An open-label, single arm, multi-center extension study evaluating long-term safety, tolerability and effectiveness of ofatumumab in subjects with relapsing multiple sclerosis

Published: 16-10-2018
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This study has been transitioned to CTIS with ID 2023-507906-15-00 check the CTIS register for the current data. This study is designed to collect long-term safety, tolerability, effectiveness and health outcomes data in RMS patients.COVID-19...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON54568

Source
ToetsingOnline

Brief title
COMB157G2399 (ALITHIOS)

Condition

- Neurological disorders NEC

Synonym
MS, Multiple Sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor/verrichter van dit onderzoek)

Intervention

Keyword: Multiple Sclerose, Ofatumumab, Relapses

Outcome measures

Primary outcome

- Proportion of subjects with adverse events

- Proportion of subjects with laboratory, or vital signs results meeting

abnormal criteria

-Proportion of subjects with electrocardiogram (ECG) meeting abnormal criteria

[through Week 240 (EOS)]

- Proportion of subjects meeting predefined criteria in Columbia Suicide

Severity Rating Scale (C-SSRS) [through Week 240/EOS]

Secondary outcome

Through Week 240/EOS:

- Annualized Relapse Rate (ARR)

- Time to 3-month Confirmed Disability Worsening (3mCDW)

- Time to 6-month Confirmed Disability Worsening (6mCDW)

- Time to 6-month Confirmed Disability Improvement (6mCDI)

- Time to 12-month Confirmed Disability Improvement (12mCDI)

- Time to 24-month Confirmed Disability Improvement (24mCDI)

- Time to 6-month Confirmed Disability Improvement (6mCDI) sustained until End

of Study (EOS)

- Change in Expanded Disability Status Scale(EDSS)

- Time to 6-month confirmed 4-point worsening on Symbol Digit Modalities Test (SDMT)

- Change in SDMT

- Annualized T2 lesion rate

- Number of T1 Gd-enhancing lesions per Magnetic Resonance Image (MRI) scan

- Annual rate of change in brain volume

- Change in neurofilament light chain (NfL) concentration in serum

- Relationship between NfL and disease activity, disease course and treatment response

- Patient Reported Outcomes (PROs)

COVID-19 substudy:

Humoral Response (antibodies against SARS-Cov-2)

- Proportion of subjects with a positive SARS-CoV-2 Immunoglobulin G (IgG) antibody test assessed over time at approximately 3, 6, 9 and 12 months after first vaccination or booster.

T-cell response (reactie T-cells against SARS-Cov-2)

- Proportion of subjects having established SARS-CoV-2 specific T-cells as defined by the detection of SARS-CoV-2 reactive Tcells, measured by e.g. enzyme-linked immunosorbent spot (ELIspot) assay from T-cells that were stimulated with SARS-CoV-2 peptide mix, assessed over time at approximately 3,

6, 9 and 12 months after first vaccination or booster.

Study description

Background summary

MS is a long-term illness where the body*s immune system attacks and damages the protective covering (called myelin) around the nerves in the central nervous system. Damaged myelin results in scar tissue or *sclerosis*. Because this scar tissue does not transfer signals from the brain as well as normal myelin, nerves stop working properly. Such scars can be seen on a scan called magnetic resonance imaging (MRI).
People with relapsing MS will have repeated attacks, or *relapses*. During these relapses, the own immune system attacks the nerves in the brain or spinal cord, damaging the myelin covering. This can result in symptoms including difficulty walking, balance problems, vision problems, and more. Some symptoms may not completely recover after the relapse leading to accumulation of disability over time.
The immune system is made up of many different types of cells that work together to fight infection, among them B-cells and lymphocytes, which are types of white blood cells. Ofatumumab targets cells in the immune system by temporarily removing the number of Bcells, a type of white blood cell. White blood cells are involved in the process of inflammation that is believed to play a role in damaging the myelin and in some of the symptoms in MS. Bcells produce *antibodies* which fight infection but are also responsible for some of the damage that is done to the nerve cells in MS.
In the Netherlands, ofatumumab is approved and *on the market* for the treatment of Chronic Lymphocytic Leukemia (CLL), a cancer of the blood which affects a type of white blood cell called lymphocytes. However, for use in CLL, the dose is much higher than will be used in this study. In CLL, the medication is administered into a vein but for this MS research study, the medication will be given by an injection under the skin (subcutaneous injection).
Ofatumumab has not yet been approved for the treatment of people with relapsing MS. Therefore, ofatumumab is currently not *on the market* for MS in any country.
Around 267 patients with relapsing-remitting MS have been treated with ofatumumab (most via injection under the skin) in completed clinical studies to date (details on these studies can be found in Section 5). In addition, there are two large trials ongoing with more than 1800 patients with relapsing MS participating (with half the patients receiving ofatumumab treatment). This study will enroll patients that have participated in other ofatumumab studies and provide the opportunity for Novartis to study ofatumumab long-term safety and efficacy.

This study does not compare ofatumumab to any other treatment for MS; all patients will be treated with ofatumumab.

COVID-19 substudy:
People taking ofatumumab have a reduced number of B-cells available to produce antibodies following vaccination which may reduce the effectiveness of vaccination. It is important to determine if people treated with ofatumumab are able to develop a protective immune response after vaccination against COVID-19.

Study objective

This study has been transitioned to CTIS with ID 2023-507906-15-00 check the CTIS register for the current data.

This study is designed to collect long-term safety, tolerability, effectiveness and health outcomes data in RMS patients.

COVID-19 substudy:
The purpose of this COVID-19 research sub-study is to determine the effects of the study treatment (ofatumumab) on the development of an immune response to selected SARS-CoV-2 (COVID-19) vaccines in participants with RMS.

Study design

This study uses an open-label, multi-center, single treatment arm design, enrolling subjects that have participated in a Novartis ofatumumab MS clinical study. This study has 3 main Parts:
* Part 1 - Screening
* Part 2 - Loading
* Part 3 - Open-Label Treatment

COVID-19 substudy:
During a number of visits of the main study, additional blood samples may be taken for a number of patients. Depending on
which visit the participant is on a C-SSRS will be completed. Participation is voluntary.
The substudy will run for a maximum of 12 months (or until the end of the main study if this is sooner).

Intervention

1. Ofatumumab (OMB157G) 20 mg sc injection on Day 1, Day 7, Day 14 and every 4 weeks (q4) from month 1.
2. Placebo sc on Day 1 and Day 14 if applicable.

COVID-19 substudy:
no intervention

Study burden and risks

Risks: Adverse events of the study medication (ofatumumab) and possibly methylprednisone (premedication), side effects of the tests (blood collection, injections, accelerated washout of teriflunomide).

Burden:
Visits: Screening, Day 1, day 7 and 14, Week 4 (W4), followed by every 12 weeks in the first 2 years, then every 24 weeks until the 5th year of the study, thereafter yearly until 8th year.
Physical examination at screening, thereafter at each visit, end of study visit(s)
Vital Signs: at screening, Day 1 and from W4 onwards at each visit in the first year, then every 24 weeks until 5th year, thereafter yearly until 8th year, end of study visit(s)
Blood tests: at screening, Day 1 and from W4 onwards at each visit in the first year, then every 24 weeks until 5th yr, thereafter yearly until 8th yr, end visit(s), M3, 6, 9 in follow-up period.
Pregnancy tests: during screening, then annually and at end of study visit(s) via blood test, monthly test at home via urine examination.
ECG at screening and at end of study visit of 5th yr.
MRI at screening, annually until 5th yr, end of study visit of 5th yr, M6 in follow-up period.
Neurological examination (EDSS) at screening, every visit until 8th year, end of study visit(s), M3,6,9 in follow-up period.
SDMT: screening, day 1, from W12 onwards every visit in the first 2 years, then every 24 weeks until 5th yr, end of study visit 5th yr.
Questionnaire 'state of mind; : Screening and Day 1, then at each visit until 5th yr, end of study visit 5th yr.
Other questionnaires: screening and day 1, annually until 5th yr, end of study visit 5th yr.
Monthly telephone call if no visit.

COVID-19 substudy:
Additional blood sampling: first visit after signing Informed Consent, at 3,6,9 and 12 months after first vaccination or booster
Suicidal questionnaire: depending on which visit the participant is on..

Contacts

Public
Novartis

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects eligible for inclusion in this study must fulfill all of the following criteria:
- Must have participated in a Novartis MS study:
• which dosed ofatumumab 20 mg sc every 4 weeks,
• was an adult (>= 18 years of age) study in RMS,
• must have completed the study on study treatment (subjects that are on temporary drug interruption at the time of End of Study are considered completers).
- Written informed consent must be obtained before any assessment is performed

Exclusion criteria

• Premature discontinuation from previous ofatumumab study or from study treatment in previous ofatumumab study • Subjects that have had their previous

ofatumumab study end of study (EOS) > 6 months prior to screening and/or been given another MS disease-modifying treatment (DMT) between EOS of previous study and screening of this study. • Less than 3.5-month washout of teriflunomide for subjects that will not complete the accelerated elimination procedure (AEP) prior to Day 1. Only applicable to subjects completing studies COMB157G2301 and COMB157G2302 • Subjects with a history of not being able or willing to cooperate or comply with study protocol requirements in the opinion of theInvestigator • Subjects that have any unresolved adverse event (AE) or condition from the previous study or prior to Day 1 that necessitates temporary interruption of the study treatment, until such time as the event or condition has resolved (the subject will be monitored within the safety follow-up of the previous study and not consented into study COMB157G2399 until the AE or condition has resolved) • Emergence of any clinically significant condition/disease during previous ofatumumab study or prior to Day 1 in which study participation might result in safety risk for subjects • Subjects with neurological findings consistent with Progressive Multifocal Leukoencephalopathy (PML) or confirmed PML • Subjects with active systemic bacterial, viral or fungal infections, or chronic infection (e.g. Acquired Immune Deficiency Syndrome (AIDS)) prior to Day 1 • Subjects that have developed or have had reactivation of syphilis, hepatitis B or tuberculosis during previous ofatumumab study or prior to Day 1

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-05-2019
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ofatumumab
Generic name:	ofatumumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-10-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-05-2019
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-08-2021
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-11-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-03-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EU-CTR	CTIS2023-507906-15-00
EudraCT	EUCTR2017-004703-51-NL
ClinicalTrials.gov	NCT03650114
CCMO	NL67272.029.18