Clinical trial results:
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)

Summary

EudraCT number	2013-003600-40
Trial protocol	GB LT CZ IT FI BG NL
Global end of trial date	11 February 2016

Results information

Result version number	v1 (current)
This version publication date	23 February 2017
First version publication date	23 February 2017

Trial information

Trial identification

Sponsor protocol code	218MS305

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02219932
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, Massachusetts,, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine whether prolonged-release fampridine (10 mg twice daily) has a clinically meaningful effect on participant-reported walking ability over a 24-week study period.

The secondary objectives are: to determine whether prolonged-release fampridine 10 mg taken twice daily (BID) has a clinically meaningful effect on dynamic and static balance, physical impact of multiple sclerosis (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 twice daily over a 24-week treatment period.

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 164
Country: Number of subjects enrolled	Bulgaria: 89
Country: Number of subjects enrolled	United Kingdom: 88
Country: Number of subjects enrolled	Czech Republic: 75
Country: Number of subjects enrolled	United States: 61
Country: Number of subjects enrolled	Russian Federation: 44
Country: Number of subjects enrolled	Serbia: 32
Country: Number of subjects enrolled	Finland: 23
Country: Number of subjects enrolled	Lithuania: 23
Country: Number of subjects enrolled	Netherlands: 22
Country: Number of subjects enrolled	Italy: 15

Worldwide total number of subjects	636
EEA total number of subjects	499

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	607
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 646 participants were enrolled. A single site in Poland was later closed due to serious Good Clinical Practice noncompliance issues observed during study conduct. There were 10 participants randomized at this site (6 to fampridine / 4 to placebo). Data from this site were excluded from all analyses (including the age and country tables).

Pre-assignment period milestones

Number of subjects started	636
Number of subjects completed	635

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Randomized but not treated: 1

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Blinding implementation details:

Study treatment was prepackaged for supply to study sites so that no site personnel would be unblinded in the course of study drug dispensing. Study treatment was stored in a secure location, and accountability for study treatment was the responsibility of the Investigator. To maintain the study blind, treatment assignments were not shared with the subjects, their families, or any member of the study team, either at the study site or at the Sponsor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo twice daily (BID) for up to 24 weeks

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo, given orally twice daily (approximately 12 hours apart) for 24 weeks.

Arm title	Fampridine 10 mg BID

Arm description:

Prolonged-release fampridine 10 mg BID for up to 24 weeks

Arm type	Experimental

Investigational medicinal product name	Fampridine
Investigational medicinal product code	BIIB041
Other name	dalfampridine, Ampyra, Fampyra, fampridine prolonged-release tablets
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Prolonged-release fampridine (10 mg), given orally twice daily (approximately 12 hours apart) for 24 weeks.

Number of subjects in period 1[1]	Placebo	Fampridine 10 mg BID
Started	319	316
Completed	254	266
Not completed	65	50
Adverse event, serious fatal	1	1
Adverse event, non-fatal	23	21
NotSpecified	5	11
Pregnancy	1	-
Lack of Efficacy (Participant Perception)	10	2
Investigator Decision	-	1
Lost to follow-up	4	2
Consent Withdrawn	11	6
Protocol deviation	10	6

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 646 participants were enrolled. A single site in Poland was later closed due to serious Good Clinical Practice noncompliance issues observed during study conduct. There were 10 participants randomized at this site (6 to fampridine / 4 to placebo). Data from this site were excluded from all analyses (including the age and country tables and subject disposition).

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo twice daily (BID) for up to 24 weeks	
Reporting group title	Fampridine 10 mg BID
Reporting group description:	
Prolonged-release fampridine 10 mg BID for up to 24 weeks	

Reporting group values	Placebo	Fampridine 10 mg BID	Total
Number of subjects	319	316	635
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	48.8	49	
standard deviation	± 10.5	± 9.82	-
Gender, Male/Female Units: Subjects			
Female	181	187	368
Male	138	129	267

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo twice daily (BID) for up to 24 weeks	
Reporting group title	Fampridine 10 mg BID
Reporting group description:	
Prolonged-release fampridine 10 mg BID for up to 24 weeks	
Subject analysis set title	Intent-to-treat population: Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants who received at least 1 dose of study drug and had at least 1 postbaseline efficacy assessment.	
Subject analysis set title	Intent-to-treat population: Fampridine 10 mg BID
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants who received at least 1 dose of study drug and had at least 1 postbaseline efficacy assessment.	

