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	

Results information

Result version number	v1
This version publication date	03 June 2016
First version publication date	03 June 2016

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	02 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 April 2015
Global end of trial reached?	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: 3
Country: Number of subjects enrolled	Brazil: 18
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Peru: 22
Country: Number of subjects enrolled	Russian Federation: 67
Country: Number of subjects enrolled	Serbia: 19
Country: Number of subjects enrolled	Tunisia: 8
Country: Number of subjects enrolled	Ukraine: 30
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	United States: 210
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 69
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Austria: 3

Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Bulgaria: 38
Country: Number of subjects enrolled	Czech Republic: 130
Country: Number of subjects enrolled	Estonia: 16
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Latvia: 12
Country: Number of subjects enrolled	Lithuania: 17
Worldwide total number of subjects	821
EEA total number of subjects	409

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 subjects were screened for entry into the study. 821 subjects were entered into the double-blind treatment period. Subjects 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	Double Blind Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Treatment was administered in a double-blind, double-dummy fashion in order to maintain blinding.

Arms

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

Arm description:

Subjects with relapsing multiple sclerosis (RMS) who experienced at least either two documented clinical relapses within 2 years or one clinical relapse within 1 year prior to screening received interferon beta-1a three times per week (with placebo infusions matching ocrelizumab every 24 weeks).

Arm type	Active comparator
Investigational medicinal product name	Interferon beta-1a
Investigational medicinal product code	
Other name	Rebif
Pharmaceutical forms	Solution for injection
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).

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

Dosage and administration details:

Subjects received placebo infusions matching ocrelizumab infusions of 300 mg on Days 1 and 15 for the first dose and as a single infusion of 600 mg for all subsequent doses every 24 weeks.

Arm title	Ocrelizumab

Arm description:

Subjects with RMS who experienced at least either two documented clinical relapses within 2 years or one clinical relapse within 1 year prior to screening received ocrelizumab 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.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received placebo injections matching interferon beta-1a SC three times per week.

Number of subjects in period 1	Interferon beta-1a 44 mcg SC	Ocrelizumab
Started	411	410
Completed	340	366
Not completed	71	44
Consent withdrawn by subject	13	8
Physician decision	-	1
Adverse Event	25	13
Death	1	-
Pregnancy	2	3
Non-compliance with study drug	3	-
Non-compliance	2	-
Protocol Violation	1	2
Unspecified	11	8
Lost to follow-up	1	1
Lack of efficacy	12	8

Baseline characteristics

Reporting groups	
Reporting group title	Interferon beta-1a 44 mcg SC
Reporting group description:	
Subjects with relapsing multiple sclerosis (RMS) who experienced at least either two documented clinical relapses within 2 years or one clinical relapse within 1 year prior to screening received interferon beta-1a three times per week (with placebo infusions matching ocrelizumab every 24 weeks).	
Reporting group title	Ocrelizumab
Reporting group description:	
Subjects with RMS who experienced at least either two documented clinical relapses within 2 years or one clinical relapse within 1 year prior to screening received ocrelizumab every 24 weeks (with placebo injections matching interferon beta-1a SC three times per week).	

Reporting group values	Interferon beta-1a 44 mcg SC	Ocrelizumab	Total
Number of subjects	411	410	821
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 36.9 ± 9.3	 37.1 ± 9.3	 -
Gender categorical Units: Subjects			
Female	272	270	542
Male	139	140	279

End points

End points reporting groups

Reporting group title	Interferon beta-1a 44 mcg SC

Reporting group description:

Subjects with relapsing multiple sclerosis (RMS) who experienced at least either two documented clinical relapses within 2 years or one clinical relapse within 1 year prior to screening received interferon beta-1a three times per week (with placebo infusions matching ocrelizumab every 24 weeks).

Reporting group title	Ocrelizumab

Reporting group description:

Subjects with RMS who experienced at least either two documented clinical relapses within 2 years or one clinical relapse within 1 year prior to screening received ocrelizumab every 24 weeks (with placebo injections matching interferon beta-1a SC three times per week).

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

End point title	Annualised Relapse Rate (ARR) in Subjects With Relapsing Multiple Sclerosis (MS) at 96 Weeks

End point description:

ARR was calculated as the total number of relapses for all subjects in the treatment group divided by the total subject-years of exposure to that treatment. Intent-to-treat (ITT) population included all randomised subjects in the study.

End point type	Primary

End point timeframe:

Week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	410		
Units: relapses				
number (confidence interval 95%)	0.292 (0.235 to 0.361)	0.156 (0.122 to 0.2)		

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 44 mcg SC v Ocrelizumab

Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Negative Binomial Model
Parameter estimate	Ratio (Ocrelizumab / Interferon beta-1a)
Point estimate	0.536
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.719

Secondary: Time to Onset of Confirmed Disability Progression (CDP) for at Least 12 and 24 Weeks During the Double Blind Treatment Period

End point title	Time to Onset of Confirmed Disability Progression (CDP) for at Least 12 and 24 Weeks During the Double Blind Treatment Period

End point description:

Disability progression was defined as an increase in the 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
This endpoint 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 or 24 weeks after the initial documentation of neurological worsening. ITT population included all randomised subjects in the study. 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 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
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:

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 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	superiority
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

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 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	superiority
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: 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 subjects in the treatment group divided by the total number of brain MRI scans. The total number of lesions is calculated as the sum of the individual number of lesions at Weeks 24, 48, and 96. ITT population included all randomised subjects in the study.

End point type	Secondary

End point timeframe:

Baseline up to week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	410		
Units: lesions				
number (not applicable)	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 44 mcg SC v Ocrelizumab
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: 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 subjects in the treatment group divided by the total number of brain MRI scans. The total number of lesions is calculated as the sum of the individual number of lesions at Weeks 24, 48, and 96. ITT population included all randomised subjects in the study.	
End point type	Secondary
End point timeframe:	
Baseline up to week 96	

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	410		
Units: lesions				
number (not applicable)	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 44 mcg SC v Ocrelizumab
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 Subjects With Confirmed Disability Improvement (CDI) for at Least 12 Weeks

End point title	Percentage of Subjects With Confirmed Disability Improvement (CDI) for at Least 12 Weeks
End point description:	
Disability improvement was assessed only for the subgroup of subjects 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. This endpoint was considered confirmatory only when results of both studies WA21092 and WA21093 were combined. ITT population included all randomised subjects in the study. Here, number of subjects analysed signifies number of subjects who were evaluable for the endpoint.	
End point type	Secondary
End point timeframe:	
Week 96	

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	306[1]	310		
Units: percentage of subjects				
number (confidence interval 95%)	12.42 (8.94 to 16.64)	20 (15.69 to 24.89)		

Notes:

[1] - Number of subjects who were evaluable for this endpoint.

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 44 mcg SC v Ocrelizumab
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 subjects in the treatment group divided by the total number of brain MRI scans. The total number of lesions is calculated as the sum of the individual number of new lesions at Weeks 24, 48, and 96. ITT population included all randomised subjects in the study.	
End point type	Secondary
End point timeframe:	
Baseline up to week 96	

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	410		
Units: lesions				
number (not applicable)	1307	564		

Statistical analyses

Statistical analysis title	T1 Hypointense Lesions

Statistical analysis description:

Adjusted by baseline T1-hypointense lesion count, baseline EDSS (<4.0 vs. >=4.0) and geographical region (US vs. ROW).

Comparison groups	Interferon beta-1a 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Adjusted rate ratio
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: 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 subjects 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 + Zcognitive} /3.0.
The results from each of these three tests are transformed into Z scores and averaged to yield a composite score for each subject at each time point. ITT population included all randomised subjects in the study. Here, n signifies the number of subjects evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	410		
Units: units on a scale				
arithmetic mean (standard error)				
Unadjusted Baseline mean (n= 359, 360)	0.028 (± 0.034)	-0.012 (± 0.04)		
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 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	superiority
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. ITT population included all
randomised subjects in the study. Here, number of subjects analysed signifies number of subjects who were evaluable for the endpoint.

End point type	Secondary

End point timeframe:

From Week 24 up to Week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	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 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0042
Method	MMRM
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.

Descriptive statistics at baseline include subjects with assessment at baseline and at least one post-baseline value. ITT population included all randomised subjects in the study. Here, n signifies the number of subjects evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	410		
Units: units on a scale				
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 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2193
Method	MMRM
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 Subjects who Have No Evidence of Disease Activity (NEDA) up to Week 96

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

End point description:

NEDA was defined only for subjects with a baseline EDSS score >=2.0. Subjects who completed the 96 week treatment period were considered as having evidence of disease activity if at least one protocol-defined relapse (PDR), a 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 subject was considered as having NEDA. ITT population included all randomised subjects in the study. Here, number of subjects analysed signifies number of subjects who were evaluable for the endpoint.

End point type	Secondary

End point timeframe:

Week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291[2]	289[3]		
Units: percentage of subjects				
number (confidence interval 95%)	27.1 (22.1 to 32.6)	47.4 (41.5 to 53.3)		

Notes:

[2] - Number of subjects who were evaluable for this endpoint.

[3] - Number of subjects who were evaluable for this endpoint.

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 44 mcg SC v Ocrelizumab
Number of subjects included in analysis	580
Analysis specification	Pre-specified
Analysis type	superiority
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 Subjects With Adverse Events (AEs)

End point title	Number of Subjects 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 Week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	409	408		
Units: subjects	331	327		

Statistical analyses

No statistical analyses for this end point

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

End point title	Exposure to Ocrelizumab (Area Under the Concentration - Time Curve)[4]

End point description:

The pharmacokinetics population included all subjects in the ocrelizumab group who had at least 1 measurable concentration value.

End point type	Secondary

End point timeframe:

Week 96

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Number of subjects positive for anti-drug antibodies (ADAs) to ocrelizumab is the number of post-baseline evaluable subjects determined to have treatment-induced ADA or treatment-enhanced ADA during the study period. Baseline evaluable subjects with an ADA assay result from a baseline sample(s). The safety population included all subjects who received any study drug. Here, n signifies the number of subjects evaluable at the specified time points.

End point type	Secondary

End point timeframe:

Baseline up to week 96

End point values	Interferon beta-1a 44 mcg SC	Ocrelizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	409	408		
Units: subjects				
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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to Week 96 (Double Blind Treatment Period)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Interferon beta-1a

Reporting group description:

Subjects with relapsing multiple sclerosis (RMS) who experienced at least either two documented clinical attacks within 2 years or one clinical attack within 1 year prior to screening received interferon beta-1a three times per week (with placebo infusions matching ocrelizumab every 24 weeks).

Reporting group title	Ocrelizumab

Reporting group description:

Subjects with RMS who experienced at least either two documented clinical attacks within 2 years or one clinical attack within 1 year prior to screening received ocrelizumab every 24 weeks (with placebo injections matching interferon beta-1a SC three times per week).

Serious adverse events	Interferon beta-1a	Ocrelizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 409 (7.82%)	28 / 408 (6.86%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 409 (0.00%)	2 / 408 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	2 / 409 (0.49%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mantle cell lymphoma			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal cancer			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland adenoma			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Mammoplasty			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 409 (0.00%)	2 / 408 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 409 (0.24%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			

subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hyperventilation			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus congestion			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 409 (0.00%)	2 / 408 (0.49%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			

subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	3 / 409 (0.73%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 409 (0.24%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 409 (0.00%)	2 / 408 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured cerebral aneurysm			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancreatitis acute			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 409 (0.00%)	2 / 408 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid Arthritis			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 409 (0.24%)	2 / 408 (0.49%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			

subjects affected / exposed	2 / 409 (0.49%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 409 (0.49%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute tonsillitis			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site cellulitis			

subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic arthritis staphylococcal			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Interferon beta-1a	Ocrelizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	257 / 409 (62.84%)	241 / 408 (59.07%)	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	30 / 409 (7.33%)	125 / 408 (30.64%)	
occurrences (all)	46	234	
Nervous system disorders			
Headache			
subjects affected / exposed	54 / 409 (13.20%)	33 / 408 (8.09%)	
occurrences (all)	64	51	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	85 / 409 (20.78%)	15 / 408 (3.68%)	
occurrences (all)	97	15	
Injection site erythema			

subjects affected / exposed	74 / 409 (18.09%)	0 / 408 (0.00%)	
occurrences (all)	76	0	
Fatigue			
subjects affected / exposed	28 / 409 (6.85%)	21 / 408 (5.15%)	
occurrences (all)	33	22	
Psychiatric disorders			
Depression			
subjects affected / exposed	24 / 409 (5.87%)	28 / 408 (6.86%)	
occurrences (all)	24	32	
Insomnia			
subjects affected / exposed	15 / 409 (3.67%)	21 / 408 (5.15%)	
occurrences (all)	17	22	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	28 / 409 (6.85%)	25 / 408 (6.13%)	
occurrences (all)	29	26	
Back pain			
subjects affected / exposed	20 / 409 (4.89%)	25 / 408 (6.13%)	
occurrences (all)	25	28	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	56 / 409 (13.69%)	52 / 408 (12.75%)	
occurrences (all)	81	93	
Upper respiratory tract infection			
subjects affected / exposed	35 / 409 (8.56%)	59 / 408 (14.46%)	
occurrences (all)	44	83	
Nasopharyngitis			
subjects affected / exposed	43 / 409 (10.51%)	43 / 408 (10.54%)	
occurrences (all)	55	61	
Sinusitis			
subjects affected / exposed	25 / 409 (6.11%)	19 / 408 (4.66%)	
occurrences (all)	27	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 June 2011	1. The study design has been changed from rater blind to double blind, double dummy design to improve the robustness of the study. 2. The 400 mg dose of ocrelizumab has been removed leaving a single dose of ocrelizumab 600 mg; as a consequence the total number of subjects has decreased from 1200 to 800 (due to the removal of the 400 mg dose arm). The 600 mg dose of ocrelizumab has been established as the lowest, maximally effective dose, based on the results from phase II study in RRMS (WA21493/ACT4422g).
15 June 2012	1. Dosing preparation and infusion guidance were revised to simplify the preparation of infusion bags and dosing procedures. 2. Specific eligibility cut-off values for immunoglobulin M (IgM) and immunoglobulin G (IgG) and the re-treatment criteria for IgG were modified to reflect the central lab reference ranges.
14 March 2013	1. Inclusion of an OLE phase under the same protocol.
04 September 2014	1. Update to the Statistical Considerations and Analytical Plan section of the protocol in line with the SAP amendment to implement European Medicines Agency (EMA) Scientific Advice and to increase statistical rigor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported