A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis

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To demonstrate that ofatumumab is superior to teriflunomide in reducing the frequency of confirmed relapses as evaluated by the annualized relapse rate (ARR) in patients with relapsing MS

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

Summary

ID

NL-OMON47697

Source
ToetsingOnline

Brief title
COMB157G2301

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 van dit onderzoek)

Intervention

Keyword: Multiple Sclerose, Ofatumumab, Relapses, Teriflunomide

Outcome measures

Primary outcome

* Annual Relapse Rate (ARR)

* Time to disability worsening as measured by 3-month confirmed worsening

(3mCDW) on Expanded Disability Status Scale (EDSS)

* Time to disability worsening as measured by 6-month confirmed worsening

(6mCDW) on EDSS

* Time to disability improvement as measured by 6-month confirmed improvement

(6mCDI) on EDSS

* Number of T1 gadolinium (Gd)-enhancing lesions per Magnetic Resonance Image

(MRI) scan

* Number of new or enlarging T2 lesions on MRI per year (annualized T2 lesion

rate)

* Neurofilament light chain (NfL) concentration in serum

* Rate of brain volume loss (BVL) based on assessments of percentage brain

volume change from baseline

Secondary outcome

* Time to first relapse

* Annualized relapse rates > 8 weeks after the onset of treatment

* Risk of a 3mCDW > 8 weeks after the onset of treatment

* Risk of a 6mCDW > 8 weeks after the onset of treatment

* Time to a 6-month confirmed cognitive decline (6mCCD), defined as a 4-point worsening on Symbol Digit Modalities Test (SDMT)

* Time to 6mCDW or 6mCCD, whichever is reached first

* Change in cognitive performance relative to baseline as measured by the SDMT

* Time to 6-month confirmed worsening of at least 20% in the timed 25 foot walk test (T25FW)

* Time to 6-month confirmed worsening of at least 20% in the 9-hole peg test (9HPT)

* Time to 6mCDI sustained until end of study as measured by EDSS

* Number of new or enlarging T2 lesions between Month 12 and End of Study (EOS)

* Change in T2 lesion volume relative to baseline

* Proportion of patients with no evidence of disease activity (NEDA) at year 1 and 2

* Physical and psychological impact of MS disease as measured by the Multiple Sclerosis Impact Scale (MSIS-29)

In the subgroup of newly diagnosed, treatment-naïve patients, evaluate if:

* High NfL (above median) concentration at baseline is predictive of higher disease activity post baseline

* Patients with a high NfL (above median) concentration at baseline benefit from a stronger relative treatment effect of ofatumumab vs teriflunomide

* The safety profile of ofatumumab vs terifluomide is comparable in patients with high NfL (above median) concentration at baseline

* To evaluate the safety and tolerability of ofatumumab compared to

teriflunomide

* To evaluate the pharmacokinetic (PK) of ofatumumab

Study description

Background summary

Multiple sclerosis is a chronic condition in which the central nervous system is affected. Inflammations occur in the nervous tissue with the result that the transfer of information is affected in the central nervous system, and nerves die off. As a result, the patient experiences more and more physical symptoms, this leads to serious limitations. It is therefore important to start with an effective treatment at an early stage to prevent permanent damage. Currently, the MS treatment consists of medication that primarily focusses on the T cells. Recent research has shown that not only the T-cells of the immune system play a role in the damage of the nervous system, but also the B-cells. B-cells have an essential function mainly in the early phase of an immune response, a.o. by the regulation of T-cells and inflammation via the production of cytokines. B-cells are present in the inflammatory lesions in the nervous system and in the cerebrospinal fluid of patients with MS.
Ofatumumab, a fully human anti-CD20 monoclonal antibody, has a similar mechanism of action as rituximab and ocrelizumab and is already registered for the treatment of patients with chronic lymphocytic leukemia in a higher dosage (under trade name Arzerra*). As a fully human antibody ofatumumab is predicted to have a reduced immunogenicity, partly supported by the very low incidence of anti-drug antibodies against ofatumumab observed in clinical trials (<1% of patients in the oncology studies). In addition, results from two Phase 2 studies in patients with MS show that subcutaneous administration of ofatumumab reduces the number of active inflammation with more than 90% (in 4-12 week after the start of the study).
In this phase 3 study, the effects (efficacy, safety and tolerability) of ofatumumab compared to the active comparator teriflunomide for the maximum period of 2.5 years. Teriflunomide (trade Aubagio®) is registered in the Netherlands as a treatment for relapsing-remitting MS. The study is followed by an open-label extension study in which all patients are treated with ofatumumab with the objective to investigate the long term safety and tolerability of ofatumumab.
There are no risky surgeries. Unlike a regular treatment is extra bled, are purchased more neurological tests and questionnaires are completed. ECG is made also.
The risk to the patient is limited to the risk of side effects of the study

medication and injection. All participating patients are treated with an active agent. The burden on the patient is acceptable.
Given the need for more opportunities to treat relapsing MS, it is justified to ask patients to participate in this study

Study objective

To demonstrate that ofatumumab is superior to teriflunomide in reducing the frequency of confirmed relapses as evaluated by the annualized relapse rate (ARR) in patients with relapsing MS

Study design

Randomized, double-blind, double-dummy, parallel-group, active-comparator controlled, adaptive design, maximal treatment duration of 30 months for an individual patient

Intervention

Ofatumumab (OMB157G) 20 mg sc injections once every 4 (q4) weeks (following initial loading regimen of three 20 mg sc doses/week in first 14 days) + teriflunomide-matching placebo capsules orally once daily
Teriflunomide 14 mg capsules orally once daily + ofatumumab-matching sc placebo injections

Study burden and risks

Risks: Adverse events of study medication (ofatumumab and teriflunomide) and methylprednisolon (evt. given before first and following injections study medication) and study assessments (drawing of blood, injecitons)

Burden:
Visits: screening, baseline, Day 1, 7 and 14, Month 1, 3, then every three months.
Physical examination at screening, baseline, every 6 months
Blood pressure, weight each visit
Blood tests: each visit plus extra for required safety testing during treatment with terflunomide (biweekly fisrt half a year) and then bimonthly
Pregnancy tests; during screening and final visit by a blood test, on day 1 every 3 months through urinalysis
ECG at screening or baseline and the final visit
MRI screening, annually
Neurological examination (EDSS) assessment, baseline or day 1 every 3 months
T25W: screening or baseline, every 3 months
9-HPT and SDMT: screening or baseline, every 6 months
Questionnaires: Screening or Baseline, then every visit

Call every month if no visits scheduled
Diary if necessary

Contacts

Public
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL
Scientific
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Male or female patients aged 18 to 55 years (inclusive) at Screening
* Relapsing MS: relapsing-remitting course (RRMS), or secondary progressive (SPMS) course with disease activity
* Disability status at Screening with an EDSS score of 0 to 5.5 (inclusive)
* Documentation of at least: 1 relapse during the previous 1 year OR 2 relapses during the previous 2 years prior to Screening OR a positive Gd-enhancing MRI scan during the year prior to randomization

* Neurologically stable within 1 month prior to randomization

Exclusion criteria

* Patients with primary progressive MS or SPMS without disease activity
* Patients meeting criteria for neuromyelitis optica
* Disease duration of more than 10 years in patients with an EDSS score of 2 or less
* Women of child-bearing potential unless using highly effective methods of contraception during study drug dosing and for 12 months post-dosing
* Sexually active males unless they agree to use condom during intercourse while on study drug
* Patients at risk of developing or having reactivation of hepatitis: positive results at Screening for serology markers for hepatitis A, B, C and E (HA, HB, HC, and HE) indicating acute or chronic infection
* Patients at risk of developing or having reactivation of syphilis or tuberculosis

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:	Recruitment stopped
Start date (anticipated):	14-02-2017
Enrollment:	20
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	08-08-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-01-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO
Date: 25-01-2017

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 07-02-2017

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 21-02-2017

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 07-03-2017

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 10-03-2017

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 09-05-2017

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 28-09-2017

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 17-10-2017

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 05-03-2018

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO

Date:	15-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-10-2018
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:	11-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	02-05-2019
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
EudraCT	EUCTR2015-005418-31-NL
ClinicalTrials.gov	NCT02792218
CCMO	NL58118.029.16