Primary: Proportion of Participants Achieving a Mean Improvement of ≥ 8 Points From Baseline on the Multiple Sclerosis Walking Scale (MSWS-12) Over 24 Weeks

End point title	Proportion of Participants Achieving a Mean Improvement of ≥ 8 Points From Baseline on the Multiple Sclerosis Walking Scale (MSWS-12) Over 24 Weeks
End point description:	
MSWS-12 is a participant self-assessment of the walking limitations due to MS during the past 2 weeks. It contains 12 items that measure the impact of MS on walking. Items are summed to generate a total score and transformed to a scale with a range of 0 to 100, where higher scores indicate greater impact on walking. A responder is defined as a participant with a mean improvement of at least 8 points over 24 weeks compared to baseline. Baseline is defined as the mean at Screening and Day 1 visits. If a participant has a mean MSWS-12 score of < 0.5 over the double-blind period, and a baseline MSWS-12 score of < 8 points, the participant is counted as a responder. A participant who indicates they cannot walk at all on MSWS-12 during any double-blind visit, and who shows severe disability and an inability to walk on other efficacy assessments is counted as a non-responder. Estimated proportion obtained from binomial proportions.	
End point type	Primary
End point timeframe:	
Baseline to 24 weeks	

End point values	Intent-to-treat population: Placebo	Intent-to-treat population: Fampridine 10 mg BID		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	318	315		
Units: proportion of participants				
number (not applicable)	0.336	0.432		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Based on logistic regression, adjusting for baseline MSWS-12 score, baseline TUG speed, age, screening Expanded Disability Status Scale (EDSS) score
and prior aminopyridine. Missing data handled by multiple imputation. Hypothesis testing was performed at the 2-sided 5% significance level overall, with adjustment for testing multiple secondary endpoints.

Comparison groups	Intent-to-treat population: Placebo v Intent-to-treat population: Fampridine 10 mg BID
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	2.26

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Based on logistic regression, adjusting for baseline MSWS-12 score, baseline TUG speed, age, screening Expanded Disability Status Scale (EDSS) score
and prior aminopyridine. Missing data handled by multiple imputation. Hypothesis testing was performed at the 2-sided 5% significance level overall, with adjustment for testing multiple secondary endpoints.

Comparison groups	Intent-to-treat population: Placebo v Intent-to-treat population: Fampridine 10 mg BID
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk Difference for Adjusted Proportions
Point estimate	0.104
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.178

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Based on logistic regression, adjusting for baseline MSWS-12 score, baseline TUG speed, age, screening Expanded Disability Status Scale (EDSS) score
and prior aminopyridine. Missing data handled by multiple imputation. Hypothesis testing was performed at the 2-sided 5% significance level overall, with adjustment for testing multiple secondary endpoints.

Comparison groups	Intent-to-treat population: Placebo v Intent-to-treat population: Fampridine 10 mg BID

Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Relative Risk
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	1.7

Secondary: Proportion of Participants Achieving a Mean Improvement From Baseline of ≥ 15% in Time Up dand Go (TUG) Speed Over 24 Weeks

End point title	Proportion of Participants Achieving a Mean Improvement From Baseline of ≥ 15% in Time Up dand Go (TUG) Speed Over 24 Weeks

End point description:

TUG is a timed walking test designed to measure gait performance and balance. It measures in seconds the time taken by an individual to stand up from a standard arm chair (approximate seat height of 46 cm [18in], arm height 65 cm [25.6 in]), walk a distance of 3 meters (118 inches, approximately 10 feet), turn, walk back to the chair, and sit down.

A responder is defined as a participant with a mean improvement of at least 15% in TUG speed over 24 weeks compared to baseline. Baseline is defined as the mean of Screening and Day 1 visits. Estimated proportion obtained from binomial proportions. There are 2 TUG tests given, and the average across the 2 tests is used to calculate average speed. Healthy participants below the age of 79 are expected to complete this task in 7-10 seconds (American College of Rheumatology). Missing data are handled using multiple imputation and baseline is defined as the mean over screening and Day 1.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Intent-to-treat population: Placebo	Intent-to-treat population: Fampridine 10 mg BID		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	318	315		
Units: proportion of participants				
number (not applicable)	0.347	0.434		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Based on logistic regression, adjusting for baseline TUG speed, screening EDSS score and prior aminopyridine. Missing data were handled using multiple imputation.

Comparison groups	Intent-to-treat population: Placebo v Intent-to-treat population: Fampridine 10 mg BID

Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	2.07

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Based on logistic regression, adjusting for baseline TUG speed, screening EDSS score and prior aminopyridine. Missing data were handled using multiple imputation.	
Comparison groups	Intent-to-treat population: Placebo v Intent-to-treat population: Fampridine 10 mg BID
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk Difference for Adjusted Proportions
Point estimate	0.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.175

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Based on logistic regression, adjusting for baseline TUG speed, screening EDSS score and prior aminopyridine. Missing data were handled using multiple imputation.	
Comparison groups	Intent-to-treat population: Placebo v Intent-to-treat population: Fampridine 10 mg BID
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Relative Risk
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.51

Secondary: Change From Baseline in Multiple Sclerosis Impact Scale-29 (MSIS-29) Physical Score Over 24 Weeks

End point title	Change From Baseline in Multiple Sclerosis Impact Scale-29 (MSIS-29) Physical Score Over 24 Weeks

End point description:

The 29-item MSIS-29 is a participant-reported outcome measure to assess the impact of MS on day-to-day life during the past 2 weeks from a participant's perspective; it measures 20 physical items and 9 psychological items. The physical score is generated by summing individual items and then transforming to a scale with a range of 0 (no impact of MS) to 100 (extreme impact of MS); a negative change indicates an improvement in function.

