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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Main Information

Primary registry identifying number
LBCTR2020033434

Protocol number
MA30143

MOH registration number

Study registered at the country of origin
Yes

Study registered at the country of origin: Specify

Type of registration
Retrospective

Type of registration: Justify
Study started before establishment of LBCTR

Date of registration in national regulatory agency
25/01/2018

Primary sponsor
F. HOFFMANN-LA ROCHE LTD

Primary sponsor: Country of origin
Switzerland

Date of registration in primary registry
02/04/2020

Date of registration in national regulatory agency
25/01/2018

Public title
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Acronym
Ensemble

Scientific title
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Brief summary of the study: English

This study is a prospective, multicenter, open-label, single-arm effectiveness 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) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion in 500 mL 0.9% sodium chloride every 24 weeks for the remainder of the study duration.
The study will consist of the following periods:
• Screening period: Up to 4 weeks
• Treatment period: Open-label treatment period of 192 weeks (i.e. 24 weeks after the last dose of ocrelizumab, which will be administered at Week 168)
• A follow-up period of at least 48 weeks, which is independent treatment (DMT) administered as explained below. 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 who complete the 192 weeks Treatment Period and, in agreement with their treating neurologist, decide not to continue in a separate long term extension (LTE) study, will be followed up for at least 48 weeks after the end of the Treatment Period (i.e. 192 weeks + 48 weeks).

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 (Continued B-cell monitoring). If the patients are receiving other B-cell targeted therapies, then
the Follow-up Period is only 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 (starting after the site visit at 8 weeks) 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 (including new or worsening neurological symptoms) and possible events or infections.

Brief summary of the study: Arabic

ان الهدف من هذه الدراسة هو معرفة ما اذا كان اوكريليزوماب (دواء الدراسة) سيوقف تفاقم اشارات واعراض التصلّب المتعدّد المبكر. تعمل الاجسام المضادة الوحيدة النسيلة مثل جهاز مناعة المريض، وتتعلّق ببعض الخاليا بهدف الهجوم على الجراثيم وغيرها من الامراض في جسم المريض. يتعلّق اوكريليزوماب ببعض انواع كريات الدم البيضاء (الخاليا البائية) التي يعتقد انها تلعب دوراً في مرض التصلّب المتعدّد.
سوف تضمّ هذه الدراسة ما لا يقل عن 1,100 مريض.
سبق ان تم اعتماد اوكريليزوماب لعلاج التصلّب المتعدد في العديد من البلدان بما فيها الواليات المتحدة االميركية واوستراليا وكندا واالتحاد االوروبي وغيرها من الدول. غير ان هذا الدواء ما زال تجريبياً في بلدان اخرى، مّما يعني ان السلطات الصحية في هذه البلدان لم تقر استعمال اوكريليزوماب لعالج التصلّب المتعدد.

Health conditions/problem studied: Specify

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

Interventions: Specify

Ocrelizumab (Ocrevus) - recombinant humanized anti-human monoclonal antibody

Key inclusion and exclusion criteria: Inclusion criteria

Patients must meet the following criteria for study entry:
• Signed informed consent form
• 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 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
• 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 after the last dose of study drug.
A woman is considered to be of childbearing potential if she is postmenarcheal, 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 following are acceptable contraceptive methods: progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, male or female condom with or without spermicide, and cap, diaphragm, or sponge with spermicide. A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods) is considered acceptable.

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

18

Key inclusion and exclusion criteria: Age maximum

55

Key inclusion and exclusion criteria: Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:
• Secondary progressive multiple sclerosis progressive relapsing MS
• Inability to complete an MRI (contraindications for MRI include but are not restricted to pacemaker, cochlear implants, presence of foreign substances in the eye, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, claustrophobia, weight>140 kg, etc.)
• Known presence of other neurological 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 or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
− History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T-lymphotropic virus 1 [HTLV-1], herpes zoster myelopathy)
− History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; MELAS [mitochondrial myopathy, encephalopathy, lactic acidosis, stroke] syndrome)
− Neuromyelitis optica
− History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjogren's syndrome, Behçet's disease, sarcoidosis)
− History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)
UExclusions Related to General Health
• Pregnancy or lactation
• 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 (New York Heart Association [NYHA] III or IV functional severity)
• Known active bacterial, viral, fungal, mycobacterial infection or other infection, (excluding fungal infection of nail beds) or any major episode of infection requiring hospitalization or treatment with intravenous (IV) antibiotics within 4 weeks prior to screening or oral antibiotics 2 weeks prior to screening.
Note: Active infections should be treated and effectively controlled before possible inclusion in the study
• History of major opportunistic infections (i.e. cryptococcosis, Pneumocystis pneumonia, progressive multifocal leukoencephalopathy [PML])
• History or known presence of recurrent or chronic infection (e.g., human immunodeficiency virus [HIV], syphilis, tuberculosis [TB])
• History of malignancy, including solid tumors and hematological malignancies, except basal cell carcinoma, in situ squamous cell carcinoma of the skin, and in situ carcinoma of the cervix of the uterus that have been previously completely excised with documented, clear margins.
• History of alcohol or drug abuse within 24 weeks prior to baseline
• History or laboratory evidence of coagulation disorders UExclusions Related to Medications
• Received any prior approved DMT with a label for MS, for example, interferons, glatiramer acetate, natalizumab, alemtuzumab, daclizumab, fingolimod, teiflunomide and dimethylfumarate.
• Receipt of a live vaccine or attenuated live vaccine within 6 weeks prior to the baseline visit. In rare cases when patient requires vaccination with a live vaccine, the screening period may be extended but cannot exceed 8 weeks.
• Treatment with any investigational agent within 24 weeks of screening (Visit 1) or five half-lives of the investigational drug (whichever is longer) or treatment with any experimental procedures for MS (e.g., treatment for chronic cerebrospinal venous insufficiency).
• Contraindications to or intolerance of oral or IV corticosteroids, including methylprednisolone administered IV, according to the country label, including:
a) Psychosis not yet controlled by a treatment;
b) Hypersensitivity to any of the constituents.
• Previous treatment with B-cell targeted therapies (i.e., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab).
• Systemic corticosteroid therapy within 4 weeks prior to screening.
• Any previous treatment with immunosuppressants/ immunomodulators/ antineoplastic therapies (cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, cladribine, mitoxantrone, laquinimod, total body irradiation, or bone marrow transplantation).
• Treatment with IV immunoglobulins (Ig) within 12 weeks prior to baseline.
• Treatment with investigational DMT
• History of recurrent aspiration pneumonia requiring antibiotic therapy
• Treatment with fampridine/dalfampridine (Fampyra®)/Ampyra®) unless on stable dose for ≥ 30 days prior to screening. Wherever possible, patients should remain on stable doses throughout the 96-week treatment period. UExclusions Related to Laboratory Findings*
• Positive serum β human chorionic gonadotropin (hCG) measured at screening
• 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])
• Lymphocyte count below lower limit of normal (LLN)
• CD4 count<250/µL.
• Aspartate aminotransferase (AST)/ serum glutamic oxaloacetic transaminase (SGOT) or alanine aminotransferase (ALT) /serum glutamic pyruvic transaminase (SGPT)≥ 3.0 × the upper limit of normal (ULN)

• Serum creatinine >1.4 mg/dL (> 124 µmol/L) for women or > 1.6 mg/dL (> 141µmol/L) for men
• Hemoglobin < 8.5 g/dL (< 5.15 mmol/L)
• Platelet count <100,000/µL (<100 × 109PP/L)
• Absolute neutrophil count <1.0 × 103PP/µL

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Other

Trial scope: Specify scope

Study design: Allocation

N/A: Single arm study

Study design: Masking

Open (masking not used)

Study design: Control

Uncontrolled

Study phase

3

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Single

Study design: Specify assignment

N/A

IMP has market authorization

Yes, Lebanon and Worldwide

IMP has market authorization: Specify

United States of America, Albania, Australia, Israel, Kosovo, Kuwait, Panama, Paraguay, Russian Federation, Ukraine, United Arab Emirates, and Canada

Name of IMP	Year of authorization	Month of authorization
Ocrelizumab	2018	10

Type of IMP

Immunological

Pharmaceutical class

Ocrelizumab is a recombinant humanized anti-human monoclonal antibody that selectively targets and eliminates CD20-expressing B cells.

Therapeutic indication

Relapsing remitting multiple sclerosis

Therapeutic benefit

The majority of the clinical trials of DMTs in MS target patients who are already progressed, for example the mean duration of disease is around six years for many clinical trials (Wiendl and Meuth. 2015). There is, however, evidence suggesting that early intervention might be effective in reducing the rate of relapses in patients with RRMS and in slowing the course of MS progression (Noyes and Weinstock-Guttman. 2013).

A follow-up of the phase 3 clinical trial (n = 160) of IFNβ-1a vs. placebo in early RRMS patients described above, patients randomized to IFNβ-1a (n=79) were significantly less likely to progress to an EDSS score of 4.0 or greater (44.3% vs 65.4%; P=.007) or 5.0 or greater (34.2% vs 54.3%; P=.01) than patients randomized to placebo (n=81) at the 8-year follow-up assessment (Rudick et al. 2010). Other long-term studies have also
demonstrated a positive impact of early therapy in patients with RRMS. In a long-term follow-up of the pivotal PRISMS study (n=560), patients originally randomized to both the 22-µg and 44-µg doses of IFNβ-1a had sustained reductions in relapses and less disease progression compared with patients originally randomized to placebo. Although all patients received IFNβ-1a treatment by year 3 of the pivotal study (patients originally randomized to placebo were switched to either the 22- or 44-µg dose), the increased disability observed in patients for whom treatment was delayed was sustained (Kappos et al. 2006), suggesting that delaying treatment for as little as 2 years may result in irreversible consequences.

Study model
N/A

Study model: Explain model
N/A

Study model: Specify model
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
None retained

Biospecimen description
NA

Target sample size
10

Actual enrollment target size
6

Date of first enrollment: Type
Actual

Date of first enrollment: Date
08/03/2018

Date of study closure: Type
Actual

Date of study closure: Date
16/01/2024

Recruitment status
Complete

Recruitment status: Specify

Date of completion
21/01/2019

IPD sharing statement plan
Yes

IPD sharing statement description

During this study, health and personal information about subjects will be collected. This section describes the protection, use, and sharing of information, which consists of the following:
• Information in the medical record, which is held by Sites.
• Information that is collected or produced during this study ("study data"), which is held by sites, Roche, Roche affiliates, and Roche's representatives.
Subject privacy is very important, and Roche uses many safeguards to protect privacy, in accordance with applicable data privacy laws and laws related to the conduct of clinical trials.
Subject study data and samples will be labelled with a patient identification (ID) number that is unique and not related to or derived from information that identifies subject (such as name, picture, or any other personally identifying information). Roche, Roche affiliates, and Roche's representatives will only have access to study data and samples labelled with a patient ID number, except as described below. Subjects medical record, which includes personal information that can identify subjects, will not be accessed for the purposes of this study, except as described below:
Information (which includes information in medical record that can identify subjects) may need to be reviewed to make sure the study is being done properly or to check the quality of the information. This information will be kept private. The following people and groups of people may and/or copy this information:
• Study monitors of Roche and/or CRO, a company hired by Roche to perform certain study activities
• The Institutional Review Board or Ethics Committee
• Regulatory authorities

Roche, Roche affiliates, and Roche's collaborators and licensees (people and companies who partner with Roche) may use study data labelled with patient ID number for research purposes or to advance science and public health.
Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. These data will not include information that identifies subjects, and extra steps will be taken to safeguard privacy.
Subject information will not be given to insurance company or employer, unless required by law. If the results from this study are published in a medical journal or presented at a scientific meeting, subjects will not be identified.
Information from this study will be retained by Sites for 15 years after the end of the study. In addition, Roche will retain the study data for up to 25 years after the end of the study.

Additional data URL

Admin comments

Trial status

Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
NA	NA

Sources of Monetary or Material Support

Name
F. HOFFMANN-LA ROCHE LTD

Secondary Sponsors

Name
NA

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Bassem Yamout	American University of Beirut, Medical Center	Lebanon	+961 01/350000	yamoutba@gmail.com	Nehme and Therese Tohme Multiple Sclerosis Center - American University of Beirut Medical Center
Scientific	Bassem Yamout	American University of Beirut, Medical Center	Lebanon	+961 01/350000	yamoutba@gmail.com	American University of Beirut, Medical Center

Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Nehme and Therese Tohme Multiple Sclerosis Center - American University of Beirut Medical Center	Dr. Bassem Yamout	Neurologist	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
American University of Beirut Medical Center	25/01/2018	Dr. Abeer Dakik	irb@aub.edu.lb	+9611350000 ext. 5445

Countries of Recruitment

Name
Lebanon
Argentina
Australia
Austria
Belgium
Brazil
Bulgaria
Canada
Croatia
Denmark
France
Germany
Hungary
Italy
Kuwait
Mexico
Norway
Netherlands
Poland
Portugal
Romania
Slovakia
Slovenia
Spain
Sweden
Switzerland

Turkey
United Kingdom
United States of America

Health Conditions or Problems Studied

Condition	Code	Keyword
Multiple Sclerosis	Multiple sclerosis (G35)	MS

Interventions

Intervention	Description	Keyword
Ocrelizumab	The investigational medicinal product (IMP) for this study is Ocrelizumab IV (OCREVUS). recombinant humanized monoclonal antibody.	Ocrevus

Primary Outcomes

Name	Time Points	Measure
• To evaluate the effectiveness of ocrelizumab in early stage of RRMS	Evaluate clinical measures related to disease progression over 4 years in patients in the early stage of their RRMS disease	Related to disability progression: • Time to onset of CDP sustained for at least 24 weeks and 48 weeks • Proportion of patients who have confirmed disability improvement (CDI), CDP for at least 24 weeks and 48 weeks at year 1, 2 and 4 • Proportion of patients who have improved, stable or worsened disability compared with baseline measured by EDSS annually • Mean change from baseline in EDSS score over the course of the study

Key Secondary Outcomes

Name	Time Points	Measure
Different effectiveness measures evaluated for ocrelizumab in early stage of RRMS	Other clinical measures and composite endpoints:	• Time to first protocol-defined event of disease activity • Time to first relapse • Annualised relapse rate • Proportion of patient relapse free by week 48, 96, 144 and 192 • Proportion of patients with no evidence of protocol- defined disease activity (NEDA) over week 96, week 144 and week 192 where disease activity is defined as at least one the following events: protocol-defined relapse; CDP based on increases in EDSS; a T1 Gd- enhanced lesion after Week 8; or a new and/or enlarging T2 hyperintense lesion on MRI after Week 8 compared to the Week 8 MRI scan. • Proportion of patients with no evidence of progression (NEP) defined as no progression sustained for at least 24 weeks on all of 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 • Proportion of patients with no evidence of progression sustained for at least 24 weeks and no active disease (NEPAD) defined as no progression on all of the three components of NEP (CDP, T25FWT, 9HPT), no new relapse and no enlarging or new T2 or T1 Gd- enhancing lesion between baseline and week 96/192 • Change from baseline of Multiple Sclerosis Functional Composite (MSFC) and its composites (T25FW, 9HP, and Paced Auditory Serial Addition Test [PASAT]) over time • Change from baseline in cognitive performance as measured by Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) performed annually
Different effectiveness measures evaluated for ocrelizumab in early stage of RRMS	Related to MRI	• Total number of T1 Gd-enhancing lesions as detected by brain MRI over time • Total number of new and/or enlarging T2 lesion as detected by brain MRI over time • Change in total T1 hypointense lesion volume over time • Total number of fluid-attenuated inversion-recovery (FLAIR) late enhancing lesions as detected by brain MRI over time • Change in brain volume (including white and grey matter fractions) as detected by brain MRI over time
Different effectiveness measures evaluated for ocrelizumab in early stage of RRMS	Other measures related to MS disease:	• Time to treatment discontinuation/switch
Different effectiveness measures evaluated for ocrelizumab in early stage of RRMS	Patient reported outcomes:	• Employment status (Work Productivity and Activity Impairment Questionnaire [WPAI]) • SymptoMScreen • Quality of life (Multiple Sclerosis Impact Scale [MSIS]-29)

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