Clinical trial results:
An Open-Label, Single-Arm Phase IV Study To Assess Ocrelizumab Efficacy, Safety, And Impact On Patient Reported Outcomes (PROS) In Patients With Active Relapsing Multiple Sclerosis

Summary

EudraCT number	2018-000780-91
Trial protocol	FR
Global end of trial date	15 February 2021

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022

Trial information

Trial identification

Sponsor protocol code	ML40359

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03589105
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	Final
Date of interim/final analysis	21 October 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

PRO-MSACTIVE is an open label, single-arm phase IV study evaluating the efficacy, safety and impact of ocrelizumab on patient reported outcomes (PROs) in patients with active relapsing multiple sclerosis (RMS).
The objective of the study was to investigate the impact of ocrelizumab on disease activity in active RMS patients according to Lublin's definition of activity (clinical and/or imaging features). Different PRO questionnaires were also evaluated in the PRO-MSACTIVE study to better understand the impact of disease on symptom severity, fatigue, health-related quality of life, work productivity and treatment satisfaction in patients with active RMS.
Participants received a maximum of 2 treatment doses of ocrelizumab: an initial dose of two 300 milligram (mg) infusions separated by 14 days, followed by one single 600 mg infusion 24 weeks after the first infusion.

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	08 September 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 422
Worldwide total number of subjects	422
EEA total number of subjects	422

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	415
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included adult patients (age ≥18 years) with active RMS (RRMS or SPMS) defined by clinical or imaging features and who might have received prior Disease-Modifying Treatment(s) (DMT).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Active Relapsing Multiple Sclerosis (RMS)

Arm description:

Each participant received an initial dose of two 300 mg infusions of Ocrelizumab each separated by 14 days followed by one single dose of 600 mg 24 weeks after the initial dose.

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:

Two infusions of 300 mg administered 14 days apart.
A single infusion of 600 mg administered 24 weeks after the initial dose.

Arm title	Active Secondary Progressive Multiple Sclerosis (SPMS)

Arm description:

Each participant received an initial dose of two 300 mg infusions of Ocrelizumab each separated by 14 days followed by one single dose of 600 mg 24 weeks after the initial dose.

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:

Two infusions of 300 mg administered 14 days apart.
A single infusion of 600 mg administered 24 weeks after the initial dose.

Number of subjects in period 1	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)
Started	376	46
Completed	343	41
Not completed	33	5
Consent withdrawn by subject	7	2
Physician decision	1	-
Adverse event, non-fatal	4	-
Pregnancy	2	-
Desire for pregnancy	14	1
Lost to follow-up	5	2

Baseline characteristics

Reporting groups

Reporting group title	Active Relapsing Multiple Sclerosis (RMS)
Reporting group description:	
Each participant received an initial dose of two 300 mg infusions of Ocrelizumab each separated by 14 days followed by one single dose of 600 mg 24 weeks after the initial dose.	
Reporting group title	Active Secondary Progressive Multiple Sclerosis (SPMS)
Reporting group description:	
Each participant received an initial dose of two 300 mg infusions of Ocrelizumab each separated by 14 days followed by one single dose of 600 mg 24 weeks after the initial dose.	

Reporting group values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)	Total
Number of subjects	376	46	422
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)	373	42	415
From 65-84 years	3	4	7
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	38.3	50.7	
full range (min-max)	18 to 71	36 to 69	-
Gender Categorical Units: Subjects			
Female	280	31	311
Male	96	15	111

Subject analysis sets

Subject analysis set title	Active Relapsing Multiple Sclerosis (RMS)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Each participant received an initial dose of two 300 mg infusions of Ocrelizumab each separated by 14 days followed by one single dose of 600 mg 24 weeks after the initial dose.	
Subject analysis set title	Active Secondary Progressive Multiple Sclerosis (SPMS)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Each participant received an initial dose of two 300 mg infusions of Ocrelizumab each separated by 14 days followed by one single dose of 600 mg 24 weeks after the initial dose.	
Subject analysis set title	All Subjects
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Each participant received an initial dose of two 300 mg infusions of Ocrelizumab each separated by 14 days followed by one single dose of 600 mg 24 weeks after the initial dose.

Reporting group values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)	All Subjects
Number of subjects	376	46	422
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)	373	42	415
From 65-84 years	3	4	7
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	38.3	50.7	39.7
full range (min-max)	18 to 71	36 to 69	18 to 71
Gender Categorical Units: Subjects			
Female	280	31	311
Male	96	15	111

End points

End points reporting groups

Reporting group title	Active Relapsing Multiple Sclerosis (RMS)
Reporting group description:	
Each participant received an initial dose of two 300 mg infusions of Ocrelizumab each separated by 14 days followed by one single dose of 600 mg 24 weeks after the initial dose.	
Reporting group title	Active Secondary Progressive Multiple Sclerosis (SPMS)
Reporting group description:	
Each participant received an initial dose of two 300 mg infusions of Ocrelizumab each separated by 14 days followed by one single dose of 600 mg 24 weeks after the initial dose.	
Subject analysis set title	Active Relapsing Multiple Sclerosis (RMS)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Each participant received an initial dose of two 300 mg infusions of Ocrelizumab each separated by 14 days followed by one single dose of 600 mg 24 weeks after the initial dose.	
Subject analysis set title	Active Secondary Progressive Multiple Sclerosis (SPMS)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Each participant received an initial dose of two 300 mg infusions of Ocrelizumab each separated by 14 days followed by one single dose of 600 mg 24 weeks after the initial dose.	
Subject analysis set title	All Subjects
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Each participant received an initial dose of two 300 mg infusions of Ocrelizumab each separated by 14 days followed by one single dose of 600 mg 24 weeks after the initial dose.	

Primary: Percentage of participants free of disease activity

End point title	Percentage of participants free of disease activity[1]
End point description:	
This outcome measure evaluates the impact of ocrelizumab on disease activity in participants with active Relapsing Multiple Sclerosis (RMS). Freedom of disease activity is defined as participant without any relapse from enrollment to Week 48 and without T1 Gadolinium-enhancing lesion detected by brain MRI at Week 48 and without any new and/or enlarging T2 lesion detected by brain MRI at Week 48.	
End point type	Primary
End point timeframe:	
From Enrollment to Week 48	

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: Statistician analysis details:
Analysis description: Evaluate the impact of ocrelizumab on disease activity at W48
Analysis type: Descriptive

Statistical test of hypothesis:
Not Applicable (no comparison)

Parameter estimate:
Parameter type: Proportion of patients free of disease activity

End point values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	46		
Units: Percentage of participants				
number (confidence interval 95%)				
Free of disease activity	62.2 (57.1 to 67.2)	71.7 (56.5 to 84.0)		
Presence of disease activity	37.8 (32.8 to 42.9)	28.3 (16.0 to 43.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized relapse rate

End point title	Annualized relapse rate

End point description:

Annualized relapse rate is defined as the total number of clinical relapses divided by the number of participant-years of study treatment exposure. This outcome measure describes the efficacy of ocrelizumab in active RMS participants.

End point type	Secondary

End point timeframe:

At Week 48

End point values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	46		
Units: Rate				
number (confidence interval 95%)				
Adjusted annualized relapse rate at W48	0.1503 (0.1089 to 0.2075)	0.0918 (0.0307 to 0.2742)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with stable, improved, or worsened expanded disability status scale (EDSS)

End point title	Percentage of participants with stable, improved, or worsened expanded disability status scale (EDSS)

End point description:

This outcome measure describes the efficacy of ocrelizumab in active RMS participants. Improvement: change <-0.5; stability: change within the range of [-0.5 ; +0.5]; worsening: change >+0.5

End point type	Secondary

End point timeframe:

From Enrollment to Week 48

End point values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	375	46		
Units: Percentage				
number (confidence interval 95%)				
Missing	0 (0 to 0)	0 (0 to 0)		
Improvement	18.9 (15.1 to 23.2)	2.2 (0.1 to 11.5)		
Stability	65.7 (60.7 to 70.5)	84.8 (71.1 to 93.7)		
Worsening	15.4 (11.9 to 19.5)	13.0 (4.9 to 26.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with disability progression at Week 24 confirmed at Week 48

End point title	Percentage of participants with disability progression at Week 24 confirmed at Week 48

End point description:

This outcome measure describes confirmed disability progression (CDP24) in active RMS participants. Disability progression is defined as an increase in the baseline EDSS score of at least 1.0 point (or 0.5 point if the baseline EDSS score was >5.5).

End point type	Secondary

End point timeframe:

At Week 48

End point values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	46		
Units: Percentage				
number (confidence interval 95%)				
Missing	0 (0 to 0)	0 (0 to 0)		
No Disability Progression	87.5 (83.7 to 90.7)	82.6 (68.6 to 92.2)		
Confirmed Disability Progression	12.5 (9.3 to 16.3)	17.4 (7.8 to 31.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in EDSS

End point title	Mean Change in EDSS

End point description:

This outcome measure describes the efficacy of ocrelizumab in active RMS participants. A Mixed-Effect Model Repeated Measures analysis (MMRM) has been used using all the longitudinal observations at each post-baseline visit.

End point type	Secondary

End point timeframe:

From Baseline to Week 48

End point values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	46		
Units: Number				
least squares mean (standard error)	-0.21 (± 0.05)	0.11 (± 0.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of relapse-free RMS participants

End point title	Percentage of relapse-free RMS participants

End point description:	
This outcome measure describes the efficacy of ocrelizumab in active RMS participants.	
End point type	Secondary
End point timeframe:	
From Enrollment to Week 24 and Week 48	

End point values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	46		
Units: Percentage				
number (confidence interval 95%)				
Relapse-free at W24	89.6 (86.1 to 92.5)	91.3 (79.2 to 97.6)		
Relapse-free at W48	87.2 (83.4 to 90.4)	89.1 (76.4 to 96.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with no T1 gadolinium-enhancing lesion as detected by brain MRI

End point title	Percentage of participants with no T1 gadolinium-enhancing lesion as detected by brain MRI
End point description:	
This outcome measure describes the efficacy of ocrelizumab in active RMS participants.	
End point type	Secondary
End point timeframe:	
At Week 48	

End point values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	46		
Units: Percentage				
number (confidence interval 95%)	82.7 (78.5 to 86.4)	89.1 (76.4 to 96.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with no T1 gadolinium-enhancing lesion and no new and/or enlarging T2 lesion as detected by brain MRI

End point title	Percentage of participants with no T1 gadolinium-enhancing lesion and no new and/or enlarging T2 lesion as detected by brain MRI

End point description:

Composite endpoint combining the absence of T1 Gd and new/enlarging T2 lesions

End point type	Secondary

End point timeframe:

At Week 48

End point values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	46		
Units: Percentage				
number (confidence interval 95%)	66.8 (61.7 to 71.5)	76.1 (61.2 to 87.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with no new and/or enlarging T2 lesion as detected by brain MRI

End point title	Percentage of participants with no new and/or enlarging T2 lesion as detected by brain MRI

End point description:

This outcome measure evaluates the impact of ocrelizumab on disease activity in participants with active RMS.

End point type	Secondary

End point timeframe:

At Week 48

End point values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	46		
Units: Percentage				
number (confidence interval 95%)	74.2 (69.7 to 78.8)	80.4 (66.1 to 90.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the score of MS symptom severity scale (SymptoMScreen)

End point title	Change from baseline in the score of MS symptom severity scale (SymptoMScreen)

End point description:

SymptoMScreen is a PRO questionnaire to rapidly assess the severity of MS symptoms. It comprises 12 distinct domains that are measured on a scale from 0 (not affected at all) to 6 (total limitation). The range of the total SymptoMScreen score is 0-72

End point type	Secondary

End point timeframe:

At Week 24 and Week 48

End point values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	46		
Units: Points on scale				
arithmetic mean (standard deviation)				
Week 24	-1.35 (± 8.36)	-1.27 (± 7.88)		
Week 48	-1.03 (± 9.32)	-0.23 (± 9.32)		
Early Treatment Discontinuation	1.80 (± 8.74)	-4.00 (± 0000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the score of Modified Fatigue Impact Scale (MFIS)

End point title	Change from baseline in the score of Modified Fatigue Impact Scale (MFIS)

End point description:

MFIS consists of 21 items rated on a scale from 0 (never) to 4 (almost always). The items can then be grouped into three subscales (physical, cognitive and psychosocial functioning) and a total score. Higher item scores indicate a greater impact of fatigue on a person's activities. The range for the total MFIS score is 0-84.

End point type	Secondary

End point timeframe:

At Week 24 and Week 48

End point values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	46		
Units: Points on scale				
arithmetic mean (standard deviation)				
Week 24	-2.54 (± 12.86)	-3.47 (± 13.24)		
Week 48	-3.46 (± 13.47)	-1.53 (± 14.24)		
Early Treatment Discontinuation	1.67 (± 11.17)	4.00 (± 0000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the score of EuroQol 5-Dimension Questionnaire (EQ-5D-5L with Visual Analogue Scale (VAS)) for health-related quality of life

End point title	Change from baseline in the score of EuroQol 5-Dimension Questionnaire (EQ-5D-5L with Visual Analogue Scale (VAS)) for health-related quality of life

End point description:

EQ-5D-5L comprise 5 dimensions which are evaluated on 5 grading levels. The VAS (Visual Analogue Scale) is used to assess the patient's health state. It provides the utility score based on the preferences of the general French population. The range for Health State Score is 0 (the worst health you can imagine) to 100 (the best health you can imagine). The range for utility score, based on the French value, is -0,530 to 1.

End point type	Secondary

End point timeframe:

At Week 24 and Week 48

End point values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	46		
Units: Points on scale				
arithmetic mean (standard deviation)				
Health State Score Week 24	3.47 (± 15.68)	0.12 (± 19.3)		
Health State Score Week 48	4.36 (± 16.10)	3.67 (± 24.40)		
Health State Score Early Treatment Discontinuation	1.50 (± 21.48)	15.00 (± 0000)		
Utility Score Week 24	0.0413 (± 0.1976)	0.0118 (± 0.1721)		
Utility Score Week 48	0.0536 (± 0.1920)	0.0180 (± 0.2346)		
Utility Score Early Treatment Discontinuation	0.0082 (± 0.1603)	0.3720 (± 0000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the score of Work Productivity and Activity Impairment scale (WPAI:SHP)

End point title	Change from baseline in the score of Work Productivity and Activity Impairment scale (WPAI:SHP)

End point description:

The WPAI:SHP scale measures productivity and activity impairment. The answers to 6 questions are used to calculate scores according to predefined algorithms.
(0: no Impairment 100: total impairment)

End point type	Secondary

End point timeframe:

At Week 24 and Week 48

End point values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	46		
Units: Points on scale				
arithmetic mean (standard deviation)				

Overall work impairment Week 24	-2.86 (± 27.15)	-0.04 (± 24.04)		
Overall work impairment Week 48	-1.08 (± 25.38)	3.05 (± 21.66)		
Overall work impairment Early Treatment Disc	-4.15 (± 46.23)	0000 (± 0000)		
Activity impairment Week 24	-3.95 (± 25.06)	-6.90 (± 19.69)		
Activity impairment Week 48	-6.01 (± 23.45)	-6.75 (± 21.65)		
Activity impairment Early Treatment Disc	0.00 (± 30.41)	0000 (± 0000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the score of Multiple Sclerosis International Quality Of Life Questionnaire (MusiQOL)

End point title	Change from baseline in the score of Multiple Sclerosis International Quality Of Life Questionnaire (MusiQOL)

End point description:

MusiQoL questionnaire assesses the quality of life of MS patients. It comprises 31 questions evaluated on a 5-point scale (from never/not at all to always/very much). Answers to the questions can be grouped into 9 dimensions and an overall index score (0 worst quality of life – 100 best quality of life). All dimension scores are linearly transformed to a 0-100 scale.

End point type	Secondary

End point timeframe:

At Week 24 and Week 48

End point values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	46		
Units: Points on scale				
arithmetic mean (standard deviation)				
Week 24	1.15 (± 10.81)	0.03 (± 14.49)		
Week 48	1.64 (± 11.29)	2.74 (± 10.01)		
Early Treatment Discontinuation	-3.16 (± 12.93)	0000 (± 0000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the score of Treatment Satisfaction Questionnaire for Medication (TSQM-14)

End point title	Change from baseline in the score of Treatment Satisfaction Questionnaire for Medication (TSQM-14)

End point description:

TSQM-14 assesses patient satisfaction with treatment. It consists of 14 questions rated on a 5 or 7-point scale (from extremely dissatisfied to extremely satisfied). Answers to the questions can be grouped into 4 areas. All dimension scores are linearly transformed to a 0-100 scale.

End point type	Secondary

End point timeframe:

At Week 24 and Week 48

End point values	Active Relapsing Multiple Sclerosis (RMS)	Active Secondary Progressive Multiple Sclerosis (SPMS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	46		
Units: Points on scale				
arithmetic mean (standard deviation)				
Week 24	4.40 (± 19.00)	7.90 (± 21.39)		
Week 48	8.52 (± 20.73)	6.68 (± 24.94)		
Early Treatment Discontinuation	-30.32 (± 33.42)	0000 (± 0000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events (AE)

End point title	Percentage of Participants with Adverse Events (AE)

End point description:

This outcome measure describes ocrelizumab safety in active RMS patients. Severity of AEs is determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0)

End point type	Secondary

End point timeframe:

From Baseline to Week 48

End point values	All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	422			
Units: Percentage				
number (not applicable)				
Any AE	89.3			
AE of grade ≥3	10.7			
SAE	8.5			
Deaths	0.0			
Withdrawals due to AE	0.9			
Temporary interruption due to AE	8.5			
AESIs: ALT and AST increased	0.2			
IRRs	47.6			
COVID-19 infection	1.2			
Pregnancy	1.9			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Week 48	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Ocrelizumab

Reporting group description:

Each participant received an initial dose of two 300 mg infusions of Ocrelizumab each separated by 14 days followed by one single dose of 600 mg 24 weeks after the initial dose.

Serious adverse events	Ocrelizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 422 (8.53%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
GLIOBLASTOMA			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MALIGNANT MELANOMA			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
PHLEBITIS			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
ECTOPIC PREGNANCY			

subjects affected / exposed	3 / 422 (0.71%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
FATIGUE			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
GAIT DISTURBANCE			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
OVARIAN CYST			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
PNEUMONITIS			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
ALCOHOL WITHDRAWAL SYNDROME			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ANXIETY			

subjects affected / exposed	1 / 422 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HALLUCINATION				
subjects affected / exposed	1 / 422 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PSYCHOTIC BEHAVIOUR				
subjects affected / exposed	1 / 422 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SUICIDAL IDEATION				
subjects affected / exposed	1 / 422 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
INFUSION RELATED REACTION				
subjects affected / exposed	1 / 422 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
POST LUMBAR PUNCTURE SYNDROME				
subjects affected / exposed	1 / 422 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HEAD INJURY				
subjects affected / exposed	1 / 422 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FEMORAL NECK FRACTURE				
subjects affected / exposed	1 / 422 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FALL				

subjects affected / exposed	1 / 422 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
EXTRADURAL HAEMATOMA				
subjects affected / exposed	1 / 422 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SPINAL FRACTURE				
subjects affected / exposed	1 / 422 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
TOXICITY TO VARIOUS AGENTS				
subjects affected / exposed	1 / 422 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
TIBIA FRACTURE				
subjects affected / exposed	1 / 422 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
CEREBROVASCULAR ACCIDENT				
subjects affected / exposed	1 / 422 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
MULTIPLE SCLEROSIS RELAPS				
subjects affected / exposed	2 / 422 (0.47%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
MENINGISM				
subjects affected / exposed	1 / 422 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
CEREBRAL HAEMORRHAGE				

subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HEADACHE			
subjects affected / exposed	2 / 422 (0.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
DIZZINESS			
subjects affected / exposed	2 / 422 (0.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
EPILEPSY			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
subjects affected / exposed	2 / 422 (0.47%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
NEUTROPENIA			
subjects affected / exposed	3 / 422 (0.71%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HYPOACUSIS			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
EXTERNAL EAR INFLAMMATION			

subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
FACIAL CELLULITIS			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
PEAU D'ORANGE			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
CALCULUS BLADDER			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
NECK PAIN			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
PYELONEPHRITIS			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
INFLUENZA			

subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19 PNEUMONIA			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 422 (0.47%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
PYELONEPHRITIS ACUTE			
subjects affected / exposed	1 / 422 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
HYPOCALCAEMIA			
subjects affected / exposed	1 / 422 (0.24%)		
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	337 / 422 (79.86%)		
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
subjects affected / exposed	206 / 422 (48.82%)		
occurrences (all)	332		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	62 / 422 (14.69%)		
occurrences (all)	88		
General disorders and administration			

site conditions			
ASTHENIA			
subjects affected / exposed	37 / 422 (8.77%)		
occurrences (all)	40		
FATIGUE			
subjects affected / exposed	25 / 422 (5.92%)		
occurrences (all)	29		
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	21 / 422 (4.98%)		
occurrences (all)	26		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	21 / 422 (4.98%)		
occurrences (all)	24		
Infections and infestations			
URINARY TRACT INFECTION			
subjects affected / exposed	42 / 422 (9.95%)		
occurrences (all)	54		
NASOPHARYNGITIS			
subjects affected / exposed	48 / 422 (11.37%)		
occurrences (all)	60		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 May 2019	Number of participant centers (n=50) Study duration (30 months) Definition of active MS (inclusion criterion) Exclusion criteria (current active infection, elimination procedure of teriflunomide, wash out period only for previous DMTs) Time intervals between ocrelizumab infusion Data collected on previous DMTs Definition of hospitalizations not considered as SAEs Pharmacovigilant contact details
22 August 2019	Time intervals between ocrelizumab infusion and pregnancy test (infusion visits: the day of infusion; non-infusion visits: within 5 days prior to the visit (matching with the wording used in clarification letter which was sent after protocol V 2.0 release)
14 April 2020	Duration of permitted concomitant therapies prior to baseline (8 weeks) In case of a W48 visit delay, the delay was applied for the W72 safety visit (to take into account the COVID-19 pandemic) Addition of safety information regarding the risk of hepatitis reactivation under ocrelizumab treatment (changes in SmPC)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported