A Phase III, multicenter, randomized, parallel-group, double blinded, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with Primary Progressive Multiple Sclerosis

Published: 12-10-2010
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Primary:To investigate the efficacy of ocrelizumab compared with placebo in patients with primary progressive multiple sclerosis, as measured by thetime to onset of confirmed disability progression over the treatment period, defined as an increase...

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

Summary

ID

NL-OMON50554

Source
ToetsingOnline

Brief title
WA25046 Oratorio

Condition

- Demyelinating disorders

Synonym
PPMS, Primary Progressive Multiple Sclerosis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Disability progression, Efficacy, Ocrelizumab, PPMS

Outcome measures

Primary outcome

Efficacy: Time to onset of of confirmed disability progression, defined as an

increase in Expanded Disability Status Scale (EDSS) score that is

sustained for at least 12 weeks

Secondary outcome

1. Time to confirmed disability progression, defined as an increase in EDSS

score that is sustained for at least 24 weeks

2. Change in timed 25-foot walk

3. Change in total volume of T2 lesions on magnetic resonance imaging (MRI)

scans of the brain

4. Safety and tolerability: Incidence of adverse events

Study description

Background summary

Primary Progressive Multiple Sclerosis (PPMS) is a rare form of Multiple Sclerosis (MS), accounting for 10-15% of all cases of MS. It's a neurologically disabling condition without a cure. To date, no therapies have shown effectiveness in PPMS and none are registered for its treatment in global region.
B cells are believed to contribute to the development of all subtypes of MS, including PPMS. Removing select B-cells from circulation may beneficially

disrupt inflammatory processes that potentially involve processes promoting chronic autoimmunity.
Ocrelizumab specifically depletes CD20+ B cells, making it an attractive agent to test therapeutic potential in patients with PPMS within clinical studies.

Study objective

Primary:
To investigate the efficacy of ocrelizumab compared with placebo in patients with primary progressive multiple sclerosis, as measured by the time to onset of confirmed disability progression over the treatment period, defined as an increase in EDSS that is sustained for at least 12 weeks, based on regularly scheduled visits.

Secondary:
To evaluate the efficacy of ocrelizumab compared with placebo, as reflected by the following:
• The time to confirmed disability progression over the treatment period, defined as an increase in EDSS that is sustained for at least 24 weeks
• The change in 25-foot timed walk from baseline to Week 120
• The change in total volume of T2 lesions on MRI scans of the brain from baseline to week 120
• The percentage change in total brain volume as detected by brain MRI from Week 24 to Week 120
• The change in SF 36 Health Survey version 2 (SF 36v2) Physical Component Summary (PCS) score from baseline to Week 120
• To evaluate the safety and tolerability of ocrelizumab300 mg × 2 (over 24 week treatment cycles) in patients with primary progressive multiple sclerosis as compared with placebo

Exploratory (clinical):
• The proportion of patients with confirmed 12-week disability progression at Week 120
• The change in EDSS score (mean change and area under the curve [AUC]) from baseline to Weeks 48, 96, and 120
• The change in Multiple Sclerosis Functional Composite Scale (MSFCS) score from baseline to Weeks 48, 96, and 120
• The time to confirmed disability progression over the treatment period, defined as an increase in EDSS that is sustained for at least 12 weeks (0.5 or 1, same criteria as for the primary endpoint time to 12-week CDP) or a 20% increase in 25-foot timed walk that is sustained for at least 12 weeks, or a 20% increase in the 9-hole peg test that is sustained for at least 12 weeks
• The time to sustained 20 percent increase in 25 foot timed walk and 9-hole peg test
• The proportion of patients with a 20 percent increase in 25 foot timed walk time

• The proportion of patients with a 20 percent increase in 9-hole peg test time
• The change in Paced Auditory Serial Addition

Open Label Extension Phase
• To evaluate the long-term safety of ocrelizumab treatment during the Open Label Extension (OLE) phase of the study.
• To evaluate the long-term effects of ocrelizumab on clinical and MRI parameters of disease activity and progression during the OLE phase of the study.

For Imaging, Patient-Reported Outcomes and Biomarkers Exploratory Objectives, please refer to the study protocol

Study design

Multicentre, randomized, parallel group, double-blind, placebo controlled study.

Intervention

A total of 630 primary progressive MS patients will be enrolled and assigned (2:1 randomization) to either an ocrelizumab arm or a placebo arm, stratified by age and region.
Ocrelizumab will be administered as a dual i.v. infusions of 300 mg x2 (on Days 1 and 15) for the first treatment cycle followed by single i.v. infusions of 600 mg every 24 weeks. Patients randomized to the placebo group will receive placebo of ocrelizumab.

Study burden and risks

- Infusion Reaction Risk with Ocrelizumab:fever, chills/rigors, muscle pain, headache, skin rash, fatigue, nausea, vomiting, abnormally low blood pressure, flu-like symptoms, difficulty breathing or shortness of breath.

- Infection Risk with Ocrelizumab: Symptoms that could be due to an infection are e.g. fever, chills, sore throat, coughing up phlegm, loin/kidney pain, pain upon urination, feeling weak, giddy or generally very unwell.

- Other Risks with Ocrelizumab: When you receive ocrelizumab, there is a small chance that your immune system might develop antibodies against the drug. If you develop these special antibodies, they may cause side effects such as rashes, they may affect your body*s ability to respond to ocrelizumab and may stop ocrelizumab from working and increase the chances of infusion reactions. It may also affect your body*s ability to respond to other drugs of similar type.

- Worsening MS: Since this study will have a long duration for the treatment period, some individuals with PPMS treated with placebo as well as ocrelizumab can be expected to experience a worsening of their symptoms that can lead to disability.

- Magnetic Resonance Imaging: The contrast agent may cause temporary nausea (a feeling of being sick to your stomach) or headache. Itching, a rash, or a drop in blood pressure are also possible.

- Blood Draws: The risks of drawing blood from a vein include discomfort at the site of the needle stick, possible bruising and swelling around the site of the needle stick, rarely an infection, and uncommonly feeling faint from the procedure.

- Lumbar Puncture: This procedure could cause discomfort and may result in bruising, stiffness, and, rarely, infection. You may experience a headache, and there is a small chance of bleeding, infection, or injury to a nerve.

Contacts

Public
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Scientific
Hoffmann-La Roche

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CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Adult patients, Ages 18-55 years inclusive
- Primary Progressive Multiple Sclerosis (according to revised McDonald criteria)
- Expanded Disability Status Scale (EDSS) 3.0 to 6.5 points
- Disease duration from the onset of MS symptoms:
a. less than 15 years in patients with an EDSS at screening > 5.0
b. less than 10 years in patients with an EDSS at screening <= 5.0
- Sexually active female and male patients of reproductive potential must use:
Female: two methods of contraception throughout the trial, including the active treatment phase AND for 48 weeks after the last dose of ocrelizumab, or until their B-cells have repleted, whichever is longer.
Male: two methods of contraception throughout trial, including the active treatment phase AND for 24 weeks after the last dose of ocrelizumab.

Exclusion criteria

- History of relapsing remitting multiple sclerosis, secondary progressive, or progressive relapsing multiple sclerosis at screening
- Contraindications for Magnetic Resonance Imaging (MRI)
- Known presence of other neurologic disorders
- Known active infection or history of or presence of recurrent or chronic infection
- History of cancer, including solid tumors and hematological malignancies (except for basal cell, in situ squamous cell carcinomas of the skin and in situ carcinoma of the cervix that have been excised and resolved)
- Previous treatment with B-cell targeted therapies (e.g. rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab)
- Any previous treatment with lymphocyte trafficking blockers, with alemtuzumab, anti-CD4, cladribine, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, or bone marrow transplantation
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study;

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:	Recruitment stopped
Start date (anticipated):	03-07-2012
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ocrelizumab
Generic name:	Ocrelizumab

Ethics review

Approved WMO Date:	12-10-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-03-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	17-04-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-05-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-07-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-05-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-06-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-07-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-07-2013

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-11-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-12-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-06-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	14-10-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-02-2018
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	17-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-10-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-01-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-01-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-06-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	09-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2010-020338-25-NL
ClinicalTrials.gov	NCT01194570
CCMO	NL33418.078.10

Study results

Results posted: 28-11-2023

First publication
20-10-2023