A PHASE IIIB MULTICENTER, RANDOMIZED, DOUBLE-BLIND, CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY AND PHARMACOKINETICS OF A HIGHER DOSE OF OCRELIZUMAB IN ADULTS WITH RELAPSING MULTIPLE SCLEROSIS

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This study will evaluate the efficacy, safety, and pharmacokinetics of a higher dose of ocrelizumab compared with the approved dose of ocrelizumab in patients with relapsing forms of multiple sclerosis.

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

Summary

ID

NL-OMON55134

Source
ToetsingOnline

Brief title
BN42082 - Musette

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: Double blind - Randomised, High dose Ocrelizumab, Phase IIIB, Relapsing Multiple Sclerosis

Outcome measures

Primary outcome

The primary efficacy objective is to demonstrate the superiority of a higher

dose of ocrelizumab over the approved dose of ocrelizumab as assessed by risk

reduction in cCDP sustained for at least 12 weeks.

Secondary outcome

The secondary efficacy objective is to demonstrate superiority of a higher dose

of ocrelizumab over the approved dose of ocrelizumab on the basis of the

endpoints stated in protocol section 2.1.2

The exploratory efficacy objective for this study is to evaluate the efficacy

of a higher dose of ocrelizumab compared with the approved dose of ocrelizumab

on the basis of, but not limited to, the endpoints described in protocol

section 2.1.3

Study description

Background summary

Multiple sclerosis (MS) is chronic, inflammatory, demyelinating, and degenerative central nervous system disease. The symptomatic deterioration associated with progression of MS results in a slow, insidious loss of a patient's motor and sensory function, as well as cognitive decline and autonomic dysfunction. Disability progression across the spectrum of MS might occur as a result of two concurrent inflammatory mechanisms: acute inflammation and chronic compartmentalized inflammation.
AEven though there are many drugs currently available that target the acute inflammatory mechanisms associated with relapses and relapse associated worsening, to date, only ocrelizumab is indicated for PPMS

Chronic inflammation is responsible for increasing disability. This progression of increasing disability has yet to be addressed in all forms of MS. And treatments that can slow or stop MS disease progression are a serious unmet medical need.

The rationale for testing a higher dose of ocrelizumab in patients with RMS and PPMS is based on (1) exposure response analyzes in the pivotal Phase III studies of RMS and PPMS, (2) data from Phase II study of RRMS with a higher dose of 2000 mg ocrelizumab, and (3) data from previous phase I to III studies with higher doses of ocrelizumab in rheumatoid arthritis (RA)

Study objective

This study will evaluate the efficacy, safety, and pharmacokinetics of a higher dose of ocrelizumab compared with the approved dose of ocrelizumab in patients with relapsing forms of multiple sclerosis.

Study design

Study BN42082 is a Phase IIIb, randomized, double blind, controlled, parallel group, multicenter study to evaluate efficacy, safety and pharmacokinetics of a higher dose of ocrelizumab (1200 mg [patient*s body weight <75 kg] or 1800 mg [patient*s body weight
=>75 kg]) per IV infusion every 24 weeks in patients with RMS, in comparison to the approved 600 mg dose of ocrelizumab. This study will consist of the following phases:screening, double blind treatment (DBT) phase, open-label extension (OLE) phase, safety follow-up (SFU), and B cell monitoring

Figure 1 (in Protocol) gives an overview of the study design

Intervention

Patients will be randomly assigned to one of two treatment arms: higher dose or approved dose of ocrelizumab. Randomization will occur in a 2:1 ratio (higher

dose to approved dose, respectively). Randomization will be stratified.

Study burden and risks

Based on the previous experience with higher doses of ocrelizumab, ocrelizumab MS Phase II/III exposure-safety correlation, the statistical modeling and prediction of Serious Infections (SIE) rates in MS population from the RA data, the higher dose of 1200 mg and 1800 mg are expected to be well tolerated.

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

• Ages 18-55 years at time of screening
• Ability to comply with the study protocol
• Diagnosis of RMS (i.e., RRMS or aSPMS where patients still experience relapses) in accordance with the revised McDonald Criteria 2017
• At least two documented clinical relapses within the last 2 years prior to screening, or one clinical relapse in the year prior to screening (with no relapse 30 days prior to screening and at baseline)
• Patients must be neurologically stable for at least 30 days prior to randomization and baseline assessments
• Expanded disability status scale (EDSS) score, at screening and baseline, from 0 to 5.5 inclusive
• Average T25FWT score over two trials at screening and over two trials at baseline respectively, up to 150 (inclusive) seconds
• Average 9HPT score over four trials at screening and over four trials at baseline respectively, up to 250 (inclusive) seconds
• Documented MRI of brain with abnormalities consistent with MS at screening
• Participants requiring symptomatic treatment for MS and/or physiotherapy must be treated at a stable dose. No initiation of symptomatic treatment for MS or physiotherapy within 4 weeks of randomization
• For females of childbearing potential, agreement to remain abstinent or use adequate contraceptive method.
• For female patients without reproductive potential: Females may be enrolled if post menopausal unless the patient is receiving a hormonal therapy for her menopause or if surgically sterile.

Exclusion criteria

• History of primary progressive MS at screening
• Any known or suspected active infection at screening or baseline, or any major episode of infection requiring hospitalization or treatment with IV anti microbials within 8 weeks prior to and during screening or treatment with oral anti microbials within 2 weeks prior to and during screening
• History of confirmed or suspected progressive multifocal leukoencephalopathy (PML)
• History of cancer, including hematologic malignancy and solid tumors,within 10 years of screening
• Immunocompromised state
• Receipt of a live or live attenuated vaccine within 6 weeks prior to randomization
• Inability to complete an MRI or contraindication to gadolinium administration
• Contraindications to mandatory pre medications for IRRs, including uncontrolled psychosis for corticosteroids or closed angle glaucoma for antihistamines
• Known presence of other neurologic disorders that could interfere withthe diagnosis of MS or assessments of efficacy and/or safety during the study

• Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
• Significant, uncontrolled disease that may preclude patient from participating in the study
• History of or currently active primary or secondary (non-drug related) immunodeficiency
• Pregnant or breastfeeding or intending to become pregnant during the study
• Lack of peripheral venous access
• History of alcohol or other drug abuse within 12 months prior to screening
• Treatment with any investigational agent within 24 weeks prior to screening or treatment with any experimental procedure for MS
• Previous use of anti-CD20s (including ocrelizumab), if in the last 2 years before screening, or if B-cell count is not normal, or if the stop of the treatment was motivated by safety reasons or lack of efficacy
• Any previous treatment with mitoxantrone, cladribine, atacicept, and alemtuzumab
• Previous treatment with fingolimod, siponimod, or ozanimod within 6 weeks of baseline
• Previous treatment with natalizumab within 4.5 months of baseline
• Previous treatment with interferons beta (1a or 1b), or glatiramer acetate within 2 weeks of baseline
• Previous treatment with any other immunomodulatory or immunosuppressive medication not already listed above without appropriate washout as described in the applicable local label (washout to be completed prior to baseline). If the washout requirements are not described in the applicable local label, then the wash out period must be five times the half-life of the medication. The PD effects of the previous medication must also be considered when determining the required time for washout.
• Any previous treatment with bone marrow transplantation and hematopoietic stem cell transplantation
• Any of previous history 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
• Positive screening tests for active, latent, or inadequately treated hepatitis B
• Sensitivity or intolerance to any ingredient (including excipients) of ocrelizumab
• Any additional exclusionary criterion as per ocrelizumab (Ocrevus) local label, if more stringent than the above

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2020
Enrollment:	10
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO

Date:	10-08-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	16-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	11-11-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-12-2020
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:	30-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-05-2021
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	EUCTR2020-000893-69-NL
CCMO	NL74512.056.20