# AN OPEN-LABEL, SINGLE-ARM 4-YEAR STUDY TO EVALUATE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB TREATMENT IN PATIENTS WITH PROGRESSIVE MULTIPLE SCLEROSIS

Published: 27-02-2018
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This study has been transitioned to CTIS with ID 2023-506429-13-00 check the CTIS register for the current data. This study will evaluate the effectiveness and safety of ocrelizumab in PMS patients.

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Demyelinating disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON56383

**Source**
ToetsingOnline

**Brief title**
CONSONANCE / MN39159

### Condition

- Demyelinating disorders

**Synonym**
ms, multiple sclerosis

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Roche Nederland B.V.
**Source(s) of monetary or material Support:** F. Hoffman - La Roche

## Intervention

**Keyword:** Ocrelizumab, Open-label, Phase III, Progressive Multiple Sclerosis

## Outcome measures

### Primary outcome

The primary objective of this study is to evaluate the effectiveness of ocrelizumab treatment in patients with PMS disease course. See section 2 of the protocol for more information (table 1).

### Secondary outcome

-To evaluate the effectiveness of ocrelizumab treatment in PMS patients using a range of patient-relevant measures and imaging outcomes.

-To evaluate the safety and tolerability of ocrelizumab in PMS patients.

See section 2 of the protocol for more information (table 1).

# Study description

### Background summary

Evidence for mitigation of disease worsening in progressive forms of MS remains sparse, particularly in patients with PPMS. Delaying or halting the progression of functional performance impairment and disability worsening is an important treatment goal in patients diagnosed with PPMS. Ocrelizumab has demonstrated a significant reduction in clinical disability outcomes as well as a reduction of MRI disease burden measures compared with placebo in PPMS patients in the Phase III ORATORIO study (NCT01194570). However, there is a need to explore the effectiveness of ocrelizumab to alter the course of the complete spectrum of progressive MS (PMS) disease; i.e. PPMS and SPMS, which will be the primary

objective of this study.

## Study objective

This study has been transitioned to CTIS with ID 2023-506429-13-00 check the CTIS register for the current data.

This study will evaluate the effectiveness and safety of ocrelizumab in PMS patients.

## Study design

This study is a prospective, multicenter, open-label, single-arm effectiveness and safety study in patients with PMS. The first dose of ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) in 250 mL 0.9% sodium chloride separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion in 500 mL 0.9% sodium chloride every 6 months for the remainder of the study duration.

This study will enroll 900 patients. The ratio between relapsing onset MS patients with PMS criteria as per Lublin et al. 2014 and PPMS patients will be 1:1. Patients will be assessed for effectiveness and safety every 24 weeks. The study will consist of the following periods:

-Screening period: up to 4 weeks.
-Treatment period: open-label treatment period of 192 weeks.
-A follow-up period of 48 weeks.

## Intervention

Patients that will be eligible for participation in this study will be treated with ocrelizumab, according to the study-specific form set out in Appendix 1 (schedule of assessments) of the study protocol. After the first dose, which is divided in 2 gifts with an interval of 14 days, study medication will be administered 8 times within 192 weeks.

## Study burden and risks

PML
PML is an important potential risk for ocrelizumab and it has only been reported with ocrelizumab where the risk for PML was pre-existing, specifically from prior immunosuppressive treatment (e.g. natalizumab or fingolimod treatment). In all of these PML cases, the causality with ocrelizumab was not considered plausible.

Hypersensitivity (allergic reactions)

Allergic reactions to ocrelizumab have not been reported to date, however, these reactions may occur and their symptoms may be difficult to distinguish from IRRs.

Decreased effectiveness of certain vaccines
Lowering the number of B cells may, in some patients, reduce the protection given by certain vaccines. It is not known to date whether ocrelizumab has this effect. While the patient is taking part in this study, he/she must not receive any vaccinations without first discussing this with the doctor. If a vaccination is considered necessary, the patient will need to wait at least 6 weeks after vaccination to receive the first dose of study drug. Vaccinations of a live or live-attenuated vaccine (using a weakened form of the germ, for example BCG against tuberculosis or vaccines against yellow fever) are not recommended during the treatment with ocrelizumab.

Increased risk of cancer
An increased risk of cancer with ocrelizumab may exist. In controlled trials in multiple sclerosis, cancers, including breast cancer, occurred more frequently in ocrelizumab-treated patients, however, the frequency is within the frequency of cancer in the patient population with multiple sclerosis.

Neutropenia
Neutropenia has been reported in some patients treated with ocrelizumab for MS, without any medical consequences, and has not been confirmed to be related to ocrelizumab.

# Contacts

**Public**
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Woerden 3446 GR
NL
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)

## Inclusion criteria

- Able to comply with the study protocol, in the investigator's judgement
- Age 18-65 years, inclusive
- Have a definite diagnosis of PMS (as per the revised McDonald 2010 criteria for PPMS or Lublin et al. 2014 criteria for PMS)
- Expanded Disability Status Scale (EDSS) <=6.5 at screening
- Have documented evidence of disability progression independent of relapse activity at any point over the 2 years prior to the screening visit. In case relapse(s) have occurred in the last 2 years, disability progression will have to be considered as independent of relapse activity as per treating physician*s judgment
- Fulfill at least one of the 21 criteria assessing the evidence of disability progression independent of relapse activity in the last 2 years using the pre-baseline disability progression rating system checklist
- Have experience of having used a smartphone and connecting a smartphone to Wi-Fi network providers
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## Exclusion criteria

- Relapsing-remitting multiple sclerosis (RRMS) at screening.
- Inability to complete an MRI
- Gadolinium (Gd) intolerance
- Known presence of other neurological disorders, including but not limited to, the following:
History of ischemic or hemorrhagic disorders of the brain or the spinal cord.
History or known presence of Central nervous system (CNS) or spinal cord tumor.
History or known presence of potential metabolic causes of myelopathy.
History or known presence of infectious causes of myelopathy.

History of genetically inherited progressive CNS degenerative disorder.
Neuromyelitis optica.
History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease.
History of severe, clinically significant brain or spinal cord trauma.
Exclusions Related to General Health
- Pregnancy
- Lactation
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressant*s during the course of the study
- History of or currently active primary or secondary immunodeficiency.
- Lack of peripheral venous access.
- Significant or uncontrolled somatic disease or any other significant disease that may preclude patient from participating in the study.
- Active infections must be treated and resolved prior to the first infusion of ocrelizumab
- Patients in a severely immunocompromised state until the condition resolves
- Patients with known active malignancies or being actively monitored for recurrence of malignancy
- Patients who have or have had confirmed progressive multifocal leukoencephalopathy (PML)

Exclusions Related to Laboratory Findings
Any abnormal screening laboratory value that is clinically relevant should be retested only once in order to rule out any progressive or uncontrolled underlying condition. The last value before randomisation must meet study criteria.
• Positive screening tests for hepatitis B: All patients must be tested for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (total HBcAb).
o If HBsAg is positive, the patient is not eligible
o If HBsAg is negative and HBcAb is positive, hepatitis B virus (HBV) DNA must be measured by polymerase chain reaction (PCR)
* If HBV DNA is positive, the patient is not eligible
* If HBV DNA is negative, the patient is eligible and HBV DNA (by PCR) must be repeated every 24 weeks.
o If HBsAg and HBcAb are both negative, the patient is eligible.
Note: Hepatitis B virus serologies measured using biotin-based immunoassays should be interpreted with caution in MS patients using high-dose biotin, as false positives have been reported in these patients. A biotin-free immunoassay is recommended in these patients; if unavailable, an appropriate correction technique should be applied.
• CD4 count <250 cells/µL
• Absolute neutrophil count (ANC) <1.0 × 103/µL
• Aspartate aminotransferase (AST)/ serum glutamic oxaloacetic transaminase (SGOT) or alanine aminotransferase (ALT) /serum glutamic pyruvic transaminase (SGPT)>=3.0 × the upper limit of normal (ULN)

Please note: based on local Ethics Committees or National Competent Authority requirements, additional diagnostic testing may be required for selected patients or selected centres to exclude tuberculosis, Lyme disease, HTLV-1 associated myelopathy (HAM), acquire immunodeficiency syndrome (AIDS), hepatitis C virus infection (HCV), SARS-CoV-2, hereditary disorders, connective tissue disorders, or sarcoidosis. Other specific diagnostic tests may be requested when deemed necessary by the Investigator.

Exclusions Related to Medications
Absolute exclusions:
- Previous treatment with Ocrelizumab
• Hypersensitivity to ocrelizumab or to any of its excipients.
• Previous treatment with B-cell targeted therapies (i.e. atacicept, tabalumab, belimumab, ofatumumab, or obinutizumab). Note: previous treatment with rituximab is allowed as long as the last dose was administered more than 6 months before the ocrelizumab infusion AND if discontinuation was due to adverse events or immunogenicity AND if B-cell levels are above the lower limit of normal (LLN) prior to screening.
• Any previous treatment with alemtuzumab (Campath/Mabcampath/Lemtrada), total body irradiation, or bone marrow transplantation.
• Previous treatment with natalizumab where PML has not been excluded according to specific algorithm in the protocol.
• Contraindications to or intolerance of oral or intravenous (IV) corticosteroids, including methylprednisolone administered IV, according to the country label, including:
a) Psychosis not yet controlled by a treatment.
b) Hypersensitivity to any of the constituents.
Relative exclusions:
2 weeks prior to screening: previous treatment with siponimod.
4 to 8 weeks prior to screening:
• Systemic corticosteroid therapy within 4 weeks prior to screening
• All vaccines should be given at least 6 weeks before the first infusion of ocrelizumab unless the local regulations allow for a shorter interval .
Live/live attenuated vaccines should be avoided during treatment and safety follow-up period until B cells are peripherally repleted.
• Previous treatment with daclizumab in the last 8 weeks.
• Treatment with fampridine/dalfampridine (Fampyra®)/Ampyra®) or other symptomatic MS treatment unless on stable dose for >=30 days prior to screening. Wherever possible, patients should remain on stable doses throughout the treatment period.
• Previous treatment with fingolimod or ozanimod in the last 8 weeks prior to screening (a different wash-out period when
switching from fingolimod or ozanimod to ocrelizumab can be used).
12 weeks prior to screening:
• Previous treatment with natalizumab in the last 12 weeks prior to screening. (A different wash-out period when switching from natalizumab to ocrelizumab can be used. An assessment should be made to balance risk of return of MS disease

activity with possible additive immunosuppressive effects of each drug.)
• Previous treatment with azathioprine, cyclophosphamide, mycophenolate mofetil or methotrexate in the last 12 weeks prior to screening.
• Treatment with teriflunomide in the last 12 weeks. This washout period can be shortened if an accelerated elimination procedure
is implemented before screening visit.
24 weeks prior to screening:
• Treatment with any investigational agent within 24 weeks of screening (Visit 1) or five half-lives of the investigational drug (whichever is longer) or
treatment with any experimental procedures for MS (e.g., treatment for chronic cerebrospinal venous
insufficiency) within 24 weeks of screening (Visit 1).
96 weeks prior to screening:
• Previous treatment with mitoxantrone, cyclosporine or cladribine in the last 96 weeks.

Exclusions for Subjects participating in the OCT assessments
• Patients with clinically relevant ocular pathologies, potentially interfering with clinical and instrumental evaluations.

Exclusions for Subjects participating in the measurement of Motor Evoked Potentials (MEP)
• History of seizures
• Prior craniotomy or skull fracture
• Movable metallic implant in the head (patients with jaw- or bone-fixed metal implants can be included)
• Implanted stimulators (e.g. cochlear implant or cardiac pacemaker, deep brain stimulator)
• Known history of high intracranial pressure.

# Study design

## Design

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|---|---|
| Study phase: | 3 |
| Study type: | Interventional |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 03-07-2018 |
| Enrollment: | 41 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Ocrevus |
| Generic name: | ocrelizumab |
| Registration: | Yes - NL intended use |

# Ethics review

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|---|---|
| Approved WMO Date: | 27-02-2018 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 27-04-2018 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 06-06-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 09-07-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO | |

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|---|---|
| Date: | 03-08-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 16-09-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 31-10-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 03-12-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 21-12-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 17-02-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 25-02-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 16-03-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek |

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| | (Assen) |
| Approved WMO Date: | 05-06-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 12-08-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 19-08-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 30-09-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 24-12-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 28-05-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 15-06-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 10-10-2021 |

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| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 25-10-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 18-12-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 14-09-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 05-10-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 20-11-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EU-CTR | CTIS2023-506429-13-00 |
| EudraCT | EUCTR2017-001313-93-NL |
| ClinicalTrials.gov | NCT03523858 |
| CCMO | NL64650.056.18 |