A Multicenter, Randomized, Double Blind, Placebo Controlled Study to Assess the Long-Term Efficacy and Safety of Prolonged Release Fampridine (BIIB041) 10 mg, Administered Twice Daily in Subjects with Multiple Sclerosis (ENHANCE)

Published: 26-11-2014
Last updated: 21-04-2024

Primary:The primary objective of Study 218MS305 is to determine whether prolonged-release fampridine (10 mg BID) has a clinically meaningful effect on patient-reported walking ability over a 24-week study period.Secondary:The secondary objectives...

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

Summary

ID

NL-OMON41721

Source
ToetsingOnline

Brief title
Enhance

Condition

- Other condition
- Central nervous system infections and inflammations

Synonym

Multiple sclerosis

Health condition

nervous system disorders, movement disorders not including parkinsonism

Research involving
Human

Sponsors and support

Primary sponsor: Biogen Idec Research Limited
Source(s) of monetary or material Support: Biogen Idec is the Sponsor of the study and is funding the study.

Intervention

Keyword: multiple sclerosis, placebo, prolonged release fampridine, walking improvement

Outcome measures

Primary outcome

The primary endpoint in this study is the proportion of subjects who achieve a mean improvement on the MSWS-12 of * 8 points from baseline over a 24-week treatment period. -12 is <8 points at baseline, the subject will be counted as having a point mean improvement from baseline if their mean MSWS-12 score during the treatment period is <0.5. Baseline will be defined as the mean of scores from Screening and Day 1 Visits. To determine whether a subject achieved a mean improvement of at least 8 points, the mean change on MSWS-12 will be calculated as the difference between the mean on-treatment score over 24 weeks and the mean pretreatment score. The primary analysis will be performed in the intent-to-treat (ITT) population and missing data will be handled using the multiple imputation procedure [Schafer 1997; Schafer 1999]. Comparisons between the fampridine and placebo treatment groups will be made using a logistic regression model adjusted for the

baseline MSWS-12 score and the Screening EDSS score. Hypothesis testing will be performed at a 2-sided 5% significance level. If an interim analysis is performed, then hypothesis testing will be performed as described in the protocol.

Secondary outcome

For the secondary endpoints, the proportion of subjects who achieve a mean improvement in TUG speed of >15% from baseline over a 24-week period will be compared between treatment groups using a logistic regression model adjustedfor the baseline TUG speed and the Screening EDSS score. Baseline will be defined as the mean speed over Screening and Day 1. The mean changes from baseline in the

MSIS-29, BBS, and ABILHAND scores will be compared using an analysis of covariance (ANCOVA) model adjusted for the corresponding baseline score and the Screening EDSS score. Baseline for MSIS-29 and BBS scores will be defined as the mean of scores from the Screening and Day 1 Visits. Baseline for the ABILHAND score will be defined as the score on Day 1 Visit. Secondary efficacy analyses on TUG speed, MSIS-29, BBS, and ABILHAND scores will be performed in the ITT population and missing data will be handled using the multiple imputation procedure [Schafer 1997; Schafer 1999]. Depending on the distribution of data for changes from baseline in MSIS-29, BBS, and ABILHAND scores, nonparametric analyses may be performed instead. Hypothesis testing will be performed at a 2-sided 5% significance level overall, with adjustment for testing multiple endpoints and the potential interim analysis. A combination of the sequential step-down procedure and the Hochberg procedure

will be used to control the overall Type I error in the testing of secondary efficacy endpoints. Analyses will also be performed to assess the predictive values of different measures of early response. For the exploratory endpoints, descriptive statistics will be used to summarize changes from Day 1 in EQ-5D-3L, SF-36, Version 2 (EQ-5D-3L visual analogue score and index score, and SF-36 subscale scores), and SDMT. If the data are normally distributed for these endpoints, least square means and 95% confidence intervals will be presented using an ANCOVA model adjusted for baseline and the Screening EDSS score. Otherwise, nonparametric analyses will be used. The proportion of subjects with an improvement on the PGIC and changes in HRU over time will also be summarized. Incidence of AEs occurring within each treatment group will be summarized overall, by severity, and by relationship to study treatment. Incidence of SAEs will be summarized by treatment group. Actual values and changes from baseline will be summarized by treatment group for laboratory assessments
and vital signs. Laboratory assessments will also be summarized for each treatment group using shift tables. Incidence of clinically meaningful changes in vital signs and ECGs will be summarized by treatment group.

Study description

Background summary

MS is an inflammatory condition that damages the myelin of the central nervous system and causes neurological impairment, often leading to severe disability. Its etiology remains unknown, although it is generally assumed that MS is mediated by an autoimmune process, possibly triggered by infection, and

superimposed upon a genetic predisposition. MS is the most common cause of neurological disability in young and middle-aged adults and has a major physical, psychological, social, and financial impact on patients and their families. In particular, walking impairment is a prominent manifestation of MS. Up to 85% of MS patients identify it as their primary complaint [Scheinberg 1980].

The prolonged-release formulation of fampridine (prolonged-release fampridine) has been approved in the United States as a treatment to improve walking in patients with MS (demonstrated by an increase in walking speed) under the proprietary name Ampyra® since 22 January 2010. Fampridine has also been approved under the brand name Fampyra® in the European Union (EU; July 2011) and other countries. The United States Adopted Name (USAN) is The effectiveness of prolonged-release fampridine 10 mg twice daily (BID), given 12 hours apart, in improving walking in patients with MS was evaluated in 2 pivotal randomized, placebo-controlled Phase 3 studies (MS-F203 and MS-F204) involving 540 subjects. The primary measure of efficacy in both trials was walking speed (in feet per second) as measured by the Timed 25-Foot Walk (T25FW), using a responder analysis. A responder was defined as a subject who showed faster walking speed for at least 3 out of a possible 4 visits during the double-blind treatment period than the maximum value achieved in the 5 nontreatment visits (4 before the double-blind period and 1 during the postdosing follow-up period).

During the double-blind treatment period, a significantly greater proportion of subjects taking prolonged-release fampridine had increases in walking speed compared with subjects taking placebo. In Study MS-F203, at least 50% of fampridine-treated subjects had more than a 10% increase in walking speed from baseline, at least 30% of the subjects had more than a 20% increase in walking speed from baseline, and at least 10% of the subjects had more than a 30% increase in walking speed from baseline, compared with a significantly lower proportion of subjects taking placebo. A similar pattern was also observed in Study MS-F204.

A recently completed Phase 2 study (218MS205) [n=132] assessed the effects of prolonged-release fampridine 10 mg BID on MS subjects* self-assessed walking disability and balance. The objectives of Study 218MS205 were to explore the impact of prolonged-release fampridine on overall walking disability, and to further elucidate the clinical relevance of changes over the 24-week treatment duration. Using the patient global impression of change as well as other anchor and distribution-based analyses, the minimum clinically important difference on the Multiple Sclerosis Walking Scale 12 (MSWS-12) was estimated at 8 points for improvement. Although formal statistical hypothesis testing was not performed in this study, a larger proportion of fampridine-treated subjects had at least an 8-point mean improvement on the MSWS-12, when compared with placebo-treated subjects (48.5% and 28.1%,respectively). Fampridine-treated subjects also exhibited improvements on the Timed Up and Go test (TUG), the Multiple Sclerosis Impact Scale (MSIS-29) physical subscale, and the Berg Balance Scale (BBS) as compared with placebo-treated subjects.

Study objective

Primary:
The primary objective of Study 218MS305 is to determine whether prolonged-release fampridine (10 mg BID) has a clinically meaningful effect on patient-reported walking ability over a 24-week study period.
Secondary:
The secondary objectives are as follows:
- To determine whether prolonged-release fampridine 10 mg BID has a clinically meaningful effect on dynamic and static balance, physical impact of MS, and upper extremity function over a 24-week study period
- To evaluate criteria for early assessment of response to fampridine that can predict clinically meaningful benefits in walking ability and balance
- To assess the safety and tolerability of prolonged-release fampridine 10 mg BID over a 24-week treatment period.

Study design

Subjects will be screened up to 14 days prior to Day 1. Eligible subjects will be enrolled into the study and, after undergoing baseline assessments, will be randomized in a 1:1 ratio to receive fampridine or placebo for 24 weeks. Randomization will be stratified by the Expanded Disability Status Scale (EDSS) score (*6 or >6) at Screening.
Assessments will be conducted at Weeks 2 and 4, and then every 4 weeks, until the last study treatment is administered at the Week 24 Visit. Not all assessments will be performed at every visit. A Follow-up Visit will be conducted at 2 weeks (±3 days) following the last study treatment administration (Week 24/Early Termination Visit).

Intervention

The treatment is to be self-administered by the subjects at home. Tablets must be swallowed whole and must not be divided, crushed, dissolved, sucked, or chewed. The tablets are to be taken without food, on an empty stomach. Water should be used to aid in swallowing the tablet. The desiccant should not be swallowed and, if removed, must be placed back into the bottle. Subjects are expected to receive prolonged-release fampridine 10 mg BID or matched placebo BID every 12 hours for up to 24 weeks.

Study burden and risks

For nature and extent of burden, please see the schedule of events section of the protocol and section E4 of this form. For the risks please see section E9. Regarding the benefit: it could be that prolonged-release fampridine (10 mg BID) has a clinically meaningful effect on patient-reported walking ability. However, there is no guarantee that the subjects condition will improve by

participation in this study. The results of the study might help people with a similar condition in the future. It is possible that the symptoms of the subjects condition will not improve during the study or may even worsen. Treatment with this study drug may also involve risks to the subjects future health that we currently don*t know about.

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

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. Aged 18 to 70 years, inclusive, at the time of informed consent.;3. Female subjects of childbearing potential must have a negative urine pregnancy test at the Screening Visit and on Day 1. All subjects must agree to practice

effective contraception during the study, and be willing and able to continue contraception for 30 days after their last dose of study treatment. For effective contraception methods, see Section 15.5.3.;4. Must have a diagnosis of primary-progressive, secondary-progressive, progressive-relapsing, or relapsing-remitting MS per revised McDonald Committee criteria [McDonald 2001; Polman 2005] as defined by Lublin and Reingold [Lublin and Reingold 1996] of at least 3 months duration.;5. Must have an EDSS score of 4 to 7, inclusive.;6. Must have walking impairment, as deemed by the Investigator.;7. Subjects must be able to understand and comply with the requirements of the protocol.

Exclusion criteria

1. History of human immunodeficiency virus (HIV).;2. Presence of acute or chronic hepatitis. Subjects who have evidence of prior hepatitis infection that has been serologically confirmed as resolved are not excluded from study participation.;3. Known allergy to fampridine, pyridine-containing substances, or any of the inactive ingredients in the prolonged-release fampridine tablet.;4. Any history of seizure, epilepsy, or other convulsive disorder, with the exception of febrile seizures in childhood.;5. CrCl of <80 mL/min.;6. 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) within the 5 years prior to the Screening Visit or at any time during the screening period.;7. Onset of MS exacerbation within 60 days prior to the Screening Visit, or at any time during the screening period.;8. History of any major surgical intervention (with the exception of skin biopsy) within the 30 days prior to the Screening Visit or Day 1, or at any time during the screening period.;9. Any non-MS-related condition or factor (as determined by the Investigator) that is likely to interfere with walking ability including, but not limited to, previous major surgery of the foot, leg, or hip; any significant trauma; or known peripheral neuropathy of the lower limb.;10. Presence of pulmonary disease including, but not limited to, chronic obstructive pulmonary disease that can impede the subject*s daily activities (as determined by the Investigator).;11. Presence of any psychiatric disorder, including clinical depression, that is likely to interfere with the subject*s participation in the study (as determined by the Investigator).;12. Uncontrolled hypertension (as determined by the Investigator) at the Screening Visit or at any time during the screening period.;13. History of any clinically significant cardiac, endocrinologic, hematologic, immunologic, metabolic, urologic, neurologic (except for MS, but including events indicative of a potentially lower seizure threshold), dermatologic, or other major disease (as determined by the Investigator).;14. Clinically significant abnormal laboratory values.;15. A body mass index (BMI) *40 (BMI formula: BMI = mass [kg]/[height(m)]2);16. History of severe allergic or anaphylactic reactions.;17. Use of off-label MS treatment including rituximab, daclizumab, or antibody (except natalizumab) within the 3 months prior to the Screening Visit, at any time during the screening period, or scheduled for use during study participation.;18. Use of mitoxantrone or cyclophosphamide within the 3 months prior to the Screening Visit, at any time during the screening period, or scheduled for use during study participation.;19. Initiation of natalizumab or alemtuzumab treatment or any change in the subject*s dose or regimen of natalizumab or alemtuzumab, within the 3 months prior to the Screening Visit, or at any time during the screening period.;20. Initiation of treatment with, or any change in the

subject*s dose or regimen of, interferon *-1b, interferon *-1a, fingolimod, teriflunomide, glatiramer acetate, or dimethyl fumarate within the 30 days prior to the Screening Visit or at any time during the screening period.;21. Pulsed steroid treatment within the 60 days prior to the Screening Visit or at any time during the screening period.;22. Any change in the subject*s medication dose or regimen for the treatment of fatigue or depression within the 30 days prior to the Screening Visit or at any time during the screening period.;23. Any change in prophylactic treatment for pain with antidepressants or anticonvulsants prescribed for this purpose within 30 days prior to the Screening Visit or at any time during the screening period.;24. Any change in the subject*s dose or regimen of antispastic agents within the 7 days prior to the Screening Visit or at any time during the screening period.;25. Treatment with an investigational drug within the 30 days (or 7 half-lives, whichever is longer) prior to the Screening Visit or at any time during the screening period.;26. Treatment with any aminopyridine (fampridine, 4-AP, or 3,4-diaminopyridine [DAP] in any formulation) within the 30 days prior to the Screening Visit or at any time during the screening period.;27. Treatment with organic cation transporter 2 (OCT2) inhibitors within 5 half-lives prior to the Screening Visit or at any time during the screening period;28. History of drug or alcohol abuse within the 2 years prior to the Screening Visit.;29. Female subjects who are currently pregnant or who are considering becoming pregnant while participating in the study.;30. Female subjects who are currently breastfeeding.;31. Inability to comply with study requirements.;32. Subject who plan to participate in another clinical study (including any observational studies) during the course of the current study.

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):	20-04-2015
Enrollment:	30

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fampyra
Generic name:	Prolonged-release fampridine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	26-11-2014
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	20-02-2015
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	03-04-2015
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	EUCTR2013-003600-40-NL
ClinicalTrials.gov	NCT02219932
CCMO	NL50685.096.14