An Extension Protocol For Multiple Sclerosis Patients Who Participated in Genzyme-Sponsored Studies of Alemtuzumab

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The objectives of this study are to examine: (1) the long-term safety and efficacy of alemtuzumab in multiple sclerosis (MS) patients who received alemtuzumab during prior Genzyme-sponsored studies including CAMMS223, CAMMS323, or CAMMS32400507 (...

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

Summary

ID

NL-OMON41482

Source
ToetsingOnline

Brief title
CARE-MS extension Study

Condition

- Demyelinating disorders

Synonym
MS, Multiple Sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Genzyme Corporation

Source(s) of monetary or material Support: farmaceutische industrie;de sponsor

Intervention

Keyword: Alemtuzumab, Extension, Multiple Sclerosis

Outcome measures

Primary outcome

Efficacy: Efficacy will be assessed by evaluation of relapses, EDSS, MRI, the Medical Outcome Study (MOS) 36-Item Short-Form Health Survey (SF 36) Version 2, the Functional Assessment of Multiple Sclerosis (FAMS), and the EuroQoL in 5 Dimensions (EQ-5D).

Safety: Safety will be assessed by evaluation of AEs, serious adverse events (SAEs), medical events of interest (MEOIs), laboratory tests (clinical chemistry including thyroid function, hematology and urinalysis, lymphocyte phenotyping, anti-alemtuzumab antibodies), and vital signs and physical examinations. Additional safety evaluations will be performed to assist in the clinical management of patients and/or for research purposes including urine pregnancy tests for women of childbearing potential, collection and storage of peripheral blood mononuclear cells (PBMCs), measures of immune system function, and enhanced surveillance for ITP (by Monthly Monitoring Surveys), anti-GBM disease, and infection.

Other: A Health Resources Utilization Questionnaire (HRUQ) will be administered to obtain pharmacoeconomic data.

Efficacy Analysis

The long-term effects of alemtuzumab in patients who received alemtuzumab prior to the extension study (eg, in studies CAMMS223, CAMMS323, or CAMMS324) will be examined by:

• Summarizing the efficacy endpoints, including sustained accumulation of disability (SAD), relapse rate, sustained reduction in disability (SRD) and change in EDSS, MRI, and QoL, from prior study baseline through Extension Month 48

• Summarizing the percentage of patients meeting criteria for as-needed retreatment (MRI vs relapse), and time to meeting criteria for retreatment.

The efficacy of alemtuzumab in patients who received SC IFNB-1a prior to the extension study will be evaluated using pre vs post alemtuzumab comparisons on the efficacy endpoints noted above.

Analyses comparing the effect of IAT with DAT on the efficacy endpoints noted above will be restricted to patients in CAMMS323 and CAMMS324 and use an integrated dataset consisting of all data from study onset in these prior studies through Extension Month 24.

Safety Analysis

All patients in the extension study will be evaluated for safety based on incidence, duration, grade/intensity, seriousness, and relationship of AEs to alemtuzumab, with a focus on infections and autoimmune disorders, notably ITP, thyroid dysfunction, and anti-GBM disease. Deaths and other SAEs will also be

evaluated.

Secondary outcome

N/A

Study description

Background summary

Alemtuzumab (Campath/MabCampath) has been used as an experimental treatment of multiple sclerosis since 1991. Currently, alemtuzumab is approved to treat some types of leukemia but is not approved for the treatment of MS.

Over 400 MS patients have been treated with Alemtuzumab in clinical research studies conducted in Europe and the US. These studies have shown that it may be an effective treatment for multiple sclerosis. For instance, there has already been a study of alemtuzumab versus one of the standard treatments for multiple sclerosis, interferon beta 1a (Rebif®), in people with relapsing-remitting multiple sclerosis, study *CAMMS223*. This showed that two years* treatment with alemtuzumab, used at the dose proposed for this current study, reduced the risk of having a relapse, compared to Rebif®, by 74% and it also reduced the risk of acquiring sustained disability by 71% compared to Rebif®. But there were more side-effects associated with alemtuzumab compared to Rebif®.

The two Phase 3 studies, CAMMS323 and CAMMS32400507 (hereafter: CAMMS324), were developed to confirm the phase 2 results and collect additional information on safety and efficacy. Both protocols specified that all patients treated with alemtuzumab would be monitored for at least 4 years after their last cycle of study medication for safety purposes. At least part of this monitoring will take place under this separate extension protocol. In addition, patients who had received SC IFNB-1a in one of the previous studies have the opportunity to receive treatment with alemtuzumab in this extension study, provided the in-and exclusion criteria are met.

Study objective

The objectives of this study are to examine: (1) the long-term safety and efficacy of alemtuzumab in multiple sclerosis (MS) patients who received alemtuzumab during prior Genzyme-sponsored studies including CAMMS223, CAMMS323, or CAMMS32400507 (referred to hereafter as CAMMS324); (2) the safety and efficacy of as-needed alemtuzumab retreatment in these previously alemtuzumab-treated patients; and (3) the safety and efficacy of 2 fixed annual alemtuzumab cycles followed by optional as-needed retreatment in patients who

previously received subcutaneous interferon beta-1a (SC IFNB-1a) during these studies. The efficacy of immediate alemtuzumab treatment (IAT, ie, alemtuzumab initiated at onset of CAMMS323 or CAMMS324) vs. delayed alemtuzumab treatment (DAT, ie, alemtuzumab initiated after completing 2 years of CAMMS323 or CAMMS324) will also be examined.

Study design

This is an open-label, rater-blinded extension study for patients who participated in CAMMS223, CAMMS323, or CAMMS324 (referred to hereafter as prior studies).
Based upon prior study enrollment, patients will have a finite period of time to enroll in this study:
• Patients who are participating in CAMMS323 or CAMMS324 should be told details of the extension study and be provided with a copy of the informed consent form (ICF) to review in advance of their CAMMS323 or CAMMS324 Month 24 visit, preferably at the Month 21 visit. Informed consent should then be obtained at, or following, the CAMMS323 or CAMMS324 Month 24 visit, but not sooner. Patients [from CAMMS323 or CAMMS324] who do not provide consent at the Month 24 visit will have 8 weeks from their scheduled Month 24 visit to consent to the extension study.
• Patients who participated in CAMMS223 will have 6 months from the date their site receives approval for this extension study to consent to the extension study. Approval refers to the official notice from Genzyme to a site following receipt of applicable approval from governing agencies (eg, Competent Authorities, Institutional Review Board [IRB]/Ethics Committee [EC]), and other required documentation that they are approved to start entering patients in the extension study.
Patients randomized to and treated with alemtuzumab in one of these prior studies will receive safety monitoring. They may also be eligible to receive additional alemtuzumab upon documented evidence of resumed disease activity, defined as >=1 protocol-defined relapse or >=2 new or enlarging brain or spinal lesions on magnetic resonance imaging (MRI), provided they meet all of the entry criteria and do not meet any of the disqualifying criteria in Section 9.2.3. All retreatment cycles will consist of 12 mg/day alemtuzumab intravenously (IV) infused once daily for 3 days. Patients will have 47 months from enrollment (ie, signing of the ICF) to qualify for and receive retreatment.
Patients randomized to and treated with SC IFNB-1a in one of these prior studies will be enrolled in this study only if they desire treatment with alemtuzumab and meet all of the entry criteria. Eligible patients will receive 2 annual cycles of alemtuzumab. The first cycle should be administered at study entry, provided the patient does not meet any of the disqualifying criteria listed in Section 9.2.3. The second cycle should be administered 12 months later, provided the patient meets none of the disqualifying criteria.
SC IFNB-1a patients who cannot receive alemtuzumab at study entry should be reassessed regularly at the discretion of the investigator and must qualify for

and receive alemtuzumab treatment by the end of the Month 2 visit window or they will be discontinued from the study. SC IFNB-1a patients who complete 2 alemtuzumab cycles will be eligible for as needed alemtuzumab retreatment according to the procedures described above for alemtuzumab patients.
Safety and efficacy assessments will be performed at scheduled visits for 48 months from enrollment in this extension study. Adverse events (AEs) and concomitant medications will be monitored continuously. Once the extension study ends, any additional safety follow-up may occur via a separate mechanism.
The Expanded Disability Status Scale (EDSS), relapse, and MRI assessments will be performed by raters who are blinded to patients* treatment history. The annual MRIs will be read and interpreted locally by qualified site personnel and/or designee (eg. neuroradiologist) for assessment of retreatment eligibility and to rule out a non-MS pathology. Annual MRIs will also be read and interpreted by blinded neuroradiologists at a central site for the analyses of efficacy endpoints.
An independent, Data Monitoring Committee (DMC) will conduct interim monitoring of data during this study until the lead-in Phase 3 studies (CAMMS323 and CAMMS324) are concluded.
A sub-study to assess the potential effects of a 5-day, 12 mg/day, IV alemtuzumab treatment cycle on cardiac repolarization as detected by prolongation of the QT corrected (QTc) interval ("QT substudy") will be performed at selected sites (excluding the Netherlands). Approximately 55 patients formerly treated with SC IFNB-1a in prior studies will be enrolled in the QT sub-study (provided that they meet additional eligibility criteria for QT assessment), in which they will have ECGs and corresponding PK samplings performed surrounding the first cycle of alemtuzumab dosing. A single dose of 400 mg of moxifloxacin will be given orally 4 days prior to th first day of alemtuzumab treatment, as a positive control to establish assay sensitivity.
For research purposes and on a voluntary basis, a blood sample will be collected from consenting patients for subsequent exploratory analysis of genetic variations related to MS disease and/or the effects of alemtuzumab. If the sample is deemed unusable, a second sample would be obtained.

Intervention

Alemtuzumab will be IV infused in a supervised medical setting. Patients previously treated with alemtuzumab who show documented evidence of resumed disease activity, do not meet any of the disqualifying safety criteria for receiving alemtuzumab, and consent to alemtuzumab retreatment will receive 12 mg/day alemtuzumab once daily for 3 consecutive days. These patients may subsequently receive additional cycles of alemtuzumab upon documented evidence of resumed disease activity, but not within the same 12-month period. They will have 35 months from enrollment to qualify for and receive retreatment.

SC IFNB-1a treated patients entering the extension study will receive 12 mg/day alemtuzumab once daily for 5 days during the first cycle, and 12 mg/day for 3

days during the second cycle, 12 months later. SC IFNB-1a patients may qualify for as needed retreatment, 12 mg/day for 3 consecutive days, after their second fixed annual cycle if they meet the eligibility requirements and are within 35 months from entry into the extension study.
All patients will receive premedication with 1 gram of IV methylprednisolone immediately prior to alemtuzumab on days 1-3 of any treatment cycle. All patients will also receive a course of acyclovir, 200 mg twice daily (or therapeutic equivalent), beginning with the first day of any alemtuzumab cycle and continuing for 28 days after the last day of any cycle.

Study burden and risks

During the study the following non-invasive assessments will be conducted: yearly brain scans with MRI (Magnetic Resonance Imaging), monthly questionnaires to evaluate how you are feeling, to determine health condition, and to find out about other medical visits, standard urinalysis, physical examination and a special neurological exam, the Expanded Disability Status Scale (EDSS).

During the study the following invasive assessments will be done: monthly blood samples taken from a vein in your arm and monthly urinsampling. Additional blood- and/or urinsamples may be taken for medical testing.

The patients entering in the study may be subjected to the following invasive treatments: Alemtuzumab: 5 days in a row intravenous infusion for approximately 4-6 hours. 1 Year later 3 days intravenous infusion for approximately 4-6 hours. Corticosteroids: 3 days infusion of methylprednisolone for approximately 1 hour every day, repeat after 12 months.

Treatment with Alemtuzumab may cause side effects: for a few hours, worsening of current or old symptoms from MS, rash in response to antihistamine medication, fever, headache, and fatigue - may last for a few hours, rigor/chills, nausea, vomiting, and/or diarrhea, shortness of breath and/or spasms in the windpipe, especially in patients with asthma, hypotension.
In addition, Alemtuzumab treatment may cause low platelet count, possibly leading to unusual bleeding, easy bruising, appearance of petechia Immune Trombocytopenic Purpura (ITP), easy bleeding of the gums, nosebleeds, and unusually heavy menstrual periods.
Alemtuzumab treated patients are at an increased risk of infections.
One person has developed *Goodpasture*s syndrome* after treatment with alemtuzumab.
Alemtuzumab treated patients may develop Graves* disease, an abnormality of the thyroid gland, with symptoms: increased sweating; anxiety; weight loss; tremor; and sometimes, pain in the neck.

The intravenous corticosteroid methylprednisolone may reduce or eliminate these symptoms, and antihistamine medication may further reduce the risk of rash.

Methylprednisolone treated patients may experience nervousness and difficulty sleeping, which resolves within a day of the last infusion. Severe damage to bone, particularly the hip, is a rare side effect of high dose intravenous steroid treatment.

Herpes Simplex Type 1 and 2: An anti-viral medication (acyclovir or similar medicine) designed to prevent herpes will be given to all alemtuzumab patients starting on the first day of each alemtuzumab cycle and continuing for 28 days after the last day of the cycle. Acyclovir is generally well-tolerated. The most common side effects associated with acyclovir are nausea and diarrhea. Abnormal kidney function has been reported in some patients, particularly elderly patients with abnormal kidney function.

The MRI contrast agent gadolinium may cause mild headache, nausea and local pain, in less than 1% of the time low blood pressure and light-headedness occurs. Less than one in one thousand patients are allergic to the contrast agent, resulting in hives and itchy eyes, but more severe reactions have been seen, which result in shortness of breath.
Other than the risks of side effects, known or unknown, one disadvantage of this study is that you will be inconvenienced by blood tests, clinic visits, and MRI brain scans.
There may be other risks or side effects which are unknown at this time.

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

Patients must meet ONE of the following criteria to participate in the;Extension Study:;-Received alemtuzumab in CAMMS323 or CAMMS324, completed the 2-;year study period, and have not subsequently received disease;modifying treatments (other than glatiramer acetate or interferon beta);;or;-Received Rebif® in CAMMS323 or CAMMS324, completed the 2-year;study period, and have not subsequently received alternative disease;modifying treatments (other than glatiramer acetate or another;interferon beta); or;-Participated in CAMMS223.;NOTE: Criteria 1 and 2 above mean that patients who enrolled in;CAMMS323 or CAMMS324 but did not complete the 2-year study period;or went on to receive non-study drug DMTs after randomization are not eligible for inclusion in the Extension Study. Patients who enrolled in;CAMMS324 after participation in CAMMS223 must meet criteria 1 or 2 to be eligible for inclusion in the Extension Study.

Exclusion criteria

Any alemtuzumab patient from CAMMS223, CAMMS323, or CAMMS324;who has received alemtuzumab off-label (ie, outside of one of the prior;Genzyme-sponsored studies) or is participating in any other;investigational study, unless approved by Genzyme. In addition, these;patients must be screened for disqualifying safety concerns before;receiving alemtuzumab retreatment.;Any Rebif® patient from CAMMS223, CAMMS323, or CAMMS324 who;meets any of the following criteria. In addition, these patients must be;screened for disqualifying safety concerns before receiving alemtuzumab treatment.;a)Does not wish to receive alemtuzumab;;b) Ongoing participation in any other investigational study , unless;approved by Genzyme;;c)Has received alemtuzumab off-label (ie, outside of one of the prior;Genzyme-sponsored studies);;d)Known bleeding disorder or therapeutic anticoagulation;;e)Diagnosis of idiopathic thrombocytopenia purpura or other;autoimmune hematologic abnormality;;f)History of malignancy, except basal cell skin carcinoma;;g)Intolerance of pulsed corticosteroids, especially a history of steroid;psychosis;h)Significant Autoimmune disorder (other than MS);;i)Major psychiatric disorder or epileptic seizures not adequately;controlled by treatment;;j)Active infection or high risk for infection;k)Unwilling to use a reliable and acceptable contraceptive method during;and for at least 6 months following each alemtuzumab treatment cycle;(fertile

patients only).

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-11-2010
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NVT
Generic name:	alemtuzumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	28-09-2009
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	07-06-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-08-2010
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-05-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-09-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-09-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-11-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-06-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-09-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	21-09-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-10-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-10-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-10-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-09-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-02-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2009-010788-18-NL
ClinicalTrials.gov	NCT00930553
CCMO	NL29272.003.09