Clinical trial results:
An Open-Label Study To Evaluate the Efficacy and Safety of Ocrelizumab in Subjects With Relapsing Multiple Sclerosis Who Have A Suboptimal Response to an Adequate Course of Disease-Modifying Treatment

Summary

EudraCT number	2015-005597-38
Trial protocol	GB IE SE ES EE DK DE NL BE CZ FI FR IT
Global end of trial date	

Results information

Result version number	v2 (current)
This version publication date	24 December 2021
First version publication date	29 October 2020
Version creation reason	• New data added to full data set Results maintenance

Trial information

Trial identification

Sponsor protocol code	MA30005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02861014
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
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	Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	20 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 October 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this prospective, multicenter, open-label, efficacy, and safety study is to assess the efficacy and safety of ocrelizumab in subjects with Relapsing Remitting Multiple Sclerosis (RRMS) who have had a suboptimal response to an adequate course of a Disease-Modifying Treatment (DMT).

Protection of trial subjects:

This study was conducted in accordance with the protocol and with the following: - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines - Applicable ICH Good Clinical Practice (GCP) Guidelines - Applicable laws and regulations

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 September 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 98
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Turkey: 26
Country: Number of subjects enrolled	United Kingdom: 48
Country: Number of subjects enrolled	Belgium: 28
Country: Number of subjects enrolled	Czech Republic: 44
Country: Number of subjects enrolled	Denmark: 17
Country: Number of subjects enrolled	Estonia: 15
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 139
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Italy: 200
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Norway: 6
Worldwide total number of subjects	680
EEA total number of subjects	651

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)	680
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

One additional subject was initially enrolled in error and the information provided is based on the ITT population.

Pre-assignment

Screening details:

The study consists of a Screening period (up to 4 weeks), an Open-label treatment period (96 weeks; with last dose administered at Week 72), and a Safety Follow-up period of at least 2 years.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ocrelizumab

Arm description:

Participants received Ocrelizumab as two 300 mg IV infusions on Days 1 and 15 followed by one 600 mg IV infusions administered at Weeks 24, 48, and 72.

Arm type	Experimental
Investigational medicinal product name	Ocrelizumab
Investigational medicinal product code	
Other name	RO4964913
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ocrelizumab is administered as two 300 mg IV infusions on Days 1 and 15 followed by one 600 mg IV infusions administered at Weeks 24, 48, and 72.

Number of subjects in period 1	Ocrelizumab
Started	680
Completed	641
Not completed	39
Physician decision	2
Consent withdrawn by subject	14
Adverse event, non-fatal	7
Study Terminated By Sponsor	3
Death	1
Pregnancy	4
Commercial Ocrelizumab	3
Lack of efficacy	3
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	Ocrelizumab
Reporting group description:	
Participants received Ocrelizumab as two 300 mg IV infusions on Days 1 and 15 followed by one 600 mg IV infusions administered at Weeks 24, 48, and 72.	

Reporting group values	Ocrelizumab	Total	
Number of subjects	680	680	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	680	680	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	34.2		
standard deviation	± 8.6	-	
Sex: Female, Male Units: Participants			
Female	436	436	
Male	244	244	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	3	3	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	625	625	
More than one race	2	2	
Unknown or Not Reported	49	49	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	27	27	
Not Hispanic or Latino	579	579	
Unknown or Not Reported	74	74	

End points

End points reporting groups

Reporting group title	Ocrelizumab

Reporting group description:

Participants received Ocrelizumab as two 300 mg IV infusions on Days 1 and 15 followed by one 600 mg IV infusions administered at Weeks 24, 48, and 72.

Primary: Percentage of Participants With No Evidence of Disease Activity (NEDA) as per Protocol Defined Events During a 96-Week Period

End point title	Percentage of Participants With No Evidence of Disease Activity (NEDA) as per Protocol Defined Events During a 96-Week Period[1]

End point description:

A protocol-defined event of disease activity was defined by the occurrence of at least one of the following while on treatment with ocrelizumab: - A protocol-defined relapse (PDR) - 24-week CDP based on increase in EDSS while on treatment with ocrelizumab - A T1 Gd-enhanced lesion after Week 8 - A new and/or enlarging T2 hyperintense lesion on MRI after Week 8 compared to the Week 8 MRI scan

End point type	Primary

End point timeframe:

Week 96

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses provided

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	658			
Units: Percentage				
number (confidence interval 95%)	74.8 (71.3 to 78.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Free From a Protocol-Defined Event of Disease Activity During 24 Weeks Period

End point title	Percentage of Participants Free From a Protocol-Defined Event of Disease Activity During 24 Weeks Period

End point description:

A protocol-defined event of disease activity was defined by the occurrence of at least one of the following while on treatment with ocrelizumab: - A protocol-defined relapse (PDR) - 24-week CDP based on increase in EDSS while on treatment with ocrelizumab - A T1 Gd-enhanced lesion after Week 8 - A new and/or enlarging T2 hyperintense lesion on MRI after Week 8 compared to the Week 8 MRI scan

End point type	Secondary

End point timeframe:

Baseline up to 24 weeks

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	673			
Units: Percentage				
number (confidence interval 95%)	87.1 (84.3 to 89.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Free From a Protocol-Defined Event of Disease Activity During 48 Weeks Period

End point title	Percentage of Participants Free From a Protocol-Defined Event of Disease Activity During 48 Weeks Period

End point description:

A protocol-defined event of disease activity was defined by the occurrence of at least one of the following while on treatment with ocrelizumab: - A protocol-defined relapse (PDR) - 24-week CDP based on increase in EDSS while on treatment with ocrelizumab - A T1 Gd-enhanced lesion after Week 8 - A new and/or enlarging T2 hyperintense lesion on MRI after Week 8 compared to the Week 8 MRI scan

End point type	Secondary

End point timeframe:

Baseline up to 48 weeks

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	665			
Units: Percentage				
number (confidence interval 95%)	82.6 (79.5 to 85.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Protocol-Defined Event of Disease Activity

End point title	Time to First Protocol-Defined Event of Disease Activity

End point description:

9999 = The median time to onset could not be estimated because more than 50% of the mITT population were event-free at the end of the study.

End point type	Secondary

End point timeframe:

Baseline up to 96 Weeks

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Weeks				
median (confidence interval 95%)	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted mean change from baseline to Week 96 in Expanded Disability Status Scale (EDSS)

End point title	Adjusted mean change from baseline to Week 96 in Expanded Disability Status Scale (EDSS)

End point description:

The EDSS is an ordinal clinical rating scale ranging from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments.

End point type	Secondary

End point timeframe:

Weeks: 24, 48, 72, 96

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Points on scale				
arithmetic mean (standard deviation)				
Week 24	-0.02 (± 0.64)			
Week 48	0.01 (± 0.82)			
Week 72	-0.03 (± 0.85)			
Week 96	-0.01 (± 0.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Confirmed Disability Improvement (CDI), Confirmed Disability Progression (CDP), or Stable Disability, as Assessed Using EDSS Scale

End point title	Percentage of Participants With Confirmed Disability Improvement (CDI), Confirmed Disability Progression (CDP), or Stable Disability, as Assessed Using EDSS Scale

End point description:

The EDSS is an ordinal clinical rating scale ranging from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments.

End point type	Secondary

End point timeframe:

Up to Week 96

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	640			
Units: Percentage				
number (not applicable)				
Confirmed Disability Progression	13.4			
Stable Disability	72.2			
Confirmed Disability Improvement	14.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with a baseline EDSS score ≥2 with CDI at Week 96

End point title	Number of participants with a baseline EDSS score ≥2 with CDI at Week 96

End point description:

The EDSS is an ordinal clinical rating scale ranging from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments.

End point type	Secondary

End point timeframe:

Week 96

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	339			
Units: Percentage				
number (not applicable)	17.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized protocol-defined relapse rate at Week 96

End point title	Annualized protocol-defined relapse rate at Week 96

End point description:

End point type	Secondary

End point timeframe:

Week 96

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Rate				
number (confidence interval 95%)	0.030 (0.023 to 0.038)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of 24-week Confirmed Disability Progression

End point title	Time to onset of 24-week Confirmed Disability Progression

End point description:

9999 = The median time to onset could not be estimated because more than 50% of the mITT population were event-free at the end of the study.

End point type	Secondary

End point timeframe:

Baseline up to 96 Weeks

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Weeks				
median (confidence interval 95%)	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of First Protocol-Defined Relapse

End point title	Time to Onset of First Protocol-Defined Relapse

End point description:

9999 = The median time to onset could not be estimated because more than 50% of the mITT population were event-free at the end of the study.

End point type	Secondary

End point timeframe:

Baseline up to 96 Weeks

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Weeks				
median (confidence interval 95%)	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of first new and/or enlarging T2 lesion

End point title	Time to onset of first new and/or enlarging T2 lesion

End point description:

9999 = The median time to event could not be estimated because more than 50% of the ITT population were event-free at the end of the study.

End point type	Secondary

End point timeframe:

Baseline up to 96 Weeks

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Weeks				
median (confidence interval 95%)	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of T1 Gd-enhancing lesions per MRI scan

End point title	Mean number of T1 Gd-enhancing lesions per MRI scan
End point description:	
9999 = No result could be obtained for Week 96, as the model did not converge.	
End point type	Secondary
End point timeframe:	
Weeks: 24, 48, 96	

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Rate				
number (confidence interval 95%)				
Week 24	0.004 (0.001 to 0.014)			
Week 48	0.004 (0.001 to 0.011)			
Week 96	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 96 in total T2 lesion volume detected by brain MRI from

End point title	Change from baseline to Week 96 in total T2 lesion volume detected by brain MRI from
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Week 96	

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	632			
Units: mL				
arithmetic mean (standard deviation)	-558.6 (± 1194.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline to Week 96 in total T2 lesion volume detected by brain MRI

End point title	Percentage change from baseline to Week 96 in total T2 lesion volume detected by brain MRI

End point description:

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	632			
Units: mL				
arithmetic mean (standard deviation)	-8.5 (± 18.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of new and/or enlarging T2 hyperintense lesions volume of lesions per MRI scan

End point title	Volume of new and/or enlarging T2 hyperintense lesions volume of lesions per MRI scan

End point description:

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: uL				
arithmetic mean (standard deviation)				
Week 24	21.4 (± 241.7)			
Week 48	23.1 (± 510.2)			
Week 96	3.7 (± 41.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of new and/or enlarging T2 hyperintense lesions per MRI scan

End point title	Mean number of new and/or enlarging T2 hyperintense lesions per MRI scan

End point description:

End point type	Secondary

End point timeframe:

Weeks 24, 48, 96

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Rate				
arithmetic mean (confidence interval 95%)				
Week 24	0.053 (0.038 to 0.075)			
Week 48	0.009 (0.004 to 0.017)			
Week 96	0.011 (0.006 to 0.020)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at Week 48 and 96 in T1 hypointense lesion volume

End point title	Change from baseline at Week 48 and 96 in T1 hypointense lesion volume

End point description:

End point type	Secondary

End point timeframe:

Weeks 48, 96

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: mL				
arithmetic mean (standard deviation)				
Week 48	-416.5 (± 1224.3)			
Week 96	-528.5 (± 1144.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline at Week 48 and 96 in T1 hypointense lesion volume

End point title	Percentage change from baseline at Week 48 and 96 in T1 hypointense lesion volume

End point description:

End point type	Secondary

End point timeframe:

Weeks 48, 96

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Percentage				
arithmetic mean (standard deviation)				
Week 48	-4.0 (± 149.7)			
Week 96	-12.5 (± 21.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted mean change from baseline at Week 48 and 96 in T1 hypointense lesion volume

End point title	Adjusted mean change from baseline at Week 48 and 96 in T1 hypointense lesion volume

End point description:

End point type	Secondary

End point timeframe:

Weeks 48, 96

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: mL				
arithmetic mean (confidence interval 95%)				
Week 48	-461.8 (-613.8 to -309.7)			
Week 96	-576.5 (-727.0 to -426.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted mean percentage change from baseline in brain volume

End point title	Adjusted mean percentage change from baseline in brain volume

End point description:

End point type	Secondary

End point timeframe:

Weeks 24, 48, 96

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Percentage				
arithmetic mean (confidence interval 95%)				
Week 24	-0.153 (-0.259 to -0.047)			
Week 48	-0.445 (-0.556 to -0.334)			
Week 96	-0.805 (-0.940 to -0.669)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted mean percentage change from baseline in cortical grey matter

volume	
End point title	Adjusted mean percentage change from baseline in cortical grey matter volume
End point description:	
End point type	Secondary
End point timeframe: Weeks 48, 96	

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Percentage				
arithmetic mean (confidence interval 95%)				
Week 48	-0.312 (-0.606 to -0.019)			
Week 96	-0.618 (-0.928 to -0.308)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted mean percentage change from baseline in white matter volume	
End point title	Adjusted mean percentage change from baseline in white matter volume
End point description:	
End point type	Secondary
End point timeframe: Weeks 48, 96	

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Percentage				
arithmetic mean (confidence interval 95%)				
Week 48	-0.382 (-0.609 to -0.154)			
Week 96	-0.745 (-0.983 to -0.507)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - SDMT Score

End point title	Change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - SDMT Score

End point description:

Brief International Cognitive Assessment for MS (BICAMS) is assessing cognitive processing speed and verbal and visual memory. Symbol Digits Modalities Test (SDMT) is assessing processing speed/working memory.

End point type	Secondary

End point timeframe:

Weeks 48, 96

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Points on scale				
arithmetic mean (standard deviation)				
Week 48	2.5 (± 9.8)			
Week 96	1.3 (± 10.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - BVMT-R Score

End point title	Change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - BVMT-R Score

End point description:

Brief International Cognitive Assessment for MS (BICAMS) is assessing cognitive processing speed and verbal and visual memory. Brief Visuospatial Memory Test-Revised (BVMT-R) is assessing learning and visuospatial memory.

End point type	Secondary

End point timeframe:

Weeks 48, 96

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Points on scale				
arithmetic mean (standard deviation)				
Week 48	-1.9 (± 5.3)			
Week 96	-1.5 (± 5.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - SDMT Score

End point title	Percentage change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - SDMT Score

End point description:

Brief International Cognitive Assessment for MS (BICAMS) is assessing cognitive processing speed and verbal and visual memory. Symbol Digits Modalities Test (SDMT) is assessing processing speed/working memory.

End point type	Secondary

End point timeframe:

Weeks 48, 96

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Percentage				
arithmetic mean (standard deviation)				
Week 48	7.2 (± 30.8)			
Week 96	4.8 (± 30.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - BVMT-R Score

End point title	Percentage change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - BVMT-R

	Score

End point description:

Brief International Cognitive Assessment for MS (BICAMS) is assessing cognitive processing speed and verbal and visual memory. Brief Visuospatial Memory Test-Revised (BVMT-R) is assessing learning and visuospatial memory.

End point type	Secondary

End point timeframe:

Weeks 48, 96

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Percentage				
arithmetic mean (standard deviation)				
Week 48	-4.4 (± 31.1)			
Week 96	-2.0 (± 33.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

End point type	Secondary

End point timeframe:

Baseline up to approximately 3 years 2 months

End point values	Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	680			
Units: Percentage				
number (not applicable)				
Any AE	89.1			
SAE	7.2			
Deaths	0.1			
AEs leading to study drug discontinuation	1.0			
SAEs leading to study drug discontinuation	0.7			
AEs leading to dose modification/interruption	15.0			

Infusion-related reactions (IRRs)	43.2			
Serious IRRs	0.1			
Infections	66.9			
Serious infections	1.6			
Malignancies	0.4			
Pregnancies	0.7			
AE of Grade >=3	11.9			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline to primary cutoff date (up to 3 years 2 months)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Ocrelizumab
Reporting group description:	
Participants received Ocrelizumab as two 300 mg IV infusions on Days 1 and 15 followed by one 600 mg IV infusions administered at Weeks 24, 48, and 72.	

Serious adverse events	Ocrelizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 680 (7.21%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
BENIGN NEOPLASM OF THYMUS			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SQUAMOUS CELL CARCINOMA OF THE CERVIX			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
SHOCK HAEMORRHAGIC			

subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
ABORTION SPONTANEOUS			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
OEDEMA			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
TESTICULAR INFARCTION			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
HAEMORRHAGIC OVARIAN CYST			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
NASAL ULCER			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
COMPLETED SUICIDE			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
DELIRIUM			

subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
DEPRESSION				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
DEPRESSION SUICIDAL				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HALLUCINATION				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
SUICIDE ATTEMPT				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
ANKLE FRACTURE				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FACIAL BONES FRACTURE				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
INFUSION RELATED REACTION				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
RIB FRACTURE				

subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
TENDON INJURY				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
URETERIC INJURY				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
UTERINE RUPTURE				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
ANGINA PECTORIS				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MYOCARDIAL INFARCTION				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
CEREBRAL VENOUS SINUS THROMBOSIS				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GENERALISED TONIC-CLONIC SEIZURE				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

HEADACHE				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MIGRAINE				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MULTIPLE SCLEROSIS RELAPSE				
subjects affected / exposed	3 / 680 (0.44%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
STATUS MIGRAINOSUS				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
SUBARACHNOID HAEMORRHAGE				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
GRANULOCYTOPENIA				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
VERTIGO				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
ABDOMINAL PAIN LOWER				

subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ANAL FISTULA				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COLITIS ULCERATIVE				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CROHN'S DISEASE				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ENTEROCOLITIS				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
LUMBAR HERNIA				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MELAENA				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
TOOTHACHE				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
HEPATITIS				

subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
DERMATITIS ATOPIC			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DERMATITIS ALLERGIC			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
GUTTATE PSORIASIS			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
URTICARIA			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
OSTEONECROSIS			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
ANAL ABSCESS			

subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GASTROENTERITIS				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
OESOPHAGITIS BACTERIAL				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
ORAL BACTERIAL INFECTION				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
SEPSIS				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA				
subjects affected / exposed	2 / 680 (0.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
SINUSITIS				
subjects affected / exposed	3 / 680 (0.44%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
SUPERINFECTION FUNGAL				
subjects affected / exposed	1 / 680 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
URINARY TRACT INFECTION				

subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VARICELLA ZOSTER VIRUS INFECTION			
subjects affected / exposed	1 / 680 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
VIRAL INFECTION			
subjects affected / exposed	1 / 680 (0.15%)		
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	Ocrelizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	531 / 680 (78.09%)		
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
subjects affected / exposed	294 / 680 (43.24%)		
occurrences (all)	569		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	154 / 680 (22.65%)		
occurrences (all)	320		
PARAESTHESIA			
subjects affected / exposed	34 / 680 (5.00%)		
occurrences (all)	47		
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	67 / 680 (9.85%)		
occurrences (all)	106		
PYREXIA			

subjects affected / exposed occurrences (all)	47 / 680 (6.91%) 62		
Gastrointestinal disorders DIARRHOEA subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all)	 42 / 680 (6.18%) 52 38 / 680 (5.59%) 40		
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all) OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	 47 / 680 (6.91%) 56 42 / 680 (6.18%) 55		
Psychiatric disorders INSOMNIA subjects affected / exposed occurrences (all)	 34 / 680 (5.00%) 43		
Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all) BACK PAIN subjects affected / exposed occurrences (all) PAIN IN EXTREMITY subjects affected / exposed occurrences (all)	 37 / 680 (5.44%) 40 57 / 680 (8.38%) 74 47 / 680 (6.91%) 58		
Infections and infestations INFLUENZA subjects affected / exposed occurrences (all) NASOPHARYNGITIS	 92 / 680 (13.53%) 137 		

subjects affected / exposed	210 / 680 (30.88%)		
occurrences (all)	449		
ORAL HERPES			
subjects affected / exposed	55 / 680 (8.09%)		
occurrences (all)	116		
SINUSITIS			
subjects affected / exposed	36 / 680 (5.29%)		
occurrences (all)	58		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	51 / 680 (7.50%)		
occurrences (all)	81		
URINARY TRACT INFECTION			
subjects affected / exposed	70 / 680 (10.29%)		
occurrences (all)	108		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2016	Updates to AE reporting period and safety information and selection criteria. Recommendation on subject observation added. Updates to screening assessments. Update to infusion preparation instructions. Extension of window for laboratory sample collection.
28 March 2017	Change in sample size from 600 to 750 (more subjects were recruited than expected, a result of screening rate being higher than anticipated)
05 October 2017	Updates to core safety text. Requirement added for antihistamine pre-treatment. Removal of California Verbal Learning Test 2 from the BICAMS test battery. Removal of the serum sampling for antibody assay. Extension of time window for laboratory assessments before ocrelizumab infusion.
04 November 2018	Updates to safety risks (substantial change). Information on use of the optional patient diary. Clarification on treatment discontinuation rules for subjects who become pregnant.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported