Clinical trial results:
A phase III, open-label, randomized, multicenter trial of ofatumumab maintenance treatment versus no further treatment in subjects with relapsed chronic lymphocytic leukemia (CLL) who have responded to induction therapy

Summary

EudraCT number	2009-012518-39
Trial protocol	IT NL PL BE CZ SE FI ES FR DK HU GR
Global end of trial date	26 June 2018

Results information

Result version number	v1 (current)
This version publication date	12 July 2019
First version publication date	12 July 2019

Trial information

Trial identification

Sponsor protocol code	112517

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01039376
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate progression free survival (PFS) of subjects treated with ofatumumab maintenance treatment compared to no further treatment after remission induction in subjects with relapsed chronic CLL. Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 May 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Belgium: 31
Country: Number of subjects enrolled	Brazil: 10
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Czech Republic: 29
Country: Number of subjects enrolled	Denmark: 17
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	Greece: 21
Country: Number of subjects enrolled	Hungary: 25
Country: Number of subjects enrolled	India: 5
Country: Number of subjects enrolled	Israel: 39
Country: Number of subjects enrolled	Italy: 31
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Netherlands: 40
Country: Number of subjects enrolled	Norway: 2

Country: Number of subjects enrolled	Poland: 42
Country: Number of subjects enrolled	Russian Federation: 39
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	Ukraine: 22
Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	480
EEA total number of subjects	285

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)	240
From 65 to 84 years	238
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eligible participants were stratified based on complete or partial remission at study entry, number of previous induction treatments (2 versus 3) and type of prior treatment (chemoimmunotherapy, only alkylating monotherapy, or other treatment). Participants were then randomized in a 1:1 ratio to receive ofatumumab or no further 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	Ofatumumab

Arm description:

Participants with relapsed CLL received IV infusions of ofatumumab on Day 1 (300 mg) and Day 8 (1000 mg) in the first cycle, followed by infusions of 1000 mg every 2 months for up to 2 years following the first 1000 mg dose.

Arm type	Experimental
Investigational medicinal product name	OMB157
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use, Intravenous drip use

Dosage and administration details:

Ofatumumab infusions were given on Day 1 (300 mg) and Day 8 (1000 mg) in the first cycle, followed by infusions of 1000 mg every 2 months.

Arm title	Observation

Arm description:

Participants with relapsed CLL received no treatment and were under observation for up to 2 years.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Ofatumumab	Observation
Started	240	240
Completed	110	114
Not completed	130	126
Physician decision	15	10
Consent withdrawn by subject	20	32
Study terminated by Sponsor	90	72
Lost to follow-up	5	12

Baseline characteristics

Reporting groups	
Reporting group title	Ofatumumab
Reporting group description:	
Participants with relapsed CLL received IV infusions of ofatumumab on Day 1 (300 mg) and Day 8 (1000 mg) in the first cycle, followed by infusions of 1000 mg every 2 months for up to 2 years following the first 1000 mg dose.	
Reporting group title	Observation
Reporting group description:	
Participants with relapsed CLL received no treatment and were under observation for up to 2 years.	

Reporting group values	Ofatumumab	Observation	Total
Number of subjects	240	240	480
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	121	120	241
>=65 years	119	120	239
Sex: Female, Male Units: Subjects			
Female	79	80	159
Male	161	160	321
Race/Ethnicity, Customized Units: Subjects			
Hispanic/Latino	15	18	33
Not Hispanic/Latino	225	221	446
Missing	0	1	1
AgeContinuous Units: Years			
arithmetic mean	63.9	64.1	
standard deviation	± 10.31	± 9.61	-

End points

End points reporting groups

Reporting group title	Ofatumumab
Reporting group description:	
Participants with relapsed CLL received IV infusions of ofatumumab on Day 1 (300 mg) and Day 8 (1000 mg) in the first cycle, followed by infusions of 1000 mg every 2 months for up to 2 years following the first 1000 mg dose.	
Reporting group title	Observation
Reporting group description:	
Participants with relapsed CLL received no treatment and were under observation for up to 2 years.	
Subject analysis set title	Ofatumumab
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants with relapsed CLL received IV infusions of ofatumumab on Day 1 (300 mg) and Day 8 (1000 mg) in the first cycle, followed by infusions of 1000 mg every 2 months for up to 2 years following the first 1000 mg dose.	
Subject analysis set title	Observation
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants with relapsed CLL received no treatment and were under observation for up to 2 years.	

Primary: Progression-free survival, as assessed by the Investigator

End point title	Progression-free survival, as assessed by the Investigator
End point description:	
Progression-free survival is defined as the time from randomization to the date of disease progression (PD) or death due to any cause. PD was determined by the investigator according to the definitions of response in the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-Sponsored Working Group (NCI-WG) guidelines. According to the guidelines, PD is characterized by at least one of the following: lymphadenopathy (appearance of any new lesion such as enlarged lymph nodes (>1.5 centimeter [cm]), spleen or liver or other infiltrates or an increase by 50% or more in the greatest diameter of any previous site); an increase by 50% or more in the previously noted enlargement of the liver or spleen; an increase by 50% or more in the numbers of blood lymphocytes with at least 5000 lymphocytes per microliter; transformation to a more aggressive histology, or occurrence of cytopenia attributable to chronic lymphocytic leukemia.	
End point type	Primary
End point timeframe:	
From randomization until progression or death (up to 79 months)	

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	240		
Units: Months				
median (confidence interval 95%)	34.17 (29.70 to 38.01)	16.89 (12.98 to 20.37)		

Statistical analyses

Statistical analysis title	PFS, as assessed by the investigator
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Stratified log rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.7

Primary: Progression-free survival, as assessed by the Independent Review Committee (IRC)

End point title	Progression-free survival, as assessed by the Independent Review Committee (IRC)

End point description:

Progression-free survival is defined as the time from randomization to the date of disease progression (PD) or death due to any cause. PD was determined by the IRC according to the definitions of response in the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-Sponsored Working Group (NCI-WG) guidelines. According to the guidelines, PD is characterized by at least one of the following: lymphadenopathy (appearance of any new lesion such as enlarged lymph nodes (>1.5 centimeter [cm]), spleen or liver or other infiltrates or an increase by 50% or more in the greatest diameter of any previous site); an increase by 50% or more in the previously noted enlargement of the liver or spleen; an increase by 50% or more in the numbers of blood lymphocytes with at least 5000 lymphocytes per microliter; transformation to a more aggressive histology, or occurrence of cytopenia attributable to chronic lymphocytic leukemia.

End point type	Primary

End point timeframe:

From randomization until progression or death (up to 79 months)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	240		
Units: Months				
median (confidence interval 95%)	33.74 (28.35 to 38.01)	14.98 (11.63 to 19.12)		

Statistical analyses

Statistical analysis title	PFS, as assessed by IRC
Comparison groups	Ofatumumab v Observation

Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Stratified log rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.68

Secondary: Overall survival

End point title	Overall survival
End point description:	
Overall survival is defined as time from randomization to date of death.	
End point type	Secondary
End point timeframe:	
From randomization until death (up to 88 months)	

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	240		
Units: Months				
median (confidence interval 95%)	999 (68.96 to 999)	73.63 (66.53 to 999)		

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6046
Method	Stratified log rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.25

Secondary: Number of participants with improvement in response from Baseline

End point title	Number of participants with improvement in response from Baseline

End point description:

Improvement in response was assessed by calculating the percentage of participants who changed from partial response (PR) at Baseline to complete response during the study.

End point type	Secondary

End point timeframe:

From Baseline until the end of the study (up to 88 months)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	192		
Units: Participants	16	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to next therapy

End point title	Time to next therapy

End point description:

Time to next therapy is defined as the time from randomization to the date of receiving the next CLL treatment.

End point type	Secondary

End point timeframe:

From randomization until the end of the study (up to 88 months)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	240		
Units: Months				
median (confidence interval 95%)	36.21 (30.49 to 41.40)	27.56 (23.49 to 32.49)		

Statistical analyses

Statistical analysis title	Time to next therapy
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0178
Method	Stratified log rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.96

Secondary: Progression-free survival after next-line therapy

End point title	Progression-free survival after next-line therapy

End point description:

Progression-free survival after next-line therapy is defined as the time from randomization until progression or death following the next-line therapy and counted as events deaths prior to next-line therapy. Participants who received next-line therapy and who did not have progression or death after next-line therapy were censored at their last date of contact. Participant who died prior to next-line therapy, was counted as an event.

End point type	Secondary

End point timeframe:

From randomization until progression or death (up to 88 months)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	180		
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Progression-free survival after next-line therapy
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3136
Method	log rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.32

Secondary: Time to progression after next-line therapy

End point title	Time to progression after next-line therapy

End point description:

Time to progression after next-line therapy is defined as the time from progression following randomization until progression or death following next-line therapy and counted as events deaths prior to next-line therapy. Participants who received next-line therapy with a PD prior to receiving next line therapy and who did not had progression or death after next-line therapy were censored at their last date of contact. If a participant died prior to next-line therapy, this was counted as an event.

End point type	Secondary

End point timeframe:

From randomization until progression or death (up to 88 months)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	170		
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Time to progression after next-line therapy
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1603
Method	log rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.19

Secondary: Change from Baseline (BL) in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Chronic Lymphocytic Leukaemia 16 Item Module (EORTC QLQ-CLL 16)

End point title	Change from Baseline (BL) in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Chronic Lymphocytic Leukaemia 16 Item Module (EORTC QLQ-CLL 16)

End point description:

The EORTC QLQ-CLL16 is comprised of 16 questions that address 5 domains of health-related quality of life (HRQoL) important in CLL. There are 4 multi-item scales – fatigue (2 items), treatment side effects ([TSE], 4 items), disease symptoms (disease effects scale [DES], 4 items), and infection (4 items) – and single-item scales (social activities [Social Problems (SP) Scale] and future health worries [Future Health (FH) Scale]). These are measured on a four-point Likert scale, where 1 = not at all and 4 = very much. These scores are transformed to give a rating from 0 – 100, where 0 = no symptoms or problems and 100 = severe symptoms or problems. Changes from Baseline were analyzed by a mixed model-repeated measures analysis of covariance (ANCOVA).

End point type	Secondary

End point timeframe:

From randomization until the end of the study (up to 47 months)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	236		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Disease Effects Scale	0.36 (± 1.81)	2.56 (± 1.78)		
Fatigue Scale	-0.16 (± 2.96)	3.63 (± 2.93)		
Future Health Scale	-8.66 (± 3.69)	-5.08 (± 3.65)		
Infection Scale	0.77 (± 2.20)	0.25 (± 2.17)		
Social Problems Scale	5.69 (± 3.20)	10.02 (± 3.16)		
Treatment Side Effects Scale	-0.54 (± 1.77)	1.95 (± 1.74)		

Statistical analyses

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-CLL 16
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0199 [1]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	-2.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.04
upper limit	-0.35

Notes:

[1] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-CLL 16
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0085 [2]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	-3.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.61
upper limit	-0.97

Notes:

[2] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-CLL 16
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0642 [3]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	-3.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.37
upper limit	0.21

Notes:

[3] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-CLL 16
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6398 [4]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	0.52

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	2.72

Notes:

[4] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-CLL 16
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0055 [5]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	-4.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.37
upper limit	-1.28

Notes:

[5] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-CLL 16
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0063 [6]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	-2.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.27
upper limit	-0.71

Notes:

[6] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Secondary: Change from Baseline in the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) score

End point title	Change from Baseline in the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) score

End point description:

The EORTC QLQ-C30 is a self-reported, 30-item cancer-specific instrument that assesses 15 domains: physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items), social functioning (2 items), pain (2 items), fatigue (3 items), nausea and vomiting (2 items), five single-item symptom scores (insomnia, loss of appetite, constipation, diarrhea, and dyspnea), a single item asking about financial difficulties, and global health status/quality of life (QOF) consisting of 2 items. Functional and symptoms scales were measured on a four-point Likert scale, where 1 = not at all and 4 = very much, whereas global health status or QOF was assessed using a 7-item Likert scale, ranging from "poor" (worse quality of life) to "excellent" (better quality of life). Changes from Baseline were analyzed by mixed model-repeated measures ANCOVA.

End point type	Secondary

End point timeframe:

From randomization until the end of the study (up to 47 months)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	236		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Appetite Loss	-0.63 (± 2.33)	0.85 (± 2.30)		
Cognitive Functioning	-1.63 (± 2.30)	-3.03 (± 2.29)		
Constipation	-1.71 (± 2.30)	0.27 (± 2.27)		
Diarrhoea	-1.99 (± 2.23)	-2.49 (± 2.20)		
Dyspnoea	0.44 (± 2.71)	2.76 (± 2.67)		
Emotional Functioning	-0.83 (± 2.47)	-4.72 (± 2.44)		
Fatigue	-0.02 (± 2.89)	4.61 (± 2.85)		
Financial Difficulties	4.09 (± 3.31)	5.85 (± 3.26)		
Nausea and Vomiting	0.28 (± 1.12)	1.50 (± 1.11)		
Pain	1.82 (± 2.89)	4.87 (± 2.87)		
Physical Functioning	-2.25 (± 2.01)	-4.07 (± 2.01)		
Global Health Status/QOL	-0.17 (± 2.52)	-1.94 (± 2.49)		
Role Functioning	-6.94 (± 3.04)	-10.51 (± 3.00)		
Social Functioning	-4.15 (± 2.71)	-7.80 (± 2.69)		
Insomnia	-4.49 (± 3.51)	-2.70 (± 3.48)		

Statistical analyses

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-C30
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1816 [7]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	-1.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.64
upper limit	0.69

Notes:

[7] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-C30
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2863 [8]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	3.97

Notes:

[8] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-C30
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0932 [9]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	-1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.28
upper limit	0.33

Notes:

[9] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-C30
Comparison groups	Ofatumumab v Observation

Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6533 [10]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	2.66

Notes:

[10] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-C30
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0963 [11]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	-2.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.06
upper limit	0.42

Notes:

[11] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-C30
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0037 [12]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	3.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.27
upper limit	6.51

Notes:

[12] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-C30
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0013 [13]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	-4.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.45
upper limit	-1.82

Notes:

[13] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-C30
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2902 [14]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	-1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.02
upper limit	1.51

Notes:

[14] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-C30
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0606 [15]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	-1.22

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.49
upper limit	0.05

Notes:

[15] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-C30
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0393 [16]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	-3.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.93
upper limit	-0.15

Notes:

[16] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-C30
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0968 [17]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	3.96

Notes:

[17] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-C30
Comparison groups	Ofatumumab v Observation

Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1449 [18]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	1.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	4.17

Notes:

[18] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-C30
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0259 [19]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	3.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	6.7

Notes:

[19] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-C30
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0175 [20]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	3.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	6.65

Notes:

[20] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline (BL) in EORTC QLQ-C30
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3209 [21]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	-1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.33
upper limit	1.75

Notes:

[21] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Secondary: Change from Baseline in the Quality of Life Status as assessed by the EuroQol-5D (EQ-5D) Scale

End point title	Change from Baseline in the Quality of Life Status as assessed by the EuroQol-5D (EQ-5D) Scale

End point description:

EQ-5D is comprised of a 5-item health status measure and a visual analogue scale (VAS) and is used to generate two scores: the utility score and the thermometer score. The utility score measures mobility, self-care, usual activities, pain, discomfort, and anxiety/depression. Responses to each of the 5 health states are measured on a 3-point scale (level 1 = no problem; level 2 = some or moderate problem[s] and level 3 = unable, or extreme problems). Responses are typically converted into health utilities or valuations on a scale ranging from 0 (worst health) to 1 (perfect health). The thermometer score ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). Changes from Baseline were analyzed by mixed model-repeated measures ANCOVA. A negative adjusted mean change from Baseline represents a worsening of quality of life.

End point type	Secondary

End point timeframe:

From screening until the end of the study (up to 47 months)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	236		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Utility Score	-0.02 (± 0.03)	-0.05 (± 0.03)		
Thermometer Score	-0.37 (± 2.05)	-1.75 (± 2.04)		

Statistical analyses

Statistical analysis title	Change from Baseline in EQ-5D
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.011 [22]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.06

Notes:

[22] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Statistical analysis title	Change from Baseline in EQ-5D
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1999 [23]
Method	Repeated measures analysis of covariance
Parameter estimate	Mean difference (final values)
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	3.49

Notes:

[23] - The analysis is adjusted for BL score, actual strata, age group, BL ECOG performance status and Binet stage at Screening using mixed-model (Proc Mixed) repeated with intercept, BL score by time and treatment by time interaction.

Secondary: Number of participants with an improvement in Eastern Cooperative Oncology Group (ECOG) Performance Status at the indicated time points

End point title	Number of participants with an improvement in Eastern Cooperative Oncology Group (ECOG) Performance Status at the indicated time points

End point description:

Improvement is defined as a decrease from Baseline by at least one step on the ECOG performance status scale (improvement categorized as yes or no). Improvement in ECOG performance status was measured.

End point type	Secondary

End point timeframe:

From randomization until the end of the study (up to 88 months)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	240		
Units: Participants				
C1 W2/M1 (n=234, 202)	10	12		
C2 W9/M3 (n= 226, 222)	20	17		
C3 W17/M5 (n=214, 203)	16	17		
C4 W25/M7 (n=200, 184)	18	16		
C5 W33/M9 (n=194, 171)	16	18		
C6 W41/M11 (n=183, 151)	14	12		
C7 W49/M13 (n= 174, 137)	18	14		
C8 W57/M15 (n=154, 119)	14	15		
C9 W65/M17 (n=140, 107)	11	12		
C10 W73/M19 (n=136, 103)	14	10		
C11 W81/M21 (n= 124, 94)	10	9		
C12 W89/M23 (n= 119, 82)	11	7		
C13 W97/M25 (n=112, 79)	9	7		
3M FU (n=106, 63)	11	6		
6M FU (n=104, 61)	9	4		
9M FU (n=92, 50)	5	5		
12M FU (n=81, 43)	6	5		
15M FU (n=66, 39)	4	4		
18M FU (n=60, 35)	4	3		
21M FU (n=51, 32)	3	3		
24M FU (n=48, 26)	3	2		
27M FU (n=40, 24)	3	1		
30M FU (n=35, 18)	3	1		
33M FU (n=30, 17)	3	1		
36M FU (n=27, 15)	3	1		
39M FU (n=22, 12)	1	2		
42M FU (n=17, 10)	0	0		
45M FU (n=14, 7)	0	1		
48M FU (n=10, 5)	0	1		
51M FU (n=8, 4)	0	1		
54M FU (n=6, 2)	1	1		
57M FU (n=3, 2)	0	1		
60M FU (n=2, 2)	0	1		
Withdrawal (n=79, 94)	5	10		
Worst-Case Post Baseline	3	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated constitutional or B-symptoms

at the indicated time points

End point title	Number of participants with the indicated constitutional or B-symptoms at the indicated time points

End point description:

Participants with the indicated constitutional or B-symptoms (night sweats [without signs of infection]; unintentional weight loss >= 10% within the previous 6 months; recurrent, unexplained fever of > 38 degrees celcius or 100.5 degrees fahrenheit for 2 weeks; and extreme fatigue) were presented. The proportion of participants with no night sweats, no weight loss, no fever and no extreme fatigue were summarized.

End point type	Secondary

End point timeframe:

From Screening until the end of the study (up to 88 months)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	240		
Units: Participants				
SCR, extreme fatigue	0	7		
SCR, fever	0	1		
SCR, night sweats	13	8		
SCR, weight loss	2	1		
C1 W2/M1, extreme fatigue (n=236, 204)	0	2		
C1 W2/M1, fever (n=236, 204)	0	0		
C1 W2/M1, night sweats (n=236, 204)	9	6		
C1 W2/M1, weight loss (n=236, 204)	4	1		
C2 W9/M3, extreme fatigue (n=227, 223)	3	3		
C2 W9/M3, fever (n=227, 223)	1	2		
C2 W9/M3, night sweats (n=227, 223)	6	10		
C2 W9/M3, weight loss (n=227, 223)	3	1		
C3 W17/M5, extreme fatigue (n=215, 206)	4	5		
C3 W17/M5, fever (n=215, 206)	1	2		
C3 W17/M5, night sweats (n=215, 206)	6	10		
C3 W17/M5, weight loss (n=215, 206)	3	3		
C4 W25/M7, extreme fatigue (n=203, 187)	1	3		
C4 W25/M7, fever (n=203, 187)	1	2		
C4 W25/M7, night sweats (n=203, 187)	5	7		
C4 W25/M7, weight loss (n=203, 187)	1	1		
C5 W33/M9, extreme fatigue (n=196, 171)	1	5		
C5 W33/M9, fever (n=196, 171)	1	0		
C5 W33/M9, night sweats fatigue (n=196, 171)	7	8		
C5 W33/M9, weight loss (n=196, 171)	0	4		
C6 W41/M11, extreme fatigue (n=184, 152)	1	2		
C6 W41/M11, fever (n=184, 152)	2	0		
C6 W41/M11, night sweats (n=184, 152)	7	7		

C6 W41/M11, weight loss (n=184, 152)	0	0		
C7 W49/M13, extreme fatigue (n=175, 138)	1	1		
C7 W49/M13, fever (n=175, 138)	0	0		
C7 W49/M13, night sweats (n=175, 138)	3	5		
C7 W49/M13, weight loss (n=175, 138)	2	1		
C8 W57/M15, extreme fatigue (n=155, 122)	1	1		
C8 W57/M15, fever (n=155, 122)	2	0		
C8 W57/M15, night sweats (n=155, 122)	4	4		
C8 W57/M15, weight loss (n=155, 122)	2	3		
C9 W65/M17, extreme fatigue (n=142, 107)	2	2		
C9 W65/M17, fever (n=142, 107)	2	0		
C9 W65/M17, night sweats (n=142, 107)	7	4		
C9 W65/M17, weight loss (n=142, 107)	1	2		
C10 W73/M19, extreme fatigue (n=137, 103)	2	2		
C10 W73/M19, fever (n=137, 103)	1	0		
C10 W73/M19, night sweats (n=137, 103)	7	4		
C10 W73/M19, weight loss (n=137, 103)	2	1		
C11 W81/M21, extreme fatigue (n=126, 96)	0	3		
C11 W81/M21, fever (n=126, 96)	1	0		
C11 W81/M21, night sweats (n=126, 96)	2	4		
C11 W81/M21, weight loss (n=126, 96)	0	0		
C12 W89/M23, extreme fatigue (n=121, 84)	1	0		
C12 W89/M23, fever (n=121, 84)	0	0		
C12 W89/M23, night sweats (n=121, 84)	3	3		
C12 W89/M23, weight loss (n=121, 84)	0	1		
C13 W97/M25, extreme fatigue (n=114, 79)	1	0		
C13 W97/M25, fever (n=114, 79)	0	0		
C13 W97/M25, night sweats (n=114, 79)	2	1		
C13 W97/M25, weight loss (n=114, 79)	1	3		
3M follow up, extreme fatigue (n=112, 64)	3	2		
3M follow up, fever (n=112, 64)	1	1		
3M follow up, night sweats (n=112, 64)	4	4		
3M follow up, weight loss (n=112, 64)	2	0		
6M follow up, extreme fatigue (n=106, 61)	3	2		
6M follow up, fever (n=106, 61)	1	0		
6M follow up, night sweats (n=106, 61)	2	2		
6M follow up, weight loss (n=106, 61)	1	1		
9M follow up, extreme fatigue (n=94, 50)	2	2		
9M follow up, fever (n=94, 50)	0	0		
9M follow up, night sweats (n=94, 50)	4	2		

9M follow up, weight loss (n=94, 50)	0	2		
12M follow up, extreme fatigue (n=82, 45)	0	3		
12M follow up, fever (n=82, 45)	1	1		
12M follow up, night sweats (n=82, 45)	2	4		
12M follow up, weight loss (n=82, 45)	0	1		
15M follow up, extreme fatigue (n=68, 41)	0	0		
15M follow up, fever (n=68, 41)	0	1		
15M follow up, night sweats (n=68, 41)	2	1		
15M follow up, weight loss (n=68, 41)	1	0		
18M follow up, extreme fatigue (n=62, 35)	1	1		
18M follow up, fever (n=62, 35)	0	0		
18M follow up, night sweats (n=62, 35)	2	1		
18M follow up, weight loss (n=62, 35)	0	0		
21M follow up, extreme fatigue (n=53, 33)	0	1		
21M follow up, fever (n=53, 32)	0	0		
21M follow up, night sweats (n=53, 32)	1	2		
21M follow up, weight loss (n=53, 33)	0	0		
27M follow up, extreme fatigue (n=40, 25)	0	0		
27M follow up, fever (n=40, 25)	0	0		
27M follow up, night sweats (n=40, 24)	2	1		
27M follow up, weight loss (n=40, 25)	1	1		
30M follow up, extreme fatigue (n=35, 18)	0	0		
30M follow up, fever (n=35, 18)	0	0		
30M follow up, night sweats (n=35, 18)	1	1		
30M follow up, weight loss (n=35, 18)	0	0		
33M follow up, extreme fatigue (n=30, 17)	0	0		
33M follow up, fever (n=30, 17)	1	0		
33M follow up, night sweats (n=30, 17)	2	2		
33M follow up, weight loss (n=30, 17)	0	0		
36M follow up, extreme fatigue (n=27, 15)	1	0		
36M follow up, fever (n=27, 15)	0	0		
36M follow up, night sweats (n=27, 15)	1	0		
36M follow up, weight loss (n=27, 15)	0	0		
39M follow up, extreme fatigue (n=23, 12)	1	0		
39M follow up, fever (n=23, 12)	0	0		
39M follow up, night sweats (n=23, 12)	1	0		
39M follow up, weight loss (n=23, 12)	0	0		
42M follow up, extreme fatigue (n=18, 10)	0	0		
42M follow up, fever (n=18, 10)	0	1		
42M follow up, night sweats (n=18, 10)	0	1		
42M follow up,, weight loss (n=18, 10)	0	0		
51M follow up, extreme fatigue (n=8, 4)	0	0		
51M follow up, fever (n=8, 4)	1	0		
51M follow up, night sweats (n=8, 4)	0	1		
51M follow up, weight loss (n=8, 4)	0	0		

54M follow up, extreme fatigue (n=6, 2)	0	0		
54M follow up, fever (n=6, 2)	1	0		
54M follow up, night sweats (n=6, 2)	0	0		
54M follow up, weight loss (n=6, 2)	0	0		
Withdrawal, extreme fatigue (n=81, 97)	9	12		
Withdrawal, fever (n=81, 97)	7	3		
Withdrawal, night sweats (n=81, 97)	14	15		
Withdrawal, weight loss (n=81, 97)	4	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Grade 3 and above adverse event of infection

End point title	Number of participants with Grade 3 and above adverse event of infection

End point description:

Participants with Grade 3, Grade 4 and Grade 5 adverse event of infection are presented. Adverse events were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) grade, version 4.0 (1=mild; 2=moderate; 3=severe; 4=life-threatening/disabling; 5=death).

End point type	Secondary

End point timeframe:

From first dose of study medication until 60 days after the last dose of study medication or until the last observation at Visit 14 (up to 26 months)

End point values	Ofatumumab	Observation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	239	241		
Units: Participants	38	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any adverse event (AE) or serious adverse event (SAE)

End point title	Number of participants with any adverse event (AE) or serious adverse event (SAE)

End point description:

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or

may require medical or surgical intervention to prevent one of the other outcomes listed. Refer to the general Adverse AE/SAE module for a complete list of AEs and SAEs.

End point type	Secondary

End point timeframe:

From first dose of study medication until 60 days after the last dose of study medication or until the last observation at Visit 14 for AEs (up to 26 months) and until end of study for SAEs (88 months)

End point values	Ofatumumab	Observation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	239	241		
Units: Participants				
Any AE	221	198		
Any SAE	120	120		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with a Grade 3 or Grade 4 myelosuppression (anemia, neutropenia, or thrombocytopenia) at indicated time points

End point title	Number of participants with a Grade 3 or Grade 4 myelosuppression (anemia, neutropenia, or thrombocytopenia) at indicated time points

End point description:

Myelosuppression is defined as the decrease in the ability of the bone marrow to produce blood cells. Number of participants who reported myelosuppression (anemia [low hemoglobin count], neutropenia [low neutrophil count], and thrombocytopenia [low platelet count]) are presented. AEs were graded according to NCI common terminology criteria for adverse events (CTCAE) grade, version 4.0 (1, mild; 2, moderate; 3, severe; 4, life-threatening/disabling; 5, death).

End point type	Secondary

End point timeframe:

From first dose of study medication until 60 days after the last dose of study medication or until the last observation at Visit 14 for AEs (up to 26 months) and until the end of the study for SAEs (88 months)

End point values	Ofatumumab	Observation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	239	241		
Units: Participants				
SCR (n=221, 199)	7	5		
C1 W1/M1 (n=3, 10)	1	1		
C1 W2/M1 (n=225, 192)	13	8		
C2 W9/M3 (n=221, 210)	12	15		
C2, unscheduled (n=5, 2)	1	0		
C3 W17/M5 9 (n=208, 195)	18	7		
C3, unscheduled (n=7, 2)	1	0		
C4 W25/M7 (n=192, 180)	12	8		

C4 Unscheduled (n= 1, 0)	1	0		
C5 W33/M9, (n= 188, 164)	15	5		
C5, unscheduled (n= 3, 0)	1	0		
C6 W41/M11 (n=180, 139)	13	5		
C6 unscheduled (n= 8, 0)	4	0		
C6 unscheduled (n= 1, 0)	1	0		
C7 W49/M13 (n= 165, 132)	9	2		
C8 W57/M15 (n=148, 120)	10	3		
C9 W65/M17 (n=135, 101)	5	1		
C9, unscheduled (n= 2, 1)	0	1		
C10 W73/M19 (n=130, 101)	2	2		
C11 W81/M21 (n=122, 92)	5	1		
C11 unscheduled (n=2, 1)	1	0		
C11 unscheduled (n=2, 0)	1	0		
C12 W89/M23 (n= 115, 81)	3	2		
C13 W97/M25 (n=109, 75)	3	2		
C13, unscheduled (n=2, 0)	1	0		
3M follow-up (n=102, 61)	2	1		
6M follow-up (n=92, 55)	2	1		
9M follow-up (n=86, 50)	2	1		
12M follow-up (n=77, 43)	1	2		
15M follow-up (n=62, 37)	1	0		
18M follow-up (n=55, 33)	0	1		
27M follow-up (n=37, 22)	0	1		
30M follow-up (n=29, 17)	0	1		
33M follow-up (n=27, 16)	1	0		
60M follow-up (n=2, 2)	1	0		
Withdrawal (n=76, 93)	11	8		
Unscheduled (n=2, 2)	0	1		
Unscheduled (n=2, 5)	0	2		
Unscheduled (n=7, 7)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who received at least one transfusion during the study

End point title	Number of participants who received at least one transfusion during the study

End point description:

Participants who received at least one transfusion (any blood products or blood supportive care product) during the study are presented.

End point type	Secondary

End point timeframe:

From randomization until the end of the study (up to 88 months)

End point values	Ofatumumab	Observation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	239	241		
Units: Participants	96	64		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants diagnosed with autoimmune hemolytic anemia (AIHA)

End point title	Number of participants diagnosed with autoimmune hemolytic anemia (AIHA)

End point description:

AIHA is a disease where the body's immune system fails to recognize red blood cells as "self" and begins destroying these red blood cells. The number of participants diagnosed with AIHA are presented.

End point type	Secondary

End point timeframe:

From randomization until the end of the study (up to 88 months)

End point values	Ofatumumab	Observation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	239	241		
Units: Participants				
Haemolytic anaemia	2	2		
Autoimmune haemolytic anaemia	1	4		
Thrombocytopenic purpura	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with a positive anti-ofatumumab antibody (human anti-human antibody; HAHA) result

End point title	Number of participants with a positive anti-ofatumumab antibody (human anti-human antibody; HAHA) result

End point description:

All serum samples for analysis of HAHA were first tested in a screening step; positive samples from the screening were further evaluated in a confirmation test. The confirmed positive samples were reported as HAHA positive and further evaluated in the titration test to obtain a titer of HAHA. A confirmed positive result at any time point means the participant is positive for HAHA.Results are reported as the number of participants positive for HAHA.

End point type	Secondary

End point timeframe:

Pre-dose (Visit 1), Months 7, 13, 19, and 25 during treatment and at 3 and 6 months after last ofatumumab dose (up to 30 months)

End point values	Ofatumumab	Observation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	239	0[24]		
Units: Participants	1			

Notes:

[24] - analysis not done for this group

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in the immunoglobulin (Ig) antibodies IgA, IgG, and IgM at indicated time points

End point title	Mean change from Baseline in the immunoglobulin (Ig) antibodies IgA, IgG, and IgM at indicated time points

End point description:

Immunoglobulins, or antibodies, are large proteins used by the immune system to identify and neutralize foreign particles such as bacteria and viruses. Their normal blood levels indicate proper immune status. Low levels indicate immuno-suppression. IgA, IgG, and IgM were measured in the blood samples of the participants. Baseline IgA, IgG, and IgM values are the last pre-dose assessment values performed on Cycle 1 Day 1. Change from Baseline was calculated as the post-baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

Baseline, every six months during treatment, and after last treatment visit and/or upon relapse (up to 88 months)

End point values	Ofatumumab	Observation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	239	241		
Units: grams per liter				
arithmetic mean (standard deviation)				
IgA, C2 W9, M3 (n=0, 2)	0.0 (± 0.0)	0.2 (± 0.23)		
IgA, C3 W17, M5 (n=6, 3)	0.0 (± 0.12)	-0.1 (± 0.24)		
IgA, C4 W25, M7 (n=189, 172)	-0.1 (± 0.17)	-0.0 (± 0.41)		
IgA, C5 W33, M9 (n= 1, 2)	-0.0 (± 999)	-0.0 (± 0.01)		
IgA, C6 W41, M11 (n=1,1)	0.0 (± 999)	-0.1 (± 999)		
IgA, C7 W49, M13 (n=157, 122)	-0.1 (± 0.24)	-0.0 (± 0.63)		
IgA, C8 W57, M15 (n=3, 2)	-0.1 (± 0.15)	0.0 (± 0.02)		
IgA, C9 W65, M17 (n=3, 2)	-0.2 (± 0.17)	0.1 (± 0.04)		
IgA, C10 W73, M19 (n=125, 91)	-0.1 (± 0.20)	0.1 (± 0.37)		
IgA, C11 W81, M21 (n=1, 2)	-0.0 (± 999)	0.2 (± 0.21)		
IgA, C12 W89, M23 (n=1, 4)	-0.3 (± 999)	0.2 (± 0.39)		
IgA, C13 W97, M25 (n=107, 74)	-0.1 (± 0.23)	0.1 (± 0.38)		
IgA, 3M FU (n=89, 51)	-0.1 (± 0.22)	0.2 (± 0.37)		
IgA, 6M FU (n=83, 50)	-0.1 (± 0.18)	0.1 (± 0.39)		

IgA, 9M FU (n=62, 40)	-0.1 (± 0.22)	0.1 (± 0.38)		
IgA, 12M FU (n=54, 35)	-0.1 (± 0.30)	0.2 (± 0.36)		
IgA, 15M FU (n=40, 31)	-0.0 (± 0.27)	0.2 (± 0.44)		
IgA, 18M FU (n=38, 23)	0.1 (± 0.57)	0.1 (± 0.25)		
IgA, 21M FU (n=33, 23)	-0.1 (± 0.40)	0.1 (± 0.34)		
IgA, 24M FU (n=29, 21)	0.2 (± 1.06)	0.1 (± 0.37)		
IgA, 27M FU (n=24, 15)	0.1 (± 0.70)	0.1 (± 0.46)		
IgA, 30M FU (n=18, 12)	0.2 (± 0.85)	0.1 (± 0.58)		
IgA, 33M FU (n=18, 11)	0.4 (± 1.48)	0.2 (± 0.60)		
IgA, 36M FU (n=18, 11)	0.2 (± 1.06)	0.2 (± 0.63)		
IgA, 39M FU (n= 14, 8)	0.2 (± 0.86)	0.3 (± 0.71)		
IgA, 42M FU (n=14, 6)	0.4 (± 1.67)	0.2 (± 0.72)		
IgA, 45M FU (n=11, 4)	-0.2 (± 0.20)	0.4 (± 0.94)		
IgA, 48M FU (n=9, 3)	-0.1 (± 0.83)	-0.0 (± 0.25)		
IgA, 51M FU (n=4, 3)	0.3 (± 1.15)	0.2 (± 0.70)		
IgA, 54M FU (n=6, 2)	0.0 (± 0.89)	0.7 (± 1.34)		
IgA, 57M FU (n=3, 2)	-0.4 (± 0.36)	0.4 (± 1.04)		
IgA, 60M FU (n=2, 2)	-0.5 (± 0.42)	0.4 (± 1.05)		
IgA, Withdrawal (n=6, 4)	0.0 (± 0.53)	-0.1 (± 0.08)		
IgG, C2 W9, M3 (n=0, 2)	0.0 (± 0.0)	-0.4 (± 0.21)		
IgG, C3 W17, M5 (n=6, 3)	0.0 (± 1.17)	0.2 (± 0.39)		
IgG, C4 W25, M7 (n=190, 172)	-0.7 (± 2.03)	-0.1 (± 1.83)		
IgG, C5 W33, M9 (n= 1, 2)	-1.0 (± 999)	0.5 (± 2.20)		
IgG, C6 W41, M11 (n=1,1)	-1.9 (± 999)	1.0 (± 999)		
IgG, C7 W49, M13 (n=157, 122)	-1.1 (± 1.9)	0.2 (± 2.88)		
IgG, C8 W57, M15 (n=3, 2)	-1.3 (± 1.03)	-0.9 (± 0.08)		
IgG, C9 W65, M17 (n=3, 2)	-3.7 (± 4.96)	0.9 (± 0.71)		
IgG, C10 W73, M19 (n=125, 91)	-1.0 (± 2.15)	0.6 (± 4.61)		
IgG, C11 W81, M21 (n=1, 2)	0.2 (± 999)	-0.3 (± 1.39)		
IgG, C12 W89, M23 (n=1, 4)	-0.5 (± 999)	0.2 (± 0.89)		
IgG, C13 W97, M25 (n=107, 74)	-1.1 (± 2.45)	0.3 (± 3.02)		
IgG, 3M FU (n=90, 51)	-0.7 (± 2.46)	0.2 (± 2.83)		
IgG, 6M FU (n=83, 50)	-0.9 (± 2.24)	0.2 (± 2.89)		
IgG, 9M FU (n=62, 40)	-0.7 (± 2.29)	0.1 (± 2.87)		
IgG, 12M FU (n=54, 35)	-0.5 (± 2.17)	-0.3 (± 3.26)		
IgG, 15M FU (n=40, 31)	-0.4 (± 2.49)	-0.1 (± 3.29)		
IgG, 18M FU (n=38, 23)	-0.5 (± 2.71)	-0.3 (± 3.45)		
IgG, 21M FU (n=33, 23)	-0.9 (± 2.39)	0.1 (± 3.81)		
IgG, 24M FU (n=29, 21)	-0.1 (± 2.17)	0.0 (± 3.43)		
IgG, 27M FU (n=24, 15)	-0.3 (± 2.32)	-0.5 (± 3.97)		
IgG, 30M FU (n=18, 12)	0.3 (± 2.67)	-0.9 (± 4.83)		
IgG, 33M FU (n= 18, 11)	0.7 (± 2.91)	-1.1 (± 5.63)		
IgG, 36M FU (n=18, 11)	-0.1 (± 2.71)	-1.2 (± 3.87)		
IgG, 39M FU (n= 14, 8)	0.3 (± 2.53)	-0.9 (± 5.60)		
IgG, 42M FU (n= 14, 6)	0.6 (± 3.03)	0.9 (± 4.82)		
IgG, 45M FU (n=11, 4)	-0.6 (± 2.11)	2.3 (± 4.00)		
IgG, 48M FU (n= 9, 3)	-0.6 (± 2.30)	3.5 (± 3.14)		
IgG, 51M FU (n=4, 3)	0.1 (± 3.25)	2.4 (± 4.02)		
IgG, 54M FU (n=6, 2)	-1.0 (± 2.35)	5.6 (± 4.14)		
IgG, 57M FU (n=3, 2)	1.3 (± 4.01)	5.3 (± 5.68)		
IgG, 60M FU (n=2, 2)	0.8 (± 4.43)	4.6 (± 4.28)		
IgG, Withdrawal (n=6, 4)	-0.7 (± 0.91)	-1.5 (± 1.86)		

IgM, C2 W9, M3 (n=0, 2)	0.0 (± 0.0)	0.1 (± 0.12)		
IgM, C3 W17, M5 (n=6, 3)	-0.0 (± 0.09)	-0.0 (± 0.06)		
IgM, C4 W25, M7 (n=190, 172)	-0.1 (± 0.43)	0.1 (± 0.42)		
IgM, C5 W33, M9 (n= 1, 2)	-0.1 (± 999)	-0.1 (± 0.07)		
IgM, C6 W41, M11 (n=1,1)	-0.5 (± 999)	0.0 (± 999)		
IgM, C7 W49, M13 (n=157, 122)	-0.1 (± 0.29)	0.2 (± 0.90)		
IgM, C8 W57, M15 (n=3, 2)	-0.0 (± 0.05)	-0.0 (± 0.01)		
IgM, C9 W65, M17 (n= 3, 2)	-0.3 (± 0.54)	0.3 (± 0.49)		
IgM, C10 W73, M19 (n=125, 91)	-0.1 (± 0.36)	0.2 (± 0.86)		
IgM, C11 W81, M21 (n=1, 2)	0.0 (± 999)	0.2 (± 0.04)		
IgM, C12 W89, M23 (n=1, 4)	0.0 (± 999)	-0.0 (± 0.11)		
IgM, C13 W97, M25 (n=107, 74)	-0.1 (± 0.45)	0.2 (± 0.79)		
IgM, 3M FU (n=90, 51)	-0.0 (± 0.35)	0.3 (± 1.30)		
IgM, 6M FU (n=83, 50)	-0.1 (± 0.36)	0.4 (± 1.60)		
IgM, 9M FU (n=62, 40)	-0.1 (± 0.17)	0.6 (± 2.93)		
IgM, 12M FU (n=54, 35)	-0.0 (± 0.18)	0.6 (± 2.49)		
IgM, 15M FU (n=40, 31)	-0.0 (± 0.15)	0.3 (± 1.08)		
IgM, 18M FU (n=38, 23)	0.1 (± 0.25)	1.2 (± 4.95)		
IgM, 21M FU (n=33, 23)	0.1 (± 0.41)	1.4 (± 5.48)		
IgM, 24M FU (n=29, 21)	0.0 (± 0.14)	2.0 (± 8.19)		
IgM, 27M FU (n=24, 15)	0.2 (± 0.41)	-0.2 (± 1.14)		
IgM, 30M FU (n=18, 12)	0.1 (± 0.17)	-0.0 (± 1.51)		
IgM, 33M FU (n=18, 11)	0.1 (± 0.22)	0.1 (± 0.36)		
IgM, 36M FU (n=18, 11)	0.2 (± 0.28)	-0.3 (± 1.31)		
IgM, 39M FU (n=14, 8)	0.1 (± 0.21)	-0.4 (± 1.54)		
IgM, 42M FU (n=14, 6)	0.1 (± 0.23)	-0.6 (± 1.79)		
IgM, 45M FU (n=11, 4)	0.2 (± 0.32)	0.2 (± 0.27)		
IgM, 48M FU (n=9, 3)	0.1 (± 0.28)	0.4 (± 0.38)		
IgM, 51M FU (n=4, 3)	-0.0 (± 0.06)	0.3 (± 0.39)		
IgM, 54M FU (n=6, 2)	0.1 (± 0.24)	0.5 (± 0.26)		
IgM, 57M FU (n=3, 2)	0.2 (± 0.49)	0.4 (± 0.41)		
IgM, 60M FU (n=2, 2)	0.6 (± 0.84)	0.4 (± 0.42)		
IgM, Withdrawal (n=6, 4)	0.3 (± 0.73)	-0.0 (± 0.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who were positive and negative for minimal residual disease (MRD) at any visit

End point title	Number of participants who were positive and negative for minimal residual disease (MRD) at any visit

End point description:

MRD refers to small number of leukemic cells that remain in the participant during treatment or after treatment at the time the participant achieved a confirmed complete remission. Number of participants who were positive and negative for minimal residual disease (MRD) at any visit is presented.

End point type	Secondary

End point timeframe:

From randomization until the end of the study (up to 88 months)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	240		
Units: Participants				
Positive	150	122		
Negative	27	37		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in cluster of differentiation (CD) CD5+CD19+ and CD5-CD19+ cell counts at the indicated time points

End point title	Change from Baseline in cluster of differentiation (CD) CD5+CD19+ and CD5-CD19+ cell counts at the indicated time points

End point description:

CD5+CD19+ cells were counted by flow cytometry. Flow cytometry is a technique for counting and examining microscopic particles with an electronic detection apparatus. Baseline CD5+CD19+ and CD5-CD19+ cell count value is the last pre-dose assessment values performed on Cycle 1 Day 1. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

Baseline and every two months from Month 3 until Month 25 and at every followup (up to 88 months)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	240		
Units: Cells per microliter				
arithmetic mean (standard deviation)				
CD5+CD19+, C2 W9, M3 (n=192, 166)	-284.1 (± 2101.26)	598.6 (± 3155.69)		
CD5+CD19+, C3 W17, M5 (n=185, 169)	52.0 (± 3554.94)	750.5 (± 1995.47)		
CD5+CD19+, C4 W25, M7 (n=170, 152)	-177.6 (± 4105.41)	2102.2 (± 9866.31)		
CD5+CD19+, C5 W33, M9 (n= 168, 147)	-113.6 (± 3336.44)	1905.2 (± 6104.84)		
CD5+CD19+, C6 W41, M11 (n=154, 129)	-450.3 (± 2851.41)	1550.9 (± 5483.76)		
CD5+CD19+, C7 W49, M13 (n=152, 122)	-505.3 (± 2716.66)	1429.2 (± 4408.69)		
CD5+CD19+, C8 W57, M15 (n=137, 108)	-625.9 (± 3003.35)	1107.6 (± 3371.04)		
CD5+CD19+, C9 W65, M17 (n=123, 90)	-649.5 (± 3057.32)	967.0 (± 1826.90)		

CD5+CD19+, C10 W73, M19 (n=120, 89)	-238.6 (± 4061.13)	1146.0 (± 1914.02)		
CD5+CD19+, C11 W81, M21 (n=112, 89)	-579.0 (± 3446.95)	1656.7 (± 2662.28)		
CD5+CD19+, C12 W89, M23, (n=110, 74)	-569.5 (± 3510.43)	1608.3 (± 3220.20)		
CD5+CD19+, C13 W97, M25 (n=100, 64)	-361.3 (± 2702.79)	2059.0 (± 4987.97)		
CD5+CD19+, 3M FU (n=92, 53)	121.1 (± 5479.03)	2143.9 (± 4280.66)		
CD5+CD19+, 6M FU (n=89, 48)	1968.3 (± 15975.52)	2363.5 (± 4937.00)		
CD5+CD19+, 9M FU (n=82, 41)	1411.3 (± 6965.41)	4008.5 (± 13550.03)		
CD5+CD19+, 12M FU (n=74, 35)	2198.5 (± 10743.58)	2316.0 (± 8763.12)		
CD5+CD19+, 15M FU (n=57, 30)	-84.4 (± 4140.77)	1246.2 (± 2894.20)		
CD5+CD19+, 18M FU (n=48, 27)	1844.1 (± 10091.28)	1250.9 (± 3182.14)		
CD5+CD19+, 21M FU (n=42, 24)	-395.1 (± 4521.30)	1147.5 (± 2191.69)		
CD5+CD19+, 24M FU (n=38, 24)	279.4 (± 6250.23)	2354.0 (± 6726.31)		
CD5+CD19+, 27M FU (n=34, 20)	-368.6 (± 4829.16)	2250.8 (± 5833.72)		
CD5+CD19+, 30M FU (n=27, 16)	-354.4 (± 5686.14)	2189.3 (± 6246.05)		
CD5+CD19+, 33M FU (n=23, 14)	-397.0 (± 2767.27)	3024.8 (± 7543.26)		
CD5+CD19+, 36M FU (n=23, 13)	-354.8 (± 2767.77)	3668.4 (± 8581.98)		
CD5+CD19+, 39M FU (n=19, 10)	-163.7 (± 3116.92)	1217.1 (± 2441.59)		
CD5+CD19+, 42M FU (n=16, 9)	-81.7 (± 3426.53)	2005.9 (± 4327.53)		
CD5+CD19+, 45M FU (n=13, 7)	466.9 (± 919.60)	450.4 (± 1031.86)		
CD5+CD19+, 48M FU (n=10, 5)	1255.3 (± 2289.34)	643.4 (± 1270.16)		
CD5+CD19+, 51M FU (n=5, 4)	4341.4 (± 8803.05)	1104.8 (± 2004.49)		
CD5+CD19+, 54M FU (n=5, 2)	1689.8 (± 2357.27)	237.5 (± 251.02)		
CD5+CD19+, 57M FU (n=3, 2)	703.3 (± 898.82)	186.0 (± 145.66)		
CD5+CD19+, 60M FU (n=2, 2)	237.0 (± 326.68)	278.5 (± 392.44)		
CD5+CD19+, withdrawal (n=73, 83)	8916.4 (± 25922.35)	13991.9 (± 23553.42)		
CD5-CD19+, C2 W9, M3 (n=192, 166)	-17.9 (± 588.42)	81.1 (± 781.76)		
CD5-CD19+, C3 W17, M5 (n=185, 169)	5.2 (± 358.12)	50.7 (± 168.87)		
CD5-CD19+, C4 W25, M7 (n=170, 152)	73.9 (± 687.62)	228.2 (± 2037.16)		
CD5-CD19+, C5 W33, M9 (168, 147)	87.5 (± 971.22)	98.9 (± 401.27)		
CD5-CD19+, C6 W41, M11 (n=154, 129)	-13.1 (± 257.81)	92.7 (± 296.23)		
CD5-CD19+, C7 W49, M13 (n=152, 122)	5.3 (± 368.66)	77.5 (± 125.81)		

CD5-CD19+, C8 W57, M15 (n=137, 108)	-13.3 (± 279.89)	95.9 (± 143.95)		
CD5-CD19+, C9 W65, M17 (n=123, 90)	-4.4 (± 349.91)	128.3 (± 294.11)		
CD5-CD19+, C10 W73, M19 (n=120, 89)	3.3 (± 421.97)	172.5 (± 555.27)		
CD5-CD19+, C11 W81, M21 (n=112, 89)	-20.7 (± 303.21)	127.2 (± 150.18)		
CD5-CD19+, C12 W89, M23 (n= 110, 74)	-13.5 (± 306.57)	143.7 (± 251.88)		
CD5-CD19+, C13 W97, M25 (100, 64)	7.9 (± 103.85)	184.0 (± 403.97)		
CD5-CD19+, 3M FU (n=92, 53)	27.4 (± 522.67)	145.7 (± 229.93)		
CD5-CD19+, 6M FU (n=89, 48)	22.6 (± 428.70)	153.8 (± 330.63)		
CD5-CD19+, 9M FU (n=82, 41)	13.2 (± 368.63)	140.9 (± 107.92)		
CD5-CD19+, 12M FU (n=74, 35)	86.4 (± 769.73)	147.2 (± 136.93)		
CD5-CD19+, 15M FU (n=57, 30)	10.8 (± 393.47)	154.8 (± 120.86)		
CD5-CD19+, 18M FU (n=48, 27)	84.7 (± 146.38)	173.5 (± 142.95)		
CD5-CD19+, 21M FU (n=42, 24)	16.2 (± 450.95)	175.9 (± 158.31)		
CD5-CD19+, 24M FU (n=38, 24)	574.7 (± 2993.58)	223.2 (± 200.06)		
CD5-CD19+, 27M FU (n=34, 20)	102.0 (± 643.44)	153.3 (± 110.37)		
CD5-CD19+, 30M FU (n=27, 16)	38.7 (± 271.84)	142.9 (± 106.57)		
CD5-CD19+, 33M FU (n=23, 14)	98.3 (± 117.18)	157.5 (± 96.69)		
CD5-CD19+, 36M FU (n=23, 13)	141.1 (± 179.33)	215.2 (± 298.90)		
CD5-CD19+, 39M FU (n=19, 10)	134.3 (± 167.33)	183.9 (± 249.78)		
CD5-CD19+, 42M FU (n=16, 9)	113.3 (± 131.48)	361.1 (± 601.36)		
CD5-CD19+, 45M FU (n=13, 7)	108.6 (± 140.97)	157.7 (± 116.04)		
CD5-CD19+, 48M FU (n=10, 5)	147.7 (± 185.10)	180.6 (± 175.93)		
CD5-CD19+, 51M FU (n=5, 4)	162.6 (± 229.87)	139.3 (± 82.75)		
CD5-CD19+, 54M FU (n=5, 2)	221.2 (± 217.75)	315.0 (± 43.84)		
CD5-CD19+, 57M FU (n=3, 2)	138.3 (± 196.32)	195.5 (± 17.68)		
CD5-CD19+, 60M FU (n=2, 2)	180.5 (± 222.74)	127.0 (± 173.95)		
CD5-CD19+, withdrawal (n=73, 83)	593.5 (± 2028.89)	552.7 (± 1799.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of covariates to compute cox proportional hazards regression model for relationship between investigator assessed progression-free survival and the indicated prognostic markers

End point title	Summary of covariates to compute cox proportional hazards regression model for relationship between investigator assessed progression-free survival and the indicated prognostic markers

End point description:

Blood samples were collected for the assessment of the following prognostic markers at Baseline (BL) and upon relapse: immunoglobulin heavy chain variable region (IgVH) mutational status; VH3-21 usage; Cytogenetics (by fluorescent in situ hybridization [FISH]) including 6q-, 11q-, +12q, 17p-, 13q- deletions; beta 2 microglobulin. Cox-regression model was used to explore the relationship between progression-free survival and the following explanatory variables: treatment group, cytogenetics (analyzed by FISH) at BL, IgVH mutational status at BL, beta 2 microglobulin at BL, BL CD20 and BL complement level. For each covariate, a hazard ratio <1 indicates a lower risk on the first effect tested compared with the other effects tested. Cytogenetics Group (based on >=20%)=CY G.

End point type	Secondary

End point timeframe:

From Baseline until the end of the study (up to 79 months)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	240		
Units: Participants				
CY G: 6q- or +12q or 13q	36	12		
CY G: 17p-	7	4		
CY G: 11q-	11	10		
CY G: no aberration	166	181		
CY G: missing	20	33		
B2 Microglobulin G 2: > 3500 µg/L	80	68		
B2 Microglobulin G 2: <=3500 µg/L	157	171		
B2 Microglobulin G 2: missing	3	1		
IgVH Mutational Status 1: mutated	54	74		
IgVH Mutational Status 1: unmutated	139	116		
IgVH Mutational Status 1: not available	3	1		
IgVH Mutational Status 1: missing	44	49		
VH3-21 Usage Flag: Yes	7	7		
VH3-21 Usage Flag: No	233	233		

Statistical analyses

Statistical analysis title	Cox proportional hazards regression model
Comparison groups	Ofatumumab v Observation

Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.547
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.051
upper limit	2.276

Statistical analysis title	Cox proportional hazards regression model
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	9.303
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.934
upper limit	17.54

Statistical analysis title	Cox proportional hazards regression model
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	4.219
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.468
upper limit	7.21

Statistical analysis title	Cox proportional hazards regression model
Comparison groups	Ofatumumab v Observation

Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.832
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.434
upper limit	2.339

Statistical analysis title	Cox proportional hazards regression model
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.573
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.432
upper limit	0.76

Statistical analysis title	Cox proportional hazards regression model
Comparison groups	Ofatumumab v Observation
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.301
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.692
upper limit	2.448

Secondary: Cmax and Ctrough of ofatumumab

End point title	Cmax and Ctrough of ofatumumab

End point description:

Blood samples were collected to assess the plasma concentration of ofatumumab. Maximum concentration (Cmax) and observed drug concentration prior to the next dose (Ctrough) were determined. Blood samples were collected at pre-dose and 0.5 hours after the end of the infusion at treatment on Month 1 Week 1 (Day 1), Month 1 Week 2 (Day 8), and at every second infusion.

End point type	Secondary

End point timeframe:

Day 1 of Month 1 (Cycle 1 Week 1); Day 8 of Month 1 (Cycle 1 Week 2); and Month 7 (Cycle 4)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	0[25]		
Units: micrograms per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
Cmax, Cycle 1 Week 1	73.8 (± 65)	()		
Cmax, Cycle 1 Week 2	264 (± 50)	()		
Cmax, Cycle 4	275 (± 31)	()		
Ctrough, Cycle 1 Week 2	16.3 (± 254)	()		
Ctrough, Cycle 4	9.9 (± 1323)	()		

Notes:

[25] - analysis not done for this group

Statistical analyses

No statistical analyses for this end point

Secondary: Total plasma clearance (CL) of ofatumumab

End point title	Total plasma clearance (CL) of ofatumumab

End point description:

Plasma clearance is defined as the plasma volume that is cleared of drug per unit of time.

End point type	Secondary

End point timeframe:

Day 1 of Month 1 (Cycle 1 Week 1); Day 8 of Month 1 (Cycle 1 Week 2); and Month 7 (Cycle 4)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	0[26]		
Units: millileters per hour (mL/hour)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Week 1	49.1 (± 38)	()		
Cycle 1 Week 2	9.6 (± 43)	()		
Cycle 4	8.1 (± 50)	()		

Notes:

[26] - analysis not done for this group.

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-tau) of ofatumumab

End point title	AUC(0-tau) of ofatumumab

End point description:

Area under the concentration time curve over the dosing interval (AUC[0-tau]) is a measure of the drug exposure over time.

End point type	Secondary

End point timeframe:

Day 1 of Month 1 (Cycle 1 Week 1); Day 8 of Month 1 (Cycle 1 Week 2); and Month 7 (Cycle 4)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	0[27]		
Units: micrograms*hour per mL (µg*hour/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Week 1	6113 (± 38)	()		
Cycle 1 Week 2	104013 (± 43)	()		
Cycle 4	122782 (± 50)	()		

Notes:

[27] - analysis not done for this group.

Statistical analyses

No statistical analyses for this end point

Secondary: Vss of ofatumumab

End point title	Vss of ofatumumab

End point description:

Volume of distribution at steady state (Vss) is defined as the apparent volume of distribution of a drug between plasma and the rest of the body at steady state. Data from all time points collected were used to calculate one Vss value for each individual.

End point type	Secondary

End point timeframe:

Day 1 Month 1 (Cycle 1) through Month 7 (Cycle 4)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	0[28]		
Units: Liters (L)				
geometric mean (geometric coefficient of variation)	6.0 (± 27)	()		

Notes:

[28] - analysis not done for this group.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma half-life (t1/2) of ofatumumab

End point title	Plasma half-life (t1/2) of ofatumumab

End point description:

The terminal half life (t1/2) of ofatumumab is defined as the time required for the plasma concentration of ofatumumab to reach half of its original value.

End point type	Secondary

End point timeframe:

Day 1 of Month 1 (Cycle 1 Week 1); Day 8 of Month 1 (Cycle 1 Week 2); and Month 7 (Cycle 4)

End point values	Ofatumumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	0[29]		
Units: hours				
geometric mean (geometric coefficient of variation)				
Cycle 1 Week 1	126 (± 35)	()		
Cycle 1 Week 2	458 (± 36)	()		
Cycle 4	542 (± 48)	()		

Notes:

[29] - analysis not done for this group.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study medication until 60 days after the last dose of study medication or until the last observation at Visit 14 for AEs (up to 26 months) and until end of study for SAEs (88 months).

Adverse event reporting additional description:

All cause mortality (deaths) was collected for as long as participants could be contacted from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV) up to a maximum of 88 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Ofatumumab

Reporting group description:

Ofatumumab Participants with relapsed CLL received IV infusions of ofatumumab on Day 1 (300 mg) and Day 8 (1000 mg) in the first cycle, followed by infusions of 1000 mg every 2 months for up to 2 years following the first 1000 mg dose.

Reporting group title	Observation

Reporting group description:

Participants with relapsed CLL received no treatment and were under observation for up to 2 years.

Reporting group title	Total

Reporting group description:

All Patients

Serious adverse events	Ofatumumab	Observation	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	120 / 239 (50.21%)	120 / 241 (49.79%)	240 / 480 (50.00%)
number of deaths (all causes)	88	87	175
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma gastric			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			

subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaplastic large cell lymphoma T- and null-cell types			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	2 / 239 (0.84%)	1 / 241 (0.41%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Brain neoplasm malignant			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extraskeletal myxoid chondrosarcoma			

subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal carcinoma			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hodgkin's disease			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma metastatic			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	2 / 239 (0.84%)	0 / 241 (0.00%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	2 / 239 (0.84%)	1 / 241 (0.41%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Metastases to central nervous system			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			

subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Myelodysplastic syndrome			
subjects affected / exposed	2 / 239 (0.84%)	2 / 241 (0.83%)	4 / 480 (0.83%)
occurrences causally related to treatment / all	1 / 3	0 / 2	1 / 5
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Neoplasm malignant			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	2 / 239 (0.84%)	0 / 241 (0.00%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Prostate cancer			
subjects affected / exposed	1 / 239 (0.42%)	2 / 241 (0.83%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Rectal cancer			

subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Refractory anaemia with an excess of blasts			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal neoplasm			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Richter's syndrome			
subjects affected / exposed	0 / 239 (0.00%)	2 / 241 (0.83%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin cancer			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Spinal meningioma benign			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	3 / 239 (1.26%)	1 / 241 (0.41%)	4 / 480 (0.83%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
T-cell lymphoma			

subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	2 / 239 (0.84%)	1 / 241 (0.41%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery aneurysm			
subjects affected / exposed	2 / 239 (0.84%)	1 / 241 (0.41%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venoocclusive disease			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			

Allogenic bone marrow transplantation therapy			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract operation			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastectomy			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septal operation			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 239 (0.00%)	2 / 241 (0.83%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Condition aggravated			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	4 / 239 (1.67%)	3 / 241 (1.24%)	7 / 480 (1.46%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 3	0 / 3	0 / 6
Malaise			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Non-cardiac chest pain			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	19 / 239 (7.95%)	18 / 241 (7.47%)	37 / 480 (7.71%)
occurrences causally related to treatment / all	3 / 31	0 / 20	3 / 51
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Acute graft versus host disease in skin			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Allergy to arthropod bite			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Allergy to immunoglobulin therapy			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 239 (0.84%)	0 / 241 (0.00%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alveolitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asphyxia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Bronchiectasis			

subjects affected / exposed	2 / 239 (0.84%)	1 / 241 (0.41%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 239 (0.42%)	2 / 241 (0.83%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 239 (0.84%)	4 / 241 (1.66%)	6 / 480 (1.25%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Epistaxis			
subjects affected / exposed	2 / 239 (0.84%)	2 / 241 (0.83%)	4 / 480 (0.83%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiccups			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 239 (0.00%)	2 / 241 (0.83%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Interstitial lung disease			
subjects affected / exposed	2 / 239 (0.84%)	0 / 241 (0.00%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			

subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 239 (0.42%)	2 / 241 (0.83%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pulmonary embolism			
subjects affected / exposed	2 / 239 (0.84%)	2 / 241 (0.83%)	4 / 480 (0.83%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Respiratory disorder			

subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 239 (0.00%)	2 / 241 (0.83%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychomotor retardation			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			

Device dislocation			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthroscopy			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calcium ionised increased			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Capillary permeability increased			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart rate irregular			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	2 / 239 (0.84%)	0 / 241 (0.00%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Platelet count decreased			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dislocation of vertebra			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face injury			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 239 (0.42%)	2 / 241 (0.83%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 239 (0.42%)	2 / 241 (0.83%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 239 (0.42%)	2 / 241 (0.83%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Humerus fracture			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle strain			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	3 / 239 (1.26%)	3 / 241 (1.24%)	6 / 480 (1.25%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 3
Upper limb fracture			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound secretion			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			

subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 239 (0.84%)	2 / 241 (0.83%)	4 / 480 (0.83%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 239 (0.42%)	2 / 241 (0.83%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 3
Cardiac failure			
subjects affected / exposed	3 / 239 (1.26%)	2 / 241 (0.83%)	5 / 480 (1.04%)
occurrences causally related to treatment / all	0 / 8	0 / 2	0 / 10
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 4
Cardiac failure acute			

subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 239 (0.42%)	3 / 241 (1.24%)	4 / 480 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Myocardial ischaemia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Carotid artery stenosis			

subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cerebrovascular accident			
subjects affected / exposed	0 / 239 (0.00%)	2 / 241 (0.83%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Depressed level of consciousness			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	2 / 239 (0.84%)	0 / 241 (0.00%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic neuropathy			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	5 / 239 (2.09%)	7 / 241 (2.90%)	12 / 480 (2.50%)
occurrences causally related to treatment / all	0 / 5	0 / 7	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 239 (0.42%)	2 / 241 (0.83%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	18 / 239 (7.53%)	10 / 241 (4.15%)	28 / 480 (5.83%)
occurrences causally related to treatment / all	6 / 21	0 / 11	6 / 32
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic anaemia			
subjects affected / exposed	2 / 239 (0.84%)	1 / 241 (0.41%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenic purpura			

subjects affected / exposed	2 / 239 (0.84%)	0 / 241 (0.00%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	5 / 239 (2.09%)	5 / 241 (2.07%)	10 / 480 (2.08%)
occurrences causally related to treatment / all	6 / 7	0 / 5	6 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 239 (0.42%)	3 / 241 (1.24%)	4 / 480 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenic purpura			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness			

subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo positional			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Colitis			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 239 (0.00%)	2 / 241 (0.83%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			

subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	2 / 239 (0.84%)	0 / 241 (0.00%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eosinophilic colitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal infarction			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Intestinal obstruction			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			

subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal spasm			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	2 / 239 (0.84%)	0 / 241 (0.00%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Small intestinal perforation			

subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			

subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Hepatic failure			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Hepatotoxicity			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema multiforme			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin lesion			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 239 (0.84%)	0 / 241 (0.00%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			

subjects affected / exposed	0 / 239 (0.00%)	2 / 241 (0.83%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 239 (0.42%)	2 / 241 (0.83%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			

subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporotic fracture			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute sinusitis			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspergillus infection			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial disease carrier			

subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blastocystis infection			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	4 / 239 (1.67%)	3 / 241 (1.24%)	7 / 480 (1.46%)
occurrences causally related to treatment / all	2 / 4	0 / 3	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 239 (0.42%)	5 / 241 (2.07%)	6 / 480 (1.25%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Campylobacter colitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 239 (0.84%)	5 / 241 (2.07%)	7 / 480 (1.46%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			

subjects affected / exposed	2 / 239 (0.84%)	0 / 241 (0.00%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus viraemia			
subjects affected / exposed	0 / 239 (0.00%)	2 / 241 (0.83%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	2 / 239 (0.84%)	0 / 241 (0.00%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis enterococcal			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterobacter bacteraemia			

subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterobacter sepsis			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal sepsis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis viral			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiglottitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			

subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal fungal infection			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genital herpes			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes virus infection			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	3 / 239 (1.26%)	4 / 241 (1.66%)	7 / 480 (1.46%)
occurrences causally related to treatment / all	2 / 3	0 / 4	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster disseminated			

subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster oticus			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	4 / 239 (1.67%)	1 / 241 (0.41%)	5 / 480 (1.04%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral discitis			
subjects affected / exposed	1 / 239 (0.42%)	2 / 241 (0.83%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JC virus infection			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leishmaniasis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Listeria sepsis			

subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Listeriosis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 8	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	5 / 239 (2.09%)	3 / 241 (1.24%)	8 / 480 (1.67%)
occurrences causally related to treatment / all	1 / 5	0 / 4	1 / 9
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Meningitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis bacterial			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis pneumococcal			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucormycosis			

subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mycobacterial infection			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroborreliosis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Nocardiosis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media acute			

subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parvovirus infection			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital cellulitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirectal abscess			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	2 / 239 (0.84%)	0 / 241 (0.00%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal bacteraemia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal sepsis			
subjects affected / exposed	0 / 239 (0.00%)	2 / 241 (0.83%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	2 / 239 (0.84%)	1 / 241 (0.41%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	2 / 2	0 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	37 / 239 (15.48%)	35 / 241 (14.52%)	72 / 480 (15.00%)
occurrences causally related to treatment / all	14 / 49	0 / 54	14 / 103
deaths causally related to treatment / all	0 / 5	0 / 6	0 / 11
Pneumonia bacterial			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pneumonia streptococcal			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Post procedural cellulitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural pneumonia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Post procedural sepsis			

subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative abscess			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pseudomonas infection			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	2 / 239 (0.84%)	0 / 241 (0.00%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Respiratory tract infection			
subjects affected / exposed	4 / 239 (1.67%)	4 / 241 (1.66%)	8 / 480 (1.67%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 9
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Sepsis			
subjects affected / exposed	8 / 239 (3.35%)	5 / 241 (2.07%)	13 / 480 (2.71%)
occurrences causally related to treatment / all	1 / 9	0 / 5	1 / 14
deaths causally related to treatment / all	0 / 5	0 / 1	0 / 6
Septic shock			
subjects affected / exposed	5 / 239 (2.09%)	3 / 241 (1.24%)	8 / 480 (1.67%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 8
deaths causally related to treatment / all	0 / 4	0 / 3	0 / 7
Sinusitis			

subjects affected / exposed	3 / 239 (1.26%)	2 / 241 (0.83%)	5 / 480 (1.04%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Staphylococcal infection			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	4 / 239 (1.67%)	2 / 241 (0.83%)	6 / 480 (1.25%)
occurrences causally related to treatment / all	2 / 5	0 / 2	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 239 (1.26%)	5 / 241 (2.07%)	8 / 480 (1.67%)
occurrences causally related to treatment / all	1 / 3	0 / 5	1 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			

subjects affected / exposed	1 / 239 (0.42%)	1 / 241 (0.41%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster virus infection			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 239 (0.42%)	2 / 241 (0.83%)	3 / 480 (0.63%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glucose tolerance impaired			
subjects affected / exposed	1 / 239 (0.42%)	0 / 241 (0.00%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			

subjects affected / exposed	0 / 239 (0.00%)	2 / 241 (0.83%)	2 / 480 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypermetabolism			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 241 (0.41%)	1 / 480 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Ofatumumab	Observation	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	202 / 239 (84.52%)	139 / 241 (57.68%)	341 / 480 (71.04%)
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	42 / 239 (17.57%)	0 / 241 (0.00%)	42 / 480 (8.75%)
occurrences (all)	67	0	67
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 239 (9.62%)	7 / 241 (2.90%)	30 / 480 (6.25%)
occurrences (all)	28	9	37
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	61 / 239 (25.52%)	22 / 241 (9.13%)	83 / 480 (17.29%)
occurrences (all)	105	24	129
Thrombocytopenia			
subjects affected / exposed	13 / 239 (5.44%)	11 / 241 (4.56%)	24 / 480 (5.00%)
occurrences (all)	15	11	26
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	33 / 239 (13.81%)	22 / 241 (9.13%)	55 / 480 (11.46%)
occurrences (all)	36	22	58
Oedema peripheral			
subjects affected / exposed	12 / 239 (5.02%)	10 / 241 (4.15%)	22 / 480 (4.58%)
occurrences (all)	14	10	24
Pyrexia			
subjects affected / exposed	41 / 239 (17.15%)	23 / 241 (9.54%)	64 / 480 (13.33%)
occurrences (all)	56	27	83
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	12 / 239 (5.02%)	2 / 241 (0.83%)	14 / 480 (2.92%)
occurrences (all)	12	2	14
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	13 / 239 (5.44%)	11 / 241 (4.56%)	24 / 480 (5.00%)
occurrences (all)	14	11	25
Diarrhoea			
subjects affected / exposed	41 / 239 (17.15%)	13 / 241 (5.39%)	54 / 480 (11.25%)
occurrences (all)	47	14	61
Nausea			
subjects affected / exposed	13 / 239 (5.44%)	8 / 241 (3.32%)	21 / 480 (4.38%)
occurrences (all)	15	8	23
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	58 / 239 (24.27%)	28 / 241 (11.62%)	86 / 480 (17.92%)
occurrences (all)	71	37	108
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	23 / 239 (9.62%)	9 / 241 (3.73%)	32 / 480 (6.67%)
occurrences (all)	29	10	39
Rash			
subjects affected / exposed	26 / 239 (10.88%)	10 / 241 (4.15%)	36 / 480 (7.50%)
occurrences (all)	27	10	37
Psychiatric disorders			
Insomnia			

subjects affected / exposed	14 / 239 (5.86%)	6 / 241 (2.49%)	20 / 480 (4.17%)
occurrences (all)	17	7	24
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	20 / 239 (8.37%)	12 / 241 (4.98%)	32 / 480 (6.67%)
occurrences (all)	23	14	37
Back pain			
subjects affected / exposed	15 / 239 (6.28%)	12 / 241 (4.98%)	27 / 480 (5.63%)
occurrences (all)	16	12	28
Infections and infestations			
Bronchitis			
subjects affected / exposed	21 / 239 (8.79%)	17 / 241 (7.05%)	38 / 480 (7.92%)
occurrences (all)	28	23	51
Herpes zoster			
subjects affected / exposed	14 / 239 (5.86%)	8 / 241 (3.32%)	22 / 480 (4.58%)
occurrences (all)	16	8	24
Influenza			
subjects affected / exposed	16 / 239 (6.69%)	10 / 241 (4.15%)	26 / 480 (5.42%)
occurrences (all)	18	12	30
Nasopharyngitis			
subjects affected / exposed	22 / 239 (9.21%)	22 / 241 (9.13%)	44 / 480 (9.17%)
occurrences (all)	27	29	56
Pneumonia			
subjects affected / exposed	17 / 239 (7.11%)	11 / 241 (4.56%)	28 / 480 (5.83%)
occurrences (all)	28	11	39
Respiratory tract infection			
subjects affected / exposed	17 / 239 (7.11%)	15 / 241 (6.22%)	32 / 480 (6.67%)
occurrences (all)	19	18	37
Rhinitis			
subjects affected / exposed	14 / 239 (5.86%)	4 / 241 (1.66%)	18 / 480 (3.75%)
occurrences (all)	15	4	19
Sinusitis			
subjects affected / exposed	22 / 239 (9.21%)	9 / 241 (3.73%)	31 / 480 (6.46%)
occurrences (all)	25	11	36
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	52 / 239 (21.76%) 75	26 / 241 (10.79%) 40	78 / 480 (16.25%) 115

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2009	Addition of baseline MRD, exploratory endpoints, post-PD PRO and clarifications.
21 May 2010	Added study name and clarifications, modified I/E
07 February 2013	At the request of the French regulatory agency related information from the Study Procedures Manual (SPM) was added into Section 6.4.6
17 December 2013	FDA request for additional HBV information and protocol clarifications
26 August 2014	As the significance level was met at the interim analysis of efficacy, further enrollment in the study was discontinued.
01 April 2016	References to GlaxoSmithKline or its staff were replaced with that of Novartis and its authorized agents to align with the change of sponsorship

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: