An Open-Label, single-arm study to evaluate the effectiveness and safety of Ocrelizumab in patients with early stage relapsing remitting multiple sclerosis

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This study will evaluate the efficacy and safety of ocrelizumab in patients with early stage relapsing remitting multiple sclerosis (RRMS).The objective of the Immune Substudy is to explore immunological changes associated with ocrelizumab treatment...

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

Summary

ID

NL-OMON50626

Source
ToetsingOnline

Brief title
ENSEMBLE / MA30143

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

The primary goal of this study is to determine the efficacy of ocrelizumab by evaluating clinical measures related to disease progression over 4 years in patients in the early stage of their RRMS disease.

Secondary outcome

1. Time to onset of confirmed disability progression (CDP) sustained for at least 24 weeks and 48 weeks

2. Proportion of patients who have confirmed disability improvement (CDI), CDP for at least 24 weeks and 48 weeks at Years 1, 2 and 4

3. Proportion of patients who have improved, stable or worsened disability compared with baseline measured by EDSS annually

4. Mean change from baseline in EDSS score over the course of the study

5. Time to first protocol-defined event of disease activity

6. Time to first relapse

7. Annualized relapse rate

8. Proportion of patient relapse free by Weeks 48, 96, 144 and 192

9. Proportion of patients with no evidence of protocol-defined disease activity (NEDA) over Week 96, Week 144 and Week 192

10. Proportion of patients with no evidence of progression sustained for at least 24 weeks on all the following three components (CDP; 20%

increase in timed 25 Foot Walk Test [T25FWT]; 20% increase in timed 9 hole peg test [9HPT]) between baseline and Week 96/192

11. Proportion of patients with no active disease between Baseline and Week 96/192

12. Change from baseline of multiple sclerosis functional composite (MSFC) and its composites (T25FW, 9HP, and Paced Auditory Serial Addition Test [PASAT]) over time

13. Change from baseline in cognitive performance as measured by Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) performed annually

14. Total number of T1 Gd-enhancing lesions; and new and/or enlarging T2 lesion as detected by brain MRI over time

15. Change in total T1 hypointense lesion volume over time

16. Total number of fluid-attenuated inversion-recovery (FLAIR) late enhancing lesions as detected by brain MRI over time

17. Change in brain volume (including white and grey matter fractions) as detected by brain MRI over time

18. Time to treatment discontinuation/switch

19. Employment status score (Work Productivity and Activity Impairment Questionnaire [WPAI])

20. SymptoMScreen score

21. Quality of life score (Multiple Sclerosis Impact Scale [MSIS]-29)

22. Rate and nature of adverse events

23. Changes in vital signs, physical and neurological examinations, clinical

laboratory results, locally reviewed MRI for safety (non-MS CNS pathology) and concomitant medications (including pre-medications and medications used during and following ocrelizumab administration)

Study description

Background summary

This study was designed to evaluate the efficacy and safety of ocrelizumab in patients with early stage relapsing remitting multiple sclerosis (RRMS). We say "relapsing remitting" because this type of MS involves attacks (relapses) of symptoms and then again a recovery phase (remitting). Suppression of disease activity and disability progression as early as possible seems to be an important goal of therapy in MS. Ocrelizumab is a recombinant humanized antibody which binds to B-cells, which are believed to play a role in MS.

One optional substudy will be offered to patients at site Zuyderland Medisch Centrum: the Immune Substudy.

The inclusion period will be reopened to include 400 patients worldwide in the Shorter Infusion Substudy, which will evaluate the safety of a shorter infusion of ocrelizumab in patients with early stage relapsing remitting multiple sclerosis (RRMS).

Study objective

This study will evaluate the efficacy and safety of ocrelizumab in patients with early stage relapsing remitting multiple sclerosis (RRMS).

The objective of the Immune Substudy is to explore immunological changes associated with ocrelizumab treatment in a treatment naïve, early stage RRMS population.

The objective of the Shorter Infusion Substudy is to evaluate the safety of a shorter infusion of ocrelizumab in patients with early stage relapsing remitting multiple sclerosis (RRMS).

Study design

This study is a prospective, multicenter, open-label, single-arm efficacy and safety study in patients with early stage RRMS. 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 192 weeks
- A follow-up period of at least 48 weeks

Follow-up Period: Patients who discontinue treatment early will be followed up for at least 48 weeks after the last infusion of study drug. Patients whose B-cells have not been repleted after 48 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 48 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.

The optional substudy will run in parallel to the main study in some selected sites (in The Netherlands, only the Immune substudy at the Zuyderland Medisch Centrum). The patients who participate in the substudies will have to perform some additional tests during the standard visits of the main study. The optional substudy described in appendix 10 of the previous protocol version has been removed. No sites participated in this substudy in The Netherlands.

The Shorter Infusion substudy is a prospective, multicentre, randomized, double-blind, controlled, parallel arm substudy evaluating the safety of a shorter duration infusion of ocrelizumab in a subgroup of patients with early stage RMS enrolled in the main MA30143 study. We expect approximately 700 patients to be enrolled in this substudy: approximately 300 patients currently participating in the main study, and at least 400 newly enrolled patients.

Intervention

Patients that will be eligible for participation in this study will be treated with 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) of the study protocol. After the first dose, which is divided into two gifts with an interval of 14 days, study medication will be administered 8 times within 192 weeks.

Study burden and risks

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.

Progressive Multifocal Leukoencephalopathy
A very rare and severe viral infection called 'progressive multifocal leukoencephalopathy (PML), which causes brain damage and can be fatal or cause severe disability, has been reported in patients treated with other MS medicines, medicines similar to ocrelizumab, and with ocrelizumab outside of clinical trials, only where the risk for PML was pre-existing, because of prior treatment with natalizumab or fingolimod. Most cases of PML, outside MS, occurred in people with severe immune deficiency, such as transplant patients on immunosuppressive medications or patients receiving certain kinds of chemotherapy (drugs to treat cancer). At each clinic visit, the study doctor will complete a thorough neurological examination to check for symptoms related to PML. If the study doctor thinks that there may be a case of PML during the study, additional tests may be carried out, including an extra brain MRI, blood and urine samples taken and possibly a lumbar puncture to check for the presence of John Cunningham virus (JCV). Samples for JCV antibody will only be tested for patients who are thought to have developed PML. These samples will be stored for up to 1 year after the last patient has made his / her last visit.

MALIGNANCIES INCLUDING BREAST CANCER
Malignancies are considered a potential risk with ocrelizumab due to the potentially decreased immune surveillance associated with B-cell depletion in the context of treatments which are used long-term to treat chronic diseases. During the controlled treatment period, the incidence rate of malignancies in the ocrelizumab treatment groups across the MS program was higher than IFN or placebo groups with overlapping CIs. The incidence rates were within the expected ranges for the MS population from epidemiology sources. The only cluster identified was for breast cancer. No firm conclusion can be made to date concerning the risk due to the low number and the limited follow-up; hence the risk remains potential to date.

NEUTROPENIA
In the controlled treatment period, decreased neutrophils were observed in 12 and 15% of MS patients treated with ocrelizumab, in PPMS and RMS respectively. Most were mild to moderate in severity, approximately 1% of the patients had Grade 3 or 4 neutropenia; and no temporal association with infections was identified.

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

- Able to comply with the study protocol, in the investigator's judgment
- Age 18 * 55 years, inclusive
- Have a definite diagnosis of RRMS, as per the revised McDonald 2010 criteria (Polman et al. 2011)
- Have a length of disease duration, from first documented clinical attack consistent with multiple sclerosis (MS) disease of <= 3 years
- Within the last 12 months: one or more clinically reported relapse(s) or one or more signs of MRI activity
- Expanded Disability Status Scale (EDSS) of 0.0 to 3.5 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 or longer after the last dose of ocrelizimab, as applicable in the ocrelizumab package

leaflet

Exclusion criteria

- Secondary progressive multiple sclerosis or history of primary progressive or progressive relapsing MS
- Inability to complete a Magnetic resonance imaging (MRI)
- Known presence of other neurological disorders, including but not limited to, the following:
• History of ischemic cerebrovascular disorders or ischemia of 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 or lactation
- Patients intending to become pregnant during the study or within 6 months after the last dose of the study drug
- 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
- Lack of peripheral venous access
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- Significant or uncontrolled somatic disease or any other significant disease that may preclude patient from participating in the study
- Congestive heart failure (NYHA III or IV functional severity)
- Known active bacterial, viral, fungal, mycobacterial infection or other infection, or any major episode of infection requiring hospitalization or treatment with intravenous antibiotics within 4 weeks prior to screening or oral antibiotics 2 weeks prior to screening
- History of major opportunistic infections
- History or known presence of recurrent or chronic infection
- History of malignancy, including solid tumors and hematological malignancies
- History of alcohol or drug abuse within 24 weeks prior to baseline
- History or laboratory evidence of coagulation disorders
Exclusions Related to Medications:
- Received any prior approved Disease modifying treatment (DMT) with a label for MS, for example, interferons, glatiramer acetate, natalizumab, alemtuzumab, daclizumab, fingolimod, teiflunomide and dimethylfumarate
- Received a live vaccine or attanuated live vaccine within 6 weeks prior to

the baseline visit
- Treatment with any investigational agent within 24 weeks of screening or five half-lives of the investigational drug or treatment with any experimental procedures for MS
- Contraindications to or intolerance of oral or intravenous (IV) corticosteroids, including methylprednisolone administered IV, according to the country label
- Previous treatment with B-cell targeted therapies
- Systemic corticosteroid therapy within 4 weeks prior to screening.
- Any previous treatment with immunosuppressants/immunomodulators/antineoplastic therapies
- Treatment with IV Immunoglobulin within 12 weeks prior to baseline
- Treatment with investigational DMT
- History of recurrent aspiration pneumonia requiring antibiotic therapy
- Treatment with fampridine/dalfamipridine unless on stable dose for >= 30 days prior to screening. Wherever possible, patients should remain on stable doses throughout the 96-week treatment period
Exclusions Related to Laboratory Findings:
- Positive serum β human chorionic gonadotropin (hCG) measured at screening
- Positive screening tests for hepatitis B
- Lymphocyte count below lower limit of normal
- CD4 count<250/µL
- Aspartate aminotransferase/ serum glutamic oxaloacetic transaminase or alanine aminotransferase/serum glutamic pyruvic transaminase >= 3.0 × Upper limit of normal
- Serum creatinine >1.4 mg/dL for women or > 1.6 mg/dL for men
- Hemoglobin < 8.5 g/dL, Platelet count <100,000/µL, Absolute neutrophil count <1.0 × 10 3/µL

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	20-11-2017
Enrollment:	24
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	15-06-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-08-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-10-2017
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:	28-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	11-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-09-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-10-2018
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:	02-12-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-12-2018
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:	24-12-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-06-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-06-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	14-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-10-2020
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:	23-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-07-2021
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)

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	EUCTR2016-002937-31-NL
ClinicalTrials.gov	NCT03085810
CCMO	NL59829.056.17

Study results

Date completed: 23-03-2023

Results posted: 10-11-2022

First publication
01-07-2022