjects affected / exposed	22 / 324 (6.79%)	29 / 324 (8.95%)	
occurrences (all)	25	35	
Mouth ulceration			
subjects affected / exposed	5 / 324 (1.54%)	10 / 324 (3.09%)	
occurrences (all)	6	11	
Skin and subcutaneous tissue disorders			
Skin haemorrhage			
subjects affected / exposed	8 / 324 (2.47%)	12 / 324 (3.70%)	
occurrences (all)	12	13	
Rash maculo-papular			
subjects affected / exposed	12 / 324 (3.70%)	7 / 324 (2.16%)	
occurrences (all)	15	10	
Rash			
subjects affected / exposed	38 / 324 (11.73%)	44 / 324 (13.58%)	
occurrences (all)	69	58	
Pruritus			
subjects affected / exposed	24 / 324 (7.41%)	9 / 324 (2.78%)	
occurrences (all)	32	10	
Petechiae			
subjects affected / exposed	32 / 324 (9.88%)	19 / 324 (5.86%)	
occurrences (all)	41	19	
Erythema			
subjects affected / exposed	11 / 324 (3.40%)	9 / 324 (2.78%)	
occurrences (all)	11	10	
Ecchymosis			
subjects affected / exposed	5 / 324 (1.54%)	11 / 324 (3.40%)	
occurrences (all)	5	12	

Actinic keratosis subjects affected / exposed occurrences (all)	8 / 324 (2.47%) 16	12 / 324 (3.70%) 15	
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	18 / 324 (5.56%) 23	13 / 324 (4.01%) 20	
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) Osteoarthritis subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Joint swelling subjects affected / exposed occurrences (all)	26 / 324 (8.02%) 30 4 / 324 (1.23%) 5 11 / 324 (3.40%) 13 13 / 324 (4.01%) 18 54 / 324 (16.67%) 69 26 / 324 (8.02%) 26 10 / 324 (3.09%) 10	26 / 324 (8.02%) 30 12 / 324 (3.70%) 14 14 / 324 (4.32%) 14 42 / 324 (12.96%) 51 63 / 324 (19.44%) 85 26 / 324 (8.02%) 30 10 / 324 (3.09%) 12	
Infections and infestations COVID-19 pneumonia subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all)	13 / 324 (4.01%) 18 19 / 324 (5.86%) 22	15 / 324 (4.63%) 20 26 / 324 (8.02%) 34	

COVID-19		
subjects affected / exposed	121 / 324 (37.35%)	84 / 324 (25.93%)
occurrences (all)	163	105
Cellulitis		
subjects affected / exposed	12 / 324 (3.70%)	13 / 324 (4.01%)
occurrences (all)	15	16
Conjunctivitis		
subjects affected / exposed	7 / 324 (2.16%)	15 / 324 (4.63%)
occurrences (all)	10	20
Ear infection		
subjects affected / exposed	10 / 324 (3.09%)	4 / 324 (1.23%)
occurrences (all)	12	5
Gastroenteritis		
subjects affected / exposed	10 / 324 (3.09%)	6 / 324 (1.85%)
occurrences (all)	10	6
Herpes zoster		
subjects affected / exposed	11 / 324 (3.40%)	10 / 324 (3.09%)
occurrences (all)	12	14
Lower respiratory tract infection		
subjects affected / exposed	12 / 324 (3.70%)	12 / 324 (3.70%)
occurrences (all)	16	14
Nasopharyngitis		
subjects affected / exposed	20 / 324 (6.17%)	16 / 324 (4.94%)
occurrences (all)	26	23
Oral herpes		
subjects affected / exposed	4 / 324 (1.23%)	13 / 324 (4.01%)
occurrences (all)	9	17
Paronychia		
subjects affected / exposed	5 / 324 (1.54%)	11 / 324 (3.40%)
occurrences (all)	6	11
Pharyngitis		
subjects affected / exposed	6 / 324 (1.85%)	12 / 324 (3.70%)
occurrences (all)	8	18
Pneumonia		
subjects affected / exposed	33 / 324 (10.19%)	37 / 324 (11.42%)
occurrences (all)	47	57

Respiratory tract infection subjects affected / exposed occurrences (all)	16 / 324 (4.94%) 20	7 / 324 (2.16%) 8	
Rhinitis subjects affected / exposed occurrences (all)	10 / 324 (3.09%) 11	10 / 324 (3.09%) 11	
Sinusitis subjects affected / exposed occurrences (all)	20 / 324 (6.17%) 26	16 / 324 (4.94%) 19	
Skin infection subjects affected / exposed occurrences (all)	7 / 324 (2.16%) 8	13 / 324 (4.01%) 16	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	95 / 324 (29.32%) 155	64 / 324 (19.75%) 105	
Urinary tract infection subjects affected / exposed occurrences (all)	35 / 324 (10.80%) 68	31 / 324 (9.57%) 58	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	12 / 324 (3.70%) 12	22 / 324 (6.79%) 23	
Gout subjects affected / exposed occurrences (all)	4 / 324 (1.23%) 10	10 / 324 (3.09%) 16	
Hyperglycaemia subjects affected / exposed occurrences (all)	13 / 324 (4.01%) 21	8 / 324 (2.47%) 8	
Hyperuricaemia subjects affected / exposed occurrences (all)	16 / 324 (4.94%) 37	22 / 324 (6.79%) 37	
Hypokalaemia subjects affected / exposed occurrences (all)	24 / 324 (7.41%) 39	24 / 324 (7.41%) 39	
Hyponatraemia			

