



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