A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy of Natalizumab on Reducing Disability Progression in Subjects With Secondary Progressive Multiple Sclerosis, With optional Open-label Extension

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

Summary

ID

NL-OMON39952

Source
ToetsingOnline

Brief title
Natalizumab ASCEND 101MS326

Condition

- Neuromuscular disorders

Synonym
Later phase MS, SPMS

Research involving
Human

Sponsors and support

Primary sponsor: Biogen Idec Limited
Source(s) of monetary or material Support: The Pharmaceutical Industry

Intervention

Keyword: Natalizumab, Phase 3b, Secondary Progressive Multiple Sclerosis, Tysabri

Outcome measures

Primary outcome

The primary endpoint is a binary outcome of confirmed progressors or non-progressors at study end. The percentage of confirmed progressors will be presented by treatment group, with the treatment comparison analyzed by the logistic regression model. The percentage of confirmed progressors in each of EDSS, T25FW, and 9HPT will also be presented with treatment comparisons by the logistic regression model.

Secondary outcome

Secondary endpoints will be summarized by presenting summary statistics for continuous or frequency distributions for categorical variables. In general, binary outcomes will be analyzed by the logistic regression model, time to event data by the Cox proportional hazards model, count data by the negative binomial regression model or Wilcoxon rank-sum test, and continuous responses by the analysis of variance or the analysis of covariance. To maintain the overall type I error rate at 5%, a closed testing procedure will be used to adjust for multiple secondary endpoints.

Study description

Background summary

Disease progression in SPMS is the result of chronic, central nervous system (CNS)-based inflammation. Natalizumab has the potential to reduce intrathecal inflammation through multiple mechanisms, including interference with chemokine-mediated inflammatory cell recruitment from the periphery, disruption of production of key molecules necessary to sustain intrathecal inflammation, including CNS ectopic lymphoid tissues, and modulation of CNS microglia/macrophage activation. Analysis of existing clinical data suggests that natalizumab may be effective in treating disease progression in SPMS for which there are limited therapies.

Study objective

Part 1:
The primary objective of the study is to investigate whether treatment with natalizumab slows the accumulation of disability not related to relapses in subjects with SPMS.

The secondary objectives of this study are to determine in this study population:
- the proportion of subjects with consistent improvement in T25FW
- the change in subject-reported ambulatory status as measured by the 12-Item MS Walking Scale (MSWS-12)
- the change in manual ability based on the ABILHAND Questionnaire
- the impact of natalizumab on subject-reported quality of life using the Multiple Sclerosis Impact Scale-29 Physical (MSIS-29 Physical)
- the change in whole brain volume between the end of study and Week 24 using MRI
- the proportion of subjects experiencing progression of disability as measured by individual physical EDSS system scores.

Part 2:
The primary objective of Part 2 of the study is to evaluate the safety profile of natalizumab in subjects with SPMS.

The secondary objectives of Part 2 are as follows:
- to investigate long-term disability (based on clinical or patient-reported assessments) in subjects with SPMS receiving natalizumab treatment for approximately 4 years
- to assess change in brain volume and T2 lesion volume.

Study design

This is a Phase 3b, multicenter, international, randomized, double-blind, placebo-controlled study to assess the efficacy of natalizumab in subjects with SPMS who are exhibiting disease progression independent of relapses. Subjects will be randomized to receive either natalizumab 300 mg or placebo intravenously (IV) every 4 weeks (q4wk) for 96 weeks.

The maximum duration of the study is 204 weeks or until availability of commercial product, whichever occurs last. (96 weeks for Part 1 + 96 weeks for Part 2 + 8 intermediate weeks when patients will receive two treatment doses).

Subjects who are not enrolling into Part 2 of the study are return to the study site for a follow-up visit 12 weeks after the last dose of study treatment (Week 108). Subjects who enroll in Part 2 are return to the study site for a follow-up visit 12 weeks after the last dose of study treatment (Week 216, or later, if commercial product is not yet available).

Intervention

An IV infusion of either natalizumab or matching placebo will be added in clinic by a study nurse monthly for 96 weeks (approximately 2 years).

Afterwards, if the patient decides to participate in the optional open-label extension, he/she will come to the clinic through week 108. Then the Part 2 begins, where the patient will come to the clinic for an IV infusion of natalizumab every 4 weeks for 96 weeks (about two years).

Study burden and risks

The patient will visit the clinic every 4 weeks. Extra visits may be needed if symptoms of an MS relapse or other significant changes in health that may be related to the use of the study drug occur. An IV infusion of either natalizumab or matching placebo will be added in clinic by a study nurse monthly for 96 weeks (approximately 2 years). For the optional Open-label extension of this study an IV infusion of natalizumab (no placebo) will be added in clinic by a study nurse monthly for another 96 weeks (approximately 2 years) or until the IP will become commercially available. A follow-up visit 12 weeks after the last infusion is needed.

During the study the following tests/assessments will be performed :
* Medical History
* Vital signs
* Blood and urine tests, including samples that will be stored for future research related to natalizumab, MS, and JC virus (human polyomavirus)
* Questionnaires about your physical functioning, and health status
* Questions about side effects
* Physical Examinations

* Neurological evaluations including relapses, dexterity, thinking, and walking
* Brain magnetic resonance imaging (MRI) scans (every 6 months and at the Week 108 follow-up visit and week 156 + 204 for OLE, 8 occasions)
* Blood and urine pregnancy tests if applicable
* Questions about new medications
More tests can be needed if indicated by the study doctor. The most blood collected at any one visit will be about 50 mL. During the complete study period, up to about 330 ml of blood may be taken for Part 1 and up to about 207 ml for Part 2. As part of the screening, blood will be tested for HIV, hepatitis B, and hepatitis C.

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

Part 1: To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time of randomization (Day 0), or at the timepoint specified in the individual eligibility criterion listed:;1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations. ;2. Be between the ages of 18 and 58, inclusive, at the time of informed consent.;3. Onset of SPMS at least 2 years prior to enrollment. SPMS is defined as relapsing-remitting disease followed by progression of disability independent of or not explained by MS relapses (Lublin, Reingold, 1996)) for at least 2 years. ;4. Have EDSS score of 3.0 to 6.5, inclusive.;5. Have an MS Severity Score (MSSS) of 4 or higher.;6. Have documented confirmed evidence of disease progression independent of clinical relapses over the 1 year prior to enrollment as defined in the Study Reference Guide.;7. Subjects must have completed those baseline assessments associated with components of the primary endpoint (EDSS, T25FW, 9HPT) prior to randomization (Day 0).;8. Subjects of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 3 months after their last infusion.;Part 2: To be eligible to participate in the Part 2 Extension Phase of this study, candidates must meet the folowing eligibility criteria at the time of consent into Part 2, or at the timepoint specified in the individual eligibility criterion listed:;1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations. ;2. Subjects must have participated in Part 1, have documented Week 108 assessment attempts for EDSS, T25FW, and 9HPT prior to first open-label dosing at Week 108 and not have missed 2 or more consecutive infusions in Part 1 of the study.;3. Subjects of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 3 months after their last infusion.

Exclusion criteria

Part 1: Candidates will be excluded from study entry if any of the following exclusion criteria exist at the time of randomization (Day 0), or at the timepoint specified in the individual criterion listed:;1.Have a diagnosis of RRMS or primary progressive MS as defined by the revised McDonald Committee criteria (Polman et al 2005).;2. Had a recent clinical relapse (within 3 months) prior to randomization. ;3. Have a T25FW test of >30 seconds during the screening period.;4. Any value below the lower limit of normal for blood levels of leukocytes, lymphocytes, or neutrophils.;5. Considered by the Investigator to be immunocompromised based on medical history, physical examination, laboratory testing, or any other testing required by local guidelines, or due to prior immunosuppressive or immunomodulating treatment.;6. Subjects for whom MRI is contraindicated (i.e., have pacemakers or other contraindicated implanted metal devices or have claustrophobia that cannot be medically managed).;7. History of any clinically significant (as determined by the Investigator) cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary,

neurologic (other than MS), dermatologic, psychiatric, and renal, or other major disease that would preclude participation in a clinical study.;8. History of malignant disease, including solid tumors and hematologic malignancies (with the exception of basal cell and squamous cell carcinomas of the skin that have been completely excised and are considered cured).;9. Known history of or positive test result for Human Immunodeficiency Virus (HIV).;10. Positive test result for hepatitis C virus (test for hepatitis C virus antibody [HCV Ab]) or hepatitis B virus (test for hepatitis B surface antigen [HBsAg] and/or hepatitis B core antibody [HBcAb]).;11. History of transplantation or any anti-rejection therapy.;12. Presence of any infectious disease (e.g., cellulitis, abscess, pneumonia, septicemia) within 30 days prior to screening.;13. History of PML or other opportunistic infections including active tuberculosis.;Treatment History;14. Any prior treatment with cell-depleting therapies, including total lymphoid irradiation, cladribine, rituximab, alemtuzumab, or bone marrow ablation.;15. Any prior treatment with natalizumab. ;16. Treatment with mitoxantrone, cyclophosphamide, cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, T cell or T cell receptor vaccination, fingolimod, daclizumab, or cytapheresis within 6 months prior to randomization.;17. Treatment with IV or oral corticosteroids, intravenous immunoglobulin (IVIg), or plasmapheresis for treatment of MS within the 3 months prior to randomization.;18. Treatment with glatiramer acetate or any interferon beta preparations within 4 weeks prior to randomization.;19. Treatment with 4-aminopyridine within 30 days prior to randomization, unless a stable dose has been maintained for at least 30 days prior to randomization and will be continued for the course of this study.;Miscellaneous;20. Female subjects considering becoming pregnant while in the study. ;21. Female subjects of childbearing potential who have a positive pregnancy test at either the Screening Visit or Week 0.;22. Female subjects who are pregnant or currently breastfeeding. ;23. History of drug or alcohol abuse, in the opinion of the Investigator, within 2 years prior to entry.;24. Unwillingness or inability to comply with the requirements of this protocol, including the presence of any condition (physical, mental, or social) that is likely to affect the subject's ability to comply with the study protocol.;25. Participation in any other investigational treatment study within the 3 months prior to screening or concurrent with this study.;26. Any pre-scheduled elective procedure during the study period that, in the opinion of the Investigator, would interfere with study parameters.;27. Any other condition, clinical finding, or reason that, in the opinion of the Investigator, is determined to be unsuitable for enrollment into this study.;28. Previous participation in this study.;Part 2: Candidates will be excluded from Part 2 Extension Phase if any of following exist at time of consent into Part 2 of study:;1. Subjects with any significant change in clinical status including laboratory tests that in opinion of Investigator would make them unsuitable to participate in extension study. Investigator must rereview the subjects's medical fitness for participation and consider any diseases that would preclude treatment.;2. Subjects sho discontinued study treatment in Part 1 OR had fewer than 20 infusions in Part 1 OR missed 2 or more consecutive infucions in Part 1;3. Considered by Investigator to be immunocompromised based on medical hsitory, physical examination, laboratory testing or any other testing required by local guidelines.;4. Part 1 exclusion ciretia no.6
5. Part 1 exclusion critearia no. 7
6. New onset of drug or alcohol abuse during Part 1 of study.
7. Part exclusion creteria no. 8
8. Signs or symptomps of PML
9. Part exclusion criteria no. 20
10. Female subjects of childbearing potential who have positive pregnancy test at either Wk

96 (serum) or Wk 108 (serum and urine)
11. Part 1 exclusion criteria no. 22
12. Part 1 exclusion criteria no. 24
13. Part 1 exclusion criteria no. 26
24. Part 1 exclusion criteria no. 27

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-07-2012
Enrollment:	45
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tysabri
Generic name:	Natalizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	12-09-2011

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-12-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-06-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-12-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2013

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2016
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	EUCTR2010-021978-11-NL
CCMO	NL37886.029.11