Clinical trial results:
A Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, PCI-32765 (Ibrutinib), in Combination with Bendamustine and Rituximab (BR) in Subjects With Newly Diagnosed Mantle Cell Lymphoma

Summary

EudraCT number	2012-004056-11
Trial protocol	SE BE GB DE HU IE IT PT SK ES NL FR PL CZ GR
Global end of trial date	24 June 2024

Results information

Result version number	v1 (current)
This version publication date	09 July 2025
First version publication date	09 July 2025

Trial information

Trial identification

Sponsor protocol code	PCI-32765MCL3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01776840
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, B-2340
Public contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.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	03 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the whether the addition of ibrutinib to bendamustine and rituximab resulted in prolongation of progression free survival (PFS) in subjects with newly diagnosed mantle cell lymphoma (MCL) who are 65 years of age or older.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 May 2013
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	Argentina: 4
Country: Number of subjects enrolled	Australia: 31
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Brazil: 21
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	China: 57
Country: Number of subjects enrolled	Czechia: 15
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Mexico: 3

Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Poland: 35
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Sweden: 18
Country: Number of subjects enrolled	Türkiye: 14
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	Ukraine: 11
Country: Number of subjects enrolled	United States: 83
Worldwide total number of subjects	523
EEA total number of subjects	188

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)	0
From 65 to 84 years	513
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

A total of 523 subjects were randomised in this study.

Pre-assignment

Screening details:

A total of 523 subjects were randomised in this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Bendamustine and Rituximab (BR) (Treatment A)

Arm description:

Subjects received 4 capsules of ibrutinib-matching placebo administered orally once daily continuously starting on Day 1, Cycle 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a maximum of 6 cycles of BR background therapy (bendamustine hydrochloride 90 milligrams per meter square [mg/m^2] intravenous [IV] infusion on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV infusion on Day 1 of each cycle), unless disease progression or unacceptable toxicity prior to Cycle 6. Subjects with complete response (CR) or partial response (PR) continued background therapy with rituximab maintenance (375 mg/m^2 IV infusion) on Day 1 every second cycle starting at Cycle 8 for maximum of 12 additional doses unless disease progression or unacceptable toxicity. Each cycle was of 28 days. Subjects received treatment A up to 100.1 months. After treatment unblinding at primary analysis, subjects discontinued placebo treatment.

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

Dosage and administration details:

Subjects received 4 capsules of ibrutinib-matching placebo orally once daily continuously from Cycle 1 Day 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first.

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

Dosage and administration details:

Subjects received rituximab 375 mg/m^2 IV infusion on Day 1 of each cycle) for a maximum of 6 cycles, unless disease progression or unacceptable toxicity prior to Cycle 6. Subjects with a CR or PR continued to receive background therapy with rituximab maintenance (375 mg/m^2 IV infusion) on Day 1 every second cycle starting at Cycle 8 for a maximum of 12 additional doses unless disease progression or unacceptable toxicity.

Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion

Routes of administration	Intravenous use

Dosage and administration details:

Subjects received bendamustine hydrochloride 90 mg/m^2 IV infusion on Days 1 and 2 of each cycle for a maximum of 6 cycles unless disease progression or unacceptable toxicity prior to Cycle 6.

Arm title	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)

Arm description:

Subjects received ibrutinib capsules 560 mg (4*140 mg capsule) administered orally once daily continuously starting on Day 1, Cycle 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a maximum of 6 cycles of BR background therapy (bendamustine hydrochloride 90 mg/m^2 IV infusion on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV infusion on Day 1 of each cycle), unless disease progression or unacceptable toxicity prior to Cycle 6. Subjects with CR or PR continued to receive background therapy with rituximab maintenance (375 mg/m^2 IV infusion) on Day 1 of every second cycle starting at Cycle 8 for maximum of 12 additional doses unless disease progression or unacceptable toxicity. Each cycle was of 28 days. Subjects received treatment B up to 117.2 months. After treatment unblinding at primary analysis, subjects continued treatment with ibrutinib at discretion of investigator.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	JNJ-54179060
Other name	IMBRUVICA, PCI-32765
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received ibrutinib capsules 560 milligrams (mg) (4*140 mg capsule) administered orally once daily continuously from Cycle 1 Day 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first.

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

Dosage and administration details:

Subjects received rituximab 375 mg/m^2 IV infusion on Day 1 of each cycle) for a maximum of 6 cycles, unless disease progression or unacceptable toxicity prior to Cycle 6. Subjects with a CR or PR continued to receive background therapy with rituximab maintenance (375 mg/m^2 IV infusion) on Day 1 every second cycle starting at Cycle 8 for a maximum of 12 additional doses unless disease progression or unacceptable toxicity.

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

Dosage and administration details:

Subjects received bendamustine hydrochloride 90 mg/m^2 IV infusion on Days 1 and 2 of each cycle for a maximum of 6 cycles, unless disease progression or unacceptable toxicity prior to Cycle 6.

Number of subjects in period 1	Placebo + Bendamustine and Rituximab (BR) (Treatment A)	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)
Started	262	261
Safety analysis set (treated)	260	259
Completed	129	119
Not completed	133	142
Consent withdrawn by subject	32	48
Lost to follow-up	12	7
Sponsor decision	89	87

Baseline characteristics

Reporting groups

Reporting group title	Placebo + Bendamustine and Rituximab (BR) (Treatment A)

Reporting group description:

Subjects received 4 capsules of ibrutinib-matching placebo administered orally once daily continuously starting on Day 1, Cycle 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a maximum of 6 cycles of BR background therapy (bendamustine hydrochloride 90 milligrams per meter square [mg/m^2] intravenous [IV] infusion on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV infusion on Day 1 of each cycle), unless disease progression or unacceptable toxicity prior to Cycle 6. Subjects with complete response (CR) or partial response (PR) continued background therapy with rituximab maintenance (375 mg/m^2 IV infusion) on Day 1 every second cycle starting at Cycle 8 for maximum of 12 additional doses unless disease progression or unacceptable toxicity. Each cycle was of 28 days. Subjects received treatment A up to 100.1 months. After treatment unblinding at primary analysis, subjects discontinued placebo treatment.

Reporting group title	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)

Reporting group description:

Subjects received ibrutinib capsules 560 mg (4*140 mg capsule) administered orally once daily continuously starting on Day 1, Cycle 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a maximum of 6 cycles of BR background therapy (bendamustine hydrochloride 90 mg/m^2 IV infusion on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV infusion on Day 1 of each cycle), unless disease progression or unacceptable toxicity prior to Cycle 6. Subjects with CR or PR continued to receive background therapy with rituximab maintenance (375 mg/m^2 IV infusion) on Day 1 of every second cycle starting at Cycle 8 for maximum of 12 additional doses unless disease progression or unacceptable toxicity. Each cycle was of 28 days. Subjects received treatment B up to 117.2 months. After treatment unblinding at primary analysis, subjects continued treatment with ibrutinib at discretion of investigator.

Reporting group values	Placebo + Bendamustine and Rituximab (BR) (Treatment A)	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)	Total
Number of subjects	262	261	523
Age categorical Units: Subjects			
In Utero	0	0	0
Preterm newborn infants (gestional age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days - 23 months)	0	0	0
Children (2 - 11 years)	0	0	0
12 - 17 years	0	0	0
Adults (18 - 64 years)	0	0	0
From 65 - 84 years	257	256	513
85 years and over	5	5	10
Age continuous Units: years			
arithmetic mean	71.7	71.8	
standard deviation	± 5.2	± 5.04	-
Gender categorical Units: Subjects			
Male	186	178	364
Female	76	83	159

End points

End points reporting groups

Reporting group title	Placebo + Bendamustine and Rituximab (BR) (Treatment A)

Reporting group description:

Subjects received 4 capsules of ibrutinib-matching placebo administered orally once daily continuously starting on Day 1, Cycle 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a maximum of 6 cycles of BR background therapy (bendamustine hydrochloride 90 milligrams per meter square [mg/m^2] intravenous [IV] infusion on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV infusion on Day 1 of each cycle), unless disease progression or unacceptable toxicity prior to Cycle 6. Subjects with complete response (CR) or partial response (PR) continued background therapy with rituximab maintenance (375 mg/m^2 IV infusion) on Day 1 every second cycle starting at Cycle 8 for maximum of 12 additional doses unless disease progression or unacceptable toxicity. Each cycle was of 28 days. Subjects received treatment A up to 100.1 months. After treatment unblinding at primary analysis, subjects discontinued placebo treatment.

Reporting group title	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)

Reporting group description:

Subjects received ibrutinib capsules 560 mg (4*140 mg capsule) administered orally once daily continuously starting on Day 1, Cycle 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a maximum of 6 cycles of BR background therapy (bendamustine hydrochloride 90 mg/m^2 IV infusion on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV infusion on Day 1 of each cycle), unless disease progression or unacceptable toxicity prior to Cycle 6. Subjects with CR or PR continued to receive background therapy with rituximab maintenance (375 mg/m^2 IV infusion) on Day 1 of every second cycle starting at Cycle 8 for maximum of 12 additional doses unless disease progression or unacceptable toxicity. Each cycle was of 28 days. Subjects received treatment B up to 117.2 months. After treatment unblinding at primary analysis, subjects continued treatment with ibrutinib at discretion of investigator.

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS was defined as the interval between the date of randomization to the date of disease progression (PD) or relapse from complete response (CR) or death, whichever was first reported. Disease assessments were based on the 2007 Revised Response Criteria for Malignant Lymphoma. PD was defined as any new lesion or increase by 50 percent (%) of previously involved sites from nadir (PD criteria: Appearance of new nodal lesion 1.5 centimeters [cm] in any axis, 50% increase in sum of product of diameters [SPD] of greater than [>] 1 node or 50% increase in longest diameter of previously identified node 1 cm in short axis). Intent-to-treat (ITT) analysis set included all randomised subjects and classified according to assigned treatment group, regardless of actual treatment received. '99999' refers that upper limit of 95% confidence interval were not estimable due to low number of subjects with events.

End point type	Primary

End point timeframe:

Up to 97 months

End point values	Placebo + Bendamustine and Rituximab (BR) (Treatment A)	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	261		
Units: months				

median (confidence interval 95%)	52.9 (43.7 to 71.0)	80.6 (61.9 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Test 1
Statistical analysis description:	
Ibrutinib + BR (Treatment B), Placebo + BR (Treatment A)	
Comparison groups	Placebo + Bendamustine and Rituximab (BR) (Treatment A) v Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)
Number of subjects included in analysis	523
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.96

Secondary: Complete Response Rate

End point title	Complete Response Rate
End point description:	
Complete response (CR) rate was defined as the percentage of subjects who achieve CR (based on investigator assessment) on or prior to the initiation of subsequent anticancer therapy. Criteria for CR: disappearance of all evidence of disease; mass of any size permitted if positron emission tomography (PET) negative; regression to normal size on computed tomography (CT); spleen and liver: not palpable, nodules disappeared; bone marrow: infiltrate cleared on repeat biopsy. ITT analysis set included all randomised subjects and classified according to the assigned treatment group, regardless of the actual treatment received.	
End point type	Secondary
End point timeframe:	
Up to 97 months	

End point values	Placebo + Bendamustine and Rituximab (BR) (Treatment A)	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	261		
Units: percentage of subjects				
number (not applicable)	57.6	65.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-Next Treatment

End point title	Time-to-Next Treatment

End point description:

Time-to-next treatment was measured from the date of randomization to the start date of any anti-mantle cell lymphoma (anti-MCL) treatment subsequent to the study treatment. ITT analysis set included all randomised subjects and classified according to the assigned treatment group, regardless of the actual treatment received. Here, '99999' refers that median, lower and upper 95% confidence interval were not estimable due to low number of subjects with events and '9999' signifies that upper limit of 95% CI could not be estimated due to low number of subjects with events.

End point type	Secondary

End point timeframe:

Up to 97 months

End point values	Placebo + Bendamustine and Rituximab (BR) (Treatment A)	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	261		
Units: months				
median (confidence interval 95%)	92.0 (71.5 to 9999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time from the date of randomization to the date of the subject’s death. Kaplan-Meier estimate was used. Intent-to-treat (ITT) analysis set included all randomised subjects and classified according to assigned treatment group, regardless of actual treatment received. Here, '99999' refers that upper limit of 95% confidence interval were not estimable due to low number of subjects with events.

End point type	Secondary

End point timeframe:

From randomisation (Day -3) up to 121 months

End point values	Placebo + Bendamustine and Rituximab (BR) (Treatment A)	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	261		
Units: months				
median (confidence interval 95%)	95.9 (86.1 to 115.3)	104.3 (81.1 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Overall Response

End point title	Percentage of Subjects With Overall Response

End point description:

Percentage of subjects with overall response was defined as the portion of subjects who achieved CR or PR. Criteria for CR: disappearance of all evidence of disease; mass of any size permitted if PET negative; regression to normal size on CT; spleen and liver: not palpable, nodules disappeared; bone marrow: infiltrate cleared on repeat biopsy. Criteria for PR: greater than or equal to (>=) 50% decrease in sum of the diameter of all target lesions compared with baseline, in absence of new lesions or unequivocal progression of non-target lesions. ITT analysis set included all randomised subjects and classified according to the assigned treatment group, regardless of the actual treatment received.

End point type	Secondary

End point timeframe:

Up to 97 months

End point values	Placebo + Bendamustine and Rituximab (BR) (Treatment A)	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	261		
Units: percentage of subjects				
number (not applicable)	88.5	89.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimal Residual Disease (MRD)-Negative Response Rate

End point title	Minimal Residual Disease (MRD)-Negative Response Rate

End point description:

Minimal residual disease negative rate was defined as the percentage of subjects with a best overall response of CR with MRD-negative disease status (that is, <5 mantle cell lymphoma [MCL] cell per 10,000 leukocytes for detection using the MRD assay), as assessed by flow cytometry of a bone marrow and/or peripheral blood sample. ITT analysis set included all randomised subjects and classified according to the assigned treatment group, regardless of the actual treatment received. CR subjects with missing MRD data and subjects who did not achieve a CR were considered non-responders.

End point type	Secondary

End point timeframe:

Up to 97 months

End point values	Placebo + Bendamustine and Rituximab (BR) (Treatment A)	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	261		
Units: percentage of subjects				
number (not applicable)	56.5	62.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

Duration of Response (DoR) was defined as the interval between the date of initial documentation of a response including PR and the date of first documented evidence of PD or death. ITT analysis set included all randomised subjects and classified according to the assigned treatment group, regardless of the actual treatment received. Subjects who achieved a PR or better were included in the analysis of duration of response. Here, "99999" refers that the upper limit of 95% confidence interval was not estimable due to a small number of subjects with events.

End point type	Secondary

End point timeframe:

Up to 97 months

End point values	Placebo + Bendamustine and Rituximab (BR) (Treatment A)	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	232	234		
Units: months				
median (confidence interval 95%)	63.5 (47 to 76.9)	81 (64.2 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Worsening (TTW) in the Lymphoma (Lym) Subscale of the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) Questionnaire

End point title	Time to Worsening (TTW) in the Lymphoma (Lym) Subscale of the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) Questionnaire

End point description:

Time to worsening in the Lymphoma subscale of the FACT-Lym, defined as the interval from the date of randomisation to the start date of worsening of subject's symptoms. Worsening was defined by a 5-point decrease from baseline, death, or a missing assessment due to being "too ill", whichever occurred first. FACT-Lym Lymphoma subscale contains 15 questions, scores from 0 to 4 for each question (higher the worse). Lymphoma subscale score was the total of reverse scores, ranged 0 to 60. Higher scores indicated a better quality of life. ITT analysis set included all randomised subjects and classified according to the assigned treatment group, regardless of the actual treatment received.

End point type	Secondary

End point timeframe:

Up to 97 months

End point values	Placebo + Bendamustine and Rituximab (BR) (Treatment A)	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	261		
Units: months				
median (confidence interval 95%)	22.2 (9.3 to 34.0)	17.4 (8.3 to 27.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response was defined as the interval between the date of randomization and the date of initial documentation of a response. ITT analysis set included all randomised subjects and classified according to the assigned treatment group, regardless of the actual treatment received. Subjects who achieved a PR or better were included in the analysis of time to response.

End point type	Secondary

End point timeframe:

Up to 97 months

End point values	Placebo + Bendamustine and Rituximab (BR) (Treatment A)	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	232	234		
Units: months				
median (full range (min-max))	2.79 (1.9 to 11.2)	2.79 (2.1 to 10.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Complete Response (DoCR)

End point title	Duration of Complete Response (DoCR)

End point description:

Duration of complete response (DoCR) was defined as the interval between the date of initial documentation of a CR and the date of first documented evidence of PD or death whichever occurs first. ITT analysis set included all randomised subjects and classified according to the assigned treatment group, regardless of the actual treatment received. Subjects who achieved a CR or better were included in the analysis of duration of complete response. Here, "99999" refers that that the median and upper limit of 95% confidence interval were not estimable due to a small number of subjects and 9999 signifies that upper limit of 95% CI could not be estimated due to low number of subjects with events. .

End point type	Secondary

End point timeframe:

Up to 97 months

End point values	Placebo + Bendamustine and Rituximab (BR) (Treatment A)	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	171		
Units: months				
median (confidence interval 95%)	78.1 (65.6 to 9999)	99999 (81.7 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point description:

Number of subjects with TEAEs were reported. An AE was any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non investigational) product. An AE does not necessarily have a causal relationship with the intervention. Treatment-emergent adverse events are defined as adverse events with onset or worsening on or after date of first dose of study treatment up to and including 30 days after date of last dose of study medication, or the initiation of subsequent anticancer therapy, whichever is earlier. Safety analysis set included all randomised subjects who received at least 1 dose of study drug (ibrutinib or placebo).

End point type	Secondary

End point timeframe:

Placebo + BR (Treatment A): From first dose of study treatment (Day 1) up to 100.1 months; Ibrutinib + BR (Treatment B): From first dose of study treatment (Day 1) up to 117.2 months

End point values	Placebo + Bendamustine and Rituximab (BR) (Treatment A)	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	260	259		
Units: subjects	257	259		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Curve of Ibrutinib During 24 Hours After Dosing at Steady State

End point title	Area Under the Concentration Curve of Ibrutinib During 24 Hours After Dosing at Steady State[1]

End point description:

Area under the concentration curve of ibrutinib during 24 hours after dosing at steady state was determined using PopPK modeling. Pharmacokinetic-evaluable population included subjects who have received at least 1 dose of ibrutinib/placebo and had at least 1 pharmacokinetic sample obtained posttreatment.

End point type	Secondary

End point timeframe:

Pre-dose on Day 2 of Cycles 1, 2 and 3; and 1, 2 and 4 hours post-dose on Day 2 of Cycles 1 and 2

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned to be reported for specified arms only.

End point values	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)			
Subject group type	Reporting group			
Number of subjects analysed	259			
Units: nanogram*hour per millilitre (ng*h/ mL)				
arithmetic mean (standard deviation)	425 (± 267)			

Statistical analyses

No statistical analyses for this end point

Secondary: Oral Volume of Distribution at Steady State of Ibrutinib

End point title	Oral Volume of Distribution at Steady State of Ibrutinib[2]

End point description:

Oral volume of distribution at steady state of ibrutinib was determined using PopPK modeling Pharmacokinetic-evaluable population included subjects who have received at least 1 dose of ibrutinib/placebo and had at least 1 pharmacokinetic sample obtained posttreatment.

End point type	Secondary

End point timeframe:

Pre-dose on Day 2 of Cycles 1, 2 and 3; and 1, 2 and 4 hours post-dose on Day 2 of Cycles 1 and 2

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for specified arms only.

End point values	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)			
Subject group type	Reporting group			
Number of subjects analysed	259			
Units: litre				
arithmetic mean (standard deviation)	7286 (± 7.87)			

Statistical analyses

No statistical analyses for this end point

Secondary: Oral Plasma Clearance (CL/F) of Ibrutinib

End point title	Oral Plasma Clearance (CL/F) of Ibrutinib[3]

End point description:

CL/F was defined as apparent total systemic clearance of ibrutinib after extravascular administration. Cl/F of Ibrutinib was determined using population pharmacokinetics (PopPK modeling). Pharmacokinetic-evaluable population included subjects who have received at least 1 dose of ibrutinib/placebo and had at least 1 pharmacokinetic sample obtained posttreatment.

End point type	Secondary

End point timeframe:

Pre-dose on Day 2 of Cycles 1, 2 and 3; and 1, 2 and 4 hours post-dose on Day 2 of Cycles 1 and 2

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for specified arms only.

End point values	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)			
Subject group type	Reporting group			
Number of subjects analysed	259			
Units: litre per hour (L/h)				
arithmetic mean (standard error)	1123 (± 4.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Plasma Concentration of Ibrutinib

End point title	Minimum Observed Plasma Concentration of Ibrutinib[4]

End point description:

Minimum observed plasma concentration of ibrutinib was determined using PopPK modeling. Pharmacokinetic-evaluable population included subjects who have received at least 1 dose of ibrutinib/placebo and had at least 1 pharmacokinetic sample obtained posttreatment.

End point type	Secondary

End point timeframe:

Pre-dose on Day 2 of Cycles 1, 2 and 3; and 1, 2 and 4 hours post-dose on Day 2 of Cycles 1 and 2

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for specified arms only.

End point values	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)			
Subject group type	Reporting group			
Number of subjects analysed	259			
Units: ng/mL				
arithmetic mean (standard deviation)	3.90 (± 2.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration of Ibrutinib

End point title	Maximum Observed Plasma Concentration of Ibrutinib[5]

End point description:

Maximum observed plasma concentration of ibrutinib was determined using PopPK modeling. Pharmacokinetic-evaluable population included subjects who have received at least 1 dose of ibrutinib/placebo and had at least 1 pharmacokinetic sample obtained posttreatment.

End point type	Secondary

End point timeframe:

Pre-dose on Day 2 of Cycles 1, 2 and 3; and 1, 2 and 4 hours post-dose on Day 2 of Cycles 1 and 2

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for specified arms only.

End point values	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)			
Subject group type	Reporting group			
Number of subjects analysed	259			
Units: ng/mL				
arithmetic mean (standard deviation)	74.5 (± 48.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Placebo + BR (Treatment A): From first dose of study treatment (Day 1) up to 100.1 months; Ibrutinib + BR (Treatment B): From first dose of study treatment (Day 1) up to 117.2 months

Adverse event reporting additional description:

Safety analysis set included all randomised subjects who received at least 1 dose of study drug (ibrutinib or placebo).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Placebo + Bendamustine and Rituximab (BR) (Treatment A)

Reporting group description:

Subjects received 4 capsules of ibrutinib-matching placebo administered orally once daily continuously starting on Day 1, Cycle 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a maximum of 6 cycles of BR background therapy (bendamustine hydrochloride 90 milligrams per meter square [mg/m^2] intravenous [IV] infusion on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV infusion on Day 1 of each cycle), unless disease progression or unacceptable toxicity prior to Cycle 6. Subjects with complete response (CR) or partial response (PR) continued background therapy with rituximab maintenance (375 mg/m^2 IV infusion) on Day 1 every second cycle starting at Cycle 8 for maximum of 12 additional doses unless disease progression or unacceptable toxicity. Each cycle was of 28 days. Subjects received treatment A up to 100.1 months. After treatment unblinding at primary analysis, subjects discontinued placebo treatment.

Reporting group title	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)

Reporting group description:

Subjects received ibrutinib capsules 560 mg (4*140 mg capsule) administered orally once daily continuously starting on Day 1, Cycle 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a maximum of 6 cycles of BR background therapy (bendamustine hydrochloride 90 mg/m^2 IV infusion on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV infusion on Day 1 of each cycle), unless disease progression or unacceptable toxicity prior to Cycle 6. Subjects with CR or PR continued to receive background therapy with rituximab maintenance (375 mg/m^2 IV infusion) on Day 1 of every second cycle starting at Cycle 8 for maximum of 12 additional doses unless disease progression or unacceptable toxicity. Each cycle was of 28 days. Subjects received treatment B up to 117.2 months. After treatment unblinding at primary analysis, subjects continued treatment with ibrutinib at discretion of investigator.

Serious adverse events	Placebo + Bendamustine and Rituximab (BR) (Treatment A)	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)	
Total subjects affected by serious adverse events			
subjects affected / exposed	157 / 260 (60.38%)	201 / 259 (77.61%)	
number of deaths (all causes)	129	120	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Gastric			

subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Myeloid Leukaemia			
subjects affected / exposed	3 / 260 (1.15%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	2 / 5	0 / 2	
deaths causally related to treatment / all	1 / 2	0 / 1	
Bladder Transitional Cell Carcinoma			
subjects affected / exposed	0 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's Disease			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain Neoplasm Malignant			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholesteatoma			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign Anorectal Neoplasm			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Cancer			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of Colon			

subjects affected / exposed	2 / 260 (0.77%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendix Cancer			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (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	4 / 260 (1.54%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Myelomonocytic Leukaemia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Adenocarcinoma			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Langerhans' Cell Histiocytosis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal Squamous Cell Carcinoma			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (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	2 / 260 (0.77%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant Melanoma			
subjects affected / exposed	2 / 260 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic Malignant Melanoma			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic Syndrome			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Non-Small Cell Lung Cancer			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ocular Neoplasm			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
subjects affected / exposed	2 / 260 (0.77%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Cell Carcinoma			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
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 / 260 (0.00%)	1 / 259 (0.39%)	
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 / 260 (0.38%)	0 / 259 (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	4 / 260 (1.54%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid Cancer			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
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 / 260 (0.38%)	0 / 259 (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 Lung			
subjects affected / exposed	2 / 260 (0.77%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic Stenosis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial Thrombosis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep Vein Thrombosis			

subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Giant Cell Arteritis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Crisis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Urgency			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 260 (0.77%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Artery Aneurysm			

subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Raynaud's Phenomenon			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary Artery Bypass			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy Closure			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 260 (0.00%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Fatigue			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Physical Health Deterioration			
subjects affected / exposed	0 / 260 (0.00%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Chills			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Asthenia			
subjects affected / exposed	2 / 260 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Discomfort			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			
subjects affected / exposed	2 / 260 (0.77%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised Oedema			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 260 (0.00%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal Inflammation			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	0 / 260 (0.00%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			

subjects affected / exposed	0 / 260 (0.00%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	14 / 260 (5.38%)	19 / 259 (7.34%)	
occurrences causally related to treatment / all	5 / 18	15 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Death			
subjects affected / exposed	0 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug Hypersensitivity			
subjects affected / exposed	1 / 260 (0.38%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serum Sickness			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 260 (0.38%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 260 (0.38%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Prostatic Obstruction			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balanoposthitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Respiratory Distress Syndrome			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute Respiratory Failure			
subjects affected / exposed	2 / 260 (0.77%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchiectasis			
subjects affected / exposed	0 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	5 / 260 (1.92%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 23	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (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	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	2 / 260 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			

subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	2 / 260 (0.77%)	7 / 259 (2.70%)	
occurrences causally related to treatment / all	2 / 3	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 260 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial Lung Disease			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infiltration			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising Pneumonia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity Pneumonitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	2 / 260 (0.77%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive Cough			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	2 / 260 (0.77%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Distress			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	1 / 260 (0.38%)	5 / 259 (1.93%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tonsillar Disorder			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Haemorrhage			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional State			

subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device End of Service			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
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 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Creatinine Increased			
subjects affected / exposed	2 / 260 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchoscopy			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Stoma Output Increased			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil Count Decreased			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet Count Decreased			
subjects affected / exposed	3 / 260 (1.15%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scan Abnormal			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus Test Positive			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Facial Bones Fracture			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion Related Reaction			
subjects affected / exposed	4 / 260 (1.54%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femur Fracture			
subjects affected / exposed	0 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head Injury			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Fracture			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus Fracture			
subjects affected / exposed	1 / 260 (0.38%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Dislocation			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
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 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Fracture			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Laceration			

subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma Complication			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural Haematoma			
subjects affected / exposed	4 / 260 (1.54%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	3 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to Various Agents			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic Intracranial Haemorrhage			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal Fracture			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Odontogenic Cyst			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute Coronary Syndrome			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	4 / 260 (1.54%)	14 / 259 (5.41%)	
occurrences causally related to treatment / all	1 / 5	8 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Pectoris			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Myocardial Infarction			
subjects affected / exposed	4 / 260 (1.54%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	1 / 260 (0.38%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 1	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			

subjects affected / exposed	1 / 260 (0.38%)	5 / 259 (1.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 4	
Coronary Artery Stenosis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-Respiratory Arrest			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiomyopathy			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary Failure			
subjects affected / exposed	2 / 260 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	1 / 260 (0.38%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Cardiomyopathy			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left Ventricular Failure			

subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral Valve Stenosis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	6 / 260 (2.31%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 7	1 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sinus Node Dysfunction			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal Rhythm			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial Effusion			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Silent Myocardial Infarction			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Bradycardia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Ischaemia			

subjects affected / exposed	0 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Extrasystoles			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amyotrophic Lateral Sclerosis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amnesia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain Oedema			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Carotid Artery Stenosis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central Nervous System Lesion			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Ischaemia			

subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	0 / 260 (0.00%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Dizziness			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial Paralysis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic Stroke			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	1 / 260 (0.38%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar Stroke			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of Consciousness			

subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Motor Neuropathy			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Herpetic Neuralgia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic Infarction			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (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	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Cord Compression			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid Haemorrhage			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	5 / 260 (1.92%)	5 / 259 (1.93%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Quadriplegia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Global Amnesia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Encephalopathy			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
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	3 / 260 (1.15%)	5 / 259 (1.93%)	
occurrences causally related to treatment / all	3 / 6	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	9 / 260 (3.46%)	16 / 259 (6.18%)	
occurrences causally related to treatment / all	8 / 12	11 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
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	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Methaemoglobinaemia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 260 (1.15%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	5 / 5	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	1 / 260 (0.38%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 260 (1.15%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	2 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Exophthalmos			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal Detachment			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative Keratitis			

subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 260 (0.00%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Abdomen			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Haemorrhage			
subjects affected / exposed	0 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 260 (0.77%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 260 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	0 / 260 (0.00%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 260 (0.77%)	8 / 259 (3.09%)	
occurrences causally related to treatment / all	2 / 2	6 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Perforation			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Ulcer			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Ulcer Haemorrhage			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental Caries			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis Haemorrhagic			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal Hernia			
subjects affected / exposed	2 / 260 (0.77%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Perforation			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth Haemorrhage			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth Ulceration			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 260 (0.38%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	1 / 1	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Obstruction			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small Intestinal Obstruction			

subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical Hernia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 260 (0.00%)	5 / 259 (1.93%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Acute			
subjects affected / exposed	1 / 260 (0.38%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Function Abnormal			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Dermatitis Allergic			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Actinic Keratosis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis Bullous			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Foot			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug Eruption			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug Reaction with Eosinophilia and Systemic Symptoms			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash Maculo-Papular			
subjects affected / exposed	0 / 260 (0.00%)	5 / 259 (1.93%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	1 / 260 (0.38%)	5 / 259 (1.93%)	
occurrences causally related to treatment / all	0 / 1	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus Urinary			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Kidney Injury			
subjects affected / exposed	2 / 260 (0.77%)	8 / 259 (3.09%)	
occurrences causally related to treatment / all	0 / 2	2 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Cyst Haemorrhage			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Impairment			
subjects affected / exposed	0 / 260 (0.00%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Obstruction			
subjects affected / exposed	0 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Colic			

subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperaldosteronism			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
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			
Arthralgia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	1 / 260 (0.38%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Finger Deformity			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Jaw Cyst			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular Weakness			
subjects affected / exposed	2 / 260 (0.77%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank Pain			
subjects affected / exposed	2 / 260 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 260 (0.77%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic Fracture			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in Extremity			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Disorder			

subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Osteoarthritis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
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 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arthritis Bacterial			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess Intestinal			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess Limb			
subjects affected / exposed	0 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 260 (0.77%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial Sepsis			

subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	4 / 260 (1.54%)	7 / 259 (2.70%)	
occurrences causally related to treatment / all	0 / 4	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary Aspergillosis			
subjects affected / exposed	0 / 260 (0.00%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Campylobacter Gastroenteritis			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida Sepsis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 260 (1.15%)	9 / 259 (3.47%)	
occurrences causally related to treatment / all	1 / 3	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Colitis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter Infection			

subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Infection			
subjects affected / exposed	0 / 260 (0.00%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19			
subjects affected / exposed	0 / 260 (0.00%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Covid-19 Pneumonia			
subjects affected / exposed	2 / 260 (0.77%)	8 / 259 (3.09%)	
occurrences causally related to treatment / all	0 / 2	2 / 12	
deaths causally related to treatment / all	0 / 0	1 / 4	
Cystitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus Infection			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Infection			
subjects affected / exposed	2 / 260 (0.77%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus Colitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 260 (0.38%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Bacteraemia			
subjects affected / exposed	0 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Infection			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal Oesophagitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 260 (0.38%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster Disseminated			

subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Viral			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatitis B Reactivation			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	3 / 260 (1.15%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Salmonella			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nosocomial Infection			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Moraxella Infection			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral Candidiasis			

subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal Candidiasis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster Oticus			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histoplasmosis Disseminated			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infective Exacerbation of Chronic Obstructive Airways Disease			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 260 (0.77%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeriosis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised Infection			

subjects affected / exposed	0 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 260 (0.38%)	5 / 259 (1.93%)	
occurrences causally related to treatment / all	0 / 1	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Abscess			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningococcal Bacteraemia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Candidiasis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis Chronic			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis Media			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parasitic Gastroenteritis			

subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	35 / 260 (13.46%)	58 / 259 (22.39%)	
occurrences causally related to treatment / all	25 / 61	52 / 85	
deaths causally related to treatment / all	0 / 1	2 / 3	
Periorbital Cellulitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal Bacteraemia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis Jirovecii Pneumonia			
subjects affected / exposed	1 / 260 (0.38%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Paronychia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Bacterial			

subjects affected / exposed	2 / 260 (0.77%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Cytomegaloviral			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Fungal			
subjects affected / exposed	0 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pseudomembranous Colitis			
subjects affected / exposed	2 / 260 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia Pseudomonal			
subjects affected / exposed	2 / 260 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Viral			
subjects affected / exposed	1 / 260 (0.38%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Postoperative Wound Infection			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive Multifocal Leukoencephalopathy			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Pneumococcal			

subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas Infection			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Sepsis			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary Tuberculosis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Chronic			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	2 / 260 (0.77%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	1 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	2 / 260 (0.77%)	5 / 259 (1.93%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	6 / 260 (2.31%)	10 / 259 (3.86%)	
occurrences causally related to treatment / all	2 / 7	8 / 12	
deaths causally related to treatment / all	1 / 1	0 / 1	
Septic Shock			
subjects affected / exposed	2 / 260 (0.77%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	3 / 3	2 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sialoadenitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Syncytial Virus Infection			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis Bacterial			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis Fungal			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Infection			
subjects affected / exposed	0 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft Tissue Infection			
subjects affected / exposed	2 / 260 (0.77%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Bacteraemia			

subjects affected / exposed	0 / 260 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Infection			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
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	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal Bacteraemia			
subjects affected / exposed	1 / 260 (0.38%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected Covid-19			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Toxoplasmosis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 260 (1.15%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	2 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	2 / 260 (0.77%)	7 / 259 (2.70%)	
occurrences causally related to treatment / all	0 / 2	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	3 / 260 (1.15%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Device Infection			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 260 (0.38%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	5 / 260 (1.92%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	2 / 6	2 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetes Mellitus			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 260 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour Lysis Syndrome			
subjects affected / exposed	3 / 260 (1.15%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	1 / 3	4 / 4	
deaths causally related to treatment / all	0 / 1	1 / 1	
Hypoglycaemia			

subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 260 (0.77%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic Acidosis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 259 (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: 5 %

Non-serious adverse events	Placebo + Bendamustine and Rituximab (BR) (Treatment A)	Ibrutinib + Bendamustine and Rituximab (BR) (Treatment B)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	255 / 260 (98.08%)	256 / 259 (98.84%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous Cell Carcinoma of Skin			
subjects affected / exposed	13 / 260 (5.00%)	12 / 259 (4.63%)	
occurrences (all)	24	16	
Vascular disorders			
Haematoma			
subjects affected / exposed	3 / 260 (1.15%)	20 / 259 (7.72%)	
occurrences (all)	4	34	

Hypertension			
subjects affected / exposed	29 / 260 (11.15%)	37 / 259 (14.29%)	
occurrences (all)	42	57	
Hypotension			
subjects affected / exposed	16 / 260 (6.15%)	22 / 259 (8.49%)	
occurrences (all)	17	24	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	25 / 260 (9.62%)	30 / 259 (11.58%)	
occurrences (all)	38	47	
Chest Pain			
subjects affected / exposed	12 / 260 (4.62%)	14 / 259 (5.41%)	
occurrences (all)	17	15	
Pyrexia			
subjects affected / exposed	76 / 260 (29.23%)	88 / 259 (33.98%)	
occurrences (all)	115	172	
Oedema Peripheral			
subjects affected / exposed	42 / 260 (16.15%)	50 / 259 (19.31%)	
occurrences (all)	60	75	
Mucosal Inflammation			
subjects affected / exposed	15 / 260 (5.77%)	14 / 259 (5.41%)	
occurrences (all)	20	20	
Malaise			
subjects affected / exposed	14 / 260 (5.38%)	12 / 259 (4.63%)	
occurrences (all)	19	13	
Influenza Like Illness			
subjects affected / exposed	13 / 260 (5.00%)	14 / 259 (5.41%)	
occurrences (all)	15	21	
Fatigue			
subjects affected / exposed	77 / 260 (29.62%)	79 / 259 (30.50%)	
occurrences (all)	134	135	
Chills			
subjects affected / exposed	39 / 260 (15.00%)	17 / 259 (6.56%)	
occurrences (all)	46	21	
Immune system disorders			

Hypogammaglobulinaemia			
subjects affected / exposed	14 / 260 (5.38%)	9 / 259 (3.47%)	
occurrences (all)	14	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	85 / 260 (32.69%)	78 / 259 (30.12%)	
occurrences (all)	139	127	
Dyspnoea			
subjects affected / exposed	45 / 260 (17.31%)	27 / 259 (10.42%)	
occurrences (all)	73	39	
Epistaxis			
subjects affected / exposed	13 / 260 (5.00%)	31 / 259 (11.97%)	
occurrences (all)	19	59	
Nasal Congestion			
subjects affected / exposed	14 / 260 (5.38%)	7 / 259 (2.70%)	
occurrences (all)	16	11	
Oropharyngeal Pain			
subjects affected / exposed	24 / 260 (9.23%)	23 / 259 (8.88%)	
occurrences (all)	26	28	
Productive Cough			
subjects affected / exposed	18 / 260 (6.92%)	16 / 259 (6.18%)	
occurrences (all)	29	22	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	28 / 260 (10.77%)	29 / 259 (11.20%)	
occurrences (all)	34	35	
Anxiety			
subjects affected / exposed	17 / 260 (6.54%)	14 / 259 (5.41%)	
occurrences (all)	21	22	
Depression			
subjects affected / exposed	12 / 260 (4.62%)	16 / 259 (6.18%)	
occurrences (all)	13	19	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	12 / 260 (4.62%)	23 / 259 (8.88%)	
occurrences (all)	17	42	

Aspartate Aminotransferase Increased			
subjects affected / exposed	14 / 260 (5.38%)	24 / 259 (9.27%)	
occurrences (all)	21	45	
Blood Creatinine Increased			
subjects affected / exposed	22 / 260 (8.46%)	23 / 259 (8.88%)	
occurrences (all)	57	32	
Lymphocyte Count Decreased			
subjects affected / exposed	26 / 260 (10.00%)	32 / 259 (12.36%)	
occurrences (all)	189	213	
Neutrophil Count Decreased			
subjects affected / exposed	43 / 260 (16.54%)	39 / 259 (15.06%)	
occurrences (all)	188	166	
Platelet Count Decreased			
subjects affected / exposed	28 / 260 (10.77%)	41 / 259 (15.83%)	
occurrences (all)	118	144	
Weight Decreased			
subjects affected / exposed	20 / 260 (7.69%)	26 / 259 (10.04%)	
occurrences (all)	24	45	
White Blood Cell Count Decreased			
subjects affected / exposed	34 / 260 (13.08%)	30 / 259 (11.58%)	
occurrences (all)	242	229	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	12 / 260 (4.62%)	23 / 259 (8.88%)	
occurrences (all)	15	30	
Fall			
subjects affected / exposed	13 / 260 (5.00%)	16 / 259 (6.18%)	
occurrences (all)	16	20	
Infusion Related Reaction			
subjects affected / exposed	26 / 260 (10.00%)	19 / 259 (7.34%)	
occurrences (all)	44	24	
Cardiac disorders			
Palpitations			
subjects affected / exposed	13 / 260 (5.00%)	9 / 259 (3.47%)	
occurrences (all)	16	17	
Atrial Fibrillation			

subjects affected / exposed	14 / 260 (5.38%)	32 / 259 (12.36%)	
occurrences (all)	14	33	
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 260 (7.31%)	22 / 259 (8.49%)	
occurrences (all)	26	26	
Headache			
subjects affected / exposed	40 / 260 (15.38%)	33 / 259 (12.74%)	
occurrences (all)	65	43	
Paraesthesia			
subjects affected / exposed	13 / 260 (5.00%)	13 / 259 (5.02%)	
occurrences (all)	15	15	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	104 / 260 (40.00%)	109 / 259 (42.08%)	
occurrences (all)	579	412	
Lymphopenia			
subjects affected / exposed	14 / 260 (5.38%)	18 / 259 (6.95%)	
occurrences (all)	139	93	
Leukopenia			
subjects affected / exposed	14 / 260 (5.38%)	27 / 259 (10.42%)	
occurrences (all)	121	85	
Anaemia			
subjects affected / exposed	60 / 260 (23.08%)	83 / 259 (32.05%)	
occurrences (all)	187	249	
Thrombocytopenia			
subjects affected / exposed	43 / 260 (16.54%)	62 / 259 (23.94%)	
occurrences (all)	146	196	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	13 / 260 (5.00%)	11 / 259 (4.25%)	
occurrences (all)	21	16	
Eye disorders			
Dry Eye			
subjects affected / exposed	5 / 260 (1.92%)	16 / 259 (6.18%)	
occurrences (all)	5	25	
Cataract			

subjects affected / exposed	17 / 260 (6.54%)	21 / 259 (8.11%)	
occurrences (all)	19	30	
Vision Blurred			
subjects affected / exposed	10 / 260 (3.85%)	14 / 259 (5.41%)	
occurrences (all)	15	24	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	29 / 260 (11.15%)	25 / 259 (9.65%)	
occurrences (all)	36	45	
Vomiting			
subjects affected / exposed	48 / 260 (18.46%)	56 / 259 (21.62%)	
occurrences (all)	86	98	
Stomatitis			
subjects affected / exposed	6 / 260 (2.31%)	23 / 259 (8.88%)	
occurrences (all)	10	33	
Nausea			
subjects affected / exposed	107 / 260 (41.15%)	109 / 259 (42.08%)	
occurrences (all)	217	241	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	16 / 260 (6.15%)	18 / 259 (6.95%)	
occurrences (all)	18	21	
Dyspepsia			
subjects affected / exposed	21 / 260 (8.08%)	21 / 259 (8.11%)	
occurrences (all)	28	28	
Dry Mouth			
subjects affected / exposed	6 / 260 (2.31%)	18 / 259 (6.95%)	
occurrences (all)	6	22	
Diarrhoea			
subjects affected / exposed	96 / 260 (36.92%)	119 / 259 (45.95%)	
occurrences (all)	176	268	
Constipation			
subjects affected / exposed	66 / 260 (25.38%)	52 / 259 (20.08%)	
occurrences (all)	87	85	
Abdominal Pain Upper			
subjects affected / exposed	10 / 260 (3.85%)	19 / 259 (7.34%)	
occurrences (all)	18	27	

Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	11 / 260 (4.23%)	21 / 259 (8.11%)	
occurrences (all)	11	23	
Erythema			
subjects affected / exposed	12 / 260 (4.62%)	13 / 259 (5.02%)	
occurrences (all)	18	15	
Pruritus			
subjects affected / exposed	56 / 260 (21.54%)	47 / 259 (18.15%)	
occurrences (all)	73	77	
Rash			
subjects affected / exposed	57 / 260 (21.92%)	95 / 259 (36.68%)	
occurrences (all)	87	193	
Rash Maculo-Papular			
subjects affected / exposed	10 / 260 (3.85%)	22 / 259 (8.49%)	
occurrences (all)	15	29	
Skin Lesion			
subjects affected / exposed	11 / 260 (4.23%)	16 / 259 (6.18%)	
occurrences (all)	16	23	
Urticaria			
subjects affected / exposed	7 / 260 (2.69%)	16 / 259 (6.18%)	
occurrences (all)	9	18	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	7 / 260 (2.69%)	16 / 259 (6.18%)	
occurrences (all)	7	23	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	44 / 260 (16.92%)	46 / 259 (17.76%)	
occurrences (all)	62	70	
Back Pain			
subjects affected / exposed	38 / 260 (14.62%)	36 / 259 (13.90%)	
occurrences (all)	50	46	
Muscle Spasms			
subjects affected / exposed	13 / 260 (5.00%)	21 / 259 (8.11%)	
occurrences (all)	14	29	

Muscular Weakness			
subjects affected / exposed	5 / 260 (1.92%)	15 / 259 (5.79%)	
occurrences (all)	7	23	
Myalgia			
subjects affected / exposed	30 / 260 (11.54%)	33 / 259 (12.74%)	
occurrences (all)	44	43	
Pain in Extremity			
subjects affected / exposed	24 / 260 (9.23%)	18 / 259 (6.95%)	
occurrences (all)	35	22	
Infections and infestations			
Bronchitis			
subjects affected / exposed	36 / 260 (13.85%)	33 / 259 (12.74%)	
occurrences (all)	55	51	
Urinary Tract Infection			
subjects affected / exposed	32 / 260 (12.31%)	36 / 259 (13.90%)	
occurrences (all)	55	76	
Conjunctivitis			
subjects affected / exposed	6 / 260 (2.31%)	26 / 259 (10.04%)	
occurrences (all)	6	36	
Covid-19			
subjects affected / exposed	3 / 260 (1.15%)	17 / 259 (6.56%)	
occurrences (all)	3	20	
Herpes Zoster			
subjects affected / exposed	27 / 260 (10.38%)	15 / 259 (5.79%)	
occurrences (all)	32	16	
Influenza			
subjects affected / exposed	16 / 260 (6.15%)	9 / 259 (3.47%)	
occurrences (all)	23	13	
Upper Respiratory Tract Infection			
subjects affected / exposed	69 / 260 (26.54%)	70 / 259 (27.03%)	
occurrences (all)	124	115	
Skin Infection			
subjects affected / exposed	5 / 260 (1.92%)	18 / 259 (6.95%)	
occurrences (all)	5	20	
Sinusitis			

subjects affected / exposed	34 / 260 (13.08%)	25 / 259 (9.65%)	
occurrences (all)	62	44	
Rhinitis			
subjects affected / exposed	13 / 260 (5.00%)	10 / 259 (3.86%)	
occurrences (all)	15	14	
Pneumonia			
subjects affected / exposed	39 / 260 (15.00%)	53 / 259 (20.46%)	
occurrences (all)	59	73	
Oral Candidiasis			
subjects affected / exposed	7 / 260 (2.69%)	19 / 259 (7.34%)	
occurrences (all)	7	31	
Nasopharyngitis			
subjects affected / exposed	28 / 260 (10.77%)	25 / 259 (9.65%)	
occurrences (all)	68	53	
Lower Respiratory Tract Infection			
subjects affected / exposed	9 / 260 (3.46%)	13 / 259 (5.02%)	
occurrences (all)	15	22	
Cellulitis			
subjects affected / exposed	4 / 260 (1.54%)	15 / 259 (5.79%)	
occurrences (all)	4	20	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	36 / 260 (13.85%)	54 / 259 (20.85%)	
occurrences (all)	57	84	
Hyperglycaemia			
subjects affected / exposed	10 / 260 (3.85%)	15 / 259 (5.79%)	
occurrences (all)	22	21	
Hyperuricaemia			
subjects affected / exposed	20 / 260 (7.69%)	24 / 259 (9.27%)	
occurrences (all)	25	44	
Hypocalcaemia			
subjects affected / exposed	7 / 260 (2.69%)	17 / 259 (6.56%)	
occurrences (all)	7	26	
Hypokalaemia			
subjects affected / exposed	30 / 260 (11.54%)	39 / 259 (15.06%)	
occurrences (all)	61	80	

Hypomagnesaemia subjects affected / exposed occurrences (all)	18 / 260 (6.92%) 44	24 / 259 (9.27%) 50	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 December 2013	The purpose of the protocol amendment 1 was to update the protocol with new safety-related information and safety instructions; further clarify study treatment dosing instructions and dose modifications; revise operational aspects of the study; provide updates based on new information, and perform minor modifications and formatting changes.
15 December 2014	The purpose of the protocol amendment 2 was to update the protocol with safety-related information for monitoring ocular events and atrial fibrillation, update to potential risks with ibrutinib, and update to administration of ibrutinib with certain concomitant medications.
20 August 2015	The purpose of the protocol amendment 3 was to update the safety language for diarrhea and other safety topics in the Introduction, the background safety information for ibrutinib had been aligned with the recently updated ibrutinib Investigator's Brochure (IB) and other protocols within the clinical development program.
29 April 2016	The purpose of the protocol amendment 4 was knowledge gained on the efficacy of ibrutinib from completed randomised clinical studies, which was not available at time of MCL3002 study design, and the lower than expected event rate, were the key drivers for this amendment. The sponsor has added a second interim analysis to occur at approximately 180 PFS events to mitigate for the potential long interval between the planned first interim analysis (134 PFS events) and the final analysis (265 PFS events).
12 July 2017	The purpose of the protocol amendment 5 was to clarify that independent Data Monitoring Committee (DMC) recommendations, including treatment unblinding and stopping placebo treatment, may be implemented following an interim analysis. This amendment also updated the protocol to align with the most recent Investigator's Brochure for ibrutinib: specifically, changes associated with dose modification for subjects with chronic hepatic impairment, and antimicrobial prophylaxis as a permitted medication in subjects who were at increased risk for opportunistic infections.
16 August 2019	The purpose of the protocol amendment 6 was to halt the collection of the complete response (CR) minimal residual disease (MRD) samples, except in subjects whose first assessment of CR was after the issue date of this amendment. Stopping the collection of MRD samples from current CR subjects will have no impact on the MRD-negative rate secondary endpoint, as all current CR subjects who were still on study and providing samples already have an MRD-negative sample.
19 December 2019	The purpose of the protocol amendment 7 was to update safety information to align with the ibrutinib Investigator's Brochure (IB) to include information regarding cerebrovascular accidents as a new safety observation identified from the post-marketing setting, and clarified that assessment of pulse/heart rate and blood pressure was expected at every protocol-specified visit until end of treatment.
27 June 2022	The purpose of the protocol amendment 8 was to update the dose modification guidance and the data that was being collected after the final analysis of PFS.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported