Clinical trial results:
A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study To Evaluate the Efficacy and Safety of Ocrelizumab in Comparison to Interferon Beta-1a (Rebif) in Patients with Relapsing Multiple Sclerosis

Summary

EudraCT number	2010-020315-36
Trial protocol	SK BE SE DE ES GB BG FR IE IT CZ
Global end of trial date	30 December 2022

Results information

Result version number	v2 (current)
This version publication date	03 January 2024
First version publication date	03 June 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	WA21093

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01412333
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4070
Public contact	F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd, +41 616878333, global.trial_information@roche.com
Scientific contact	Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This randomized, double-blind, double-dummy, parallel-group study evaluated the efficacy and safety of ocrelizumab in comparison with interferon beta-1a (Rebif) in participants with relapsing multiple sclerosis. Participants were randomized to receive either ocrelizumab 600 mg or matching placebo intravenous (IV) as 300 mg infusions on Days 1 and 15 for the first dose and as a single infusion of 600 mg for all subsequent infusions every 24 weeks, with placebo injections matching interferon beta-1a SC three times per week; or interferon beta-1a 44 mcg SC injections three times per week (with placebo infusions matching ocrelizumab infusions every 24 weeks).

Protection of trial subjects:

his study was conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. All participants were required to read and sign an informed consent form prior to participation in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 September 2011
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	Slovakia: 18
Country: Number of subjects enrolled	Sweden: 17
Country: Number of subjects enrolled	Türkiye: 13
Country: Number of subjects enrolled	Ukraine: 31
Country: Number of subjects enrolled	United States: 228
Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Bulgaria: 18
Country: Number of subjects enrolled	Bosnia and Herzegovina: 6
Country: Number of subjects enrolled	Belarus: 15
Country: Number of subjects enrolled	Brazil: 10
Country: Number of subjects enrolled	Canada: 84
Country: Number of subjects enrolled	Czechia: 16
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Spain: 52
Country: Number of subjects enrolled	France: 8

Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Croatia: 19
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Mexico: 31
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Poland: 139
Country: Number of subjects enrolled	Russian Federation: 43
Worldwide total number of subjects	835
EEA total number of subjects	356

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)	835
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1045 participants were screened for entry into the study. Of these, 210 participants failed screening; the main reasons were failure to meet the inclusion/exclusion criteria or unacceptable laboratory values. A total of 835 participants were enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Interferon beta-1a 44 mcg SC

Arm description:

Interferon beta-1a 44 mcg SC injections three times per week (with placebo infusions matching ocrelizumab infusions every 24 weeks).

Arm type	Placebo
Investigational medicinal product name	Interferon beta-1a
Investigational medicinal product code	
Other name	Rebif
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Interferon beta-1a 44 mcg SC injections three times per week (with placebo infusions matching ocrelizumab infusions every 24 weeks).

Investigational medicinal product name	Ocrelizumab
Investigational medicinal product code	
Other name	RO4964913
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During the OLE phase, all participants received ocrelizumab 600-mg IV infusion every 24 weeks.

Investigational medicinal product name	Ocrelizumab-matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo infusions matching ocrelizumab infusions every 24 week

Arm title	Ocrelizumab

Arm description:

Ocrelizumab 600 mg or matching placebo intravenous (IV) as 300 mg infusions on Days 1 and 15 for the first dose and as a single infusion of 600 mg for all subsequent infusions every 24 weeks, with placebo injections matching interferon beta-1a SC three times per week.

Arm type	Experimental

Investigational medicinal product name	Interferon beta-1a-matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo injections matching interferon beta-1a SC three times per week.

Investigational medicinal product name	Ocrelizumab
Investigational medicinal product code	
Other name	RO4964913
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ocrelizumab 600 mg or matching placebo intravenous (IV) as 300 mg infusions on Days 1 and 15 for the first dose and as a single infusion of 600 mg for all subsequent infusions every 24 weeks, with placebo injections matching interferon beta-1a SC three times per week. During the OLE phase, all participants received ocrelizumab 600-mg IV infusion every 24 weeks. During the OLE phase, all participants received ocrelizumab 600-mg IV infusion every 24 weeks.

Number of subjects in period 1	Interferon beta-1a 44 mcg SC	Ocrelizumab
Started	418	417
Completed	229	225
Not completed	189	192
Adverse event, serious fatal	5	6
Physician decision	11	16
Missing	1	3
Non-Compliance	3	7
Consent withdrawn by subject	51	54
Adverse event, non-fatal	40	42
Study Terminated By Sponsor	3	2
Non-Compliance With Study Drug	1	1
Not Specified	30	33
Pregnancy	6	4
Lost to follow-up	15	12
Lack of efficacy	22	10
Protocol deviation	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Interferon beta-1a 44 mcg SC
Reporting group description:	
Interferon beta-1a 44 mcg SC injections three times per week (with placebo infusions matching ocrelizumab infusions every 24 weeks).	
Reporting group title	Ocrelizumab
Reporting group description:	
Ocrelizumab 600 mg or matching placebo intravenous (IV) as 300 mg infusions on Days 1 and 15 for the first dose and as a single infusion of 600 mg for all subsequent infusions every 24 weeks, with placebo injections matching interferon beta-1a SC three times per week.	

Reporting group values	Interferon beta-1a 44 mcg SC	Ocrelizumab	Total
Number of subjects	418	417	835
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	418	417	835
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	37.4	37.2	
standard deviation	± 9.0	± 9.1	-
Sex: Female, Male Units:			
Female	280	271	551
Male	138	146	284
Race Units: Subjects			
American Indian or Alaska Native	4	1	5
Asian	2	2	4
Black or African American	20	22	42
White	382	368	750
Native Hawaiian or other Pacific Islander	0	1	1
Other	9	19	28
Multiple	1	4	5
Ethnicity Units: Subjects			
Hispanic or Latino	49	56	105
Not Hispanic or Latino	340	336	676

Not Stated	29	25	54

End points

End points reporting groups

Reporting group title	Interferon beta-1a 44 mcg SC
Reporting group description:	
Interferon beta-1a 44 mcg SC injections three times per week (with placebo infusions matching ocrelizumab infusions every 24 weeks).	
Reporting group title	Ocrelizumab
Reporting group description:	
Ocrelizumab 600 mg or matching placebo intravenous (IV) as 300 mg infusions on Days 1 and 15 for the first dose and as a single infusion of 600 mg for all subsequent infusions every 24 weeks, with placebo injections matching interferon beta-1a SC three times per week.	
Subject analysis set title	Interferon Beta-1a + Placebo (Open Label Extension)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
During the OLE phase, all participants received ocrelizumab 600-mg IV infusion every 24 weeks.	
Subject analysis set title	Ocrelizumab + Placebo (Open Label Extension)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
During the OLE phase, all participants received ocrelizumab 600-mg IV infusion every 24 weeks.	

Primary: Annualized Relapse Rate (ARR) in Participants With Relapsing Multiple Sclerosis (MS) at 96 Weeks

End point title	Annualized Relapse Rate (ARR) in Participants With Relapsing Multiple Sclerosis (MS) at 96 Weeks
End point description:	
ARR was protocol-defined and calculated as the total number of relapses for all participants in the treatment group divided by the total participant-years of exposure to that treatment.	
End point type	Primary
End point timeframe:	
Week 96	

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	418	417		
Units: relapses/participant year of treatment				
number (confidence interval 95%)	0.290 (0.234 to 0.361)	0.155 (0.121 to 0.198)		

Statistical analyses

Statistical analysis title	Adjusted by Geographical Region and baseline EDSS
Statistical analysis description:	
Adjusted by Geographical Region (US vs. Rest of World) and baseline EDSS (<4.0 vs. >=4.0).	
Comparison groups	Interferon beta-1a 44 mcg SC v Ocrelizumab

Number of subjects included in analysis	835
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Negative Binomial Model
Parameter estimate	Rate Ratio
Point estimate	0.532
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.397
upper limit	0.714

Secondary: Number of T1 Gadolinium (Gd)-Enhancing Lesions as Detected by Brain Magnetic Resonance Imaging (MRI) During the Double-Blind Treatment

End point title	Number of T1 Gadolinium (Gd)-Enhancing Lesions as Detected by Brain Magnetic Resonance Imaging (MRI) During the Double-Blind Treatment

End point description:

The total number of T1 gadolinium-enhancing lesions for all participants in the treatment group was calculated as the sum of the individual number of lesions at Weeks 24, 48, and 96.

End point type	Secondary

End point timeframe:

Baseline up to week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	418	417		
Units: lesions	465	21		

Statistical analyses

Statistical analysis title	Negative Binomial Model
Comparison groups	Interferon beta-1a 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	835
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Negative Binomial Model
Parameter estimate	Adjusted rate ratio
Point estimate	0.051

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.029
upper limit	0.089

Secondary: Time to Onset of Confirmed Disability Progression (CDP) for at Least 12 Weeks During the Double-Blind Treatment Period

End point title	Time to Onset of Confirmed Disability Progression (CDP) for at Least 12 Weeks During the Double-Blind Treatment Period

End point description:

Disability progression was defined as an increase in the Expanded Disability Status Scale (EDSS) score of: A) >=1.0 point from the baseline EDSS score when the baseline score was less than or equal to (<=) 5.5 B) >=0.5 point from the baseline EDSS score when the baseline score was >5.5 The EDSS scale ranges from 0 (normal neurological exam) to 10 (death due to multiple sclerosis). This outcome measure was considered confirmatory only when results of both studies WA21092 and WA21093 were combined. Disability progression was considered confirmed when the increase in the EDSS was confirmed at a regularly scheduled visit at least 12 weeks after the initial documentation of neurological worsening. Participants who had initial disability progression with no confirmatory EDSS assessment and who were on treatment at time of clinical cut-off date were censored at the date of their last EDSS assessment.

End point type	Secondary

End point timeframe:

Week 104

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	418[1]	417[2]		
Units: weeks				
median (full range (min-max))	0000 (0 to 102)	0000 (0 to 104)		

Notes:

[1] - Not achieved due to low number of participants with events.

[2] - Not achieved due to low number of participants with events.

Statistical analyses

Statistical analysis title	Time to onset of CDP at week 12
Comparison groups	Interferon beta-1a 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	835
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0169
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.92

Secondary: Number of New, and/or Enlarging T2 Hyperintense Lesions as Detected by Brain Magnetic Resonance Imaging (MRI) During the Double Blind Treatment

End point title	Number of New, and/or Enlarging T2 Hyperintense Lesions as Detected by Brain Magnetic Resonance Imaging (MRI) During the Double Blind Treatment

End point description:

The total number of new and/or enlarging T2 lesions for all participants in the treatment group was calculated as the sum of the individual number of lesions at Weeks 24, 48, and 96.

End point type	Secondary

End point timeframe:

Baseline up to week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	418	417		
Units: lesions	2103	380		

Statistical analyses

Statistical analysis title	Negative Binomial Model
Comparison groups	Interferon beta-1a 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	835
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Negative Binomial Model
Parameter estimate	Adjusted rate ratio
Point estimate	0.171
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	0.225

Secondary: Percentage of Participants With Confirmed Disability Improvement

(CDI) for at Least 12 Weeks	
End point title	Percentage of Participants With Confirmed Disability Improvement (CDI) for at Least 12 Weeks

End point description:

Disability improvement was assessed only for the subgroup of participants with a baseline EDSS score of >= 2.0. It was defined as a reduction in EDSS score of: A) >=1.0 from the baseline EDSS score when the baseline score was >=2 and <=5.5 B) >= 0.5 when the baseline EDSS score > 5.5. The EDSS scale ranges from 0 (normal neurological exam) to 10 (death due to multiple sclerosis). This outcome measure was considered confirmatory only when results of both studies WA21092 and WA21093 were combined.

End point type	Secondary

End point timeframe:

Week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	318		
Units: percentage of participants				
number (confidence interval 95%)	18.83 (14.62 to 23.65)	21.38 (17.01 to 26.30)		

Statistical analyses

Statistical analysis title	CMH Chi-Squared test (stratified)
Comparison groups	Interferon beta-1a 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	626
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4019
Method	CMH Chi-Squared test (stratified)
Parameter estimate	Relative risk (stratified)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.56

Secondary: Number of T1 Hypointense Lesions During the Double-Blind Treatment	
End point title	Number of T1 Hypointense Lesions During the Double-Blind Treatment

End point description:

The total number of new T1-Hypo-Intense Lesions (Chronic Black Holes) for all participants in the treatment group was calculated as the sum of the individual number of new lesions at Weeks 24, 48, and 96.

End point type	Secondary
End point timeframe:	
Baseline up to week 96	

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	418	417		
Units: lesions	1484	567		

Statistical analyses

Statistical analysis title	Negative Binomial Model
Comparison groups	Interferon beta-1a 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	835
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Negative Binomial Model
Parameter estimate	Adjusted rate ratio
Point estimate	0.357
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.272
upper limit	0.47

Secondary: Time to Onset of Confirmed Disability Progression (CDP) for at Least 24 Weeks During the Double-Blind Treatment Period

End point title	Time to Onset of Confirmed Disability Progression (CDP) for at Least 24 Weeks During the Double-Blind Treatment Period

End point description:

Disability progression was defined as an increase in the Expanded Disability Status Scale (EDSS) score of: A) >=1.0 point from the baseline EDSS score when the baseline score was less than or equal to (<=) 5.5 B) >=0.5 point from the baseline EDSS score when the baseline score was >5.5 The EDSS scale ranges from 0 (normal neurological exam) to 10 (death due to multiple sclerosis). This outcome measure was considered confirmatory only when results of both studies WA21092 and WA21093 were combined. Disability progression was considered confirmed when the increase in the EDSS was confirmed at a regularly scheduled visit at least 24 weeks after the initial documentation of neurological worsening. Participants who had initial disability progression with no confirmatory EDSS assessment and who were on treatment at time of clinical cut-off date were censored at the date of their last EDSS assessment.

End point type	Secondary
End point timeframe:	
Week 104	

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	418[3]	417[4]		
Units: weeks				
median (full range (min-max))	0000 (0 to 102)	0000 (0 to 104)		

Notes:

[3] - Not achieved due to low number of participants with events.

[4] - Not achieved due to low number of participants with events.

Statistical analyses

Statistical analysis title	Log Rank
Statistical analysis description: Time to onset of CDP at week 24	
Comparison groups	Interferon beta-1a 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	835
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.037
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.98

Secondary: Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score to Week 96

End point title	Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score to Week 96

End point description:

MSFC score consists of: A) Timed 25-Foot walk; B) 9-Hole Peg Test (9-HPT); and C) Paced Auditory Serial Addition Test (PASAT-3 version). The MSFCS is based on the concept that scores for these three dimensions (arm, leg, and cognitive function) are combined to create a single score (the MSFC) that can be used to detect change over time in a group of participants with MS. Since the three primary measures differ in what they actually measure, a common composite score for the three different measures i.e., Z- score was selected for the purpose. MSFC Score = {Z arm, average + Z leg, average + Z cognitive} / 3.0. The results from each of these three tests are transformed into Z-scores and averaged to yield a composite score for each participant at each time point. A score of +1 indicates that, on average, an individual scored 1 standard deviation (SD) better than the reference population and a score of -1 indicates that an individual scored 1 SD worse than the reference population.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	418	417		
Units: Z-score				
arithmetic mean (standard error)				
Unadjusted Baseline mean (n= 342, 358)	-0.001 (± 0.033)	0.026 (± 0.034)		
Adjusted Week 96 mean (n= 269, 308)	0.169 (± 0.029)	0.276 (± 0.028)		

Statistical analyses

Statistical analysis title	Mixed-effect model of repeated measures
Comparison groups	Interferon beta-1a 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	835
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.004
Method	mixed-effect model of repeated measures
Parameter estimate	Difference in Adjusted Means
Point estimate	0.107
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.034
upper limit	0.18
Variability estimate	Standard error of the mean
Dispersion value	0.037

Secondary: Percent Change in Brain Volume as Detected by Brain Magnetic Resonance Imaging (MRI) From Week 24 to Week 96

End point title	Percent Change in Brain Volume as Detected by Brain Magnetic Resonance Imaging (MRI) From Week 24 to Week 96

End point description:

Brain volume was recorded as an absolute "normalized" value at the baseline visit then recorded at subsequent visits as a percentage change relative to the absolute value at the baseline visit. Therefore, brain volume at Week 24 was calculated as the brain volume at the baseline visit multiplied by 1 + ([percentage change in brain volume from baseline visit to Week 24]/100). Estimates are from analysis based on mixed-effect model of repeated measures (MMRM) using unstructured covariance matrix: Percentage Change = Brain Volume at Week 24 + Geographical Region (US vs. ROW) + Baseline EDSS (< 4.0 vs. >= 4.0) + Week + Treatment + Treatment*Week (repeated values over Week) + Brain Volume at Week 24*Week. The EDSS scale ranges from 0 (normal neurological exam) to 10 (death due to multiple sclerosis).

End point type	Secondary

End point timeframe:

From week 24 up to week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	287		
Units: percent change				
arithmetic mean (standard error)	-0.75 (± 0.051)	-0.638 (± 0.049)		

Statistical analyses

Statistical analysis title	Mixed-effect model of repeated measures
Comparison groups	Interferon beta-1a 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	546
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.09
Method	mixed-effect model of repeated measures
Parameter estimate	Difference in Adjusted Means
Point estimate	0.112
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.018
upper limit	0.241
Variability estimate	Standard error of the mean
Dispersion value	0.066

Secondary: Change From Baseline in Short Form Health Survey-36 (SF-36) Physical Component Summary (PCS) Score at Week 96

End point title	Change From Baseline in Short Form Health Survey-36 (SF-36) Physical Component Summary (PCS) Score at Week 96

End point description:

The SF-36 is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores (domains) as well as psychometrically based physical and mental health summary measures. The SF-36 taps 8 health concepts: physical functioning, bodily pain, physical role functioning, emotional role functioning, emotional well-being, social functioning, vitality, and general health perceptions. The 8 scales are further summarized to 2 distinct higher-ordered clusters: the PCS and mental composite t-score (MCS). The range for all 8 domains as well as for the composite t-scores is from 0 to 100 with 100 as best possible health status and 0 as worst health status.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	418	417		
Units: t-score				
arithmetic mean (standard error)				
Unadjusted Baseline mean (n= 319, 355)	44.552 (± 0.544)	44.307 (± 0.541)		
Adjusted mean change at week 96(n=276, 315)	-0.833 (± 0.472)	0.326 (± 0.444)		

Statistical analyses

Statistical analysis title	Mixed-effect model of repeated measures
Comparison groups	Interferon beta-1a 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	835
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0404
Method	mixed-effect model of repeated measures
Parameter estimate	Difference in Adjusted Means
Point estimate	1.159
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	2.268
Variability estimate	Standard error of the mean
Dispersion value	0.564

Secondary: Percentage of Participants Who Have No Evidence of Disease Activity (NEDA) up to Week 96

End point title	Percentage of Participants Who Have No Evidence of Disease Activity (NEDA) up to Week 96

End point description:

NEDA was defined only for participants with a baseline EDSS score >=2.0. The EDSS scale ranges from 0 (normal neurological exam) to 10 (death due to multiple sclerosis). Participants who completed the 96- week treatment period were considered as having evidence of disease activity if at least one protocol- defined relapse (PDR), a confirmed disability progression (CDP) event or at least one MRI scan showing MRI activity (defined as Gd-enhancing T1 lesions, or new or enlarging T2 lesions) was reported during the 96-week treatment period, otherwise the participant was considered as having NEDA.

End point type	Secondary

End point timeframe:

Week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	289		
Units: percentage of participants				
number (confidence interval 95%)	24.1 (19.1 to 29.6)	43.9 (38.1 to 49.9)		

Statistical analyses

Statistical analysis title	CMH Chi-Squared test (stratified)
Comparison groups	Interferon beta-1a 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	CMH Chi-Squared test (stratified)
Parameter estimate	Relative risk (stratified)
Point estimate	1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.41
upper limit	2.32

Secondary: Number of Participants With Adverse Events (AEs)

End point title	Number of Participants With Adverse Events (AEs)

End point description:

AEs included infusion related reactions (IRRs) and serious MS relapses, but excluded non-serious MS relapses. Serious Adverse Events (SAEs) included serious MS relapses and serious IRRs.

End point type	Secondary

End point timeframe:

Baseline up to Week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab	Interferon Beta-1a + Placebo (Open Label Extension)	Ocrelizumab + Placebo (Open Label Extension)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	417	417	297	350

Units: participants				
Serious Adverse Events	40	29	71	121
Adverse Events	357	360	281	333

Statistical analyses

No statistical analyses for this end point

Secondary: Exposure to Ocrelizumab (Area Under the Concentration - Time Curve, AUC)

End point title	Exposure to Ocrelizumab (Area Under the Concentration - Time Curve, AUC)[5]

End point description:

AUC represents total drug exposure for one dosing interval after the 4th dose.

End point type	Secondary

End point timeframe:

Pre-infusion at Weeks 1, 24, 48, 72; and 30 minutes post-infusion at Week 72; at any time during Weeks 84 and 96

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No analysis reported

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	389			
Units: micrograms per milliter*day				
arithmetic mean (standard deviation)	3513 (± 955)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Anti-Drug Antibodies (ADAs) to Ocrelizumab

End point title	Number of Participants With Anti-Drug Antibodies (ADAs) to Ocrelizumab

End point description:

Number of participants positive for anti-drug antibodies (ADAs) to ocrelizumab is the number of post-baseline evaluable participants determined to have treatment-induced ADA or treatment-enhanced ADA during the study period.

End point type	Secondary

End point timeframe:

Baseline up to Week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	417	417		
Units: participants				
Positive sample at baseline (n= 407, 402)	2	4		
Positive for ADA post-baseline (n= 403, 405)	5	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to approximately 588 weeks

Adverse event reporting additional description:

The safety population included all participants who received any study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Interferon Beta-1a + Ocrelizumab Placebo (DB)

Reporting group description:

Interferon beta-1a 44 mcg SC injections three times per week (with placebo infusions matching ocrelizumab infusions every 24 weeks).

Reporting group title	Ocrelizumab + Interferon Beta-1a Placebo DB Ocrelizumab OLE

Reporting group description:

In DB phase participants received Ocrelizumab + Interferon Beta-1a Placebo. During the OLE phase, all participants received ocrelizumab 600-mg IV infusion every 24 weeks.

Reporting group title	Interferon Beta-1a + Ocrelizumab Placebo DB Ocrelizumab OLE

Reporting group description:

In DB phase participants received Interferon Beta-1a and Ocrelizumab Placebo. During the OLE phase, all participants received ocrelizumab 600-mg IV infusion every 24 weeks.

Reporting group title	Ocrelizumab + Interferon Beta-1a Placebo (DB)

Reporting group description:

Ocrelizumab 600 mg or matching placebo intravenous (IV) as 300 mg infusions on Days 1 and 15 for the first dose and as a single infusion of 600 mg for all subsequent infusions every 24 weeks, with placebo injections matching interferon beta-1a SC three times per week.

Serious adverse events	Interferon Beta-1a + Ocrelizumab Placebo (DB)	Ocrelizumab + Interferon Beta-1a Placebo DB Ocrelizumab OLE	Interferon Beta-1a + Ocrelizumab Placebo DB Ocrelizumab OLE
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 417 (9.59%)	121 / 350 (34.57%)	71 / 297 (23.91%)
number of deaths (all causes)	1	6	5
number of deaths resulting from adverse events	1	6	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MALIGNANT MELANOMA			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FIBROADENOMA OF BREAST			

subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UTERINE LEIOMYOMA			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROSTATE CANCER			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THYROID ADENOMA			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BREAST CANCER			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUMOUR HAEMORRHAGE			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLADDER CANCER			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEIOMYOMA			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTRADUCTAL PROLIFERATIVE BREAST LESION			

subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHONDROSARCOMA			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OVARIAN GERM CELL TERATOMA BENIGN			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUMOUR RUPTURE			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METASTATIC MALIGNANT MELANOMA			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TESTIS CANCER			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VARICOSE VEIN			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL VENOUS DISEASE			

subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
STERILISATION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
ABORTION SPONTANEOUS			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BREECH PRESENTATION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	0 / 417 (0.00%)	3 / 350 (0.86%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHEST PAIN			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEATH			

subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune system disorders			
HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
UTERINE POLYP			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEAVY MENSTRUAL BLEEDING			
subjects affected / exposed	1 / 417 (0.24%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ADENOMYOSIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OVARIAN CYST			
subjects affected / exposed	1 / 417 (0.24%)	1 / 350 (0.29%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COITAL BLEEDING			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSMENORRHOEA			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

ENDOMETRIOSIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENOMETRORRHAGIA			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
PULMONARY INFARCTION			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LARYNGEAL OEDEMA			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
TONSILLAR INFLAMMATION			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERSENSITIVITY PNEUMONITIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASTHMA			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRACHEAL STENOSIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
PARANASAL SINUS INFLAMMATION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 417 (0.00%)	3 / 350 (0.86%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUICIDAL IDEATION			
subjects affected / exposed	1 / 417 (0.24%)	2 / 350 (0.57%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEPRESSIVE DELUSION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MAJOR DEPRESSION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENTAL STATUS CHANGES			

subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COMPLETED SUICIDE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
CONVERSION DISORDER			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEPRESSION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APATHY			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEPRESSION SUICIDAL			
subjects affected / exposed	2 / 417 (0.48%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PSYCHOTIC DISORDER			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STRESS			

subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
SPINAL CORD INJURY CAUDA EQUINA			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENISCUS INJURY			
subjects affected / exposed	0 / 417 (0.00%)	2 / 350 (0.57%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARTILAGE INJURY			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRAUMATIC INTRACRANIAL HAEMORRHAGE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JAW FRACTURE			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JOINT INJURY			

subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLAVICLE FRACTURE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANASTOMOTIC LEAK			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRAIN CONTUSION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INCISIONAL HERNIA			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPICONDYLITIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MULTIPLE INJURIES			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANKLE FRACTURE			

subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HIP FRACTURE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FRACTURE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMUR FRACTURE			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER LIMB FRACTURE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFUSION RELATED REACTION			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL HAEMATOMA			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JOINT DISLOCATION			
subjects affected / exposed	0 / 417 (0.00%)	2 / 350 (0.57%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBDURAL HAEMATOMA			

subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACETABULUM FRACTURE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TIBIA FRACTURE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	1 / 297 (0.34%)
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 LIMB FRACTURE			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SKULL FRACTURE			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FIBULA FRACTURE			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ALCOHOL POISONING			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TOXICITY TO VARIOUS AGENTS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FRACTURE DISPLACEMENT			

subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAND FRACTURE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
TRISOMY 21			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANGINA UNSTABLE			
subjects affected / exposed	1 / 417 (0.24%)	2 / 350 (0.57%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
SPINAL CORD COMPRESSION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

HEAD DISCOMFORT			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYDROCEPHALUS			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBOSACRAL RADICULOPATHY			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIZZINESS			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CAROTID ARTERY STENOSIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PRESYNCOPE			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRIGEMINAL NEURALGIA			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OPTIC NEURITIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL INFARCTION			

subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPILEPSY			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MULTIPLE SCLEROSIS PSEUDO RELAPSE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MULTIPLE SCLEROSIS			
subjects affected / exposed	0 / 417 (0.00%)	2 / 350 (0.57%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RADICULOPATHY			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COGNITIVE DISORDER			
subjects affected / exposed	0 / 417 (0.00%)	2 / 350 (0.57%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MULTIPLE SCLEROSIS RELAPSE			
subjects affected / exposed	2 / 417 (0.48%)	2 / 350 (0.57%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEIZURE			
subjects affected / exposed	1 / 417 (0.24%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FACIAL PARALYSIS			

subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ISCHAEMIC STROKE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUROLOGICAL SYMPTOM			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
NEUTROPENIA			
subjects affected / exposed	0 / 417 (0.00%)	2 / 350 (0.57%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPLENIC INFARCTION			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPLENIC VEIN THROMBOSIS			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPONTANEOUS HAEMATOMA			

subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAEMIA			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
RETINAL DETACHMENT			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CATARACT			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
GASTROINTESTINAL INFLAMMATION			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UMBILICAL HERNIA			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ILEUS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRITIS			

subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULUM			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APPENDICITIS NONINFECTIVE			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INGUINAL HERNIA			
subjects affected / exposed	1 / 417 (0.24%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROVESICAL FISTULA			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OESOPHAGITIS			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ILEUS PARALYTIC			

subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MECHANICAL ILEUS			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CROHN'S DISEASE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN			
subjects affected / exposed	1 / 417 (0.24%)	1 / 350 (0.29%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	0 / 417 (0.00%)	3 / 350 (0.86%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATITIS FULMINANT			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATITIS ACUTE			

subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLELITHIASIS			
subjects affected / exposed	1 / 417 (0.24%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS ACUTE			
subjects affected / exposed	1 / 417 (0.24%)	2 / 350 (0.57%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BILE DUCT STENOSIS			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LIVER DISORDER			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
DRUG ERUPTION			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
NEPHROLITHIASIS			
subjects affected / exposed	2 / 417 (0.48%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CALCULUS BLADDER			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE KIDNEY INJURY			

subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHRITIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETHRAL CYST			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
GOITRE			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THYROIDITIS SUBACUTE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
VERTEBRAL OSTEOPHYTE			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNOVIAL CYST			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

OSTEOARTHRITIS			
subjects affected / exposed	1 / 417 (0.24%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTHRITIS			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERVERTEBRAL DISC DISORDER			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACK PAIN			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHITIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROCOCCAL INFECTION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
FURUNCLE			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA VIRAL			

subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA HAEMOPHILUS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHRONIC SINUSITIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIRECTAL ABSCESS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 417 (0.24%)	3 / 350 (0.86%)	4 / 297 (1.35%)
occurrences causally related to treatment / all	0 / 1	1 / 3	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTION			
subjects affected / exposed	0 / 417 (0.00%)	2 / 350 (0.57%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENCEPHALITIS			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS			

subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 417 (0.00%)	13 / 350 (3.71%)	9 / 297 (3.03%)
occurrences causally related to treatment / all	0 / 0	1 / 13	1 / 9
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 3
STAPHYLOCOCCAL SEPSIS			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIC SEPSIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OTITIS MEDIA			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER			
subjects affected / exposed	0 / 417 (0.00%)	2 / 350 (0.57%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ORCHITIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CELLULITIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYSTITIS			

subjects affected / exposed	1 / 417 (0.24%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROVIRUS INFECTION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPTIC SHOCK			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGITIS ASEPTIC			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MASTOIDITIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SKIN INFECTION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAL ABSCESS			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOCOCCAL SEPSIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			

subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATYPICAL PNEUMONIA			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE SINUSITIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL INFECTION			
subjects affected / exposed	1 / 417 (0.24%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRITIS VIRAL			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS INFECTIVE			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL SEPSIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VASCULAR DEVICE INFECTION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APPENDICITIS			

subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CELLULITIS PHARYNGEAL			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 PNEUMONIA			
subjects affected / exposed	0 / 417 (0.00%)	23 / 350 (6.57%)	13 / 297 (4.38%)
occurrences causally related to treatment / all	0 / 0	1 / 24	0 / 13
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
PHARYNGITIS			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGITIS VIRAL			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARASITIC GASTROENTERITIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INJECTION SITE CELLULITIS			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYURIA			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTOPERATIVE WOUND INFECTION			

subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PASTEURELLA INFECTION			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE HEPATITIS C			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UROSEPSIS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TOOTH INFECTION			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA BACTERIAL			
subjects affected / exposed	0 / 417 (0.00%)	2 / 350 (0.57%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	2 / 417 (0.48%)	15 / 350 (4.29%)	6 / 297 (2.02%)
occurrences causally related to treatment / all	1 / 2	4 / 15	6 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PELVIC INFLAMMATORY DISEASE			

subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	1 / 297 (0.34%)
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 PERICARDITIS			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LYME DISEASE			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL ABSCESS			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS ACUTE			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPOGLYCAEMIA			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOKALAEMIA			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DECREASED APPETITE			

subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IMPAIRED INSULIN SECRETION			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GOUT			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHYDRATION			
subjects affected / exposed	0 / 417 (0.00%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTRIGLYCERIDAEMIA			
subjects affected / exposed	1 / 417 (0.24%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOPROTEINAEMIA			
subjects affected / exposed	0 / 417 (0.00%)	1 / 350 (0.29%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Ocrelizumab + Interferon Beta-1a Placebo (DB)		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 417 (6.95%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MALIGNANT MELANOMA			

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
FIBROADENOMA OF BREAST				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
UTERINE LEIOMYOMA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PROSTATE CANCER				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
THYROID ADENOMA				
subjects affected / exposed	2 / 417 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
BREAST CANCER				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
TUMOUR HAEMORRHAGE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
BLADDER CANCER				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LEIOMYOMA				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INTRADUCTAL PROLIFERATIVE BREAST LESION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CHONDROSARCOMA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
OVARIAN GERM CELL TERATOMA BENIGN				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
TUMOUR RUPTURE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
METASTATIC MALIGNANT MELANOMA				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
TESTIS CANCER				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
DEEP VEIN THROMBOSIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

VARICOSE VEIN			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PERIPHERAL VENOUS DISEASE			
subjects affected / exposed	1 / 417 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
STERILISATION			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
ABORTION SPONTANEOUS			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
BREECH PRESENTATION			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PYREXIA			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CHEST PAIN			

subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
DEATH				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
UTERINE POLYP				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HEAVY MENSTRUAL BLEEDING				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ADENOMYOSIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
OVARIAN CYST				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COITAL BLEEDING				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

DYSMENORRHOEA				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ENDOMETRIOSIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MENOMETRORRHAGIA				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
PULMONARY INFARCTION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LARYNGEAL OEDEMA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
RESPIRATORY FAILURE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
TONSILLAR INFLAMMATION				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HYPERSENSITIVITY PNEUMONITIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

ASTHMA				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ACUTE RESPIRATORY FAILURE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
TRACHEAL STENOSIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PARANASAL SINUS INFLAMMATION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PULMONARY EMBOLISM				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
ANXIETY				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SUICIDAL IDEATION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DEPRESSIVE DELUSION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MAJOR DEPRESSION				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MENTAL STATUS CHANGES				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COMPLETED SUICIDE				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
CONVERSION DISORDER				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DEPRESSION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
APATHY				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SUICIDE ATTEMPT				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DEPRESSION SUICIDAL				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PSYCHOTIC DISORDER				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
STRESS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
HEPATIC ENZYME INCREASED				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
SPINAL CORD INJURY CAUDA EQUINA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MENISCUS INJURY				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CARTILAGE INJURY				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
TRAUMATIC INTRACRANIAL HAEMORRHAGE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
JAW FRACTURE				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
JOINT INJURY				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CLAVICLE FRACTURE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LUMBAR VERTEBRAL FRACTURE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ANASTOMOTIC LEAK				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
BRAIN CONTUSION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INCISIONAL HERNIA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
EPICONDYLITIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MULTIPLE INJURIES				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ANKLE FRACTURE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HIP FRACTURE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
FRACTURE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
FEMUR FRACTURE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
UPPER LIMB FRACTURE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INFUSION RELATED REACTION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
POST PROCEDURAL HAEMATOMA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
JOINT DISLOCATION				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SUBDURAL HAEMATOMA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ACETABULUM FRACTURE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
TIBIA FRACTURE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LOWER LIMB FRACTURE				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SKULL FRACTURE				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FIBULA FRACTURE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ALCOHOL POISONING				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
TOXICITY TO VARIOUS AGENTS				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
FRACTURE DISPLACEMENT				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HAND FRACTURE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
TRISOMY 21				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
ACUTE MYOCARDIAL INFARCTION				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
ANGINA UNSTABLE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MYOCARDIAL INFARCTION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SUPRAVENTRICULAR TACHYCARDIA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Nervous system disorders			
SPINAL CORD COMPRESSION			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HEAD DISCOMFORT			
subjects affected / exposed	1 / 417 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
HYDROCEPHALUS			
subjects affected / exposed	1 / 417 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
LUMBOSACRAL RADICULOPATHY			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
DIZZINESS			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CAROTID ARTERY STENOSIS			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PRESYNCOPE			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
TRIGEMINAL NEURALGIA			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
OPTIC NEURITIS			

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CEREBRAL INFARCTION				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
EPILEPSY				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MULTIPLE SCLEROSIS PSEUDO RELAPSE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MULTIPLE SCLEROSIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
RADICULOPATHY				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COGNITIVE DISORDER				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MULTIPLE SCLEROSIS RELAPSE				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SEIZURE				

subjects affected / exposed	2 / 417 (0.48%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
FACIAL PARALYSIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ISCHAEMIC STROKE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CEREBROVASCULAR ACCIDENT				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
NEUROLOGICAL SYMPTOM				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
NEUTROPENIA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
FEBRILE NEUTROPENIA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SPLENIC INFARCTION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SPLENIC VEIN THROMBOSIS				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SPONTANEOUS HAEMATOMA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ANAEMIA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
RETINAL DETACHMENT				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CATARACT				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
GASTROINTESTINAL INFLAMMATION				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
UMBILICAL HERNIA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
RECTAL HAEMORRHAGE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ILEUS				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
GASTRITIS				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
DIVERTICULUM				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PANCREATITIS ACUTE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
APPENDICITIS NONINFECTIVE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INGUINAL HERNIA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ENTEROVESICAL FISTULA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
OESOPHAGITIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PANCREATITIS				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ILEUS PARALYTIC				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MECHANICAL ILEUS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SMALL INTESTINAL OBSTRUCTION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COLITIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CROHN'S DISEASE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ABDOMINAL PAIN				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
CHOLECYSTITIS				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HEPATITIS FULMINANT				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HEPATITIS ACUTE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CHOLELITHIASIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CHOLECYSTITIS ACUTE				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
BILE DUCT STENOSIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LIVER DISORDER				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
DRUG ERUPTION				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
NEPHROLITHIASIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CALCULUS BLADDER				

subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
NEPHRITIS			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
URETHRAL CYST			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
GOITRE			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
THYROIDITIS SUBACUTE			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
VERTEBRAL OSTEOPHYTE			
subjects affected / exposed	1 / 417 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SYNOVIAL CYST			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

INTERVERTEBRAL DISC PROTRUSION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
OSTEOARTHRITIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ARTHRITIS				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
INTERVERTEBRAL DISC DISORDER				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
BACK PAIN				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
GASTROENTERITIS VIRAL				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
BRONCHITIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ENTEROCOCCAL INFECTION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

FURUNCLE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA VIRAL				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA HAEMOPHILUS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CHRONIC SINUSITIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PERIRECTAL ABSCESS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
URINARY TRACT INFECTION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INFECTION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA ASPIRATION				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ENCEPHALITIS				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PYELONEPHRITIS				
subjects affected / exposed	2 / 417 (0.48%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
STAPHYLOCOCCAL SEPSIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
NEUTROPENIC SEPSIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
OTITIS MEDIA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HERPES ZOSTER				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ORCHITIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CELLULITIS				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CYSTITIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ENTEROVIRUS INFECTION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SEPTIC SHOCK				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MENINGITIS ASEPTIC				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MASTOIDITIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SKIN INFECTION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ANAL ABSCESS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PNEUMOCOCCAL SEPSIS				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SEPSIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ATYPICAL PNEUMONIA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ACUTE SINUSITIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
VIRAL INFECTION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
GASTRITIS VIRAL				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CHOLECYSTITIS INFECTIVE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
VIRAL SEPSIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
VASCULAR DEVICE INFECTION				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
APPENDICITIS				
subjects affected / exposed	3 / 417 (0.72%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
CELLULITIS PHARYNGEAL				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COVID-19 PNEUMONIA				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PHARYNGITIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MENINGITIS VIRAL				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PARASITIC GASTROENTERITIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INJECTION SITE CELLULITIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PYURIA				

subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
POSTOPERATIVE WOUND INFECTION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PASTEURELLA INFECTION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ACUTE HEPATITIS C				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
UPPER RESPIRATORY TRACT INFECTION				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
UROSEPSIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
TOOTH INFECTION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA BACTERIAL				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA				

subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PELVIC INFLAMMATORY DISEASE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
VIRAL PERICARDITIS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
STAPHYLOCOCCAL INFECTION				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LYME DISEASE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ABDOMINAL ABSCESS				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PYELONEPHRITIS ACUTE				
subjects affected / exposed	0 / 417 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
HYPOGLYCAEMIA				
subjects affected / exposed	1 / 417 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HYPOKALAEMIA				

subjects affected / exposed	1 / 417 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
DECREASED APPETITE			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
IMPAIRED INSULIN SECRETION			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
GOUT			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
DEHYDRATION			
subjects affected / exposed	1 / 417 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HYPERTRIGLYCERIDAEMIA			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HYPOPROTEINAEMIA			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Interferon Beta-1a + Ocrelizumab Placebo (DB)	Ocrelizumab + Interferon Beta-1a Placebo DB Ocrelizumab OLE	Interferon Beta-1a + Ocrelizumab Placebo DB Ocrelizumab OLE
Total subjects affected by non-serious adverse events			
subjects affected / exposed	357 / 417 (85.61%)	333 / 350 (95.14%)	281 / 297 (94.61%)
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	0 / 417 (0.00%)	15 / 350 (4.29%)	15 / 297 (5.05%)
occurrences (all)	0	21	15
FALL			
subjects affected / exposed	0 / 417 (0.00%)	20 / 350 (5.71%)	24 / 297 (8.08%)
occurrences (all)	0	32	38
INFUSION RELATED REACTION			
subjects affected / exposed	50 / 417 (11.99%)	63 / 350 (18.00%)	97 / 297 (32.66%)
occurrences (all)	64	168	177
LIGAMENT SPRAIN			
subjects affected / exposed	0 / 417 (0.00%)	23 / 350 (6.57%)	18 / 297 (6.06%)
occurrences (all)	0	27	19
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	0 / 417 (0.00%)	26 / 350 (7.43%)	14 / 297 (4.71%)
occurrences (all)	0	27	15
Nervous system disorders			
MIGRAINE			
subjects affected / exposed	0 / 417 (0.00%)	20 / 350 (5.71%)	9 / 297 (3.03%)
occurrences (all)	0	29	19
HYPOAESTHESIA			
subjects affected / exposed	0 / 417 (0.00%)	24 / 350 (6.86%)	21 / 297 (7.07%)
occurrences (all)	0	38	41
DIZZINESS			
subjects affected / exposed	23 / 417 (5.52%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences (all)	27	0	0
HEADACHE			
subjects affected / exposed	71 / 417 (17.03%)	68 / 350 (19.43%)	49 / 297 (16.50%)
occurrences (all)	106	95	73
MULTIPLE SCLEROSIS RELAPSE			

subjects affected / exposed	142 / 417 (34.05%)	82 / 350 (23.43%)	70 / 297 (23.57%)
occurrences (all)	209	157	150
PARAESTHESIA			
subjects affected / exposed	0 / 417 (0.00%)	26 / 350 (7.43%)	21 / 297 (7.07%)
occurrences (all)	0	39	27
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	25 / 417 (6.00%)	34 / 350 (9.71%)	20 / 297 (6.73%)
occurrences (all)	34	53	22
INJECTION SITE REACTION			
subjects affected / exposed	28 / 417 (6.71%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences (all)	28	0	0
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	92 / 417 (22.06%)	26 / 350 (7.43%)	15 / 297 (5.05%)
occurrences (all)	106	28	17
FATIGUE			
subjects affected / exposed	39 / 417 (9.35%)	50 / 350 (14.29%)	39 / 297 (13.13%)
occurrences (all)	52	70	55
INJECTION SITE ERYTHEMA			
subjects affected / exposed	55 / 417 (13.19%)	0 / 350 (0.00%)	0 / 297 (0.00%)
occurrences (all)	59	0	0
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	0 / 417 (0.00%)	30 / 350 (8.57%)	19 / 297 (6.40%)
occurrences (all)	0	37	32
CONSTIPATION			
subjects affected / exposed	0 / 417 (0.00%)	20 / 350 (5.71%)	13 / 297 (4.38%)
occurrences (all)	0	22	15
NAUSEA			
subjects affected / exposed	0 / 417 (0.00%)	22 / 350 (6.29%)	17 / 297 (5.72%)
occurrences (all)	0	25	25
Respiratory, thoracic and mediastinal disorders			
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 417 (0.00%)	21 / 350 (6.00%)	17 / 297 (5.72%)
occurrences (all)	0	25	22
COUGH			

subjects affected / exposed	0 / 417 (0.00%)	58 / 350 (16.57%)	26 / 297 (8.75%)
occurrences (all)	0	89	43
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	0 / 417 (0.00%)	25 / 350 (7.14%)	23 / 297 (7.74%)
occurrences (all)	0	30	28
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 417 (0.00%)	21 / 350 (6.00%)	22 / 297 (7.41%)
occurrences (all)	0	23	28
DEPRESSION			
subjects affected / exposed	31 / 417 (7.43%)	38 / 350 (10.86%)	35 / 297 (11.78%)
occurrences (all)	34	45	40
INSOMNIA			
subjects affected / exposed	23 / 417 (5.52%)	21 / 350 (6.00%)	22 / 297 (7.41%)
occurrences (all)	24	26	25
Musculoskeletal and connective tissue disorders			
NECK PAIN			
subjects affected / exposed	0 / 417 (0.00%)	16 / 350 (4.57%)	15 / 297 (5.05%)
occurrences (all)	0	20	16
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 417 (0.00%)	19 / 350 (5.43%)	15 / 297 (5.05%)
occurrences (all)	0	27	28
MUSCLE SPASMS			
subjects affected / exposed	0 / 417 (0.00%)	20 / 350 (5.71%)	14 / 297 (4.71%)
occurrences (all)	0	25	20
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 417 (0.00%)	42 / 350 (12.00%)	33 / 297 (11.11%)
occurrences (all)	0	60	60
MYALGIA			
subjects affected / exposed	27 / 417 (6.47%)	15 / 350 (4.29%)	17 / 297 (5.72%)
occurrences (all)	30	16	29
ARTHRALGIA			
subjects affected / exposed	27 / 417 (6.47%)	53 / 350 (15.14%)	44 / 297 (14.81%)
occurrences (all)	33	68	57
BACK PAIN			

subjects affected / exposed	18 / 417 (4.32%)	48 / 350 (13.71%)	44 / 297 (14.81%)
occurrences (all)	19	61	65
Infections and infestations			
HERPES ZOSTER			
subjects affected / exposed	0 / 417 (0.00%)	21 / 350 (6.00%)	7 / 297 (2.36%)
occurrences (all)	0	31	7
INFLUENZA			
subjects affected / exposed	20 / 417 (4.80%)	55 / 350 (15.71%)	38 / 297 (12.79%)
occurrences (all)	25	66	54
NASOPHARYNGITIS			
subjects affected / exposed	41 / 417 (9.83%)	96 / 350 (27.43%)	65 / 297 (21.89%)
occurrences (all)	60	327	120
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	53 / 417 (12.71%)	107 / 350 (30.57%)	86 / 297 (28.96%)
occurrences (all)	89	325	267
BRONCHITIS			
subjects affected / exposed	13 / 417 (3.12%)	57 / 350 (16.29%)	25 / 297 (8.42%)
occurrences (all)	15	85	33
SINUSITIS			
subjects affected / exposed	20 / 417 (4.80%)	47 / 350 (13.43%)	34 / 297 (11.45%)
occurrences (all)	25	84	46
PNEUMONIA			
subjects affected / exposed	0 / 417 (0.00%)	23 / 350 (6.57%)	11 / 297 (3.70%)
occurrences (all)	0	28	11
PHARYNGITIS			
subjects affected / exposed	0 / 417 (0.00%)	17 / 350 (4.86%)	23 / 297 (7.74%)
occurrences (all)	0	24	44
ORAL HERPES			
subjects affected / exposed	0 / 417 (0.00%)	21 / 350 (6.00%)	10 / 297 (3.37%)
occurrences (all)	0	50	16
CYSTITIS			
subjects affected / exposed	0 / 417 (0.00%)	21 / 350 (6.00%)	15 / 297 (5.05%)
occurrences (all)	0	37	26
RHINITIS			

subjects affected / exposed	0 / 417 (0.00%)	18 / 350 (5.14%)	6 / 297 (2.02%)
occurrences (all)	0	19	7
COVID-19			
subjects affected / exposed	0 / 417 (0.00%)	96 / 350 (27.43%)	66 / 297 (22.22%)
occurrences (all)	0	120	79
GASTROENTERITIS			
subjects affected / exposed	0 / 417 (0.00%)	24 / 350 (6.86%)	15 / 297 (5.05%)
occurrences (all)	0	28	17
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 417 (0.00%)	25 / 350 (7.14%)	16 / 297 (5.39%)
occurrences (all)	0	41	20
URINARY TRACT INFECTION			
subjects affected / exposed	39 / 417 (9.35%)	96 / 350 (27.43%)	79 / 297 (26.60%)
occurrences (all)	48	257	212

Non-serious adverse events	Ocrelizumab + Interferon Beta-1a Placebo (DB)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	360 / 417 (86.33%)		
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
FALL			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
INFUSION RELATED REACTION			
subjects affected / exposed	158 / 417 (37.89%)		
occurrences (all)	271		
LIGAMENT SPRAIN			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

MIGRAINE subjects affected / exposed occurrences (all)	0 / 417 (0.00%) 0		
HYPOAESTHESIA subjects affected / exposed occurrences (all)	0 / 417 (0.00%) 0		
DIZZINESS subjects affected / exposed occurrences (all)	17 / 417 (4.08%) 19		
HEADACHE subjects affected / exposed occurrences (all)	60 / 417 (14.39%) 88		
MULTIPLE SCLEROSIS RELAPSE subjects affected / exposed occurrences (all)	94 / 417 (22.54%) 133		
PARAESTHESIA subjects affected / exposed occurrences (all)	0 / 417 (0.00%) 0		
General disorders and administration site conditions			
PYREXIA subjects affected / exposed occurrences (all)	15 / 417 (3.60%) 18		
INJECTION SITE REACTION subjects affected / exposed occurrences (all)	2 / 417 (0.48%) 2		
INFLUENZA LIKE ILLNESS subjects affected / exposed occurrences (all)	23 / 417 (5.52%) 25		
FATIGUE subjects affected / exposed occurrences (all)	44 / 417 (10.55%) 57		
INJECTION SITE ERYTHEMA subjects affected / exposed occurrences (all)	1 / 417 (0.24%) 1		
Gastrointestinal disorders			

DIARRHOEA			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
CONSTIPATION			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
NAUSEA			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
COUGH			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
DEPRESSION			
subjects affected / exposed	29 / 417 (6.95%)		
occurrences (all)	32		
INSOMNIA			
subjects affected / exposed	23 / 417 (5.52%)		
occurrences (all)	28		
Musculoskeletal and connective tissue disorders			
NECK PAIN			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
MUSCULAR WEAKNESS			

subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
MUSCLE SPASMS			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
MYALGIA			
subjects affected / exposed	12 / 417 (2.88%)		
occurrences (all)	13		
ARTHRALGIA			
subjects affected / exposed	22 / 417 (5.28%)		
occurrences (all)	28		
BACK PAIN			
subjects affected / exposed	28 / 417 (6.71%)		
occurrences (all)	31		
Infections and infestations			
HERPES ZOSTER			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
INFLUENZA			
subjects affected / exposed	24 / 417 (5.76%)		
occurrences (all)	30		
NASOPHARYNGITIS			
subjects affected / exposed	80 / 417 (19.18%)		
occurrences (all)	128		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	65 / 417 (15.59%)		
occurrences (all)	109		
BRONCHITIS			
subjects affected / exposed	22 / 417 (5.28%)		
occurrences (all)	28		
SINUSITIS			

subjects affected / exposed	27 / 417 (6.47%)		
occurrences (all)	35		
PNEUMONIA			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
PHARYNGITIS			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
ORAL HERPES			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
CYSTITIS			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
RHINITIS			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
COVID-19			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
GASTROENTERITIS			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 417 (0.00%)		
occurrences (all)	0		
URINARY TRACT INFECTION			
subjects affected / exposed	43 / 417 (10.31%)		
occurrences (all)	74		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2012	1. Provide greater clarity in the protocol language around expedited reporting of serious adverse events (SAEs) 2. Revise the dosing preparation and infusion guidance to simplify the procedures 3. Refine some aspects of the inclusion/exclusion criteria 4. Refine several operational aspects of the study conduct 5. Inform sites of additional, optional sub-studies conducted at select centers in which patients in this trial may be eligible to participate
28 March 2013	Study WA21093 has been amended to include an Open-Label Extension Phase and clarify how sustained disability progression is calculated. Additional changes to the protocol are as follows: • Provided Sponsor update on anti-CD20 therapies • Added the following exploratory objective: • Proportion of disease activity free patients, defined as absence of both relapses and sustained accumulation of disability, and absence of magnetic resonance imaging (MRI) activity by Week 96 • Amended wording for premature withdrawal • Updated Medical Monitor responsible for the trial
04 September 2014	An update to the Statistical Considerations and Analytical Plan section of the protocol in line with the Statistical Analysis Plan (SAP) for the study. The SAP was amended recently to implement European Medicines Agency (EMA) Scientific Advice and to increase ststistical rigor.
04 March 2016	1. Clarification of the objectives of the open-label extension (OLE) phase. 2. Clarification regarding permittance of alternative MS treatments and prolongation of the safety follow-up period for patients switching to other MS therapies post-ocrelizumab.
04 October 2017	Updates to the core safety wording; Additional wording changes were made to align with the most recent version of the core safety text; Addition of Adverse Events of Special Interest (AESI)
03 August 2018	Addition of optional collection of biosamples for the Research Biosample Repository taken at a single timepoint during the OLE Phase; Extension of the WA21092 OLE treatment phase to 31 December 2020
18 December 2019	OLE treatment phase has been extended to 31 December 2022; The safety risks for ocrelizumab have been updated; The pharmacokinetic/human anti-human antibody (HAHA) collection/analysis has been removed; The plasma and urine sample collections for John Cunningham virus (JCV) have been removed
27 July 2020	The goal of this amendment is to reduce patient burden and facilitate patient management at the infusion center during the ongoing open-label extension phase.

18 November 2021	The Sponsor has now made the decision not to extend this study further and; therefore, this study will end on 31 December 2022. Instead, the new rollover extension study (MN43964) is being set up to ensure that participants of Study WA21093 (together with participants from other Parent studies) can continue their ocrelizumab treatment or safety follow-up as applicable without interruption and allowing for valuable long-term data to continue to be collected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported