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	2010-020337-99
Trial protocol	GB FR CZ LV HU FI DE BE SK AT NL LT EE PT BG ES PL IT
Global end of trial date	31 December 2022

Results information

Result version number	v2 (current)
This version publication date	01 January 2024
First version publication date	03 June 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	WA21092

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01247324
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche, Ltd.
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	F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd., +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	31 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of ocrelizumab compared with interferon beta-1a 44 mcg subcutaneous (SC) in patients with relapsing multiple sclerosis (RMS).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 August 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	11 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 8
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Bulgaria: 38
Country: Number of subjects enrolled	Brazil: 18
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	Czechia: 130
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Estonia: 16
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Lithuania: 17
Country: Number of subjects enrolled	Latvia: 12

Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Peru: 22
Country: Number of subjects enrolled	Poland: 69
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Russian Federation: 67
Country: Number of subjects enrolled	Serbia: 19
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	Tunisia: 8
Country: Number of subjects enrolled	Ukraine: 30
Country: Number of subjects enrolled	United States: 210
Country: Number of subjects enrolled	South Africa: 4
Worldwide total number of subjects	821
EEA total number of subjects	405

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)	821
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1051 participants were screened for entry into the study. 821 participants were entered into the double-blind treatment period. Participants who completed the 96-week double-blind treatment had an option to enter a single group, active treatment open label extension, providing they fulfilled the eligibility criteria.

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	Investigator, Monitor, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Interferon Beta-1a + Placebo

Arm description:

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

Arm type	Active comparator
Investigational medicinal product name	Interferon beta-1a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Solution for injection in cartridge
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received interferon beta-1a 44 microgram (mcg) subcutaneous (SC) injections three times per week (with placebo infusions matching ocrelizumab infusions every 24 weeks).

Arm title	Ocrelizumab + Placebo

Arm description:

Ocrelizumab 600 mg 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	Ocrelizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received ocrelizumab 600 milligram (mg) 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 doses every 24 weeks.

Number of subjects in period 1	Interferon Beta-1a + Placebo	Ocrelizumab + Placebo
Started	411	410
Completed	226	239
Not completed	185	171
Physician decision	2	3
Study Terminated by Sponsor	4	1
Reason not specified	42	32
Consent withdrawn by participant	41	56
Missing	2	1
Adverse event, non-fatal	49	35
Death	6	10
Pregnancy	5	10
Non-compliance with study drug	3	-
Non-compliance	3	2
Lost to follow-up	3	6
Lack of efficacy	24	14
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Interferon Beta-1a + Placebo
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 + Placebo
Reporting group description:	
Ocrelizumab 600 mg 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 + Placebo	Ocrelizumab + Placebo	Total
Number of subjects	411	410	821
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)	411	410	821
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	36.9	37.1	
standard deviation	± 9.3	± 9.3	-
Gender, Male/Female Units:			
Female	272	270	542
Male	139	140	279
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	1	0	1
Black or African American	12	19	31
White	375	375	750
Other	14	10	24
Multiple	9	5	14
Ethnicity Units: Subjects			
Hispanic or Latino	58	44	102
Not Hispanic or Latino	318	329	647
Not Stated	35	37	72

Subject analysis sets	
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.	

Reporting group values	Interferon Beta-1a + Placebo (Open Label Extension)	Ocrelizumab + Placebo (Open Label Extension)	
Number of subjects	326	352	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years			
arithmetic mean	39.24	39.30	
standard deviation	± 9.31	± 9.36	
Gender, Male/Female Units:			
Female Male			
Race Units: Subjects			
American Indian or Alaska Native Asian Black or African American White Other Multiple			
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Not Stated			

End points

End points reporting groups

Reporting group title	Interferon Beta-1a + Placebo
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 + Placebo
Reporting group description:	
Ocrelizumab 600 mg 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 + Placebo	Ocrelizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	410		
Units: relapses/participant year of treatment				
number (confidence interval 95%)	0.292 (0.235 to 0.361)	0.156 (0.122 to 0.200)		

Statistical analyses

Statistical analysis title	ARR by Week 96
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 + Placebo v Ocrelizumab + Placebo

Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Negative Binomial Model
Parameter estimate	Rate Ratio
Point estimate	0.536
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.719

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 + Placebo	Ocrelizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	410		
Units: lesions	337	21		

Statistical analyses

Statistical analysis title	T1-Gd lesions

Statistical analysis description:

Adjusted by baseline T1 Gd lesion (present or not), baseline EDSS (<4.0 vs. >=4.0) and geographical region (US vs. ROW).

Comparison groups	Interferon Beta-1a + Placebo v Ocrelizumab + Placebo
Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Negative Binomial Model
Parameter estimate	Adjusted rate ratio
Point estimate	0.058

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.032
upper limit	0.104

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. EDSS assessment and who were on treatment at time of clinical cut-off date were censored at the date of their last EDSS assessment. Here, 99999 indicates median and -99999 and 99999 minimum and maximum of full range as less than 50% of subjects experience onset of CDP.

End point type	Secondary

End point timeframe:

Week 108

End point values	Interferon Beta-1a + Placebo	Ocrelizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	410		
Units: weeks				
median (full range (min-max))	99999 (-99999 to 99999)	99999 (-99999 to 99999)		

Statistical analyses

Statistical analysis title	Time to onset CDP at week 12

Statistical analysis description:

Time to onset CDP at week 12

Comparison groups	Interferon Beta-1a + Placebo v Ocrelizumab + Placebo
Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0139
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.9

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 + Placebo	Ocrelizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	410		
Units: lesions	1916	430		

Statistical analyses

Statistical analysis title	Enlarging T2 hyperintense lesions

Statistical analysis description:

Adjusted by baseline T2 lesion count, baseline EDSS (<4.0 vs. >=4.0) and geographical region (US vs. ROW).

Comparison groups	Interferon Beta-1a + Placebo v Ocrelizumab + Placebo
Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Negative Binomial Model
Parameter estimate	Adjusted rate ratio
Point estimate	0.229
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.174
upper limit	0.3

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 + Placebo	Ocrelizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	306	310		
Units: percentage of participants				
number (confidence interval 95%)	12.42 (8.94 to 16.64)	20.00 (15.69 to 24.89)		

Statistical analyses

Statistical analysis title	Confirmed Disability Improvement for 12 weeks

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) Chi-Squared test was used, stratified by Geographical Region (US vs. Rest of World) and Baseline EDSS (<4.0 vs. >=4.0). 95 percent (%) confidence interval (CI) of proportion was constructed using Pearson-Clopper method.

Comparison groups	Interferon Beta-1a + Placebo v Ocrelizumab + Placebo
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0106
Method	CMH Chi-Squared test (stratified)
Parameter estimate	Relative risk (stratified)
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	2.33

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 + Placebo	Ocrelizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	410		
Units: lesions	1307	564		

Statistical analyses

Statistical analysis title	T1-Gd lesions

Statistical analysis description:

Adjusted by baseline T1 Gd lesion (present or not), baseline EDSS (<4.0 vs. >=4.0) and geographical region (US vs. ROW).

Comparison groups	Interferon Beta-1a + Placebo v Ocrelizumab + Placebo
Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Negative Binomial Model
Parameter estimate	Adjusted rate ratio
Point estimate	0.428
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.328
upper limit	0.557

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 Expanded Disability Status Scale (EDSS) score of: A) >=1.0 point from baseline EDSS score when baseline score was less than or equal to (<=) 5.5 B) >=0.5 point from baseline EDSS score when 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 increase in EDSS was confirmed at a regularly scheduled visit at least 24 weeks after 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 date of their last EDSS assessment. Here, 99999 indicates median and -99999 and 99999 min & max of full range as less than 50% of subjects experience onset of CDP.

End point type	Secondary

End point timeframe:

Week 108

End point values	Interferon Beta-1a + Placebo	Ocrelizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	410		
Units: weeks				
median (full range (min-max))	99999 (-99999 to 99999)	99999 (-99999 to 99999)		

Statistical analyses

Statistical analysis title	Time to onset CDP at week 24

Statistical analysis description:

Hazard ratios (HR) were estimated by stratified Cox regression. Stratification factors were Geographical Region (US vs. Rest of World) and baseline EDSS (<4.0 vs. >=4.0).

Comparison groups	Interferon Beta-1a + Placebo v Ocrelizumab + Placebo
Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0278
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.95

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 + Placebo	Ocrelizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	410		
Units: Z-score				
arithmetic mean (standard error)				
Unadjusted Baseline mean (n= 359, 360)	0.028 (± 0.034)	-0.012 (± 0.040)		
Adjusted Week 96 mean (n= 308, 322)	0.174 (± 0.031)	0.213 (± 0.031)		

Statistical analyses

Statistical analysis title	MSFC score baseline to week 96

Statistical analysis description:

Estimates are from analysis based on mixed-effect model of repeated measures (MMRM) using unstructured covariance matrix: Change = Baseline MSFCS Score + Geographical Region + Baseline EDSS (< 4.0 vs. >= 4.0) + Week + Treatment + Treatment*Week (repeated values over Week) + Baseline MSFCS Score*Week.

Comparison groups	Interferon Beta-1a + Placebo v Ocrelizumab + Placebo
Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3261
Method	mixed-effect model of repeated measures
Parameter estimate	Difference in Adjusted Means
Point estimate	0.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.039
upper limit	0.116
Variability estimate	Standard error of the mean
Dispersion value	0.039

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.

End point type	Secondary

End point timeframe:

From Week 24 up to Week 96

End point values	Interferon Beta-1a + Placebo	Ocrelizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267	281		
Units: percent change				
arithmetic mean (standard error)	-0.741 (± 0.046)	-0.572 (± 0.044)		

Statistical analyses

Statistical analysis title	Percent change in brain volume

Statistical analysis description:

Estimates are from analysis based on MMRM using unstructured covariance matrix: Percentage Change = Brain Volume at Week 24 + Geographical Region + Baseline EDSS (< 4.0 vs. >= 4.0) + Week + Treatment +Treatment*Week (repeated values over Week) + Brain Volume at Week 24*Week.

Comparison groups	Interferon Beta-1a + Placebo v Ocrelizumab + Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0042
Method	mixed-effect model of repeated measures
Parameter estimate	Difference in Adjusted Means
Point estimate	0.168
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.053
upper limit	0.283

Variability estimate	Standard error of the mean
Dispersion value	0.058

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 + Placebo	Ocrelizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	410		
Units: t-score				
arithmetic mean (standard error)				
Unadjusted Baseline mean (n= 338, 357)	45.399 (± 0.529)	45.065 (± 0.507)		
Adjusted mean change at week 96 (n= 276, 315)	-0.657 (± 0.475)	0.036 (± 0.456)		

Statistical analyses

Statistical analysis title	SF-36 PCS score at week 96

Statistical analysis description:

Estimates are from analysis based on MMRM using unstructured covariance matrix: Change = Baseline PCS Score + Geographical Region + Baseline EDSS (< 4.0 vs. >= 4.0) + Week + Treatment + Treatment*Week (repeated values over Week) + Baseline PCS Score*Week.

Comparison groups	Interferon Beta-1a + Placebo v Ocrelizumab + Placebo
Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2193
Method	mixed-effect model of repeated measures
Parameter estimate	Difference in Adjusted Means
Point estimate	0.693

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.414
upper limit	1.8
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 + Placebo	Ocrelizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	289		
Units: percentage of participants				
number (confidence interval 95%)	27.1 (22.1 to 32.6)	47.4 (41.5 to 53.3)		

Statistical analyses

Statistical analysis title	NEDA at week 96

Statistical analysis description:

Analysed using CMH test, stratified by Geographical Region (US vs. Rest of World) and Baseline EDSS (<4.0 vs. >=4.0). 95% CI of proportion was constructed using Pearson-Clopper method

Comparison groups	Interferon Beta-1a + Placebo v Ocrelizumab + Placebo
Number of subjects included in analysis	580
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	CMH Chi-Squared test (stratified)
Parameter estimate	Relative risk (stratified)
Point estimate	1.74

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.39
upper limit	2.17

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 + Placebo	Ocrelizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	409	408		
Units: Participants				
Positive sample at baseline (n= 397, 396)	2	1		
Positive for ADA post-baseline (n= 401, 402)	2	1		

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)[1]

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:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint did not have statistical analyses performed.

End point values	Ocrelizumab + Placebo			
Subject group type	Reporting group			
Number of subjects analysed	393			
Units: micrograms per milliliter*day				
arithmetic mean (standard deviation)	3513 (± 955)			

Statistical analyses

No statistical analyses for this end point

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

End point type	Secondary

End point timeframe:

Baseline up to 588 weeks

End point values	Interferon Beta-1a + Placebo	Ocrelizumab + Placebo	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	409	408	326	352
Units: Participants	331	327	302	319

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to approximately 588 weeks

Adverse event reporting additional description:

The safety population includes all enrolled patients who have received at least one dose of any study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Interferon Beta- 1a + Placebo (Double Blind Period)

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 + Placebo (Double Blind Period)

Reporting group description:

Ocrelizumab 600 mg 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 title	Interferon Beta-1a + Placebo (Open Label Extension)

Reporting group description:

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

Reporting group title	Ocrelizumab + Placebo (Open Label Extension)

Reporting group description:

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

Serious adverse events	Interferon Beta- 1a + Placebo (Double Blind Period)	Ocrelizumab + Placebo (Double Blind Period)	Interferon Beta-1a + Placebo (Open Label Extension)
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 409 (7.82%)	28 / 408 (6.86%)	109 / 326 (33.44%)
number of deaths (all causes)	1	0	6
number of deaths resulting from adverse events	0	0	6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA OF COLON			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INVASIVE DUCTAL BREAST CARCINOMA			

subjects affected / exposed	0 / 409 (0.00%)	2 / 408 (0.49%)	2 / 326 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BREAST NEOPLASM			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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 CANCER			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
CERVIX CARCINOMA STAGE II			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
ENDOMETRIAL ADENOCARCINOMA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALIGNANT MELANOMA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DERMATOFIBROSARCOMA PROTUBERANS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
OESOPHAGEAL ADENOCARCINOMA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
COLON CANCER			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAPILLARY THYROID CANCER			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
BASAL CELL CARCINOMA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
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 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UTERINE LEIOMYOMA			
subjects affected / exposed	2 / 409 (0.49%)	0 / 408 (0.00%)	3 / 326 (0.92%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLESTEATOMA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MANTLE CELL LYMPHOMA			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
SQUAMOUS CELL CARCINOMA			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGIOMA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INVASIVE BREAST CARCINOMA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
SALIVARY GLAND ADENOMA			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
Vascular disorders			
VARICOSE VEIN			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
SHOCK HAEMORRHAGIC			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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			
MAMMOPLASTY			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
Pregnancy, puerperium and perinatal conditions			
CERVICAL INCOMPETENCE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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

ANEMBRYONIC GESTATION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PRE-ECLAMPSIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
ABORTION SPONTANEOUS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHEST PAIN			
subjects affected / exposed	0 / 409 (0.00%)	2 / 408 (0.49%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFLAMMATION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	1 / 409 (0.24%)	1 / 408 (0.25%)	0 / 326 (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
Reproductive system and breast disorders			
PROSTATITIS			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSMENORRHOEA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
GENITAL PROLAPSE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEAVY MENSTRUAL BLEEDING			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
MENOPAUSAL SYMPTOMS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CERVICAL POLYP			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OVARIAN CYST			

subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	2 / 326 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABNORMAL UTERINE BLEEDING			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENDOMETRIAL HYPERTROPHY			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
OVARIAN CYST RUPTURED			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UTERINE PROLAPSE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
MENORRHAGIA			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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, thoracic and mediastinal disorders			
SINUS CONGESTION			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
HYPERVENTILATION			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
PLEURAL EFFUSION			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASTHMA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	2 / 326 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NASAL SEPTUM DEVIATION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	4 / 326 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	0 / 409 (0.00%)	2 / 408 (0.49%)	0 / 326 (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
MENTAL STATUS CHANGES			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
PSYCHOGENIC TREMOR			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
SUICIDAL IDEATION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
AFFECTIVE DISORDER			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
COMPLETED SUICIDE			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
ANXIETY			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
DEVICE DISLOCATION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

PORTAL VEIN THROMBOSIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
CHOLECYSTITIS			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLELITHIASIS			
subjects affected / exposed	0 / 409 (0.00%)	2 / 408 (0.49%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LIVER DISORDER			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
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 INJURY			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GALLBLADDER MUCOCOELE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS CHRONIC			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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

WEIGHT DECREASED			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
Injury, poisoning and procedural complications			
TENDON DISLOCATION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OVERDOSE			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
MUSCLE RUPTURE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROCEDURAL PAIN			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
CRANIOCEREBRAL INJURY			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
HUMERUS FRACTURE			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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

CONCUSSION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	2 / 326 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RADIUS FRACTURE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
MULTIPLE INJURIES			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
ACETABULUM FRACTURE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
SUBDURAL HAEMATOMA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
FEMUR FRACTURE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	2 / 326 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FOOT FRACTURE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL HAEMATOMA			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
INFUSION RELATED REACTION			

subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
UPPER LIMB FRACTURE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
JOINT DISLOCATION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCLE STRAIN			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
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	1 / 409 (0.24%)	0 / 408 (0.00%)	2 / 326 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST LUMBAR PUNCTURE SYNDROME			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
TIBIA FRACTURE			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAND FRACTURE			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
COMMINUTED FRACTURE			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPROSTHETIC FRACTURE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
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 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FIBULA FRACTURE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	2 / 326 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTOPERATIVE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
TENDON RUPTURE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FRACTURE DISPLACEMENT			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
HYPERTROPHIC CARDIOMYOPATHY			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
PHIMOSIS			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
CORONARY ARTERY OCCLUSION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIOVENTRICULAR BLOCK COMPLETE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANGINA UNSTABLE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONGESTIVE CARDIOMYOPATHY			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
PERICARDITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FLUTTER			

subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	3 / 326 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC ARREST			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
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 CORONARY SYNDROME			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
LEFT VENTRICULAR DYSFUNCTION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
ANGINA PECTORIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
Nervous system disorders			
CEREBRAL ISCHAEMIA			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
POLYNEUROPATHY			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
MIGRAINE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SCIATICA			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
HEMIPARESIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
DIZZINESS			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
CARPAL TUNNEL SYNDROME			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARTIAL SEIZURES WITH SECONDARY GENERALISATION			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPILEPSY			
subjects affected / exposed	1 / 409 (0.24%)	1 / 408 (0.25%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRIGEMINAL NEURALGIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYELOPATHY			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
FACIAL PARESIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
RUPTURED CEREBRAL ANEURYSM			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
CERVICAL RADICULOPATHY			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
MULTIPLE SCLEROSIS RELAPSE			

subjects affected / exposed	3 / 409 (0.73%)	0 / 408 (0.00%)	3 / 326 (0.92%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEADACHE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSARTHRIA			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
SEIZURE			
subjects affected / exposed	0 / 409 (0.00%)	2 / 408 (0.49%)	0 / 326 (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
APHASIA			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
Blood and lymphatic system disorders			
IRON DEFICIENCY ANAEMIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
ANAEMIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEUKOPENIA			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	2 / 326 (0.61%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

VESTIBULAR DISORDER			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
Eye disorders			
VISION BLURRED			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL ARTERY OCCLUSION			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
UVEITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
CATARACT			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL DETACHMENT			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
Gastrointestinal disorders			
COLITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CROHN'S DISEASE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

INGUINAL HERNIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
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 INFLAMMATION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
INTRA-ABDOMINAL FLUID COLLECTION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
GASTRIC PERFORATION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
GASTROINTESTINAL ULCER HAEMORRHAGE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL INCARCERATED HERNIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
IMPAIRED GASTRIC EMPTYING			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
GASTRITIS			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
DIARRHOEA			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
DYSPHAGIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
FUNCTIONAL GASTROINTESTINAL DISORDER			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
ABDOMINAL PAIN			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
SUBILEUS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LARGE INTESTINAL STENOSIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
PEPTIC ULCER			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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 and subcutaneous tissue disorders			
ERYTHEMA MULTIFORME			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ERYTHEMA NODOSUM			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HIDRADENITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETEROLITHIASIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
URINARY RETENTION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHROLITHIASIS			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
Musculoskeletal and connective tissue disorders			
MUSCULOSKELETAL DISCOMFORT			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RHABDOMYOLYSIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
SPINAL RETROLISTHESIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
MUSCLE SPASMS			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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 CYST			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THORACIC SPINAL STENOSIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
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 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTHRALGIA			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACK PAIN			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRIGGER FINGER			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMARTHROSIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOARTHRITIS			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RHEUMATOID ARTHRITIS			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
CERVICAL SPINAL STENOSIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIORBITAL CELLULITIS			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SALPINGITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
SALPINGO-OOPHORITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
ENCEPHALITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
PYELONEPHRITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTIVE THROMBOSIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
COVID-19			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	6 / 326 (1.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
CHRONIC SINUSITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
INFLUENZA			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
POST-ACUTE COVID-19 SYNDROME			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SINUSITIS			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
TONSILLITIS			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
ANAL ABSCESS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
MASTOIDITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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 SYNCYTIAL VIRUS INFECTION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
PERIRECTAL ABSCESS			

subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
NEUROBORRELIOSIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUBERCULOSIS BLADDER			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	4 / 326 (1.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY SEPSIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
BILIARY SEPSIS			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
CYSTITIS			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CELLULITIS			
subjects affected / exposed	1 / 409 (0.24%)	2 / 408 (0.49%)	0 / 326 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APPENDICITIS PERFORATED			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPTIC SHOCK			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS INFECTIVE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
TOOTH ABSCESS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL INFECTION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
PILONIDAL DISEASE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
GASTROENTERITIS			

subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUBO-OVARIAN ABSCESS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
DENGUE FEVER			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY TUBERCULOSIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APPENDICITIS			
subjects affected / exposed	2 / 409 (0.49%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 PNEUMONIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	17 / 326 (5.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 18
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
SEPTIC ARTHRITIS STAPHYLOCOCCAL			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	11 / 326 (3.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	5 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA BACTERIAL			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES SIMPLEX			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
SYSTEMIC CANDIDA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES SIMPLEX MENINGITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
ENTEROCOLITIS INFECTIOUS			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
PYELONEPHRITIS ACUTE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERITONITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INJECTION SITE CELLULITIS			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	0 / 326 (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
INFECTED DERMAL CYST			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
DEVICE RELATED INFECTION			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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
ENDOCARDITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LYME DISEASE			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	2 / 326 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABSCESS LIMB			
subjects affected / exposed	2 / 409 (0.49%)	0 / 408 (0.00%)	0 / 326 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENITAL HERPES SIMPLEX			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	0 / 326 (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
PELVIC INFLAMMATORY DISEASE			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
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			
GLUCOSE TOLERANCE IMPAIRED			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERNATRAEMIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	1 / 326 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TYPE 2 DIABETES MELLITUS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	0 / 326 (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

Serious adverse events	Ocrelizumab + Placebo (Open Label Extension)		
Total subjects affected by serious adverse events			
subjects affected / exposed	116 / 352 (32.95%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events	11		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA OF COLON			

subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INVASIVE DUCTAL BREAST CARCINOMA			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
BREAST NEOPLASM			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
RENAL CANCER			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CERVIX CARCINOMA STAGE II			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ENDOMETRIAL ADENOCARCINOMA			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MALIGNANT MELANOMA			
subjects affected / exposed	2 / 352 (0.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
DERMATOFIBROSARCOMA PROTUBERANS			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
OESOPHAGEAL ADENOCARCINOMA			

subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
BREAST CANCER				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
COLON CANCER				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PAPILLARY THYROID CANCER				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
BASAL CELL CARCINOMA				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PROSTATE CANCER				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
UTERINE LEIOMYOMA				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CHOLESTEATOMA				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MANTLE CELL LYMPHOMA				

subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MENINGIOMA			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INVASIVE BREAST CARCINOMA			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SALIVARY GLAND ADENOMA			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
VARICOSE VEIN			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SHOCK HAEMORRHAGIC			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
MAMMOPLASTY			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal			

conditions				
CERVICAL INCOMPETENCE				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ANEMBRYONIC GESTATION				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PRE-ECLAMPSIA				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ABORTION SPONTANEOUS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
PYREXIA				
subjects affected / exposed	5 / 352 (1.42%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
CHEST PAIN				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INFLAMMATION				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
DRUG HYPERSENSITIVITY				

subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
PROSTATITIS			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
DYSMENORRHOEA			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
GENITAL PROLAPSE			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HEAVY MENSTRUAL BLEEDING			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MENOPAUSAL SYMPTOMS			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ENDOMETRIOSIS			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CERVICAL POLYP			

subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
OVARIAN CYST				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
ABNORMAL UTERINE BLEEDING				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ENDOMETRIAL HYPERTROPHY				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
OVARIAN CYST RUPTURED				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
UTERINE PROLAPSE				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MENORRHAGIA				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
SINUS CONGESTION				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HYPERVENTILATION				

subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PLEURAL EFFUSION				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DYSPNOEA				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ASTHMA				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CHRONIC OBSTRUCTIVE PULMONARY DISEASE				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
NASAL SEPTUM DEVIATION				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PULMONARY EMBOLISM				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ACUTE RESPIRATORY FAILURE				
subjects affected / exposed	2 / 352 (0.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
DEPRESSION				

subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MENTAL STATUS CHANGES				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PSYCHOGENIC TREMOR				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SUICIDAL IDEATION				
subjects affected / exposed	2 / 352 (0.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
AFFECTIVE DISORDER				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COMPLETED SUICIDE				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
ANXIETY				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SUICIDE ATTEMPT				
subjects affected / exposed	2 / 352 (0.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Product issues				
DEVICE DISLOCATION				

subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
PORTAL VEIN THROMBOSIS			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
CHOLECYSTITIS			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CHOLELITHIASIS			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
LIVER DISORDER			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
LIVER INJURY			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
GALLBLADDER MUCOCOELE			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CHOLECYSTITIS CHRONIC			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			

ALANINE AMINOTRANSFERASE INCREASED				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
WEIGHT DECREASED				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
TENDON DISLOCATION				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
OVERDOSE				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MUSCLE RUPTURE				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FEMORAL NECK FRACTURE				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PROCEDURAL PAIN				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CRANIOCEREBRAL INJURY				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

HUMERUS FRACTURE			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CONCUSSION			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
RADIUS FRACTURE			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MULTIPLE INJURIES			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ACETABULUM FRACTURE			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SUBDURAL HAEMATOMA			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
FEMUR FRACTURE			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
FOOT FRACTURE			
subjects affected / exposed	0 / 352 (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 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INFUSION RELATED REACTION				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
UPPER LIMB FRACTURE				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
JOINT DISLOCATION				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MUSCLE STRAIN				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ANKLE FRACTURE				
subjects affected / exposed	2 / 352 (0.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
POST LUMBAR PUNCTURE SYNDROME				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
TIBIA FRACTURE				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HAND FRACTURE				

subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COMMINUTED FRACTURE				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PERIPROSTHETIC FRACTURE				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ALCOHOL POISONING				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
FIBULA FRACTURE				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
POSTOPERATIVE RESPIRATORY FAILURE				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
TENDON RUPTURE				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
FRACTURE DISPLACEMENT				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				

HYPERTROPHIC CARDIOMYOPATHY				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PHIMOSIS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
CORONARY ARTERY OCCLUSION				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ATRIOVENTRICULAR BLOCK COMPLETE				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ANGINA UNSTABLE				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CONGESTIVE CARDIOMYOPATHY				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CORONARY ARTERY DISEASE				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ATRIAL FIBRILLATION				
subjects affected / exposed	2 / 352 (0.57%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			

PERICARDITIS			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ATRIAL FLUTTER			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CARDIAC ARREST			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ACUTE CORONARY SYNDROME			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
LEFT VENTRICULAR DYSFUNCTION			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MYOCARDIAL INFARCTION			
subjects affected / exposed	4 / 352 (1.14%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
ANGINA PECTORIS			

subjects affected / exposed	4 / 352 (1.14%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
CEREBRAL ISCHAEMIA			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
POLYNEUROPATHY			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SYNCOPE			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MIGRAINE			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SCIATICA			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HEMIPARESIS			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DIZZINESS			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CARPAL TUNNEL SYNDROME			

subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PARTIAL SEIZURES WITH SECONDARY GENERALISATION				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CEREBROVASCULAR ACCIDENT				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
EPILEPSY				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
TRIGEMINAL NEURALGIA				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MYELOPATHY				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FACIAL PARESIS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
RUPTURED CEREBRAL ANEURYSM				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CERVICAL RADICULOPATHY				

subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MULTIPLE SCLEROSIS RELAPSE				
subjects affected / exposed	5 / 352 (1.42%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
HEADACHE				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
DYSARTHRIA				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SEIZURE				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
APHASIA				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
IRON DEFICIENCY ANAEMIA				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ANAEMIA				
subjects affected / exposed	2 / 352 (0.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
LEUKOPENIA				

subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
VESTIBULAR DISORDER			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
VISION BLURRED			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
RETINAL ARTERY OCCLUSION			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
UVEITIS			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
CATARACT			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
RETINAL DETACHMENT			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
COLITIS			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

CROHN'S DISEASE				
subjects affected / exposed	2 / 352 (0.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
INGUINAL HERNIA				
subjects affected / exposed	2 / 352 (0.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
GASTROINTESTINAL INFLAMMATION				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
INTRA-ABDOMINAL FLUID COLLECTION				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GASTRIC PERFORATION				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GASTROINTESTINAL ULCER HAEMORRHAGE				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ABDOMINAL INCARCERATED HERNIA				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
IMPAIRED GASTRIC EMPTYING				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GASTRITIS				

subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DIARRHOEA				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
DYSPHAGIA				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
SMALL INTESTINAL OBSTRUCTION				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FUNCTIONAL GASTROINTESTINAL DISORDER				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ABDOMINAL PAIN				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PANCREATITIS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SUBILEUS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LARGE INTESTINAL STENOSIS				

subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PEPTIC ULCER				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PANCREATITIS ACUTE				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
ERYTHEMA MULTIFORME				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ERYTHEMA NODOSUM				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HIDRADENITIS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
ACUTE KIDNEY INJURY				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
URETEROLITHIASIS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
URINARY RETENTION				

subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
NEPHROLITHIASIS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
MUSCULOSKELETAL DISCOMFORT				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
RHABDOMYOLYSIS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SPINAL RETROLISTHESIS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MUSCLE SPASMS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
JAW CYST				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
THORACIC SPINAL STENOSIS				
subjects affected / exposed	0 / 352 (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 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ARTHRALGIA				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
BACK PAIN				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
TRIGGER FINGER				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HAEMARTHROSIS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
OSTEOARTHRITIS				
subjects affected / exposed	2 / 352 (0.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
RHEUMATOID ARTHRITIS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CERVICAL SPINAL STENOSIS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
BRONCHITIS				

subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PERIORBITAL CELLULITIS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SALPINGITIS				
subjects affected / exposed	2 / 352 (0.57%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
SALPINGO-OOPHORITIS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ENCEPHALITIS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PYELONEPHRITIS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
INFECTIVE THROMBOSIS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	8 / 352 (2.27%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 3			
CHRONIC SINUSITIS				

subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
INFLUENZA				
subjects affected / exposed	2 / 352 (0.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
POST-ACUTE COVID-19 SYNDROME				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MENINGITIS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SINUSITIS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
TONSILLITIS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ANAL ABSCESS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
MASTOIDITIS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
RESPIRATORY SYNCYTIAL VIRUS INFECTION				

subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PERIRECTAL ABSCESS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
NEUROBORRELIOSIS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
TUBERCULOSIS BLADDER				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
URINARY TRACT INFECTION				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PULMONARY SEPSIS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SEPSIS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA ASPIRATION				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
BILIARY SEPSIS				

subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CYSTITIS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
CELLULITIS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
APPENDICITIS PERFORATED				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SEPTIC SHOCK				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CHOLECYSTITIS INFECTIVE				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
TOOTH ABSCESS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
VIRAL INFECTION				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PILONIDAL DISEASE				

subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
GASTROENTERITIS			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
TUBO-OVARIAN ABSCESS			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DENGUE FEVER			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PULMONARY TUBERCULOSIS			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
APPENDICITIS			
subjects affected / exposed	3 / 352 (0.85%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
COVID-19 PNEUMONIA			
subjects affected / exposed	20 / 352 (5.68%)		
occurrences causally related to treatment / all	6 / 23		
deaths causally related to treatment / all	1 / 5		
SEPTIC ARTHRITIS STAPHYLOCOCCAL			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			

subjects affected / exposed	6 / 352 (1.70%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA BACTERIAL				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HERPES SIMPLEX				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SYSTEMIC CANDIDA				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HERPES SIMPLEX MENINGITIS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ENTEROCOLITIS INFECTIOUS				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PYELONEPHRITIS ACUTE				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PERITONITIS				
subjects affected / exposed	0 / 352 (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 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INFECTED DERMAL CYST				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
DEVICE RELATED INFECTION				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ABDOMINAL ABSCESS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ENDOCARDITIS				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
LYME DISEASE				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ABSCESS LIMB				
subjects affected / exposed	0 / 352 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
RESPIRATORY TRACT INFECTION				
subjects affected / exposed	1 / 352 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GENITAL HERPES SIMPLEX				

subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
PELVIC INFLAMMATORY DISEASE			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
WOUND INFECTION			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
GLUCOSE TOLERANCE IMPAIRED			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HYPERNATRAEMIA			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
TYPE 2 DIABETES MELLITUS			
subjects affected / exposed	1 / 352 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Interferon Beta- 1a + Placebo (Double Blind Period)	Ocrelizumab + Placebo (Double Blind Period)	Interferon Beta-1a + Placebo (Open Label Extension)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	303 / 409 (74.08%)	264 / 408 (64.71%)	285 / 326 (87.42%)
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
subjects affected / exposed	31 / 409 (7.58%)	126 / 408 (30.88%)	83 / 326 (25.46%)
occurrences (all)	47	236	172
FALL			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	19 / 326 (5.83%)
occurrences (all)	0	0	22
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	23 / 326 (7.06%)
occurrences (all)	0	0	24
Nervous system disorders			
HEADACHE			
subjects affected / exposed	53 / 409 (12.96%)	33 / 408 (8.09%)	46 / 326 (14.11%)
occurrences (all)	62	52	57
MULTIPLE SCLEROSIS RELAPSE			
subjects affected / exposed	132 / 409 (32.27%)	90 / 408 (22.06%)	82 / 326 (25.15%)
occurrences (all)	206	133	163
PARAESTHESIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	17 / 326 (5.21%)
occurrences (all)	0	0	28
HYPOAESTHESIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	19 / 326 (5.83%)
occurrences (all)	0	0	40
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	24 / 326 (7.36%)
occurrences (all)	0	0	35
FATIGUE			
subjects affected / exposed	29 / 409 (7.09%)	21 / 408 (5.15%)	34 / 326 (10.43%)
occurrences (all)	33	22	52
INFLUENZA LIKE ILLNESS			

subjects affected / exposed	85 / 409 (20.78%)	14 / 408 (3.43%)	0 / 326 (0.00%)
occurrences (all)	97	14	0
INJECTION SITE ERYTHEMA			
subjects affected / exposed	73 / 409 (17.85%)	0 / 408 (0.00%)	0 / 326 (0.00%)
occurrences (all)	75	0	0
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	22 / 326 (6.75%)
occurrences (all)	0	0	25
NAUSEA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	12 / 326 (3.68%)
occurrences (all)	0	0	13
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	26 / 326 (7.98%)
occurrences (all)	0	0	32
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	19 / 326 (5.83%)
occurrences (all)	0	0	23
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	15 / 409 (3.67%)	21 / 408 (5.15%)	0 / 326 (0.00%)
occurrences (all)	15	22	0
ANXIETY			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	15 / 326 (4.60%)
occurrences (all)	0	0	17
DEPRESSION			
subjects affected / exposed	26 / 409 (6.36%)	27 / 408 (6.62%)	24 / 326 (7.36%)
occurrences (all)	26	31	28
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	20 / 409 (4.89%)	24 / 408 (5.88%)	32 / 326 (9.82%)
occurrences (all)	24	27	40
MUSCLE SPASMS			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	19 / 326 (5.83%)
occurrences (all)	0	0	24
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	27 / 326 (8.28%)
occurrences (all)	0	0	34
ARTHRALGIA			
subjects affected / exposed	30 / 409 (7.33%)	27 / 408 (6.62%)	46 / 326 (14.11%)
occurrences (all)	35	31	57
Infections and infestations			
PNEUMONIA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	19 / 326 (5.83%)
occurrences (all)	0	0	24
SINUSITIS			
subjects affected / exposed	25 / 409 (6.11%)	18 / 408 (4.41%)	41 / 326 (12.58%)
occurrences (all)	28	22	68
BRONCHITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	46 / 326 (14.11%)
occurrences (all)	0	0	65
HERPES ZOSTER			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	18 / 326 (5.52%)
occurrences (all)	0	0	20
INFLUENZA			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	30 / 326 (9.20%)
occurrences (all)	0	0	33
NASOPHARYNGITIS			
subjects affected / exposed	40 / 409 (9.78%)	42 / 408 (10.29%)	68 / 326 (20.86%)
occurrences (all)	52	60	138
CONJUNCTIVITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	11 / 326 (3.37%)
occurrences (all)	0	0	11
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	35 / 409 (8.56%)	59 / 408 (14.46%)	89 / 326 (27.30%)
occurrences (all)	44	82	181
COVID-19			

subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	96 / 326 (29.45%)
occurrences (all)	0	0	117
GASTROENTERITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	18 / 326 (5.52%)
occurrences (all)	0	0	22
CYSTITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	21 / 326 (6.44%)
occurrences (all)	0	0	25
ORAL HERPES			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	18 / 326 (5.52%)
occurrences (all)	0	0	59
PHARYNGITIS			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	17 / 326 (5.21%)
occurrences (all)	0	0	20
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	24 / 326 (7.36%)
occurrences (all)	0	0	29
URINARY TRACT INFECTION			
subjects affected / exposed	56 / 409 (13.69%)	52 / 408 (12.75%)	80 / 326 (24.54%)
occurrences (all)	81	92	236
VIRAL INFECTION			
subjects affected / exposed	0 / 409 (0.00%)	0 / 408 (0.00%)	19 / 326 (5.83%)
occurrences (all)	0	0	32

Non-serious adverse events	Ocrelizumab + Placebo (Open Label Extension)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	286 / 352 (81.25%)		
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
subjects affected / exposed	71 / 352 (20.17%)		
occurrences (all)	179		
FALL			
subjects affected / exposed	8 / 352 (2.27%)		
occurrences (all)	11		
Vascular disorders			

HYPERTENSION			
subjects affected / exposed	20 / 352 (5.68%)		
occurrences (all)	23		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	40 / 352 (11.36%)		
occurrences (all)	47		
MULTIPLE SCLEROSIS RELAPSE			
subjects affected / exposed	84 / 352 (23.86%)		
occurrences (all)	158		
PARAESTHESIA			
subjects affected / exposed	18 / 352 (5.11%)		
occurrences (all)	23		
HYPOAESTHESIA			
subjects affected / exposed	16 / 352 (4.55%)		
occurrences (all)	23		
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	25 / 352 (7.10%)		
occurrences (all)	29		
FATIGUE			
subjects affected / exposed	36 / 352 (10.23%)		
occurrences (all)	45		
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences (all)	0		
INJECTION SITE ERYTHEMA			
subjects affected / exposed	0 / 352 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	16 / 352 (4.55%)		
occurrences (all)	18		
NAUSEA			
subjects affected / exposed	19 / 352 (5.40%)		
occurrences (all)	22		

Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	 30 / 352 (8.52%) 46		
Skin and subcutaneous tissue disorders RASH subjects affected / exposed occurrences (all)	 8 / 352 (2.27%) 12		
Psychiatric disorders INSOMNIA subjects affected / exposed occurrences (all) ANXIETY subjects affected / exposed occurrences (all) DEPRESSION subjects affected / exposed occurrences (all)	 0 / 352 (0.00%) 0 23 / 352 (6.53%) 28 45 / 352 (12.78%) 55		
Musculoskeletal and connective tissue disorders BACK PAIN subjects affected / exposed occurrences (all) MUSCLE SPASMS subjects affected / exposed occurrences (all) PAIN IN EXTREMITY subjects affected / exposed occurrences (all) ARTHRALGIA subjects affected / exposed occurrences (all)	 36 / 352 (10.23%) 46 11 / 352 (3.13%) 12 24 / 352 (6.82%) 34 29 / 352 (8.24%) 43		
Infections and infestations PNEUMONIA subjects affected / exposed occurrences (all) SINUSITIS	 15 / 352 (4.26%) 15 		

subjects affected / exposed	49 / 352 (13.92%)			
occurrences (all)	75			
BRONCHITIS				
subjects affected / exposed	51 / 352 (14.49%)			
occurrences (all)	91			
HERPES ZOSTER				
subjects affected / exposed	13 / 352 (3.69%)			
occurrences (all)	18			
INFLUENZA				
subjects affected / exposed	24 / 352 (6.82%)			
occurrences (all)	30			
NASOPHARYNGITIS				
subjects affected / exposed	73 / 352 (20.74%)			
occurrences (all)	156			
CONJUNCTIVITIS				
subjects affected / exposed	19 / 352 (5.40%)			
occurrences (all)	26			
UPPER RESPIRATORY TRACT INFECTION				
subjects affected / exposed	90 / 352 (25.57%)			
occurrences (all)	182			
COVID-19				
subjects affected / exposed	96 / 352 (27.27%)			
occurrences (all)	110			
GASTROENTERITIS				
subjects affected / exposed	16 / 352 (4.55%)			
occurrences (all)	25			
CYSTITIS				
subjects affected / exposed	16 / 352 (4.55%)			
occurrences (all)	21			
ORAL HERPES				
subjects affected / exposed	21 / 352 (5.97%)			
occurrences (all)	63			
PHARYNGITIS				
subjects affected / exposed	16 / 352 (4.55%)			
occurrences (all)	23			

RESPIRATORY TRACT INFECTION			
subjects affected / exposed	24 / 352 (6.82%)		
occurrences (all)	31		
URINARY TRACT INFECTION			
subjects affected / exposed	101 / 352 (28.69%)		
occurrences (all)	296		
VIRAL INFECTION			
subjects affected / exposed	17 / 352 (4.83%)		
occurrences (all)	24		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 June 2011	Study design was changed from rater blind to double blind, double dummy design to improve robustness of the study. - 400 mg dose of ocrelizumab was removed leaving a single dose of ocrelizumab 600 mg; therefore total number of patients was decreased from 1200 to 800 - eligibility criteria was amended to further characterize benefits of treatment with ocrelizumab in wide range of patients with different disease activity and severity of RMS. - screening period has been decreased from 4 weeks to 2 weeks -Biomarkers DNA sampling was added to protocol to identify dynamic biomarkers that are predictive of response to ocrelizumab treatment - Karnofsky Performance Scale, Low Contrast Vision Acuity testing and Symbol Digit Modality Test were implemented to support assessment of disability and to facilitate evaluation of benefit risk profile of ocrelizumab. - open-label extension phase of study will be conducted as separate extension study under new protocol.
15 June 2012	Protocol was amended to provide greater clarity in protocol language around expedited reporting of SAEs - Revised dosing preparation and infusion guidance to simplify procedures - Refined some aspects of inclusion/exclusion criteria - Refined several operational aspects of the study conduct -Informed sites of additional, optional sub-studies conducted at select centers in which patients in this trial may be eligible to participate
14 March 2013	Protocol amended to include an Open-Label Extension Phase and clarify how sustained disability progression is calculated. - Provided Sponsor update on anti-CD20 therapies - added 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. - Optional investigator-sponsored Roche-supported exploratory sub-studies being conducted at selected sites have been converted to Roche-sponsored studies as per current policy of the sponsor. - Mandatory biomarker analysis plan was revised and will include but is not limited to interleukin-6; the B-cell activating factor (BAFF) and Complement Factor H (CFH) will not be analyzed. - Inclusion of ocrelizumab concentration sample during the open label extension phase of the study. - Optional Roche Clinical Repository Sampling (RCR sampling) has now been discontinued from the open-label extension and safety follow-up phases of the study. -Local versions of WA21092 protocol (UK, GER) was consolidated into main body of revised protocol - WA21092 Coordinating Investigator for study was specified in protocol - Various minor changes and clarifications was made to improve clarity and consistency of protocol
04 March 2016	Clarification of the following: 1. objectives of the open-label extension (OLE) phase, 2. permittance of alternative MS treatments and prolongation of safety follow-up period for patients switching to other MS therapies post-ocrelizumab, 3. Patient Agreement for Continuation in the Study in Case of Confirmed Disability Progression, 4. duration of OLE phase. 5. schedule of assessments in OLE phase of study to improve consistency and data collection - Voluntary collection of pregnancy outcomes and infant health information on first year of life. - Update to telephone interview script. - Visual Evoked Potential (VEP) assessments in the OCT sub-study schedule of assessments have been amended - A change in version of ocrelizumab that will be administered across programme has been detailed in protocol.

04 October 2017	The protocol safety wording was substantially amended. - 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) - Requirement for antihistamines pre-treatment -Removal of contraception requirements for male patients and female partner reporting - Changes to contraception requirements, duration of contraception, and procedures for pregnant women during the OLE - End of study for optical coherence tomography exploratory substudy
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 - Updated language pertaining to impairment of vaccination response -Clarification regarding re-treatment with ocrelizumab for patients with active tuberculosis (TB) and for pregnant or breastfeeding female patients - Addition of information regarding exposure in utero to ocrelizumab and vaccination of neonates and infants with live or live-attenuated viruses.
18 December 2019	The WA21092 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 - Guidance for diagnosis of PML has been updated - Guidance for reporting abortions has been updated - Reference to Medical Monitor has been changed where applicable and the emergency contact information has been updated - Language has been added to clarify that, after withdrawal of consent for participation in the Research Biosample Repository (RBR), remaining RBR samples will be destroyed or will no longer be linked to the patient
27 July 2020	Protocol was amended to incorporate the option of a shorter study drug infusion regimen - shorter infusion regimen of 2 hours (about 3.5 to 4 hours in total)
19 November 2021	Introduced the option of a rollover study (MN43964), into which all ongoing participants can enroll during the course of 2022. -a reduction in the safety follow-up period and the incorporation of the risk assessment of vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for the participant population were implemented in the protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported