Clinical trial results:
A Study of Obinutuzumab in Combination With CHOP Chemotherapy Versus Rituximab With CHOP in Participants With CD20-Positive Diffuse Large B-Cell Lymphoma (GOYA)

Summary

EudraCT number	2010-024194-39
Trial protocol	ES GB SK CZ HU IT DE AT DK PL
Global end of trial date	

Results information

Result version number	v1
This version publication date	23 April 2017
First version publication date	23 April 2017

Trial information

Trial identification

Sponsor protocol code	BO21005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01287741
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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	Interim
Date of interim/final analysis	29 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 April 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to demonstrate superiority in progression-free survival (PFS) with obinutuzumab (GA101) plus cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (G-CHOP), compared with rituximab plus chemotherapy (R-CHOP) in previously untreated subjects with CD20-positive diffuse large B-cell lymphoma (DLBCL), based on investigator-assessed PFS.

Protection of trial subjects:

Each subject, or the subject's representative, signed an informed consent form prior to screening.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 July 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	78 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 252
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Japan: 111
Country: Number of subjects enrolled	Korea, Republic of: 59
Country: Number of subjects enrolled	Thailand: 86
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Colombia: 6
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Panama: 4
Country: Number of subjects enrolled	Peru: 8
Country: Number of subjects enrolled	Hungary: 68
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Russian Federation: 31
Country: Number of subjects enrolled	Serbia: 5
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Canada: 120
Country: Number of subjects enrolled	United States: 96
Country: Number of subjects enrolled	Australia: 22

Country: Number of subjects enrolled	South Africa: 8
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Switzerland: 21
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	Spain: 79
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Italy: 259
Country: Number of subjects enrolled	Czech Republic: 74
Worldwide total number of subjects	1418
EEA total number of subjects	565

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)	850
From 65 to 84 years	566
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eleven subjects withdrew from the study after randomization but prior to receiving study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab+Chemotherapy

Arm description:

Subjects received eight 21-day cycles of rituximab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera, Rituxan
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab at a dose of 375 milligrams per square metre (mg/m^2), administered by intravenous (IV) infusion on Day 1 of each 21-day cycle for 8 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cyclophosphamide 750 mg/m^2, administered intravenously (IV) on Day 1 of each 21-day cycle.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Doxorubicin 50 mg/m^2 IV, administered on Day 1 of each 21-day cycle.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vincristine 1.4 mg/m^2 (maximum 2 mg) IV, administered on Day 1 of each 21-day cycle.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 100 mg (or equivalent prednisolone or methylprednisolone), administered orally on Days 1-5 of each 21-day cycle.

Arm title	Obinutuzumab+Chemotherapy

Arm description:

Subjects received eight 21-day cycles of obinutuzumab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Participants received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	GA101, RO5072759
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Obinutuzumab 1000 mg IV infusion, administered on Day 1 of each 21-day cycle for 8 cycles. During Cycle 1, obinutuzumab was also infused on Days 8 and 15.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cyclophosphamide 750 milligrams per square metre (mg/m^2), administered intravenously (IV) on Day 1 of each 21-day cycle.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Doxorubicin 50 mg/m^2 IV, administered on Day 1 of each 21-day cycle.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vincristine 1.4 mg/m^2 (maximum 2 mg) IV, administered on Day 1 of each 21-day cycle.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 100 mg (or equivalent prednisolone or methylprednisolone), administered orally on Days 1-5 of each 21-day cycle.

Number of subjects in period 1	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy
Started	712	706
Completed	0	0
Not completed	712	706
Adverse event, serious fatal	31	38
Physician decision	12	19
Continued in the study	446	455
Adverse event, non-fatal	3	4
Non-compliance	2	3
Withdrawal by Subject	25	22
Protocol Violation	1	-
Lost to follow-up	5	8
Progressive disease	173	148
Reason not specified	14	9

Baseline characteristics

Reporting groups	
Reporting group title	Rituximab+Chemotherapy
Reporting group description:	
Subjects received eight 21-day cycles of rituximab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.	
Reporting group title	Obinutuzumab+Chemotherapy
Reporting group description:	
Subjects received eight 21-day cycles of obinutuzumab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Participants received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.	

Reporting group values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy	Total
Number of subjects	712	706	1418
Age categorical Units: Subjects			
Adults (18-64 years)	432	418	850
Elderly (From 65-84 years)	280	286	566
Elderly 85 years and over	0	2	2
Age continuous Units: years			
arithmetic mean	59.1	59.4	
standard deviation	± 13.6	± 13.3	-
Gender categorical Units: Subjects			
Female	329	337	666
Male	383	369	752

End points

End points reporting groups

Reporting group title	Rituximab+Chemotherapy

Reporting group description:

Subjects received eight 21-day cycles of rituximab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.

Reporting group title	Obinutuzumab+Chemotherapy

Reporting group description:

Subjects received eight 21-day cycles of obinutuzumab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Participants received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.

Primary: Progression-Free Survival (PFS), Investigator-Assessed

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

End point description:

Progression-free survival was defined as the time from randomization until the first documented day of disease progression or death from any cause, whichever occurred first, on the basis of investigator assessments according to the Revised Response Criteria for Malignant Lymphoma. Progression was defined as at least 50% increase in nodal lesions or >/=50% increase in any node > 1 centimeter (cm) or >/= 50% increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or >/= 50% increase in any previously involved node with a diameter </= 1 cm such that it is now >1.5 cm. Tumor measurements were obtained by computed tomography (CT) or magnetic resonance imaging (MRI). The intent-to-treat (ITT) population included all randomized subjects.

End point type	Primary

End point timeframe:

Baseline up to data cut-off (up to approximately 4 years and 9 months)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	712	706		
Units: percentage of subjects with event				
number (not applicable)	30.2	28.5		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy

Number of subjects included in analysis	1418
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3868 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.11

Notes:

[1] - Stratified by International Prognostic Index (IPI) score (low/low−intermediate (excluding participants having an IPI score 0 without bulky disease).

Secondary: Progression-Free Survival (PFS), Independent Review Committee (IRC)-Assessed

End point title	Progression-Free Survival (PFS), Independent Review Committee (IRC)-Assessed

End point description:

Progression-free survival was defined as the time from randomization until the first documented day of disease progression or death from any cause, whichever occurred first, on the basis of IRC assessments according to the Revised Response Criteria for Malignant Lymphoma. Progression was defined as at least 50% increase in nodal lesions or >/=50% increase in any node > 1 centimeter (cm) or >/= 50% increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or >/= 50% increase in any previously involved node with a diameter </= 1 cm such that it is now >1.5 cm. Tumor measurements were obtained by CT/MRI. An FDG-PET was mandatory where a PET scanner was available. The intent-to-treat (ITT) population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline up to data cut-off (up to approximately 4 years and 9 months)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	712	706		
Units: percentage of subjects with event				
number (not applicable)	26.1	24.2		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy

Number of subjects included in analysis	1418
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2736 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.1

Notes:

[2] - Stratified by International Prognostic Index (IPI) score (low/low−intermediate (excluding participants having an IPI score 0 without bulky disease).

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival in the overall study population was defined as the time from the date of randomization to the date of death from any cause. Reported is the percentage of subjects with event. The intent-to-treat (ITT) population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline up to data cut-off (up to approximately 4 years and 9 months)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	712	706		
Units: percentage of subjects with event				
number (not applicable)	17.7	17.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR), Investigator-Assessed

End point title	Overall Response Rate (ORR), Investigator-Assessed

End point description:

Overall response was determined on the basis of investigator assessments according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma, 2007. Tumor assessments were performed with CT/MRI with or without PET. Overall response was defined as the disappearance of all evidence of disease, regression of measurable disease, and no new sites. The intent-to-treat (ITT) population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline up to data cut-off (up to approximately 4 years and 9 months)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	712	706		
Units: percentage of subjects with event				
number (not applicable)				
Without PET (n= 712, 706)	80.3	81.7		
With PET (n=665, 669)	77.9	77.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR), IRC-Assessed

End point title	Overall Response Rate (ORR), IRC-Assessed

End point description:

Overall response was determined on the basis of IRC assessments according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma, 2007. Tumor assessments were performed with CT/MRI with or without PET. Overall response was defined as the disappearance of all evidence of disease, regression of measurable disease, and no new sites. The intent-to-treat (ITT) population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline up to data cut-off (up to approximately 4 years and 9 months)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	712	706		
Units: percentage of subjects with event				
number (not applicable)				
Without PET (n= 712, 706)	80.2	82.3		
With PET (n=665, 669)	81.1	82.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response (CR) at the End of Treatment, Investigator-Assessed

End point title	Complete Response (CR) at the End of Treatment, Investigator-Assessed

End point description:

Percentage of subjects with complete response was determined on the basis of investigator assessments according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma, 2007. Tumor assessments were performed with CT/MRI with or without PET. Complete response was defined as the disappearance of all evidence of disease. The intent-to-treat (ITT) population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline up to data cut-off (up to approximately 4 years and 9 months)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	712	706		
Units: percentage of subjects with event				
number (not applicable)				
Without PET (n= 712, 706)	33.8	35.1		
With PET (n=665, 669)	59.5	56.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response (CR) at the End of Treatment, IRC-Assessed

End point title	Complete Response (CR) at the End of Treatment, IRC-Assessed

End point description:

Percentage of subjects with complete response was determined on the basis of IRC assessments according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma, 2007. Tumor assessments were performed with CT/MRI with or without PET. Complete response was defined as the disappearance of all evidence of disease. The intent-to-treat (ITT) population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline up to data cut-off (up to approximately 4 years and 9 months)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	712	706		
Units: percentage of subjects with event				
number (not applicable)				
Without PET (n= 712, 706)	34.4	39.1		
With PET (n=665, 669)	65.3	66.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS), Investigator-Assessed

End point title	Event-Free Survival (EFS), Investigator-Assessed

End point description:

Event-free survival was defined as the time from the date of randomization until the date of disease progression, relapse, initiation of a new non–protocol-specified anti-lymphoma treatment, or death from any cause on the basis of investigator assessments with the use of Revised Response Criteria for Malignant Lymphoma. Disease progression/relapse was defined as at least 50% increase in nodal lesions or >/=50% increase in any node > 1 centimeter (cm) or >/= 50% increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or >/= 50% increase in any previously involved node with a diameter </= 1 cm such that it is now >1.5 cm. Tumor measurements were obtained by CT/MRI. Reported is the percentage of subjects with event.

End point type	Secondary

End point timeframe:

Baseline up to death or disease progression, or initiation of new anti-lymphoma treatment (NALT), whichever occurred first, to data cut-off (up to approximately 4 years and 9 months)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	712	706		
Units: percentage of subjects with event				
number (not applicable)	35.1	33.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival (DFS), Investigator-Assessed

End point title	Disease-Free Survival (DFS), Investigator-Assessed

End point description:

Disease-free survival was defined as the time from the date of the first occurrence of a documented CR to the date of disease progression/relapse or death from any cause on the basis of investigator assessments with the use of Revised Response Criteria for Malignant Lymphoma. Tumor assessments were performed with CT/MRI. CR was defined as disappearance of all target lesions. Progression/relapse was defined as at least 50% increase in nodal lesions or >/=50% increase in any node > 1 centimeter (cm) or >/= 50% increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or >/= 50% increase in any previously involved node with a diameter </= 1 cm such that it is now >1.5 cm. Reported is the percentage of subjects with event. The intent-to-treat (ITT) population included all

randomized subjects.

End point type	Secondary

End point timeframe:

Baseline up to death or disease progression, whichever occurred first, to data cut-off (up to approximately 4 years and 9 months)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	369	397		
Units: percentage of subjects with event				
number (not applicable)	17.3	19.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR), Investigator-Assessed

End point title	Duration of Response (DOR), Investigator-Assessed

End point description:

DOR: the time from first occurrence of a documented CR or PR to disease progression/relapse, or death from any cause for subjects with a response of CR or PR. Tumor assessments were performed with CT/MRI. CR: disappearance of all target lesions. PR: >/=50% decrease target lesions in up to six dominant lesions identified at baseline, no new lesions and no increase in the size of the liver, spleen, or other nodes. Splenic and hepatic nodules must have regressed by >/= 50%. Progression/relapse was defined as at least 50% increase in nodal lesions or >/=50% increase in any node > 1 centimeter (cm) or >/= 50% increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or >/= 50% increase in any previously involved node with a diameter </= 1 cm such that it is now >1.5 cm. The intent-to-treat (ITT) population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline up to death or disease progression, whichever occurs first, to data cut-off (up to approximately 4 years and 9 months)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	642	659		
Units: percentage of subjects with event				
number (not applicable)	26.8	26.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Next Anti-Lymphoma Treatment (TTNALT)

End point title	Time to Next Anti-Lymphoma Treatment (TTNALT)

End point description:

Time to next anti-lymphoma treatment was defined as the time from the date of randomization to the start date of the next anti-lymphoma treatment or death from any cause. Reported is the percentage of subjects with event. The intent-to-treat (ITT) population included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline up to start of next anti-lymphoma treatment or death due to any cause, whichever occurred first, to data cut-off (up to approximately 4 years and 9 months)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	712	706		
Units: percentage of subjects with event				
number (not applicable)	32.3	30.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events (AEs)