subjects affected / exposed	10 / 324 (3.09%)	8 / 324 (2.47%)	
occurrences (all)	18	13	
Type 2 diabetes mellitus			
subjects affected / exposed	14 / 324 (4.32%)	3 / 324 (0.93%)	
occurrences (all)	15	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 August 2018	<p>Key changes to the conduct of the study implemented with Amendment 1 were as follows:</p> <ul style="list-style-type: none">• Revised the inclusion criterion 9c: increased the upper limit of serum bilirubin to 3.0.• Revised exclusion criterion 11a of HBV reactivation monitoring.• Initial confirmation of progressive disease assessed by CT was sufficient for patients with SLL.
29 August 2019	<p>Key changes to the conduct of the study implemented with Amendment 2 were as follows:</p> <ul style="list-style-type: none">• Updated background information of zanubrutinib, including nonclinical data, clinical pharmacology, preliminary efficacy and safety data.• Added "ORR determined by investigator assessment" as one of the secondary objectives and endpoints.• Revised exploratory objectives and endpoints: included MRD as one of the exploratory endpoints.• Updated study duration from 7 years to 60 months.• Updated study drug access at study closure to clarify patients who benefit from zanubrutinib or ibrutinib may enroll in Zanubrutinib Long-Term Extension Study.• Revision of inclusion criteria.• Revision of exclusion criteria.• Added that patients must sign an informed consent form before any screening procedures are conducted.• Revision of Safety Follow-up Visit to End-of-Treatment Visit. Clarified the separation of Long-term Follow-up and Survival follow-up throughout the document.• Revised efficacy assessments including primary endpoint.• Revised CT assessment.• Revised bone marrow examination.• Added new optional assessment of QoL, activity, and corresponding sections to protocol.• Added that laboratory assessments may be done with either central or local laboratory; same should be used throughout the study. The contents of applicable laboratory tests were revised accordingly.• Added HIV testing.• Added assessment of del(17p) and cytogenetics, MRD, TP53 mutations and other molecular analysis.• Added section of future research (optional).• Updated information of ibrutinib for administration, dose reduction/modification per local labeling.• Revised guidelines to follow for dose interruption or modification of zanubrutinib.• Added toxicity management recommendations.• Updated information for serious adverse events for reporting and record.• Deleted the appendix of medications known to prolong QT interval.

31 January 2020	<p>Key changes to the conduct of the study implemented with Amendment 3 were as follows:</p> <ul style="list-style-type: none"> • Increased the sample size from approximately 400 patients to approximately 600 patients. • Updated study duration to approximately 51 months. • Clarified that the CT or MRI would be performed as specified per the Schedule of Assessments, independent of possible study drug hold. • Clarified that samples taken at progression leading to permanent study drug discontinuation would be used for the assessment of relevant BTK pathway genes. • Added information on warnings and precautions for zanubrutinib. • Revised zanubrutinib dose reduction for nonhematologic toxicity. • Revised the summary of tumor lysis syndrome events in clinical studies for permitted medications. • Revised the summary for the primary endpoint (ORR) analysis to state that ORR was assessed by investigator, with assessment by independent central review performed to support the primary analysis and as the basis of regulatory decisions (in the United States). • Revised the summary for the key secondary endpoint (PFS) analyses to state that PFS was assessed by investigator, with assessment by independent central review performed to support the key secondary endpoint analysis and as the basis of regulatory decisions (in the United States). • Updated the noninferiority and superiority testing analysis summary for the primary endpoint (ORR). • Updated analysis summary for key secondary endpoint (PFS) to remove the interim analysis and state that a single analysis would be performed. • Deleted summary of planned sensitivity analyses for the primary efficacy endpoint (ORR) and the key secondary endpoint (PFS). • Added to the note of Appendix 2 and Appendix 3 that patient may continue study treatment post first assessed PD due to drug hold if it was perceived that the patient would benefit from continued treatment.
03 April 2023	<p>Key changes to the conduct of the study implemented with Amendment 4 were as follows:</p> <ul style="list-style-type: none"> • Added "Demographic factors such as age, gender, race, and ethnicity could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. Race and ethnicity data are collected in accordance with International Council for Harmonisation (ICH) guidance (ICH E5 1998, ICH E17 2017) adopted by the European Medicines Agency (EMA) and US FDA, to understand whether race/ethnicity could influence the PK, safety, and/or efficacy of the study drug. For example, population PK analysis is a well-established, quantitative method that can quantify and explain the variability in drug concentrations among patients. Such variability can be attributed to intrinsic factors (eg, body weight, age, gender, race/ethnicity), or to extrinsic factors (eg, concomitant medications), and can lead to clinically relevant changes in drug concentrations that require a change in the dose or dosing regimen. Results from race/ethnicity and other demographic analyses will be incorporated into drug product labeling to provide guidance on safety and efficacy variations (if any) linked to certain populations (eg, race or ethnic group) as well as any potential dose adjustment needed for those populations. Therefore, collecting race/ethnicity data in the study is essential to understand whether race/ethnicity could influence the PK, safety, and/or efficacy." • Added Section 5.6.5 Survival Status language. • Added schedule and window for survival follow-up of every 24 weeks +/- 14 days.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported