A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study With Optional Open-Label Extension in Subjects With Relapsing Multiple Sclerosis to Evaluate the Efficacy and Safety of BIIB033 as an Add-on Therapy to Anti-Inflammatory Disease-Modifying Therapies

Published: 12-09-2017
Last updated: 12-04-2024

Part 1: To evaluate the effects of BIIB033 versus placebo on disability improvement over 72 weeks.Part 2: evaluate long-term safety profile of BIIB033 as an add-on therapy in subjects with MS.

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

Summary

ID

NL-OMON48632

Source
ToetsingOnline

Brief title
AFFINITY - 215MS202

Condition

- Neurological disorders NEC

Synonym
damage central nervous system, multiple-sclerose

Research involving
Human

Sponsors and support

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

Intervention

Keyword: add on therapy, efficacy, multiple-sclerose, safety

Outcome measures

Primary outcome

Part 1: The primary endpoint is the Overall Response Score, assessed over 72 weeks of the study.The Overall Response Score is a multicomponent score based on 4 components: EDSS, T25FW, 9HPT-D, and 9HPT-ND. It assesses overall changes in disability over time.

At each visit, each assessment is given a score compared to baseline. Meeting or exceeding the threshold for improvement in an assessment results in a +1 score for that assessment; meeting or exceeding the threshold for worsening in an assessment results in a -1 score for that assessment; no change or subthreshold changes in an assessment results in a score of 0 for that assessment. The scores of individual assessments are summed up to provide a total Overall Response Score that ranges from +4 to -4 for each visit.

Part 2: Incidence of AEs and SAEs over 96 weeks in Part 2

Secondary outcome

Part 1:

Percentage of Participants with 12-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND

*

Percentage of Participants with 12-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, or PASAT-3

Percentage of Participants with 12-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND, and without confirmed worsening in any of the 4 assessments during the 72 weeks of the study

Percentage of Participantswith 12-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, and SDMT

Percentage of Participantswith 12-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND (20% thresholds for T25FW and 9HPT)

Part 2:

* Overall Response Score over 96 weeks in Part 2

* Proportion of subjects with 24-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND (improvement in T25FW and 9HPT is defined as a *15% decrease from BIIB033 Treatment Baseline)

* Proportion of subjects with 24-week confirmed improvement in at least 1 of

the following assessments: EDSS, T25FW, 9HPT-D, 9HPT ND, PASAT-3 (improvement in PASAT-3 is defined as a *15% increase from BIIB033 Treatment Baseline)

* Proportion of subjects with 24-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, or 9HPT ND, and without confirmed worsening in any of the 4 assessments during the 96 weeks of the study

* Proportion of subjects with 24-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT ND, SDMT (improvement in SDMT is defined as a *4-point increase from BIIB033 Treatment Baseline)

* Proportion of subjects with 24-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT ND (20% thresholds for T25FW and 9HPT)

* Potentially clinically significant abnormal laboratory, ECG, vital signs, and weight values over 96 weeks in Part 2

* C SSRS score over 96 weeks in Part 2

Study description

Background summary

BIIB033 is a first-in-class human monoclonal antibody directed against LINGO-1, a negative regulator of oligodendrocyte progenitor cells (OPCs) differentiation and myelination. Specifically, LINGO-1 expression is increased in OPCs from demyelinated white matter of multiple sclerosis (MS) brain tissues. LINGO-1 negatively regulates oligodendrocyte differentiation and myelination, neuronal survival, and axonal regeneration by activating ras homolog gene family member A and inhibiting Protein kinase B phosphorylation signaling pathways BIIB033 enhances differentiation of primary rat, monkey, and human oligodendrocytes in vitro and enhances axonal myelination in an in vitro rat dorsal root ganglion/OPC co-culture bioassay. Additionally, BIIB033 enhances remyelination and functional recovery in the rat lysophosphatidylcholine (LPC), cuprizone, myelin oligodendrocyte glycoprotein-experimental autoimmune encephalomyelitis

(MOG-EAE), and MOG-EAE optic neuritis models The therapeutic hypothesis is that BIIB033 will act in the central nervous system (CNS) to block LINGO-1, which is expressed on both oligodendrocytes and neurons. In turn, the inhibition of LINGO-1 may promote remyelination via differentiation of OPCs normally present in the CNS and promote axonal regeneration by blocking signaling from myelin debris on the Nogo66 receptor 1 complex in neurons. Therefore, BIIB033 treatment in demyelinating diseases such as MS may lead to improved CNS repair with corresponding beneficial effects on neurological function and disability.

Three Phase 1 studies and 2 Phase 2 studies have been completed. The Phase 1 studies included Studies 215HV101 (single-ascending dose study in healthy volunteers), 215MS101 (multiple-ascending dose study in subjects with RRMS or SPMS), and 215HV102 (single- and
multiple-dose study in healthy Japanese volunteers). The Phase 2 studies included Study 215ON201 in subjects with acute optic neuritis (AON) and Study 215MS201 in subjects with relapsing form of MS. In the Phase 1 studies, BIIB033 exposure was dose proportional over the studied dose levels and dose ranges, with doses ranging from 0.1 to 100 mg/kg. BIIB033 was well tolerated, and laboratory findings revealed no clinically meaningful abnormalities. BIIB033 pharmacokinetics (PK) in subjects with MS was similar to that observed in healthy adults, and BIIB033 PK doesnot appear to be altered by the concurrent treatment of IFN* or GA. Additionally, the clinical study portions of an additional Phase 1 study have been completed. Study 215HV103 is a single-dose study in healthy volunteers using study drug from 2 different manufacturing processes (referred to as BIIB033-A and BIIB033-B). Preliminary data indicate that the PK parameters (area under the concentration-time curve from time 0 to infinity [AUCinf] and maximum observed concentration [Cmax]) are very similar for the BIIB033-A material and the
BIIB033-B material. The completed Phase 2 Study 215ON201 was a 24-week, randomized study designed to assess the efficacy, safety, tolerability, and PK of BIIB033 (100 mg/kg) versus placebo in 82 subjects with their first episode of AON.
A trend in improvement was observed for the intent-to-treat (ITT) population in fullfield visual evoked potential latency of the affected eye at both Weeks 24 and 32 with BIIB033 over placebo, compared with the baseline of the unaffected fellow eye. This improvement reached statistical significance in the
per-protocol population at Week 32. These data provided proof-of-biology evidence for CNS remyelination with
BIIB033 treatment. No treatment effects were observed in retinal thinning or visual acuity tests with
BIIB033 over placebo. In this study, 100 mg/kg of BIIB033 infused IV every 4 weeks was well tolerated,
and the overall incidence of adverse events (AEs) was the same in the placebo and BIIB033 groups (83%). Hypersensitivity reactions occurred in 2 subjects (5% of BIIB033-treated subjects who received 100-mg/kg dose), and postbaseline weight
gain was also observed.

The completed Phase 2 Study 215MS201 was a 72-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study to assess the efficacy, safety, tolerability, and PK of BIIB033, when used concurrently with Avonex, in subjects with relapsing forms of MS. BIIB033 was evaluated at doses of 3, 10, 30, and 100 mg/kg. * The primary endpoint was confirmed improvement in 1 or more assessments of a multicomponent disability endpoint over 72 weeks. A statistically significant linear dose-response on primary endpoint was not observed with BIIB033 treatment versus placebo (p=0.9831). Analyses showed a non-monotonic, inverted U-shaped dose response to BIIB033 with more favorable outcomes in the 10- and 30-mg/kg groups. Prespecified univariate subgroup analyses suggested enhanced efficacy in younger subjects and in those with clinical and magnetic resonance imaging (MRI) features suggestive of more preserved brain tissue integrity. Analyses of individual functional assessments as well as the Overall Response Score also suggested a more pronounced favorable effect of BIIB033 at the 10-mg/kg dose, although there was a waning effect over time. Post hoc multivariate analysis showed a greater and more durable efficacy in a subpopulation (approximately 25% to 30% of the ITT population) defined by shorter disease duration and baseline MRI characteristics consistent with lower myelin content but higher tissue integrity in T2 lesions, especially in the 10-mg/kg group. BIIB033 was generally well tolerated, with hypersensitivity reactions seen only at the 100-mg/kg dose (4 subjects [1% of BIIB033-treated subjects]) and a trend for dose-dependent weight gain over 72 weeks, with a mean increase between 0.9 and 1.9 kg in 4 BIIB033 dosing groups. The study showed no change in the PK profile of BIIB033 and no new safety signals. The efficacy results observed in Study 215MS201, combined with the favorable safety profile demonstrated by the Phase 1 and Phase 2 studies as well as the proof of biology achieved in Study 215ON201, support the continued evaluation of BIIB033.

The proposed study (215MS202) will further investigate the efficacy and safety of BIIB033 as an add-on therapy in subjects with RMS who are on a stable dose of an anti-inflammatory disease-modifying therapy (DMT) and with baseline characteristics consistent with projected enhanced treatment effect of BIIB033 as identified in the post hoc analysis from Study 215MS201. To reduce variability and potential confounding factors from different background DMTs while allowing for the evaluation of the effect of BIIB033 across a range of background therapies, 3 specific groups of background DMTs will be included in this study. The DMTs are IFN* (Avonex, Plegridy, Betaferon/Betaseron, or Rebif), DMF (Tecfidera), and natalizumab (Tysabri), representing different mechanisms of action, anti-inflammatory activities, and routes of administration. Randomization will be stratified by MS type (RRMS versus SPMS), background DMT group, and baseline MTR/DTI characteristics.

Study objective

Part 1: To evaluate the effects of BIIB033 versus placebo on disability improvement over 72 weeks.
Part 2: evaluate long-term safety profile of BIIB033 as an add-on therapy in subjects with MS.

Study design

Part 1 is a 72-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2 study to evaluate the efficacy and safety of BIIB033 (750 mg infused IV every 4 weeks) as an add-on therapy to a background DMT in subjects with RMS.
Subjects who have completed study treatment (BIIB033 or placebo) in Part 1 will have the option to take part in Part 2, which is a 96 week multicenter, OLE phase that will evaluate BIIB033 treated subjects for long-term safety and efficacy of BIIB033 treatment, and explore novel biomarkers and patient reported outcomes (PROs) for remyelination/neurorepair MS therapies. Subjects will continue the anti-inflammatory DMT used at the end of Part 1. DMT treatment in Part 2 will continue to be managed by the Investigator. The study will include clinical assessments every 24 weeks and 4 brain MRI measurements.

Intervention

Part 1: The study treatment includes BIIB033 or placebo, administered once every 4 weeks by IV infusion (at site) for a total of 19 doses over 72 weeks.
Part 2: All subjects will receive IV infusions of open-label BIIB033 750 mg once every 4 weeks as an add-on therapy to anti inflammatory DMT.

Study burden and risks

Study (215MS202) will further investigate the efficacy and safety of BIIB033 as an add-on therapy in subjects with RMS who are on a stable dose of an anti-inflammatory disease-modifying therapy (DMT) and with baseline characteristics consistent with projected enhanced treatment effect of BIIB033 as identified in the post hoc analysis from Study 215MS201. Another object of the study is to learn more about side effects of the study drug. Like all medicines, BIIB033 can cause side effects, although not everybody experiences them. The most common side effects (which may or may not be related to BIIB033) are: headache, urinary tract infection, upper respiratory tract infection, common cold, stomach upset, fatigue, MS relapse, symptoms associated with lumbar puncture (headache, nausea, neck pain, and double vision), a sensation of tingling, numbness, or burning in arms or legs, flu-like illness, and fever. Liver problems including jaundice (eyes and or skin turning yellow) along with elevations in liver enzymes also occured. It is not known whether these effects were related to BIIB033.

As with any new drug, there is a risk of rare or previously unknown side effects, and/or a chance that BIIB033 might interact with other drugs.
If patients participate in this study, it will not mean that they suffer less from RMS. RMS may get worse, improve, or stay the same. But patients will contribute to increased knowledge about the treatment of RMS.

Contacts

Public
Biogen Idec Research Limited

Innovation House, Norden Road 70
Maidenhead, Berkshire SL6 4AY
GB
Scientific
Biogen Idec Research Limited

Innovation House, Norden Road 70
Maidenhead, Berkshire SL6 4AY
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Part 1:
1. Ability of the subject to understand the purpose and risks of the study and provide signed
and dated informed consent and authorization to use confidential health information in

accordance with national and local subject privacy regulations.
2. Age 18 to 58 years old, inclusive, at the time of informed consent.
3. Diagnosis of RRMS per the 2010 McDonald*s criteria [Polman 2011] or onset of SPMS
per the Lublin and Reingold criteria [Lublin 2014].
4. Baseline EDSS score of 2.0 to 6.0.
5. MS disease duration of *20 years from first MS symptom(s).
6. Must have at least one of the following occurring within 24 months prior to Day 1/Baseline:
* Clinical relapse(s) [but not within 24 weeks prior to Day 1/Baseline]
* Gadolinium (Gd)-enhancing lesion(s) on brain or spinal cord MRI
* New T2 lesion(s) on brain or spinal cord MRI
7. Must have been taking one of the following DMTs at a stable dose for at least 24 weeks
prior to Day 1/Baseline:
* IFN* (Avonex, Plegridy, Betaferon/Betaseron, or Rebif [at 44 *g by subcutaneous
injection 3 times per week])
* DMF (Tecfidera)
* Natalizumab (Tysabri)
Subjects who missed no more than a single dose of natalizumab during the 24-week
period may still enter the study.
8. At enrollment, subject is not anticipated to require switching of background anti-inflammatory DMT, in the opinion of the Investigator.
9. All subjects must meet the following MRI criteria on the Screening/Baseline brain MRI:
* MTR in T2 lesions *-0.17 normalized MTR unit (nMTRu)
and
* DTI * radial diffusivity (DTI-RD) in T2 lesions *0.98 × 10-3 mm2/s
10. All female subjects of childbearing potential and all male subjects must practice effective
contraception during the study and be willing and able to continue contraception for at
least 24 weeks after their last dose of study treatment (BIIB033 or placebo). In addition,
subjects should not donate sperm or eggs during the study and for at least 24 weeks after
their last dose of study treatment. For further details of contraceptive requirements for
this study, please refer to Section 15.5 of the protocol.
Part 2:
-Ability to understand purpose and risks of study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
-Subjects who complete study treatment (BIIB033 or placebo) at Part 1/Week 72 Visit.

- All female subjects of childbearing potential and all male subjects must practice effective contraception during study and continue contraception for at least 24 weeks after their last dose of BIIB033. In addition, subjects should not donate sperm or eggs during study and for at least 24 weeks after their last dose of study treatment.

Exclusion criteria

Part 1:
1. Primary progressive MS [Polman 2011].
2. T25FW >30 seconds (based on an average of 2 consecutive trials at Screening).
3. An MS relapse that has occurred within 24 weeks prior to Day 1/Baseline or the subject
has not stabilized from a previous relapse at the time of Screening.
4. A history of clinically significant persistent neutralizing antibody against IFN* or
natalizumab, in the opinion of the Investigator, for subjects treated with an interferon or
with natalizumab, respectively.
5. Prior exposure to BIIB033 (opicinumab).
6. Treatment with any chemotherapeutic agents (e.g., mitoxantrone, cyclophosphamide,
cladribine), cell-depleting mAbs (e.g., rituximab, ocrelizumab, alemtuzumab), total
lymphoid irradiation, T-cell or T-cell receptor vaccination, or teriflunomide within 1 year
prior to Day 1/Baseline.
Treatment with other anti-inflammatory DMTs (e.g., GA, fingolimod, daclizumab) or
plasmapheresis within 24 weeks prior to Day1/Baseline.
8. Treatment with Botox for limb spasticity within 24 weeks before Day 1/Baseline.
9. Treatment with any investigational drug within 24 weeks or 5 t1/2 (whichever is longer)
prior to Day 1/Baseline.
10. Treatment with 4-aminopyridine (4-AP) within 30 days prior to Day 1/Baseline, unless a
stable dose has been maintained for at least 30 days prior to Day 1/Baseline and will be
continued for the course of this study.
11. Treatment with high-dose oral or IV steroids within 30 days before Day 1/Baseline.
12. Contraindications to MRI, for example, presence of pacemakers or other implanted metal
devices (excluding dental braces), an allergy to Gd, renal impairment, or

claustrophobia
that cannot be medically managed.
13. Current enrollment or a plan to enroll in any interventional clinical study in which an
investigational treatment or approved therapy for investigational use is administered
within 5 half-lives of the agent prior to the Baseline Visit. Participation in a
noninterventional study can be allowed as long as this participation does not interfere
with this protocol or is not likely to affect the subject*s ability to comply with the
protocol.
14. History of suicidal ideation or an episode of clinically severe depression (as determined
by the Investigator) within 12 weeks of enrollment. Note: Subjects receiving ongoing
antidepressant therapy will not be excluded from the study unless the medication has
been increased within 24 weeks prior to enrollment.
15. History of human immunodeficiency virus or other immunodeficient conditions.
16. Positive test result at Screening for hepatitis C virus antibody or hepatitis B virus (defined
as positive for hepatitis B surface antigen or hepatitis B core antibody).
17. History of malignancy; however, subjects with a history of excised or treated basal cell
carcinoma or fewer than 3 squamous cell carcinomas are eligible to participate in this
study.
18. History of drug or alcohol abuse (as defined by the Investigator) within 2 years prior to
Day 1/Baseline.
19. History of abnormal laboratory results that, in the opinion of the Investigator, are
indicative of a significant cardiac, endocrine, hematologic, immunologic, metabolic,
urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, neurologic (other
than MS), and/or other major diseases.
20. Any of the following abnormal blood tests at Screening:
* hemoglobin *9.0 g/dL
* platelets *100 × 109/L
* lymphocytes *1.0 × 109/L
* neutrophils *1.5 × 109/L
* alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), or
gamma-glutamyl-transferase *2 times the upper limit of normal

* creatinine clearance <60 mL/min (estimated by Cockcroft-Gault equation)
21. Female subjects who have a positive pregnancy test result, are pregnant, or are currently
breast feeding.
22. Plans to undergo elective major procedures/surgeries at any time during the study.
23. Inability to comply with study requirements.
24. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the
subject unsuitable for enrollment.
Part 2:
- Subjects who did not complete study treatment in Part 1/Week 72 Visit
- Subjects who have a duration >12 weeks between their Part 1/Week 72 Visit and Part 2/Day 1.
- Any significant change in clinical status that would make the subject unsuitable to participate in Part 2, in the opinion of the Investigator. The Investigator must reassess the subject's medical fitness for participation and consider any diseases that would preclude study treatment.
- A history of clinically significant and persistent neutralizing antibody against IFN* or natalizumab, in the opinion of the Investigator, for subjects treated with an interferon or with natalizumab, respectively.
- Treatment with any investigational drug within 12 weeks prior to Part 2/Day 1.
- Treatment with 4-aminopyridine (4-AP) within 30 days prior to Part 2/Day 1, unless a stable dose has been maintained for at least 30 days prior to Part 2/Day 1. Treatment with medical marijuana for MS symptoms is not exclusionary, if it is consistent with local MS treatment guidelines and local regulations.
- Treatment with high-dose oral or IV steroids within 30 days before Part 2/Day 1.
-Contraindications to MRI, as presence of pacemakers or other implanted metal devices (excluding dental braces), an allergy to Gd, renal impairment, or claustrophobia that cannot be medically managed.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-04-2018
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Opicinumab
Generic name:	Opicinumab

Ethics review

Approved WMO Date:	12-09-2017
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	11-01-2018
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	07-02-2018
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	15-03-2018
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	20-03-2018

Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	31-05-2018
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	28-03-2019
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	22-07-2019
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	26-08-2019
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	27-01-2020
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	23-11-2020
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	EUCTR2017-001224-22-NL
ClinicalTrials.gov	NCT03222973
CCMO	NL62541.096.17