An open-label study to evaluate the efficacy and safety of ocrelizumab in patients with relapsing remitting multiple sclerosis who have a suboptimal response to an adequate course of disease-modifying treatment

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This study will evaluate the efficacy and safety of ocrelizumab in patients with relapsing remitting multiple sclerosis (RRMS) who have a suboptimal response to an adequate course of a disease modifying treatment (DMT).

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Demyelinating disorders
Study type	Interventional

Summary

ID

NL-OMON45923

Source
ToetsingOnline

Brief title
CASTING / MA30005

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 IIIb, relapsing remitting multiple sclerosis

Outcome measures

Primary outcome

PRIMARY EFFICACY OBJECTIVE

The primary objective for this study is to assess the efficacy of ocrelizumab 600 mg intravenous (IV) given every 24 weeks on the basis of the following endpoint:

* -Proportion of patients who have no evidence of disease activity (NEDA, as per protocol defined events) during a 96-week period. The magnetic resonance imaging (MRI) activity will be calculated on the events starting from week 8 (baseline reset) when drug is fully active.

The definition of a protocol-defined event of disease activity is the occurrence of at least one of the following while on treatment with ocrelizumab:

* -A protocol-defined relapse as defined below
* -24 weeks confirmed disability progression based on increases in Expanded Disability Status Scale (EDSS) while on treatment with ocrelizumab
* -A T1 gadolinium (Gd)-enhanced lesion after Week 8 *

-A new and/or enlarging T2 hyperintense lesion on MRI after Week 8

compared to the Week 8 MRI scan

A protocol-defined MS relapse is an occurrence of new or worsening neurological symptoms attributable to MS that meets the following criteria:

* -Symptoms must persist for >24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to medications)
* -Symptoms should be preceded by neurological stability for at least 30 days
* -Symptoms should be accompanied by new objective neurological worsening determined with a timely EDSS/ Functional Systems Score (FSS) assessment, consistent with an increase of at least:
* ** 0.5 points on EDSS scale
* *or * 2 points on one of the following FSS scales: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual
* *or * 1 point on two or more of the following FSS scales: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual

PRIMARY SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of ocrelizumab 600 mg IV given every 24 weeks on the basis of the following endpoints:

- Rate and nature of adverse events
- Changes in vital signs, physical and neurological examinations, clinical laboratory results, locally reviewed MRI for safety (non-MS central nervous

system [CNS] pathology) and concomitant medications (including pre-medications and medications used during and following ocrelizumab administration).

Secondary outcome

SECONDARY EFFICACY OBJECTIVE

The secondary objective for this study is to evaluate the efficacy of ocrelizumab 600 mg IV given every 24 weeks on the basis of the following endpoints:

-The proportions of patients free from a protocol-defined event of disease activity during a 24-week period and a 48-week period

-Time to first protocol-defined event of disease activity

-Change in EDSS from baseline to Week 96

-Proportion of patients who, over a 96-week period, have Confirmed Disability Improvement (CDI) Confirmed Disability Progression (CDP) or stable disability (i.e. neither CDI nor CDP).

-Annualized rate of protocol-defined relapses at Week 96

-Time to onset of first protocol-defined relapse

-Time to onset of 24 weeks CDP

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

-Total number of T1 Gd-enhanced lesions detected by brain MRI at Weeks 24, 48 and 96

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

-Volume and number of new and/or enlarging T2 hyperintense lesions from baseline to Weeks 24, 48 and 96

-Change in T1 hypointense volume from baseline to Weeks 48 and 96

-Change in brain volume from baseline measured at Weeks 24, 48 and 96

-Change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS (Brief International Cognitive Assessment for Multiple Sclerosis)

EXPLORATORY EFFICACY OBJECTIVE

The exploratory efficacy objective for this study is to further assess the efficacy of ocrelizumab 600 mg IV given every 24 weeks by monitoring patient-reported outcomes (PROs) related to quality of life (QoL), treatment satisfaction and other endpoints or analyses as follows:

- Multiple Sclerosis Impact Scale (MSIS)-29 (MS-specific QoL questionnaire)

-Treatment satisfaction questionnaire for medication (TSQM II)

- Patient reported outcome: SymptoMScreen

- MRI and clinical outcomes at 6 months and 1 year

- Predictors of NEDA and association between NEDA and disability or other efficacy parameters

- Severity of relapses (hospitalization for MS relapse, use of corticosteroids, residual disability)

- Employment status (WPAI)

- Proportion of patients who have NEDA, as per protocol defined events during a 96-week period and starting from baseline

Study description

Background summary

This study was designed to evaluate the efficacy and safety of ocrelizumab in patients with relapsing remitting multiple sclerosis (RRMS) showing a suboptimal response to adequate courses of disease modifying treatment. One speaks of "relapsing remitting" because this type of MS involves attacks (relapses) of symptoms and then again a recovery phase (remitting).

Ocrelizumab, a recombinant humanized antibody which binds to B-cells, which are believed to play a role in MS.

Study objective

This study will evaluate the efficacy and safety of ocrelizumab in patients with relapsing remitting multiple sclerosis (RRMS) who have a suboptimal response to an adequate course of a disease modifying treatment (DMT).

Study design

This study is a prospective, multicenter, open-label, efficacy, and safety study in patients with RRMS who have a suboptimal response to an adequate course of a DMT. An adequate course of prior DMT is defined as a stable dose of the same DMT administered for at least 6 months. The first dose of ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion every 24 weeks for the study duration.
Patients will be assessed for efficacy 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 96 weeks (last dose administered at Week 72)
* -A follow-up period of at least 2 years, which is independent of the DMT administered
Follow-up Period: Patients who discontinue treatment early will be followed up for at least 96 weeks after the last infusion of study drug. Patients who complete the 96 weeks Treatment Period and, in agreement with their treating neurologist, decide not to continue in a separate long term extension (LTE) study, will be followed up for at least 96 weeks after the end of the Treatment Period.

Patients whose B-cells have not been repleted after 96 weeks of Follow-up Period will continue with visits every 24 weeks, and telephone contacts every 8 weeks, until B-cell repletion (Prolonged B-cell monitoring). If the patients are receiving other B-cell targeted therapies, then the Follow-up Period will be stopped at 96 weeks regardless of their B-cell count.

A structured telephone interview will be conducted by site personnel every 8 weeks between the study visits during the treatment period and follow-up to identify and collect information on any changes in the patient*s health status that warrant an unscheduled visit

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 Appendices 1 (schedule of assessments: screening through the end of treatment period) and 2 (follow-up schedule of assessments)1 and 2 of the study Protocol.
In 2 years time study medication will be administered 4 times with the first dose divided in two gifts with an interval of 14 days.

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 preexisting, specifically because of prior natalizumab treatment.

HYPERSENSITIVITY REACTIONS
No hypersensitivity reactions to ocrelizumab were reported in the controlled clinical trials.
Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms. A hypersensitivity reaction may present during any infusion, although typically would not present during the first infusion. For subsequent infusions, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. If a hypersensitivity reaction is suspected during infusion, the infusion must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated.

IMPAIRED RESPONSE TO VACCINATION
The degree of impairment of B-cell dependent humoral response to neo-antigens and polysaccharide antigens and its clinical relevance are currently unknown in patients with MS.
After treatment with ocrelizumab over 2 years, the proportion of patients with positive antibody titers against S. pneumoniae, mumps, rubella, and varicella were generally similar to the proportions at baseline.
No data are available on the effects of vaccination in patients receiving ocrelizumab. Physicians should review the immunization status of patients being considered for treatment with ocrelizumab. Patients who require vaccination should complete it at least 6 weeks prior to initiation of ocrelizumab.
The safety of immunization with live or live-attenuated viral vaccines, following ocrelizumab therapy has not been studied and vaccination with

live-attenuated or live vaccines is not recommended while B cells are depleted.

MALIGNANCIES INCLUDING BREAST CANCER
In controlled trials in multiple sclerosis, 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. Patients should follow standard breast cancer screening guidelines.

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.

RISKS ASSOCIATED WITH CORTICOSTEROIDS
Subjects will be receiving a low dose of a corticosteroid as an intravenous infusion to reduce the risk of infusion reactions before each study drug infusion. Corticosteroids if taken in high doses may cause side effects such as increased blood pressure, mood changes, and reduced resistance to infection and avascular necrosis of the hip.

RISKS ASSOCIATED WITH ANTIHISTAMINES
Depending on the specific type of antihistamine administered, the subject may experience transitory side effects such as drowsiness, nausea, headaches, dry mouth, and allergic reactions such as a rash.

Contacts

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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Age 18-55 years, inclusive
- Have a length of disease duration, from first symptom, of < 10 years. If the date of first symptom is unknown, then the diagnosis of RRMS (as per the revised McDonald 2010 criteria) should be of * 5 years
- Have received no more than two prior disease modifying treatments (DMTs), and the discontinuation of the most recent DMT was due to lack of efficacy
- Suboptimal disease control while on a DMT
- EDSS of 0.0 to 4.0, inclusive, at screening
- For women of childbearing potential: agreement to use an acceptable birth control method during the treatment period and for at least 6 months after the last dose of study drug

Exclusion criteria

- Secondary progressive multiple sclerosis (SPMS) or history of primary progressive or progressive relapsing MS
- Inability to complete an MRI
- Known presence of other neurological disorders
Exclusions Related to General Health
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- History or currently active primary or secondary immunodeficiency
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- History of opportunistic infections
- History or known presence of recurrent or chronic infection
- History of malignancy
- Congestive heart failure
- Known active bacterial, viral, fungal, mycobacterial infection or other infection, excluding fungal infection of nail beds
Exclusions Related to Medications
- Receipt of a live vaccine or attenuated live vaccine within 6 weeks prior to the baseline visit

- 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
- Contraindications to or intolerance of oral or IV corticosteroids, according to the country label, including a) Psychosis not yet controlled by a treatment; b) Hypersensitivity to any of the constituents
- Previous treatment with B-cell targeted therapies (i.e., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab)
- Systemic corticosteroid therapy within 4 weeks prior to screening
- Any previous treatment with alemtuzumab (Campath/Mabcampath/Lemtrada), cladribine, mitoxantrone, daclizumab, laquinimod, total body irradiation, or bone marrow transplantation
- Treatment with cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine or methotrexate
- Previous treatment with natalizumab unless natalizumab was discontinued because of persistent anti-natalizumab antibodies
- Treatment with IV immunoglobulin (Ig) within 12 weeks prior to baseline
- Any previous treatment with an investigational MS DMT not yet approved at time of screening

Exclusions Related to Laboratory Findings
- Positive serum * human chorionic gonadotropin (hCG) measured at screening
- 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 [PCR]) or hepatitis C (HepCAb)
- Lymphocyte count below lower limit of normal (LLN)
- CD4 count < 250/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)
- Platelet count <100,000/µL (<100 × 109/L)
- Absolute neutrophil count < 1.0 × 103/µL

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-01-2017
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ocrelizumab
Generic name:	ocrelizumab

Ethics review

Approved WMO Date:	01-06-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-07-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-08-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-08-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-10-2016

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	16-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-12-2017
Application type:	Amendment
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:	21-12-2018
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
EudraCT	EUCTR2015-005597-38-NL
ClinicalTrials.gov	NCT02637856

Register	ID
CCMO	NL57336.056.16