End point title	Percentage of Subjects With Adverse Events (AEs)

End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. The safety analysis population included all subjects who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to data cut-off (up to approximately 4 years and 9 months)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	703	704		
Units: percentage of subjects				
number (not applicable)	94.9	97.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Human Anti-Human Antibodies (HAHAs) to Obinutuzumab

End point title	Percentage of Subjects With Human Anti-Human Antibodies (HAHAs) to Obinutuzumab[3]

End point description:

The presence of HAHAs to obinutuzumab was assessed in the first 100 randomized subjects. The safety analysis population included all subjects who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Pre-dose (Hour 0) on Cycle (C) 1 Day (D) 1, C4D1, at end of treatment/early termination (up to Month 6), every 6 months thereafter for 30 months (cycle length = 21 days)

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 assessed in the reported arm only.

End point values	Obinutuzumab +Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: percentage of subjects				
number (not applicable)				
Screening (n=70)	2.9			
Cycle 1 Day 1 (n=29)	0			
Cycle 4 Day 1 (n=89)	0			
Study Completion / Early Discontinuation (n=67)	0			
Follow-Up Month 6 (n=41)	0			
Follow-Up Month 12 (n=40)	0			
Follow-Up Month 18 (n=27)	0			
Follow-Up Month 24 (n=25)	0			
Follow-Up Month 30 (n=19)	0			
Follow-Up Completion/ Early Discontinuation (n=6)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Cancer Therapy-

Lymphoma (FACT-Lym) Subscale Score

End point title	Change From Baseline in Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) Subscale Score

End point description:

The FACT-Lym subscale was developed to assess health-related quality of life in patients with non-Hodgkin lymphoma. The score range is 0-60, with higher scores indicating better outcomes. A positive change from baseline indicates an improvement. The intent-to-treat (ITT) population included all randomized subjects. 9999=NE=Not estimable based on 0 or 1 subject evaluated.

End point type	Secondary

End point timeframe:

Baseline (pre-dose [Hour 0] on C1D1), C3D1, end of treatment (up to Month 6), every 12 months thereafter up to data cut-off, up to approximately 4 years and 9 months, (cycle length = 21 days)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	712	706		
Units: Unitless score				
arithmetic mean (standard deviation)				
Baseline (n=607, 641)	45.36 (± 10.15)	45.12 (± 9.96)		
Score Change, Cycle 3 Day 1 (n=553, 565)	3.84 (± 8.69)	3.74 (± 9.23)		
Score Change, Study Compl./Discont. (n=526, 529)	5.04 (± 10.26)	4.43 (± 11.09)		
Score Change, Follow-Up Month 12 (n=370, 412)	6.38 (± 10.13)	6.21 (± 10.49)		
Score Change, Follow-Up Month 24 (n=232, 248)	7.79 (± 10.26)	5.95 (± 10.38)		
Score Change, Follow-Up Month 30 (n=0, 1)	99999 (± 99999)	25 (± 99999)		
Score Change, Follow-Up Month 36 (n=94, 100)	7.13 (± 10.18)	6.88 (± 10.74)		
Score Change, Follow-Up Month 48 (n=6, 10)	3.06 (± 4.67)	4 (± 7.8)		
Score Change, Follow-Up Term./Compl. (n=50, 48)	3.54 (± 12.57)	3.6 (± 11.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) Domain Scores

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) Domain Scores

End point description:

The EORTC QLQ-C30 is a health-related quality of life questionnaire. A higher score indicates better quality of life, with changes of 5 to 10 points considered to be a minimally important difference to subjects. The intent-to-treat (ITT) population included all randomized subjects. 9999=NE=Not estimable based on 0 or 1 subject evaluated.

End point type	Secondary

End point timeframe:

Baseline (pre-dose [Hour 0] on C1D1), C3D1, end of treatment (up to Month 6), every 12 months thereafter up to data cut-off, up to approximately 4 years and 9 months, (cycle length = 21 days)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	712	706		
Units: Unitless score				
arithmetic mean (standard deviation)				
Baseline (n=610, 643)	59.78 (± 24.47)	58.51 (± 25.22)		
Change Baseline, Cycle 1 Day 1 (n=0, 0)	99999 (± 99999)	99999 (± 99999)		
Change Baseline, Cycle 3 Day 1 (n=555, 567)	6.28 (± 24.08)	7.52 (± 25.95)		
Change Baseline, Study Completion (n=526, 532)	9.97 (± 26.14)	10.29 (± 30.16)		
Change Baseline, Follow-Up Month 12 (n=370, 414)	12.73 (± 26.32)	13.89 (± 30.02)		
Change Baseline, Follow-Up Month 24 (n=234, 247)	16.84 (± 26.3)	14.74 (± 29.57)		
Change Baseline, Follow-Up Month 30 (n=0, 1)	99999 (± 99999)	58.33 (± 99999)		
Change Baseline, Follow-Up Month 36 (n=94, 99)	14.36 (± 31.4)	14.31 (± 31.34)		
Change Baseline, Follow-Up Month 48 (n=7, 10)	-4.76 (± 39.04)	14.17 (± 33.34)		
Change Baseline, Follow-Up Completion (n=50, 48)	1.17 (± 33.25)	-0.69 (± 24.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentrations of Obinutuzumab in Japanese Participants with Diffuse Large B-Cell Lymphoma (DLBCL)

End point title	Serum Concentrations of Obinutuzumab in Japanese Participants with Diffuse Large B-Cell Lymphoma (DLBCL)[4]

End point description:

Serum samples for assessment of obinutuzumab serum concentrations were collected only from a subset of Japanese subjects following administration of 1000 mg obinutuzumab.

End point type	Secondary

End point timeframe:

C1: D1 post-infusion and 20-28 and 66-80 hours after end of infusion, D8 and D15 pre-and post-infusion; C2: D1 pre- and post-infusion; C4: D1 pre- and post-infusion; C6: D1 pre- and post-infusion; C8: D1 pre- and post-infusion (cycle length = 21 days)

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 assessed in the reported arm only.

End point values	Obinutuzumab +Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: micrograms per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 8 pre-infusion	174 (± 38.7)			
Cycle 1, Day 15 pre-infusion	320 (± 39.2)			
Cycle 2, Day 1 pre-infusion	431 (± 39.8)			
Cycle 4, Day 1 pre-infusion	352 (± 42.1)			
Cycle 6, Day 1 pre-infusion	378 (± 45.9)			
Cycle 8, Day 1 pre-infusion	478 (± 43.9)			
Cycle 1, Day 1 post-infusion	435 (± 32.3)			
Cycle 1, Day 1 20-28 hours after end of infusion	259 (± 56.3)			
Cycle 1, Day 1 66-80 hours after end of infusion	219 (± 51.2)			
Cycle 1, Day 8 post-infusion	578 (± 37.8)			
Cycle 1, Day 15 post-infusion	718 (± 32.9)			
Cycle 2, Day 1 post-infusion	938 (± 31.3)			
Cycle 4, Day 1 post-infusion	817 (± 28.6)			
Cycle 6, Day 1 post-infusion	813 (± 32.6)			
Cycle 8, Day 1 post-infusion	881 (± 35.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
4 years and 9 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Obinutuzumab+Chemotherapy

Reporting group description:

Subjects received eight 21-day cycles of obinutuzumab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Participants received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.

Reporting group title	Rituximab+Chemotherapy

Reporting group description:

Subjects received eight 21-day cycles of rituximab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.

Serious adverse events	Obinutuzumab+Chemotherapy	Rituximab+Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	300 / 704 (42.61%)	264 / 703 (37.55%)	
number of deaths (all causes)	126	122	
number of deaths resulting from adverse events	17	19	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 704 (0.14%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 704 (0.00%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			

subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 704 (0.14%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 704 (0.00%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Colorectal cancer			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Liposarcoma			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (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	3 / 704 (0.43%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neuroendocrine tumour			

subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Marginal zone lymphoma			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary cystadenoma lymphomatosum			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (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 / 704 (0.28%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer metastatic			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour perforation			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 704 (0.28%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			

subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypertension			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	3 / 704 (0.43%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 704 (0.00%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous occlusion			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			

subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (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			
Asthenia			
subjects affected / exposed	2 / 704 (0.28%)	4 / 703 (0.57%)	
occurrences causally related to treatment / all	2 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axillary pain			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (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	0 / 704 (0.00%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	2 / 704 (0.28%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 704 (0.43%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 3	2 / 2	
deaths causally related to treatment / all	0 / 3	2 / 2	
Extravasation			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			

subjects affected / exposed	4 / 704 (0.57%)	5 / 703 (0.71%)	
occurrences causally related to treatment / all	1 / 4	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 704 (0.28%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hernia			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperpyrexia			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated hernia			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 704 (0.28%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 704 (0.00%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			

subjects affected / exposed	2 / 704 (0.28%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	17 / 704 (2.41%)	11 / 703 (1.56%)	
occurrences causally related to treatment / all	11 / 23	10 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acquired tracheo-oesophageal fistula			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute respiratory distress syndrome			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 704 (0.14%)	3 / 703 (0.43%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 1	1 / 1	
Alveolitis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 704 (0.28%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea exertional			

subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	2 / 704 (0.28%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	3 / 704 (0.43%)	4 / 703 (0.57%)	
occurrences causally related to treatment / all	3 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infiltration			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (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 / 704 (0.00%)	1 / 703 (0.14%)	
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	4 / 704 (0.57%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	5 / 704 (0.71%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	3 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 704 (0.57%)	4 / 703 (0.57%)	
occurrences causally related to treatment / all	1 / 4	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory disorder			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	0 / 704 (0.00%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Anxiety			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (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 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emotional distress			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIV antibody positive			

subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Facial bones fracture			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 704 (0.14%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (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	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	8 / 704 (1.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	8 / 8	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney rupture			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve injury			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative respiratory failure			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			

subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	3 / 704 (0.43%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haemorrhage			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 704 (0.14%)	5 / 703 (0.71%)	
occurrences causally related to treatment / all	0 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 704 (0.00%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	9 / 704 (1.28%)	4 / 703 (0.57%)	
occurrences causally related to treatment / all	3 / 10	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Cardiac failure			
subjects affected / exposed	7 / 704 (0.99%)	3 / 703 (0.43%)	
occurrences causally related to treatment / all	3 / 7	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	3 / 704 (0.43%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac perforation			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			

subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Congestive cardiomyopathy			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery thrombosis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve disease			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 704 (0.43%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Myocardial ischaemia			

subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular flutter			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (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	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	3 / 704 (0.43%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 2	1 / 2	
Depressed level of consciousness			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 704 (0.28%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	3 / 704 (0.43%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iiird nerve paralysis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	2 / 704 (0.28%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke in evolution			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			

subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Syncope			
subjects affected / exposed	0 / 704 (0.00%)	3 / 703 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Transient ischaemic attack			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 704 (1.28%)	6 / 703 (0.85%)	
occurrences causally related to treatment / all	7 / 10	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	81 / 704 (11.51%)	72 / 703 (10.24%)	
occurrences causally related to treatment / all	97 / 103	86 / 89	
deaths causally related to treatment / all	1 / 1	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histiocytosis haematophagic			

subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	10 / 704 (1.42%)	5 / 703 (0.71%)	
occurrences causally related to treatment / all	10 / 10	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	52 / 704 (7.39%)	40 / 703 (5.69%)	
occurrences causally related to treatment / all	55 / 59	41 / 42	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic haematoma			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	8 / 704 (1.14%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	9 / 11	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 704 (0.00%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacrimation increased			

subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 704 (0.57%)	6 / 703 (0.85%)	
occurrences causally related to treatment / all	2 / 5	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 704 (0.28%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 704 (0.28%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 704 (0.57%)	6 / 703 (0.85%)	
occurrences causally related to treatment / all	2 / 6	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			

subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 704 (0.14%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastric perforation			
subjects affected / exposed	1 / 704 (0.14%)	3 / 703 (0.43%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 704 (0.28%)	3 / 703 (0.43%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematemesis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			

subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	2 / 704 (0.28%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 704 (0.14%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Inguinal hernia			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			

subjects affected / exposed	2 / 704 (0.28%)	4 / 703 (0.57%)	
occurrences causally related to treatment / all	1 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Intestinal perforation			
subjects affected / exposed	3 / 704 (0.43%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Large intestine polyp			
subjects affected / exposed	2 / 704 (0.28%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
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 / 704 (0.14%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			

subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 704 (0.28%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 704 (0.43%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 704 (0.28%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 704 (0.14%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	2 / 704 (0.28%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 704 (0.28%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute prerenal failure			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis glandularis			

subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 704 (0.28%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Addison's disease			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Goitre			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
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	1 / 704 (0.14%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 704 (0.28%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Anal abscess			
subjects affected / exposed	2 / 704 (0.28%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendiceal abscess			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 704 (0.14%)	3 / 703 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (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	1 / 704 (0.14%)	4 / 703 (0.57%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Candida sepsis			

subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	2 / 704 (0.28%)	3 / 703 (0.43%)	
occurrences causally related to treatment / all	1 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus chorioretinitis			
subjects affected / exposed	3 / 704 (0.43%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 704 (0.00%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	1 / 704 (0.14%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	2 / 704 (0.28%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fungal infection			

subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 704 (0.43%)	3 / 703 (0.43%)	
occurrences causally related to treatment / all	3 / 5	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	2 / 704 (0.28%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	4 / 704 (0.57%)	3 / 703 (0.43%)	
occurrences causally related to treatment / all	3 / 4	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster disseminated			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			

subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 704 (0.28%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	2 / 704 (0.28%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective glossitis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 704 (0.14%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	3 / 704 (0.43%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	6 / 704 (0.85%)	3 / 703 (0.43%)	
occurrences causally related to treatment / all	6 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Measles			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis cryptococcal			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 704 (0.00%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			

subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	3 / 704 (0.43%)	3 / 703 (0.43%)	
occurrences causally related to treatment / all	3 / 3	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral infection			
subjects affected / exposed	0 / 704 (0.00%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (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 / 704 (0.14%)	3 / 703 (0.43%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	40 / 704 (5.68%)	32 / 703 (4.55%)	
occurrences causally related to treatment / all	26 / 42	24 / 36	
deaths causally related to treatment / all	2 / 5	4 / 6	
Pneumonia bacterial			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic abscess			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
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	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 704 (0.28%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			

subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	15 / 704 (2.13%)	10 / 703 (1.42%)	
occurrences causally related to treatment / all	9 / 16	8 / 10	
deaths causally related to treatment / all	1 / 1	2 / 3	
Sepsis syndrome			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	12 / 704 (1.70%)	3 / 703 (0.43%)	
occurrences causally related to treatment / all	6 / 12	2 / 3	
deaths causally related to treatment / all	3 / 6	0 / 0	
Sinusitis fungal			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis of central nervous system			

subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 704 (0.43%)	3 / 703 (0.43%)	
occurrences causally related to treatment / all	2 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (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			
Cachexia			

subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 704 (0.14%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	5 / 704 (0.71%)	4 / 703 (0.57%)	
occurrences causally related to treatment / all	3 / 5	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 704 (0.00%)	3 / 703 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperglycaemia			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 704 (0.14%)	0 / 703 (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	2 / 704 (0.28%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	0 / 704 (0.00%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	0 / 704 (0.00%)	1 / 703 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 704 (0.14%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 704 (0.14%)	2 / 703 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Obinutuzumab+Chemotherapy	Rituximab+Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	642 / 704 (91.19%)	604 / 703 (85.92%)	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	249 / 704 (35.37%)	164 / 703 (23.33%)	
occurrences (all)	312	195	
Vascular disorders			
Hypertension			
subjects affected / exposed	40 / 704 (5.68%)	27 / 703 (3.84%)	
occurrences (all)	45	34	
Nervous system disorders			
Dizziness			
subjects affected / exposed	47 / 704 (6.68%)	27 / 703 (3.84%)	
occurrences (all)	52	32	
Dysgeusia			

subjects affected / exposed	44 / 704 (6.25%)	37 / 703 (5.26%)	
occurrences (all)	53	41	
Headache			
subjects affected / exposed	73 / 704 (10.37%)	56 / 703 (7.97%)	
occurrences (all)	81	68	
Neuropathy peripheral			
subjects affected / exposed	87 / 704 (12.36%)	88 / 703 (12.52%)	
occurrences (all)	96	94	
Paraesthesia			
subjects affected / exposed	55 / 704 (7.81%)	51 / 703 (7.25%)	
occurrences (all)	65	54	
Peripheral sensory neuropathy			
subjects affected / exposed	54 / 704 (7.67%)	56 / 703 (7.97%)	
occurrences (all)	61	60	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	88 / 704 (12.50%)	96 / 703 (13.66%)	
occurrences (all)	135	123	
Febrile neutropenia			
subjects affected / exposed	52 / 704 (7.39%)	44 / 703 (6.26%)	
occurrences (all)	68	58	
Leukopenia			
subjects affected / exposed	109 / 704 (15.48%)	84 / 703 (11.95%)	
occurrences (all)	272	222	
Neutropenia			
subjects affected / exposed	304 / 704 (43.18%)	261 / 703 (37.13%)	
occurrences (all)	676	671	
Thrombocytopenia			
subjects affected / exposed	47 / 704 (6.68%)	16 / 703 (2.28%)	
occurrences (all)	61	17	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	71 / 704 (10.09%)	73 / 703 (10.38%)	
occurrences (all)	89	83	
Chills			

subjects affected / exposed	131 / 704 (18.61%)	36 / 703 (5.12%)	
occurrences (all)	141	37	
Fatigue			
subjects affected / exposed	133 / 704 (18.89%)	120 / 703 (17.07%)	
occurrences (all)	181	147	
Mucosal inflammation			
subjects affected / exposed	45 / 704 (6.39%)	37 / 703 (5.26%)	
occurrences (all)	56	42	
Oedema peripheral			
subjects affected / exposed	35 / 704 (4.97%)	40 / 703 (5.69%)	
occurrences (all)	38	48	
Pyrexia			
subjects affected / exposed	129 / 704 (18.32%)	73 / 703 (10.38%)	
occurrences (all)	170	91	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	47 / 704 (6.68%)	46 / 703 (6.54%)	
occurrences (all)	52	56	
Abdominal pain upper			
subjects affected / exposed	35 / 704 (4.97%)	39 / 703 (5.55%)	
occurrences (all)	43	43	
Constipation			
subjects affected / exposed	165 / 704 (23.44%)	171 / 703 (24.32%)	
occurrences (all)	189	209	
Diarrhoea			
subjects affected / exposed	110 / 704 (15.63%)	89 / 703 (12.66%)	
occurrences (all)	146	112	
Dyspepsia			
subjects affected / exposed	44 / 704 (6.25%)	42 / 703 (5.97%)	
occurrences (all)	51	46	
Nausea			
subjects affected / exposed	206 / 704 (29.26%)	197 / 703 (28.02%)	
occurrences (all)	323	270	
Stomatitis			
subjects affected / exposed	46 / 704 (6.53%)	63 / 703 (8.96%)	
occurrences (all)	57	80	

Vomiting			
subjects affected / exposed	102 / 704 (14.49%)	72 / 703 (10.24%)	
occurrences (all)	141	99	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	83 / 704 (11.79%)	60 / 703 (8.53%)	
occurrences (all)	94	69	
Dyspnoea			
subjects affected / exposed	52 / 704 (7.39%)	31 / 703 (4.41%)	
occurrences (all)	57	31	
Oropharyngeal pain			
subjects affected / exposed	41 / 704 (5.82%)	37 / 703 (5.26%)	
occurrences (all)	46	39	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	145 / 704 (20.60%)	142 / 703 (20.20%)	
occurrences (all)	148	145	
Rash			
subjects affected / exposed	16 / 704 (2.27%)	45 / 703 (6.40%)	
occurrences (all)	19	47	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	76 / 704 (10.80%)	58 / 703 (8.25%)	
occurrences (all)	78	63	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	57 / 704 (8.10%)	42 / 703 (5.97%)	
occurrences (all)	70	49	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	43 / 704 (6.11%)	46 / 703 (6.54%)	
occurrences (all)	55	53	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	96 / 704 (13.64%)	70 / 703 (9.96%)	
occurrences (all)	120	80	
Hypokalaemia			

subjects affected / exposed occurrences (all)	60 / 704 (8.52%) 83	49 / 703 (6.97%) 74	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2011	Protocol Amendment 1 included the following: an early futility analysis of the end-of-treatment complete response rate for the first 200 randomized subjects; inclusion of fluorodeoxyglucose positron-emission tomography (FDG-PET) information for determination of the overall response rate and complete response rate at the end of treatment for subjects for whom FDG-PET information was available; inclusion of a pharmacokinetic sampling schedule and analysis plan for a subset of up to 40 Japanese subjects enrolled and treated in the obinutuzumab+chemotherapy arm.
31 August 2012	Protocol Amendment 2 included updated guidelines for dose-delays and modifications due to toxicities to make the modifications more consistent with standard practice.
22 May 2013	Protocol Amendment 3 included the following: removal of the existing cap on the recruitment of subjects with occult or prior hepatitis B infection; progression-free survival (PFS), as assessed by the independent review committee (IRC), was added to the primary outcome measure to clarify that it would be analyzed to support the primary analysis and that, in the United States, IRC-assessed PFS would be the basis for regulatory decisions.
24 March 2014	Protocol Amendment 4 included new guidelines regarding the management of subjects with thrombocytopenia, especially during the first cycle of obinutuzumab, including those subjects receiving concomitant anticoagulants or platelet inhibitors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported