A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study To Evaluate The Efficacy And Safety Of Ocrelizumab In Comparison To Interferon Beta-1a (Rebif®) In Patients With Relapsing Multiple Sclerosis

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The primary objective of this study is to assess whether the efficacy of ocrelizumab given as two dose regimens of 600 mg (given as 300 mg infusions on days 1 and 15 and 600 mg infusion in the following cycles) or 400 mg (given as 200 mg infusions...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Central nervous system infections and inflammations
Study type	Interventional

Summary

ID

NL-OMON43603

Source
ToetsingOnline

Brief title
OPERA 1

Condition

- Central nervous system infections and inflammations

Synonym
Autoimmune disorder of the central nervous system, MS

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Ocrelizumab, Rebif, relapsing Multiple Sclerose

Outcome measures

Primary outcome

The primary efficacy endpoint is annualized protocol-defined relapse rate at two years (96 weeks). Protocol-defined relapse, is defined as the occurrence of new or worsening neurological symptoms attributable to MS.

Secondary outcome

The key secondary objectives of this study are to evaluate whether the efficacy of ocrelizumab is superior to Rebif®, as reflected by the following measures:

* The time to onset of confirmed disability progression for at least 12 weeks with the initial event of neurological worsening occurring during the 96-week, double-blind, double-dummy, treatment period.

* The total number of new T1 Gd-enhancing lesions as detected by brain MRI at Weeks 24, 48, and 96.

* The total number of new, and/or enlarging T2 hyperintense lesions as detected by brain MRI at Weeks 24, 48, and 96.

* The proportion of patients who have confirmed disability improvement for at least 12 weeks with the initial event of neurological improvement occurring

during the 96-week doubleblind, double-dummy treatment period.

* The time to onset of confirmed disability progression for at least 24 weeks,

with the initial event of neurological worsening occurring

during the 96-week, double-blind, double-dummy, treatment period.

* The total number of T1-hypo-intense lesions (Chronic Black Holes) at Weeks

24, 48, and 96.

* The change in Multiple Sclerosis Functional Composite Scale (MSFCS) score

from baseline to Week 96.

* The percentage change in brain volume as detected by brain MRI from Week 24

to Week 96.

* The change in SF-36 Physical Component Summary (PCS) Score from baseline to

Week 96.

* The proportion of patients who have no evidence of disease activity (NEDA) by

Week 96.

Exploratory Objectives:

* To evaluate the long-term safety, tolerability, and efficacy of ocrelizumab

in patients with the relapsing form of MS who are enrolled in the OLE Phase.

See further protocol section 2.3.

Study description

Background summary

Multiple sclerosis (MS) is an inflammatory and degenerative demyelinating disease of the human central nervous system (CNS). Multiple sclerosis affects

around 2.5 million people worldwide: it is one of the most common neurological disorders and cause of disability of young adults. The condition manifests as neurological deficits referable to damage to the spinal cord, brainstem, optic nerves, cerebellum, and cerebrum. Resulting symptoms may include weakness, pain, visual loss, bowel/bladder dysfunction, and cognitive dysfunction. Diagnosis of MS typically occurs through the application of highly structured diagnostic criteria that rely on clinical observation, neurological examination, brain and spinal cord Magnetic Resonance Imaging (MRI) scans, evoked potentials, and examination of cerebrospinal fluid (CSF). The term relapsing MS (RMS) applies to those patients either with a relapsing remitting MS (RRMS) form or a secondary progressive MS (SPMS) form that are suffering relapses. Patients with RMS, in spite of suffering from different MS forms, constitute a common target for current treatments. Currently available first-line therapies for the treatment of either relapsing MS or relapsing-remitting MS include interferon (IFN)- *-1a (Rebif® and Avonex®), IFN-*-1b (Betaferon® / Extavia®) and glatiramer acetate (Copaxone®). Natalizumab (Tysabri®) use due to a risk of Progressive Multifocal Leukoencephalopathy (PML) is limited to RRMS nonresponsive to immunomodulatory treatment or to highly active RRMS. Mitoxantrone (Novantrone®) is also approved for treatment of relapsing MS, but is generally reserved for secondary progressive and severe relapsing*remitting forms of disease. Other drugs have been used with varying degrees of success, including corticosteroids, methotrexate, cyclophosphamide, azathioprine, and intravenous immunoglobulin. The currently approved first-line treatments are modestly effective in reducing the frequency of relapses and in prevention of disability in patients with RMS. The magnitude of these disease modifying effects are an approximately 30% relative improvement versus placebo. Licensed disease modifying agents reduce the frequency of new episodes but do not reverse fixed deficits and have questionable effects on the long-term accumulation of disability and disease progression. Despite significant advances in MS therapy many patients continue to experience disease activity; therefore there remains a need to develop more effective and better tolerated therapies for the treatment of RMS.

This study serves as a pivotal Phase III clinical trial, and is composed of the following periods: a double-blind, double-dummy treatment period, a Safety Follow-Up Period, and an Open-Label Extension Phase. The double-blind, double-dummy treatment period is designed to demonstrate the efficacy and safety of ocrelizumab in relapsing MS in comparison to high-dose, high-frequency (HDHF) IFN (Rebif®). The Open-Label Extension Phase serves to evaluate long-term safety, tolerability, and efficacy of ocrelizumab treatment in patients with relapsing forms of MS.
Rationale open label:
Results of long-term, follow-up exploratory studies suggest that exposure to DMT for more than 2 years improves outcomes by delaying the time to disability progression. Furthermore, there is accumulating evidence that, in MS, inflammatory damage is a continuous process leading to demyelination and axonal transection, and is the substrate of permanent disability in MS. Based on the

long-term efficacy and safety data of the Phase II study WA21493/ACT4422G, it is justified to offer ocrelizumab to patients who would otherwise receive treatment that, in the majority of cases, is modestly effective in reducing the frequency of relapses and in preventing sustained disability.
Thus, patients who complete the 96-week, double-blind, double-dummy treatment period will be offered participation in an OLE Phase of the study. Providing patients with the opportunity to prolong treatment with ocrelizumab beyond 2 years will provide more information on the long-term safety of ocrelizumab in RMS, (e.g., the risk of infections/serious infections/opportunistic infections or potential loss of previously acquired immunity [e.g., hypogammaglobulinemia, specific serological titers]), as well as further collection of tolerability and efficacy information from patients with long-term exposure. Furthermore, the OLE Phase will increase the overall number of patients exposed and patient-year exposure, thus increasing the likelihood of detecting rare events prior to launch, and understanding the safety/efficacy profile. Analyzing the long-term safety, tolerability, and efficacy of ocrelizumab is of critical importance to eventually help clinicians make informed decisions on therapy for patients.

Study objective

The primary objective of this study is to assess whether the efficacy of ocrelizumab given as two dose regimens of 600 mg (given as 300 mg infusions on days 1 and 15 and 600 mg infusion in the following cycles) or 400 mg (given as 200 mg infusions on days 1 and 15 and 400 mg infusion in the following cycles) intravenously every 24 weeks is superior to Rebif® as measured by the annualized protocol-defined relapse rate at two years (96 weeks) in patients with relapsing MS.

Study design

Multicentre, randomized, double-blind, double-dummy, parallel-group study and Open-label extension.

Intervention

Patients will be randomized 1:1 to receive the following treatments: Group A: a dual i.v. infusion of 300 mg ocrelizumab (on days 1 and 15) in the first 24week cycle followed by a single infusions of 600 mg every 24 weeks (in subsequent cycles). Group B: Initiating treatment: * during weeks one and two, Rebif® 8.8 µg (one pre-filled syringe (0.2 ml) containing 8.8 µg (2.4 MIU) of interferon beta-1a) will be injected subcutaneously three times per week * during weeks three and four, Rebif® 22 µg (one pre-filled syringe (0.5 ml) containing 22 µg (6 MIU) of interferon beta-1a)syringe will be injected three times per week. Treatment continuation: * From the fifth week onwards, Rebif® 44 µg (one pre-filled syringe (0.5 ml) containing 44 µg (12 MIU) of interferon beta-1a)

will be given three times per week by subcutaneous injection * A lower dose of 22 µg, also given three times per week by subcutaneous injection, is recommended for patients who cannot tolerate the higher dose of Rebif®.

Patients randomized to active ocrelizumab group will also receive dummy placebo of Rebif® (administered via subcutaneous injection three times per week). Patients randomized to active Rebif® group will also receive dummy placebo of ocrelizumab (administered as intravenous infusions at similar time points to those of the ocrelizumab group)

Study burden and risks

Patients should be informed of the risks associated with taking ocrelizumab and Rebif®. Below are listed specific major risks of Ocrelizumab of which the patients should be made aware. Further information on ocrelizumab is given in the current version of IB. Infusion-Related Reactions - All CD20 depleting agents including ocrelizumab have been associated with acute infusion-related reactions Infection Risks - Prolonged peripheral B-cell depletion is the expected outcome of ocrelizumab treatment. Infection is a potentially serious complication of B-cell depleting therapy and thus requires vigilant attention and prompt investigation and treatment in patients that exhibit signs of infection at any time following anti-CD20 antibody therapy. Prolonged B-cell Depletion - In patients with Reumatoid Arthritis (RA) that were treated with rituximab, prolonged peripheral B-cell depletion has been reported up to 4 years following a single course of therapy. Cardiovascular Disorders - Rarely, cardiac arrhythmias, cardiac ischemia and death due to myocardial dysfunction have been associated with rituximab administration in patients with oncologic disorders. Immunogenicity - Positive HAHA responses were observed and were most frequent in the lower dose groups in both RA studies; no HAHA responses were observed in the NHL study. Immunization - The effect of ocrelizumab on the response to immunization is not known The investigator must refer to the local Rebif label for details on major risks of Rebif®.

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

- adult patients, 18 - 55 years of age inclusive
- multiple sclerosis confirmed according to revised McDonald criteria (2010)
- relapsed-remitting or secondary progressive disease
- At least 2 documented clinical attacks within the last 2 years prior to screening or one clinical attack in the year prior to screening (but not within 30 days prior to screening).
- Neurological stability for * 30 days prior to both screening and baseline
- EDSS, at screening, from 0 to 5.5 inclusive
Patients who meet the following entry criteria may participate in the OLE Phase:
-Complete the 96-week, double-blind, double-dummy treatment period, and who, in the opinion of the Investigator, may benefit from treatment with ocrelizumab;
-Are able and willing to provide written informed consent for the OLE Phase (e.g., before the first infusion at Cycle 5) and to comply with the study protocol;
-Are willing to continue to use at least two contraceptive methods;
-Meet re-treatment criteria with ocrelizumab (see Section 6.1.4).

Exclusion criteria

1. Diagnosis of primary progressive MS.
2. Disease duration of more than 10 years in patients with an EDSS * 2.0 at screening.
3. Inability to complete an MRI
4. Known presence of other neurological disorders which may mimic MS.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-06-2018
Enrollment:	1
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	Ocrelizumab
Product type:	Medicine
Brand name:	Rebif
Generic name:	Interferon beta -1a
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	09-08-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	12-03-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-04-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-04-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-05-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-06-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-06-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-07-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-07-2012
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-07-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-08-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-08-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-03-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-05-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-09-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	01-10-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-12-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-05-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-06-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-07-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-11-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	16-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-02-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-03-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-06-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-02-2019

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2010-020337-99-NL
ClinicalTrials.gov	NCT10063399
CCMO	NL37276.100.11