A Study to Evaluate the Efficacy and Safety of Ocrelizumab in Adults With Primary Progressive Multiple Sclerosis

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Main Information

Primary registry identifying number
LBCTR2021114915

Protocol number
WA40404

MOH registration number
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Study registered at the country of origin
No

Study registered at the country of origin: Specify
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Type of registration
Prospective

Type of registration: Justify
N/A

Date of registration in national regulatory agency
08/11/2021

Primary sponsor
F. Hoffmann-La Roche Ltd

Primary sponsor: Country of origin
Switzerland

Date of registration in primary registry
18/02/2022

Date of registration in national regulatory agency
08/11/2021

Public title
A Study to Evaluate the Efficacy and Safety of Ocrelizumab in Adults With Primary Progressive Multiple Sclerosis

Acronym
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Scientific title
A PHASE IIIb MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN ADULTS WITH PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS

Acronym
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Brief summary of the study: English

This study will evaluate the efficacy and safety of ocrelizumab (Ocrevus®) compared with placebo in patients with primary progressive multiple sclerosis (PPMS), including patients later in their disease course.
The primary efficacy objective for this study is to evaluate the efficacy of ocrelizumab-treated patients compared with placebo-treated patients on upper extremity disability progression. This objective is measured on upper limbs on the basis of the following endpoint:
1- upper limb disability progression defined as time to 20% worsening from baseline in 9-Hole Peg Test (9-HPT) confirmed for at least 12 weeks in all randomized patients and in patients with magnetic resonance imaging (MRI) activity (MRI activity is defined as presence of T1 gadolinium (Gd)+lesion[s] and/or new and/or enlarging T2 lesion[s] as detected by MRI scans during the screening phase).
The safety objectives for this study are to evaluate the safety of ocrelizumab compared with placebo, as well as over time, for all patients who received ocrelizumab and until they receive any other immunomodulatory or immunosuppressive treatments.

Brief summary of the study: Arabic

وسلامته مقارنة مع الدواء الوهمي لدى مرضى التصلب المتعدد المترقي (Ocrevus®) (سوف تقيّم هذه الدراسة فعّالية أوكرليزوماب
الأولي(PPMS)، بما في ذلك المرضى في مرحلة لاحقة من مراحل .المرض لديهم
الهدف الأساسي للفعالية في هذه الدراسة هو تقييم الفعالية لدى المرضى المعالجين بعقار أوكرليزوماب مقارنة بالمرضى المعالجين بالدواء الوهمي
على تفاقم الإعاقة في الأطراف العلوية. يُقاس هذا الهدف على الأطراف العلوية على أساس نقطة النهاية التالية:
- 9-HPT % من خط الأساس في اختبار بيج ذو التسع ثقوب) 20تفاقم الإعاقة للطرف العلوي المعرّف على أنه الوقت حتى التفاقم بنسبة
(أسبوعًا على الأقل في جميع المرضى الموزعين عشوائيًا وفي المرضى الذين يعانون من نشاط التصويربالرنين المغناطيسي12المؤكد لمدة)
جديدة و/ أو T2 آفة)آفات(و/أو آفة +) Gd) T1 يتم تعريف نشاط التصوير بالرنين المغناطيسي على أنه وجود الجادولينيوم(MRI)
(متضخمة كما تم اكتشافها بواسطة فحوص التصوير بالرنين المغناطيسي أثناء مرحلة الفرز
تتمثل أهداف السلامة لهذه الدراسة في تقييم سلامة أوكرليزوماب مقارنة بالدواء الوهمي، وكذلك مع مرور الوقت، لجميع المرضى الذين
تلقواأوكرليزوماب وحتى يتلقوا أي علاجات تغيير مناعي أخرى أو علاجات مثبطة للمناعة.

Health conditions/problem studied: Specify

Primary progressive multiple sclerosis

Interventions: Specify

Eligible patients will be randomized (1:1) in a blinded fashion to either placebo or ocrelizumab.
The expected sample size will be approximately 1000 patients, with at least 350 patients in the MRI active subgroup. The MRI active subgroup will consist of patients with T1 Gd+ lesion(s) and/or new and/or enlarging T2 lesion(s) as detected by MRI scan during screening.
The first dose of ocrelizumab will be administered as two 300 mg IV infusions given 14 days apart. For the subsequent doses, ocrelizumab will be administered as a single 600 mg infusion every 24 weeks. A minimum interval of 20 or 22 weeks, depending if the previous dose was administered in one or two infusion, should be maintained between each infusion.
The first dose of placebo will be administered as two 300 mg IV infusions given 14 days apart. For the subsequent doses, placebo will be administered as a single 600 mg infusion every 24 weeks, with a minimum interval of 20 or 22 weeks, depending if the previous dose was administered in one or two infusion, should be maintained between each infusion.

Key inclusion and exclusion criteria: Inclusion criteria

Patients must meet the following criteria for study entry:
1-Ability to provide written informed consent and be compliant with the study protocol

2-Diagnosis of PPMS in accordance with the McDonald criteria (Thompson et al.2017).

3-Age 18-65 years at time of signing Informed Consent Form

4-Expanded Disability Status Scale (EDSS) score at screening and baseline ≥ 3.0 to 8.0, inclusive

5-Disease duration from the onset of MS symptoms relative to randomization date:
Less than 20 years in patients with an EDSS score at screening 7-8.0
Less than 15 years in patients with an EDSS at screening 5.5-6.5
Less than 10 years in patients with an EDSS at screening ≤5.0

6-Documented history or presence at screening of at least one of the following laboratory findings in a cerebrospinal fluid specimen (source documentation of laboratory results and method must be verified)
- Elevated IgG index
- One or more IgG oligoclonal bands detected by isoelectric focusing

7-Screening and baseline 9-HPT completed in > 25 seconds (average of the two hands)

8-Ability to complete the 9-HPT within 240 seconds with each hand at screening and baseline

9-Neurological stability for ≥ 30 days prior to baseline.

10-Patients previously treated with immunosuppressants, immunomodulators, or other immunomodulatory therapies must undergo an appropriate washout period according to the local label of the immunosuppressant/immunomodulatory drug used.
Patients screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility for the trial. Patients who discontinue their current therapy for non-medical reasons should specifically be informed before deciding to enter the study of their treatment options and, that by participating in this study, they may be randomized to placebo for a period of 120 weeks or greater.

11-For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraceptive methods during the treatment period and for 6 or 12 months (as applicable by the Ocrevus local label) after the final dose of ocrelizumab.
A woman is considered to be of childbearing potential if she is post menarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.
The following are considered adequate contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception.
For female patients without reproductive potential:
Women may be enrolled if surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy) or post-menopausal (i.e., spontaneous amenorrhea for the past year confirmed by a follicle-stimulating hormone [FSH] level > 40 mIU/mL) unless the patient is receiving a hormonal therapy for her menopause.

Key inclusion and exclusion criteria: Gender

Key inclusion and exclusion criteria: Specify gender

Both

Key inclusion and exclusion criteria: Age minimum

18

Key inclusion and exclusion criteria: Age maximum

65

Key inclusion and exclusion criteria: Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:
1- History of relapsing-remitting or secondary progressive MS at screening

2- Confirmed serious opportunistic infection including: active bacterial, viral, fungal, mycobacterial infection or other infection, including tuberculosis or atypical mycobacterial disease

3- Patients who have or have had confirmed or a high degree of suspicion of progressive multifocal leukoencephalopathy (PML)

4- Known active malignancy or are being actively monitored for recurrence of malignancy

5- Immunocompromised state, defined as one or more of the following:
-CD4 count < 250/microlitre
-Absolute neutrophil count <1.5 x 10^3/microlitre
-Serum IgG < 4.6 g/L

6- Receipt of a live-attenuated vaccine within 6 weeks prior to randomization

7- Inability to complete an MRI (contraindications for MRI, including but not restricted to pacemaker, cochlear implants, intracranial vascular clips, surgery within 6 weeks of entry in the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, etc.) or contraindication to Gd administration.

8- Patients requiring symptomatic treatment of MS (e.g., fampridine) and/or physiotherapy who are not on a stable regimen. Patients must not initiate symptomatic treatment of MS or physiotherapy within 4 weeks of randomization.

9- Contraindications to mandatory premedications (i.e., corticosteroids and antihistamines) for infusion-related reactions, including:
-Uncontrolled psychosis for corticosteroids
-Closed-angle glaucoma for antihistamines

10- Known presence of other neurologic disorders, including but not limited to, the following:
History of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)
History of metabolic myelopathy or known presence of untreated causes of metabolic myelopathy (e.g., untreated vitamin B12 deficiency) disease, HTLV 1, herpes zoster)
History of genetically inherited progressive CNS degenerative disorder (e.g., mitochondrial myopathy, encephalopathy, lactic acidosis, stroke [MELAS]syndrome, and hereditary paraparesis)
Neuromyelitis optica
History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjögren syndrome, Behçet disease)
History or known presence of sarcoidosis
History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)

11- Pregnant or breastfeeding, or intending to become pregnant during the study and for 6 or 12 months (as applicable by the Ocrevus local label) after last infusion of the study drug

12- Lack of peripheral venous access

13- Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine or gastrointestinal, or any other significant disease that may preclude patient from participating in the study

14- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study

15- History of alcohol or other drug abuse

16- History of primary or secondary (non-drug-related) immunodeficiency

17- Treatment with any investigational agent within 24 weeks prior to screening (Visit 1) or 5 half-lives of the investigational drug (whichever is longer), or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)

18- Previous treatment with B-cell targeting therapies (e.g., rituximab, ocrelizumab, atacicept, belimumab, ofatumumab, and alemtuzumab)

19- Any previous treatment with bone marrow transplantation and hematopoietic stem cell transplantation
Any previous history of transplantation or anti-rejection therapy

20- Treatment with IV Ig or plasmapheresis within 12 weeks prior to randomization

21- Systemic corticosteroid therapy within 4 weeks prior to screening
The screening period may be extended for patients who have used systemic corticosteroids for MS before screening. For a patient to be eligible, systemic corticosteroids should also not have been administered between screening and baseline.

22- Positive serum beta-hCG measured at screening or positive urine beta-hCG at baseline

23- 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])

24- Any additional exclusionary criterion as per ocrelizumab (Ocrevus®) local label, if more stringent than the above

25- Lack of MRI activity at screening/baseline if more than 650 patients without MRI activity have already been enrolled, as defined by T1 Gd+ lesion(s) and/or new and/or enlarged T2 lesion(s) in the screening, to ensure that at least 350 patients with MRI activity will be randomized

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Therapy

Trial scope: Specify scope

N/A

Study design: Allocation

Randomized controlled trial

Study design: Masking

Blinded (masking used)

Study design: Control

Placebo

Study phase

3

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Parallel

Study design: Specify assignment

N/A

IMP has market authorization

Yes, Worldwide

IMP has market authorization: Specify

Europe Union

Name of IMP	Year of authorization	Month of authorization
OCRELIZUMAB	2017	3

Type of IMP

Immunological

Pharmaceutical class

Ocrelizumab is a recombinant humanized monoclonal antibody based on the human immunoglobulin (Ig) G1 framework that contains heavy chain VHIII and light chain Vkl subgroup sequences.

Therapeutic indication

Primary progressive multiple sclerosis

Therapeutic benefit

In clinical trials, data from more than 5000 patients treated with ocrelizumab for autoimmune disease (that is, when the body's immune system attacks and destroys healthy body tissue) like multiple sclerosis, rheumatoid arthritis, lupus nephritis, and systemic lupus erythematosus (an autoimmune connective tissue disease) have been analyzed. Ocrelizumab was given at doses of up to 2000 mg; the maximum dose to be given in this study is 600 mg.

Study model

N/A

Study model: Explain model

Study model: Specify model

N/A

N/A

Time perspective

N/A

Time perspective: Explain time perspective

N/A

Time perspective: Specify perspective

N/A

Target follow-up duration

Target follow-up duration: Unit

Number of groups/cohorts

Biospecimen retention

Samples with DNA**

Biospecimen description

-At participating sites, blood samples will be collected for DNA extraction to enable whole genome sequencing (WGS) or other genotype analysis to assess the patient's germline genotype for allelic variations or mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology.
-The blood samples may be sent to one or more laboratories for analysis.
-Blood samples collected for WGS are to be stored until they are no longer needed or until they are exhausted.
-Patient medical information associated with WGS specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Target sample size

1000

Actual enrollment target size

Date of first enrollment: Type

Anticipated

Date of first enrollment: Date

01/02/2022

Date of study closure: Type

Anticipated

Date of study closure: Date

01/02/2028

Recruitment status

Pending

Recruitment status: Specify

Date of completion

IPD sharing statement plan

No

IPD sharing statement description

No IPD sharing statement plan

Additional data URL

https://clinicaltrials.gov/ct2/show/NCT04035005

Admin comments

Trial status

Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
nap	nap

Sources of Monetary or Material Support

Name
F. Hoffmann-La Roche Ltd

Secondary Sponsors

Name
NAP

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Aziz Zoghbi	MCT-CRO, Berytech Technology and Health, 5th Floor Damascus Road, Beirut, Lebanon	Lebanon	00961 71008269	aziz.zoghbi@mct-cro.com	Director of Country Oversight and Management MENA, Gulf and Africa
Scientific	Halim Abboud	Hotel Dieu de France	Lebanon	00961 03535711	halim.abboud@usj.edu.lb	PI

Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Hotel Dieu de France	Halim Abboud	Neurologist	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Hotel Dieu de France	26/07/2021	Nancy Choucair Alam	nancy.alam@usj.edu.lb	961 1421000-2335

Countries of Recruitment

Name
Australia
Austria
Belgium
Bulgaria
Canada
Colombia
Croatia
France
Georgia
Hungary
Ireland
Italy
Mexico
New Zealand
Poland
Portugal
Romania
Russian Federation
Republic of Serbia
Spain
Ukraine
United Kingdom
United States of America

Health Conditions or Problems Studied

Condition	Code	Keyword
Primary progressive multiple sclerosis	Multiple sclerosis (G35)	Primary progressive multiple sclerosis

Interventions

Intervention	Description	Keyword
OCRELIZUMAB	Eligible patients will be randomized (1:1) in a blinded fashion to either placebo or ocrelizumab.	Treatment

Primary Outcomes

Name	Time Points	Measure
The primary efficacy objective for this study is to evaluate the efficacy of ocrelizumab-treated patients compared with placebo-treated patients on upper extremity disability progression	12 weeks from baseline	upper limb disability progression defined as time to 20% worsening from baseline in 9-Hole Peg Test (9-HPT) confirmed for at least 12 weeks in all randomized patients and in patients with magnetic resonance imaging (MRI) activity (MRI activity is defined as presence of T1 gadolinium (Gd)+ lesion[s] and/or new and/or enlarging T2 lesion[s] as detected by MRI scans during the screening phase).

Key Secondary Outcomes

Name	Time Points	Measure
The secondary efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo for all randomized patients	1	Upper limb disability progression defined as time to 20% increase from baseline in 9-HPT confirmed for at least 24 weeks
The secondary efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo for all randomized patients	2	Time to 12-week Confirmed Disability Progression (CDP) in EDSS, defined as an increase in EDSS score that is confirmed for at least 12 weeks (an increase of ≥1.0 point from baseline EDSS score in patients with a baseline EDSS score ≤ 5.5 or an increase of ≥ 0.5 point in patients with a baseline EDSS score of > 5.5)
The secondary efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo for all randomized patients	3	Time to 24-week CDP in EDSS, defined as an increase in EDSS score that is confirmed for at least 24 weeks (an increase of ≥ 1.0 point from baseline EDSS in patients with a baseline EDSS score ≤ 5.5 or an increase of ≥0.5 point in patients with a baseline EDSS score of > 5.5)
The secondary efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo for all randomized patients	4	Percent change in total volume of T2 lesions from baseline up to Week 120
The secondary efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo for all randomized patients	5	Percent change in total brain volume from Week 24 to Week 120

Trial Results

Summary results

Study results globally

Date of posting of results summaries

Date of first journal publication of results

Results URL link

Baseline characteristics

Participant flow

Adverse events

Outcome measures

URL to protocol files