A PHASE IIIb MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN ADULTS WITH PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS

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This study will evaluate the efficacy and safety of ocrelizumab (Ocrevus®) compared with placebo in patients with PPMS, including patients later in their disease course.

Ethical review	Not approved
Status	Will not start
Health condition type	Demyelinating disorders
Study type	Interventional

Summary

ID

NL-OMON48188

Source
ToetsingOnline

Brief title
ORATORIO-HAND

Condition

- Demyelinating disorders

Synonym
MS, Primary progressive multiple sclerosis (PPMS)

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: Adults, Ocrelizumab, Placebo, Primary Progressive MS

Outcome measures

Primary outcome

The primary efficacy objective for this study is to evaluate the efficacy of ocrelizumab treated patients compared with placebo treated patients on upper extremity disability progression. This objective is measured on upper limbs on the basis of the following endpoint: upper limb disability progression defined as time to 20% worsening from baseline in 9 Hole Peg Test (9 HPT) confirmed for at least 12 weeks in all randomized patients and in patients with magnetic resonance imaging (MRI) activity (MRI activity is defined as presence of T1 gadolinium (Gd)+ lesion[s] and/or new and/or enlarging T2 lesion[s] as detected by MRI scans during the screening phase).

Secondary outcome

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo for all randomized patients on the basis of the endpoints below, in hierarchical order. The secondary efficacy endpoints will also be evaluated as exploratory analyses for the MRI active subgroup.

Upper limb disability progression defined as time to 20% increase from baseline in 9 HPT confirmed for at least 24 weeks

Time to 12 week confirmed disability progression (CDP) in Expanded Disability Status Scale (EDSS), defined as an increase in EDSS score that is confirmed for at least 12 weeks (an increase of * 1.0 point from baseline EDSS score in patients with a baseline EDSS score * 5.5 or an increase of * 0.5 point in patients with a baseline EDSS score of * 5.5)

Time to 24 week CDP in EDSS, defined as an increase in EDSS score that is confirmed for at least 24 weeks (an increase of * 1.0 point from baseline EDSS in patients with a baseline EDSS score * 5.5 or an increase of * 0.5 point in patients with a baseline EDSS score of * 5.5)

Percent change in total volume of T2 lesions from baseline up to Week 120

Percent change in total brain volume from Week 24 to Week 120

Exploratory Efficacy Objective

An exploratory efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo in patients, as measured by the primary and secondary endpoints in the following patient subgroups:

Age * 55 versus * 55

EDSS score * 6.5 versus * 6.5

MRI inactive versus MRI-active

Additional exploratory objectives include the efficacy of ocrelizumab compared with placebo in patients from the intent-to-treat (ITT) population and MRI active subgroup as measured by the following endpoints:

Proportion of patients free of disability progression on upper limbs by 9 HPT

at Week 120 and at time of clinical cutoff of primary analysis

Change from baseline to Week 120 in fatigue as measured by Modified Fatigue Impact Scale (MFIS)

Change from baseline to Week 120 and from Week 24 to Week 120 in cervical spinal cord volume on MRI scans

Change from baseline to Week 120 in a measure of manual ability for adults with upper limb impairments (ABILHAND)

Change from baseline to Week 120 in the upper limb domain of a life quality measure for patients with neurological disorders (Quality of Life in Neurological Disorders Upper Extremity Function [Neuro QoL UE])

Change from baseline to Week 120 in the Patient Global Impression of Change for upper limb function (PGIC-UL)

Change from baseline to Week 120 in the Patient Global Impression of Change for fatigue (PDIC-F)

Change from baseline to Week 120 in the Multiple Sclerosis Impact Scale (MSIS) 29 physical score

Proportion of patients at Week 120 with a clinically meaningful decline on the MSIS 29

Change from baseline to Week 120 in the Symbol Digit Modalities Test (SDMT)

Rate of decline in fine motor skills of upper extremities and manual/finger dexterity as measured by smartphone-based digital outcome assessment (Floodlight remote patient monitoring [RPM])

Safety Objectives

The safety objectives for this study are to evaluate the safety of ocrelizumab compared with placebo, as well as over time, for all patients who received ocrelizumab and until they receive any other immunomodulatory or immunosuppressive treatments.

Safety endpoints considered include adverse events, serious adverse events, adverse events leading to study treatment withdrawal, vital signs, change from baseline in laboratory test results, association of decrease in certain laboratory parameters, and serious infections.

Immunogenicity Objective

The immunogenicity objective is as follows:

Immunogenicity, as the presence of anti drug antibody (ADA) during the study relative to baseline. The relationship between ADA status and pharmacokinetics, pharmacodynamics, efficacy and safety may be explored.

Pharmacokinetic and Pharmacodynamic Objectives

The pharmacokinetic (PK) and pharmacodynamic objectives are as follows:

Characterization of the ocrelizumab PK profile

Evaluation of ocrelizumab pharmacodynamics, as measured by B cell levels in blood

Biomarker Objective

The exploratory biomarker objective for this study is to identify biomarkers that are predictive of response to ocrelizumab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more

severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to ocrelizumab, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of ocrelizumab activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

Relationship between biomarkers in blood (plasma and/or serum) and/or cerebrospinal fluid (CSF) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Health Status Utility Objective

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with ocrelizumab on the basis of the following endpoint:

Relationship between EuroQol 5 Dimension, 5 Level (EQ 5D 5L) index score and clinical measurements that may support pharmacoeconomic modeling.

Study description

Background summary

Multiple sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the CNS that affects approximately 2.3 million people worldwide (MSIF 2013). While MS is a global disease, its prevalence is highest in North America and Europe (140 and 108 per 100,000 people, respectively) (MSIF 2013). MS is commonly diagnosed during reproductive age, between 20 and 40 years (Tullman 2013). Overall, MS is approximately twice as prevalent in women as in

men, except in individuals with the primary progressive form of the disease, where there is no gender prevalence difference (MSIF 2013; Tullman 2013). Reasons for these observed differences are unclear. However, progression, once it begins, continues at similar rates in women and men (Leray et al. 2010).
In approximately 85% of patients, MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery (referred to as relapsing remitting MS [RRMS]). If left untreated, the majority of these patients will transition to a progressive form characterized by worsening neurologic disability, either with or without occasional super imposed relapses (relapsing or non relapsing secondary progressive MS). Patients accumulate disability as a result of incomplete recovery from acute relapses and/or gradual disease progression (Tullman 2013). Primary progressive MS (PPMS) is a less common form of MS, accounting for approximately 10% of all cases (approximately 40,000 individuals in the United States). PPMS is characterized by a progressive course from disease onset, with infrequent superimposed discrete clinical attacks or relapses (Lublin et al. 2014). Unlike RRMS, the typical age of onset for PPMS is older at approximately 40 years, and men are affected nearly as often as women (Cottrell et al. 1999). The absence of relapses imposes special challenges for diagnosis, requiring clinical evidence that the disease has advanced for at least 1 year from symptom onset independent of clinical relapse (Thompson et al. 2018).
Ocrelizumab is a recombinant humanized, glycosylated, monoclonal IgG1 antibody that selectively targets and depletes CD20 expressing B cells, while preserving the capacity of B cell reconstitution and preexisting humoral immunity. CD20 is a B cell surface molecule that is restricted in expression to pre*B cells and mature B cells but is not expressed earlier in the development of B cells (Banchereau and Rousset 1992). Based on the results of ocrelizumab Phase III studies in patient populations with relapsing MS (RMS) and PPMS, ocrelizumab was approved by the US Food and Drug Administration (FDA) on 28 March 2017 for the treatment of adult patients with RMS and PPMS and by the European Medicines Agency (EMA) on 12 January 2018 for patients with active relapsing forms of MS defined by clinical or imaging features and for patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.
Two identical randomized, active controlled studies (OPERA I [Study WA21092] and OPERA II [Study WA21093]) have demonstrated superior efficacy outcomes versus interferon * 1a in patients with RMS (Hauser et al. 2017); one randomized placebo controlled study (ORATORIO [Study WA25046]) has demonstrated superior efficacy in PPMS versus placebo (Montalban et al. 2017). Results of these studies show that depletion of CD20+ B cells leads to a significant impact on a broad range of clinical measures of disease, including disability progression, in addition to an impact on magnetic resonance imaging (MRI) outcomes related to disease progression and reflective of neural tissue loss, thus further supporting the hypothesis that B cells are central to the pathogenesis of both RMS and PPMS. Ocrelizumab has demonstrated a favorable safety profile in patients with RMS and PPMS (Hauser et al. 2017; Montalban et al. 2017). The proportion of patients with adverse events was similar in

patients treated with ocrelizumab compared with interferon * 1a (both 83.3%) or placebo (95.1% vs. 90.0%). The proportion of patients experiencing a serious adverse event was similar between ocrelizumab and the comparator groups (in RMS: 6.9% [ocrelizumab] and 8.7% [interferon * 1a]; in PPMS: 20.4% [ocrelizumab] and 22.2% [placebo]).
The pivotal Phase III Study WA25046 (ORATORIO) was a global, multicenter, randomized, parallel group, double blind, placebo controlled trial evaluating the efficacy and safety of ocrelizumab in adults with PPMS. Therefore, given the encouraging results from Study WA25046, the primary objective of this study is to evaluate the efficacy of ocrelizumab compared with placebo on the preservation of upper limb function in a population that also includes patients with more advanced PPMS who acquired significant lower extremity impairment.

Study objective

This study will evaluate the efficacy and safety of ocrelizumab (Ocrevus®) compared with placebo in patients with PPMS, including patients later in their disease course.

Study design

Study WA40404 is a Phase IIIb, randomized, double blind, placebo controlled, parallel group, multicenter study to evaluate efficacy on upper limb function and safety of ocrelizumab administered at 600 mg IV infusions every 24 weeks in patients with PPMS, including patients later in their disease course. This study will consist of the following phases: screening, double blind treatment, follow up 1 (FU1), an optional open label extension (OLE), follow up 2 (FU2), and B cell monitoring (BCM).
The screening phase will last up to 24 weeks. Two brain MRI scans performed at least 6 weeks apart or one brain MRI that can be compared with a brain MRI performed in the previous 1 year will be performed to verify the brain MRI activity status of the patient. For patients who fail the initial screening, a maximum of two re screenings will be allowed.
Eligible patients will be randomized (1:1) in a blinded fashion to either placebo or ocrelizumab. The expected sample size will be approximately 1000 patients, with at least 350 patients in the MRI active subgroup. The MRI active subgroup will consist of patients with T1 Gd * lesion(s) and/or new and/or enlarging T2 lesion(s) as detected by MRI scan during screening.
Patients will be treated for a minimum of 120 weeks (minimum of 5 study drug doses, with each dose 24 weeks apart) and until approximately 362 events of 12-week confirmed upper limb disability progression (9 HPT events) have occurred in the study and until 131 events of 12 week confirmed upper limb disability progression (9 HPT events) have occurred in the MRI active subgroup. The primary efficacy analysis will be performed after the above-mentioned number of events has been reached (in accordance to the definition of events for the primary analysis).

Patients who experience a double-progression event (DPE; defined as a confirmed 20% increase in 9 HPT time sustained for 24 weeks and a CDP sustained for 12 weeks) during the double blind treatment phase will be given the option to switch to post*double progression ocrelizumab (PDP OCR) after completing at least 120 weeks of the double-blind treatment phase.
All patients who prematurely discontinue from the double blind treatment phase will enter the FU1 phase, including patients who receive PDP OCR treatment, other immunomodulatory or immunosuppressive treatment(s) for MS, commercial ocrelizumab, or no treatment. The FU1 phase will run in parallel with the double blind treatment phase until the primary analysis is performed. Scheduled visits will be performed every 12 weeks. In the FU1 phase, patients will remain blinded to their original (randomized) treatment assignment. Patients who withdraw from treatment should be encouraged to remain in the study for the full duration of the FU1. All patients who are ongoing in the FU1 and not on PDP OCR treatment at the time of the primary analysis will continue in the FU2.
If the primary analysis is positive, an optional OLE phase is planned for eligible patients who either have remained in the double-blind treatment phase or are on PDP OCR treatment at the time of the primary analysis and, in the opinion of the investigator, could benefit from ocrelizumab treatment. Patients who are ongoing in the FU1 and not on PDP OCR treatment at the time of the primary analysis will not participate in the OLE.
The OLE will be carried out for approximately 2 years (4 doses of ocrelizumab). The 2 year duration of the OLE phase serves to further evaluate long term safety and efficacy of ocrelizumab treatment in patients with PPMS.
The FU2 phase will begin after the primary analysis is performed. The following patients will move into the FU2 phase: are ongoing in the FU1 and not on PDP OCR treatment at the time of the primary analysis, are ongoing in the double blind treatment phase or receiving PDP OCR at the time of the primary analysis and do not enter the OLE phase, or complete or withdraw from the OLE phase.
Laboratory and safety assessments for FU2 will be performed during the clinic visits that occur every 24 weeks. All patients will continue in the FU2 until the end of the phase. The end of FU2 is defined as 48 weeks after the last patient to enter the OLE has had his or her last OLE visit.
At the end of the FU2, all patients will move into BCM phase until the end of the study. This study will end when all patients who are not being treated with an alternative B cell depleting therapy have repleted his or her B cells. A patient*s B-cells will be considered to be repleted once B cell levels have returned to baseline value or the lower limit of normal (whichever is lower).
An independent Data Monitoring Committee will be employed to monitor and evaluate patient safety throughout the study, until the primary analysis is performed.

End of Study
The end of the study will occur when all patients who are not being treated with an alternative B cell depleting therapy have repleted his or her B-cells

(i.e., B cell level of the patient has returned to the baseline value or the lower limit of normal, whichever is lower).
Length of Study
The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 8.5 years (assuming that the last patient randomized after 3 years from the study start receives blinded treatment over 120 weeks, followed by 96 weeks of OLE, 48 weeks of FU2 and [variable] BCM phase).

Intervention

The dose level of ocrelizumab administered in this study is 600 mg every 24 weeks.
Ocrelizumab will be administered intravenously as dual infusions (300 mg on Days 1 [Dose 1 Infusion 1] and 15 [Dose 1 Infusion 2]) for the first dose and subsequently as a single IV infusion (600 mg) every 24 weeks in 500 mL 0.9% sodium chloride. This dosing regimen is consistent with the dosing regimen used in ocrelizumab Phase III/IV studies, as well as with the summary of product characteristics (SmPC) and the U.S.
prescribing information (USPI). In the double-blind treatment phase, study drug for patients randomized to the placebo
group will be administered analogously to those receiving ocrelizumab.

Rationale for Control Group
Given that no standard therapy exists in the European Union and some other parts of the world for the treatment of patients with PPMS later in their disease course/without imaging features characteristic of inflammatory activity, a placebo controlled trial is acceptable provided that appropriate patient consent and safeguards are instituted to minimize the risk of serious or irreversible harm resulting from exposure to placebo. In this study, patients randomized to placebo who experience a DPE during the double blind treatment phase will be given the option to switch to ocrelizumab (see Section 3.1.1.2).
The Sponsor recognizes that a treatment period lasting 2.5*5.5 years poses risks to patients randomized to placebo. For this reason, several study elements will be employed to protect the well being of study participants:
The Informed Consent Form clearly defines the duration of the study including the double blind treatment phase, OLE phase, and follow up phases. The probabilities of assignment to placebo and ocrelizumab are indicated in easily understood terms in multiple sections of the Informed Consent Form.
Patients who experience a DPE during the double-blind treatment phase will be given the option to switch to PDP OCR after they have completed at least 120 weeks of double-blind treatment (see Section 3.1.1.2 for definition of DPE). Patients will have to provide their informed consent prior to switching to PDP OCR.
A thorough medical monitoring plan will be implemented by the study Sponsor to ensure the safety of all study participants. Moreover, an iDMC will be

instituted to further protect the wellbeing of patients in the study.
Upon withdrawal from study treatment for any reason, patients will be recommended to stay in the study for follow up but may be eligible for treatment with some alternative therapies at the discretion of and in consultation with their Treating Investigator.

Rationale for the Use of Premedications (Methylprednisolone and Antihistamines)
To reduce the frequency and severity of infusion-related reactions (IRRs), patients will be premedicated with 100 mg methylprednisolone IV and an antihistamine approximately 30 minutes prior to administration of ocrelizumab (see Section 4.3.2.2). An integrated analysis of patients with MS who were treated with ocrelizumab revealed that the addition of antihistamines to the pretreatment with methylprednisolone decreased the incidence of IRRs by 2 fold (OCREVUS® U.S. Package Insert). Administered infrequently at a low dose, methylprednisolone is not anticipated to affect the efficacy or safety outcomes of the study. Methylprednisolone (or an alternative steroid in patients where methylprednisolone is contraindicated) will be administered to patients in both treatment groups during the treatment period to maintain the treatment blind.

Rationale for Biomarker Assessments
A blood protein biomarker sample (plasma and serum) will be taken. Assessment of the sample may include, but will not be limited to, neurofilament light chain (NfL), a marker of neuronal injury and/or other neurodegeneration/inflammatory markers. If the patient requires a CSF sample to screen for IgG index or the presence of oligoclonal bands at screening, the leftover CSF will be stored and the assessment of the sample may include, but will not be limited to, NfL. Patients for whom screening CSF was collected will have the option to participate in a collection of CSF at Week 48; this sample will be used for exploratory biomarker determination that may include, but may not be limited to, NfL. NfL, in addition to other possible markers, may be used to assess the patient*s disease activity, and/or as a pharmacodynamic, prognostic, or predictive biomarker(s) for disease progression and/or to assess drug activity, efficacy, safety, or MS pathogenesis.

Study burden and risks

Side effects and discomforts caused by the the study drug and procedures can be found in the study documents in this dossier (ICF, IB).

The sponsor feels that the side effects and the burden associated with participation are in proportion considering the
positive effects that participation in the study might have on the patient's quality of life.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Patients must meet the following criteria for study entry:
- Ability to provide written informed consent and be compliant with the study protocol
- Diagnosis of PPMS in accordance with the McDonald criteria
- Age 18*65 years at time of signing Informed Consent Form
- EDSS score at screening and baseline * 3.0 to 8.0, inclusive
- Disease duration from the onset of MS symptoms:
* Less than 15 years in patients with an EDSS at screening * 5.0
* Less than 10 years in patients with an EDSS at screening * 5.0
- Documented history or presence at screening of at least one of the following laboratory findings in a cerebrospinal fluid specimen (source documentation of laboratory results and method must be verified)

* Elevated IgG index
* One or more IgG oligoclonal bands detected by isoelectric focusing
- Screening and baseline 9 HPT completed in * 25 seconds (average of the two hands)
- Ability to complete the 9 HPT within 240 seconds with each hand at screening and baseline
- Patients previously treated with immunosuppressants, immunomodulators, or other immunomodulatory therapies must undergo an appropriate washout period according to the local label of the immunosuppressant/immunomodulatory drug used
- Patients screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility for the trial. Patients who discontinue their current therapy for non medical reasons should specifically be informed before deciding to enter the study of their treatment options and, that by participating in this study, they may be randomized to placebo for a period of 120 weeks or greater.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraceptive methods during the treatment period and for 6 months after the final dose of ocrelizumab. Adherence to local requirements, if more stringent, is required.
A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (* 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.
The following are considered adequate contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.
The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For female patients without reproductive potential:
Women may be enrolled if post menopausal (i.e., spontaneous amenorrhea for the past year confirmed by a follicle-stimulating hormone [FSH] level * 40 mIU/mL) unless the patient is receiving a hormonal therapy for her menopause or if surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy).

Eligibility Criteria for Open Label Extension Phase
- Patients who meet the following entry criteria may participate in the OLE phase:
* Completed the double blind treatment phase of the trial or have received PDP OCR in the FU1 phase, and who, in the opinion of the investigator, may benefit from treatment with ocrelizumab
* Patients who withdrew from study treatment and received another

disease-modifying therapy (DMT) or commercial ocrelizumab will not be allowed to enter in the OLE phase.
* Able and willing to provide written informed consent to participate in the OLE phase and to comply with the study protocol
* Meet the re treatment criteria for ocrelizumab
* For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraceptive methods during the treatment period and for 6 months after the final dose of ocrelizumab. Adherence to local requirements, if more stringent, is required.
A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (* 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.
The following are considered adequate contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.
The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
* For female patients without reproductive potential:
Women may be enrolled if post menopausal (i.e., spontaneous amenorrhea for the past year confirmed by a FSH level * 40 mIU/mL) unless the patient is receiving a hormonal therapy for her menopause or if surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)

Exclusion criteria

- Patients who meet any of the following criteria will be excluded from study entry:
- History of relapsing remitting or secondary progressive MS at screening
- Confirmed serious opportunistic infection including: active bacterial, viral, fungal, mycobacterial infection or other infection, including tuberculosis or atypical mycobacterial disease
- Patients who have or have had confirmed or a high degree of suspicion of progressive multifocal leukoencephalopathy (PML)
- Known active malignancy or are being actively monitored for recurrence of malignancy
- Immunocompromised state, defined as one or more of the following:
* CD4 count * 250/*L
* Absolute neutrophil count * 1.5 * 103/*L

* Serum IgG * 4.6 g/L
- Receipt of a live attenuated vaccine within 6 weeks prior to randomization
- Inability to complete an MRI (contraindications for MRI, including but not restricted to pacemaker, cochlear implants, intracranial vascular clips, surgery within 6 weeks of entry in the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, etc.) or contraindication to Gd administration.
- Patients requiring symptomatic treatment of MS (e.g., fampridine) and/or physiotherapy who are not on a stable regimen. Patients must not initiate symptomatic treatment of MS or physiotherapy within 4 weeks of randomization.
- Contraindications to mandatory premedications (i.e., corticosteroids and antihistamines) for infusion related reactions, including:
* Uncontrolled psychosis for corticosteroids
* Closed angle glaucoma for antihistamines
- Known presence of other neurologic disorders, including but not limited to, the following:
* History of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
* History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)
* History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
* History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, HTLV 1, herpes zoster myelopathy)
* History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis, mitochondrial myopathy, encephalopathy, lactic acidosis, stroke [MELAS] syndrome)
* Neuromyelitis optica
* History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti phospholipid antibody syndrome, Sjögren syndrome, Behçet disease)
* History or known presence of sarcoidosis
* History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)
- Pregnant or breastfeeding, or intending to become pregnant during the study and 6 months after last infusion of the study drug
- Lack of peripheral venous access
- Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine or gastrointestinal, or any other significant disease that may preclude patient from participating in the study
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- History of alcohol or other drug abuse
- History of primary or secondary (non*drug-related) immunodeficiency
- Treatment with any investigational agent within 24 weeks prior to screening (Visit 1) or 5 half lives of the investigational drug (whichever is longer), or

treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Previous treatment with B cell targeting therapies (e.g., rituximab, ocrelizumab, atacicept, belimumab, ofatumumab)
- Any previous treatment with bone marrow transplantation and hematopoietic stem cell transplantation
- Any previous history of transplantation or anti-rejection therapy
- Treatment with IV Ig or plasmapheresis within 12 weeks prior to randomization
- Systemic corticosteroid therapy within 4 weeks prior to screening
The screening period may be extended for patients who have used systemic corticosteroids for MS before screening. For a patient to be eligible, systemic corticosteroids should also not have been administered between screening and baseline.
- Positive serum * hCG measured at screening or positive urine * hCG at baseline
- Positive screening tests for hepatitis B (hepatitis B surface antigen [HBsAg] positive, or positive hepatitis B core antibody [total HBcAb] confirmed by a positive viral DNA polymerase chain reaction)
- Any additional exclusionary criterion as per ocrelizumab (Ocrevus®) local label, if more stringent than the above
- Lack of MRI activity at screening/baseline if more than 650 patients without MRI activity have already been enrolled, as defined by T1 Gd+ lesion(s) and/or new and/or enlarged T2 lesion(s) in the screening, to ensure that at least 350 patients with MRI activity will be randomized

Re testing before baseline: In rare cases in which the screening laboratory samples are rejected by the central laboratory (e.g., hemolyzed sample) or the result is not assessable (e.g., indeterminate) or abnormal, the tests need to be repeated within 4 weeks. Any abnormal screening laboratory value that is clinically relevant should be retested to rule out any progressive or uncontrolled underlying condition. The last value before randomization must meet study criteria.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO

Date:	24-07-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Not approved

Date:	16-01-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

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
EudraCT	EUCTR2018-001511-73-NL
ClinicalTrials.gov	NCT04035005
CCMO	NL69679.028.19