A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose Ranging Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of BIIB033 in Subjects with Relapsing Forms of Multiple Sclerosis When Used Concurrently with Avonex®

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Primary: The primary objective of the study is to evaluate the efficacy of BIIB033 in subjects with active relapsing MS when used concurrently with Avonex. Secondary: Secondary objectives of this study in this study population are to assess the...

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

Summary

ID

NL-OMON38864

Source
ToetsingOnline

Brief title
Biogen 215MS201

Condition

- Demyelinating disorders

Synonym
MS with relapses, relapsing forms of multiple sclerosis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BIIB033, Interferon beta-1a, Relapsing Multiple Sclerosis, remyelination

Outcome measures

Primary outcome

Primary Efficacy Endpoint:

Percentage of subjects experiencing confirmed improvement of neuro-physical and/or cognitive function over 72 weeks (approximately 18 months) of treatment as measured by a composite endpoint comprising the Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk (T25FW), 9 Hole Peg Test (9HPT), and (3 Second) Paced Auditory Serial Addition Test (PASAT).

Improvement on neuro-physical and/or cognitive function is defined as at least 1 of the following:

* A *1.0 point decrease in EDSS from a baseline score of *6.0 (decrease sustained for 3 months or greater).

* A *15% improvement from baseline in T25FW (improvement sustained for 3 months or greater).

* A *15% improvement from baseline in 9HPT (improvement sustained for 3 months or greater).

* A *15% improvement from baseline in PASAT (improvement sustained for 3 months

or greater).

Secondary outcome

Secondary Efficacy Endpoints:

Percentage of subjects experiencing confirmed worsening of neuro-physical and/or cognitive function and/or disability over 72 weeks (approximately 18 months) of treatment as measured by a composite endpoint of the EDSS, T25FW, 9HPT, and PASAT.

Progression of disability or worsening of neuro-physical and/or cognitive function is defined as at least 1 of the following:

* A *1.0 point increase in EDSS from a baseline score of *5.5 or a *0.5 point increase from a baseline score equal to 6.0 (increase sustained for 3 months or greater).
* A *15% worsening from baseline in T25FW (worsening sustained for 3 months or greater).
* A *15% worsening from baseline in 9HPT (worsening sustained for 3 months or greater).
* A *15% worsening from baseline in PASAT (worsening sustained for 3 months or greater).

Exploratory Efficacy Endpoints:

Clinical Efficacy Endpoints:

* Change from baseline to 72 weeks (approximately 18 months) in cognitive

function as measured by an MS cognitive composite endpoint comprising 2 tests of processing speed (the PASAT and the Symbol Digit Modalities Test [SDMT]) and 2 tests of memory and learning (the Selective Reminding Test [SRT] for verbal memory and the Brief Visuospatial Memory Test-Revised [BVMT-R] for visual memory).

* Severity of clinical relapses as determined by the Scripps Neurological Rating Scale (SNRS).

* A *15% worsening from baseline in Six Minute Walk (6MW) walking time (worsening sustained for 3 months or greater).

MRI Efficacy Endpoints:

There will be analysis of brain MRI focused on measures of repair at the focal and diffuse levels with both new and pre-existing lesions.

The MRI analysis will include the following:

* Analysis of new brain lesions

* Analysis of pre-existing brain lesions (lesions that are present at baseline scan)

* Analysis of diffuse brain MRI metrics

Patient-Reported Outcomes Efficacy Endpoints:

* 12-Item Multiple Sclerosis Walking Scale (MSWS 12)

* ABILHAND 56-Item Questionnaire

* 29-Item Multiple Sclerosis Impact Scale (MSIS-29)

* The Short Form (36) Health Survey (SF-36)

Safety Endpoints:

* Adverse events (AEs)

* Serious adverse events (SAEs)

* Clinical laboratory test results

* Physical examination findings

* Electrocardiogram (ECG)

* Vital signs results

* Weight

* Serum antibodies (Ab) to BIIB033

* Disease activity by brain MRI metrics

* MS signs and symptoms

* Columbia Suicide Severity Rating Scale (C-SSRS) score

Pharmacokinetic Endpoint:

* BIIB033 population PK assessment

Exploratory Pharmacodynamic Endpoints:

Pharmacodynamic (PD) endpoints are exploratory cellular and molecular biomarkers. Whole blood, serum, plasma, urine (all subjects), and cerebrospinal fluid (CSF) (optional) will be collected to assess the modulation of potential PD/other biomarkers that may be related to BIIB033 activity or MS disease activity. The assessment may include but is not limited to the expression of soluble proteins, lipids, sugars, messenger RNA (mRNA), and other

substances.

Study description

Background summary

BIIB033 is a first-in-class human monoclonal antibody (mAb) directed against LINGO-1, a negative regulator of myelination and neuroaxonal growth. Antagonizing LINGO-1 with BIIB033 has the potential to enhance remyelination and neuroaxonal protection in the central nervous system (CNS).
The rationale for this study is to explore the potential efficacy of BIIB033 on enhancing CNS repair through remyelination and neuroaxonal protection in MS, while treating the inflammatory aspect of the disease with an approved immunomodulatory agent, Avonex.

This study specifically will evaluate patients with relapsing MS, (which includes both RRMS and SPMS) who have ongoing clinical exacerbations and/or subclinical activity as shown by magnetic resonance imaging (MRI). The selection of patients with relapsing MS who have ongoing disease activity is considered appropriate based on the generally recognized assumption that newly developed MS lesions should be easier to repair and remyelinate due to their greater preservation of axons and lesser interference from glial scar.

The therapeutic hypothesis for the use of BIIB033 in this study is that it will reach the CNS in sufficient concentrations to block LINGO-1 in both axons and oligodendrocytes. This, in turn, will promote remyelination via differentiation of oligodendrocyte precursor cells (OPC) normally present in the brain of MS patients. It is also hypothesized that binding of BIIB033 to LINGO-1 in axons and neurons may provide neuroaxonal protection via blockade of signaling by myelin debris on the NgR1 receptor complex in the CNS.

Analysis of pre-existing MRI lesions is needed to investigate if BIIB033 can also enhance repair of pre-existing lesions of different severity. The potential efficacy of BIIB033 in pre-existing lesions is supported by the finding that OPCs are found in chronically demyelinated MS lesions, by published animal studies that show the ability of chronically demyelinated lesions to be remyelinated, and Biogen Idec studies that show enhancement of remyelination by LINGO-1 blockade in established demyelinated lesions.

Study objective

Primary: The primary objective of the study is to evaluate the efficacy of BIIB033 in subjects with active relapsing MS when used concurrently with Avonex.

Secondary: Secondary objectives of this study in this study population are to assess the safety, tolerability, and population PK of BIIB033 when used concurrently with Avonex.

Study design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate BIIB033 when used concurrently with Avonex versus placebo and Avonex in subjects with active relapsing MS.

The study treatment includes BIIB033, placebo, and Avonex. BIIB033 or placebo will be administered once every 4 weeks by IV infusion for a total of 19 doses in addition to once-weekly Avonex intramuscular (IM) injections for 72 weeks.

Intervention

There will be 5 parallel treatment groups: IV infusions of 3 mg/kg BIIB033, 10 mg/kg BIIB033, 30 mg/kg BIIB033, 100 mg/kg BIIB033, or placebo used concurrently with once-weekly Avonex IM injections. Eligible subjects will be randomized into an active treatment group (3, 10, 30, or 100 mg/kg BIIB033 plus Avonex) or the placebo plus Avonex treatment group in a 1:2:2:2:2 ratio.

Study burden and risks

Study participation for each subject will be approximately 84 to 88 weeks (approximately 21 to 22 months), including a Screening Period of 1 to 28 days, a Treatment Period of 72 weeks (18 months), and a Follow-Up Period of 12 weeks (3 months).
Subjects are to return to the study site for a post-treatment End of Study (EOS) Visit at Week 84. This final study visit will occur 12 weeks ±10 days after the last dose of BIIB033 or placebo administration.

During the 21 planned study visits, the subject will undergo the following assessments:
physical exam 9x, height 1x, weight 9x, vital signs 21x, ECG 5x, questionnaires 8x, C-SSRS 4x, MS tests 9x, Cognitive Function Tests 4x, MS signs & symptoms 9x, blood tests 13x, urine tests 13x, blood pregnancy test (women of child-bearing potential only) 1x, urine pregnancy test (women of child-bearing potential only) 13x, brain MRI 11x, lumbar puncture (optional) 2x.

The most common side effects reported by people who received BIIB033 are: headache, common cold, bladder infection, stomach upset, MS relapse, and symptoms associated with lumbar puncture (headache, nausea, neck pain and double vision). We do not know if these events were related to BIIB033. No serious side effects have been seen as of this date.

The most common side effects associated with Avonex are "flu-like symptoms,* headache, and dizziness. *Flu-like symptoms* such as fever, chills, sweating, muscle aches, and tiredness may be relieved with over the counter pain and fever reducers. For many people, these symptoms lessen or go away over time.

The examinations and administration of study treatment may cause discomfort. IV administration of BIIB033 or placebo may cause pain, redness, swelling, tenderness, and/or bruising at the IV site. Taking blood from a vein may cause bruising, localized bleeding, infection, faintness, or a small amount of pain from the needle stick. IM administration of Avonex may cause pain or discomfort.
During an MRI scan, a person may find that they feel afraid of small, enclosed spaces. A severe allergic reaction can rarely occur with use of the imaging agent (gadolinium). The imaging agent may also cause headache, dizziness or faintness, a decrease in blood pressure, nausea, vomiting, sweating, changes in taste, and injection site symptoms. In addition, a rare, but serious and sometimes fatal condition (Nephrogenic Systemic Fibrosis) has been associated with some gadolinium contrast agents in patients with severely impaired kidney function.

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

- Aged 18 to 58 years old, inclusive, at the time of informed consent.
- Diagnosis of RRMS per the 2005 McDonald*s criteria [Polman et al, 2005] or onset of SPMS per the Lublin and Reingold criteria [Lublin and Reingold 1996].
- For RRMS, subjects must have disease activity as defined by 2 or more distinct occurrences of any of the following 3 events within 12 months of enrollment:
* Clinical relapse
* Gd+ lesion on MRI (brain or spinal cord MRI)
* New T2 lesion on MRI (brain or spinal cord MRI)
- For SPMS, subjects must have disease activity as defined by 1 or more distinct occurrences of any of the following 2 events within 12 months of enrollment:
* Clinical relapse
* Gd+ lesion on MRI (brain or spinal cord MRI)
- Baseline EDSS score of 2 to 6.

Exclusion criteria

- Treatment with Botox for limb spasticity within 6 months before Day 1/Baseline.
- Treatment with any investigational MS drugs within 3 weeks or 5 t1/2 (whichever is longer) prior to Day 1/Baseline.
- Treatment with high dose oral or IV steroids *30 days before Day 1/Baseline.
- History of suicidal ideation or an episode of clinically severe depression (as determined by the Investigator) within 3 months of enrollment.
- RRMS subjects with any history of inadequate response to any approved (in country of residence) interferon * preparation (e.g., Avonex, Rebif, interferon * 1b, or any generic interferon *).
- History of human immunodeficiency virus or other immunodeficient conditions.
- T25FW >30 seconds (any of the 2 tests at Screening).
- History of malignancy; however subjects with a history or excised or treated basal cell carcinoma or fewer than 3 squamous cell carcinomas are eligible to participate in this study.
- Renal impairment with a creatinine clearance <80 mL/minute at Screening (creatinine clearance estimated by Cockcroft Gault equation).
- In the opinion of the Investigator, a history of clinically significant persistent neutralizing Ab against interferon *.
- Known intolerance, contraindication to, or history of noncompliance with Avonex.
- Treatment with fingolimod or investigational sphingosine 1-phosphate receptor 1 (S1P1)

agonists within 3 months prior to Day 1/Baseline.
- Treatment with natalizumab within 3 months prior to Day 1/Baseline.
- Initiation of treatment or dose adjustment of commercially available 4-aminopyridine (4 AP) or related products within the last 28 days.
- An MS relapse that has occurred within the 90 days prior to Day 1/Baseline and/or the subject has not stabilized from a previous relapse prior to Screening.

Study design

Design

Study phase:	2
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):	13-08-2013
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avonex
Generic name:	Interferon beta-1a
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	BIIB033
Generic name:	-

Ethics review

Approved WMO Date:	10-04-2013
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	03-07-2013
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	15-10-2013
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	06-01-2016
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

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	EUCTR2011-006262-40-NL
CCMO	NL43605.096.13