Data are based on a mixed model for repeated measures (MMRM) model using a common variance AR(1) variance-covariance matrix structure. Treatment, visit and treatment by visit interaction were included in the model as explanatory variables, adjusting for screening EDSS, baseline MSIS-29 physical score and prior aminopyridine as covariates. Missing data are handled using multiple imputation and baseline is defined as the mean over screening and Day 1.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Intent-to-treat population: Placebo	Intent-to-treat population: Fampridine 10 mg BID		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	318	315		
Units: units on a scale				
least squares mean (standard error)	-4.68 (± 0.936)	-8 (± 0.911)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Intent-to-treat population: Placebo v Intent-to-treat population: Fampridine 10 mg BID
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	mixed model for repeated measures
Parameter estimate	LS Mean Difference
Point estimate	-3.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.13
upper limit	-1.5

Variability estimate	Standard error of the mean
Dispersion value	0.925

Secondary: Change From Baseline in Berg Balance Scale (BBS) Over 24 Weeks

End point title	Change From Baseline in Berg Balance Scale (BBS) Over 24 Weeks

End point description:

The BBS is a widely used assessment tool to identify balance impairment. Functional activities such as reaching, bending, transferring, and standing are evaluated on the test to evaluate balance. Participants are asked to complete 14 tasks that are rated from 0 (cannot perform) to 4 (normal performance) for a total of 56 points. BBS scores range from 0 (poor balance) to 56 (good balance); a positive change indicates improvement.

Data are based on a MMRM model using a common variance AR(1) variance-covariance matrix structure. Treatment, visit and treatment by visit interaction were included in the model as explanatory variables, adjusting for screening EDSS, baseline BBS and prior aminopyridine as covariates. Missing data are handled using multiple imputation and baseline is defined as the mean over screening and Day 1.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Intent-to-treat population: Placebo	Intent-to-treat population: Fampridine 10 mg BID		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	318	315		
Units: units on a scale				
least squares mean (standard error)	1.34 (± 0.284)	1.75 (± 0.278)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Intent-to-treat population: Placebo v Intent-to-treat population: Fampridine 10 mg BID
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.141
Method	mixed model for repeated measures
Parameter estimate	LS Mean Difference
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.95

Variability estimate	Standard error of the mean
Dispersion value	0.277

Secondary: Change From Baseline in ABILHAND Score Over 24 Weeks

End point title	Change From Baseline in ABILHAND Score Over 24 Weeks

End point description:

The ABILHAND Questionnaire measures a participant's perceived difficulty in performing everyday manual activities in the last 3 months. The participant completes a 56-item questionnaire by estimating their own difficulty or ease in performing each of 56 activities. Items are summed to generate a total score and transformed to a scale with a range of 0 (poor manual ability) to 100 (good manual ability); a positive change indicates an improvement in manual ability.

Data are based on a MMRM model using a common variance AR(1) variance-covariance matrix structure. Treatment, visit and treatment by visit interaction were included in the model as explanatory variables, adjusting for screening EDSS, baseline ABILHAND and prior aminopyridine as covariates. Missing data are handled using multiple imputation and baseline is defined as the Day 1 assessment.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Intent-to-treat population: Placebo	Intent-to-treat population: Fampridine 10 mg BID		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	315[1]	312[2]		
Units: units on a scale				
least squares mean (standard error)	0.75 (± 0.593)	1.49 (± 0.574)		

Notes:

[1] - subjects evaluable for analysis

[2] - subjects evaluable for analysis

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Intent-to-treat population: Placebo v Intent-to-treat population: Fampridine 10 mg BID
Number of subjects included in analysis	627
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.197
Method	mixed model for repeated measures
Parameter estimate	LS Mean Difference
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	1.86

Variability estimate	Standard error of the mean
Dispersion value	0.573

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Collected through follow-up (14 [±3] days following Week 24/Early Termination). Serious adverse events collected from signing of informed consent; adverse events collected from first dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Fampridine 10mg BID

Reporting group description:

Prolonged-release fampridine 10 mg BID for up to 24 weeks

Reporting group title	Placebo

Reporting group description:

Placebo BID for up to 24 weeks

Serious adverse events	Fampridine 10mg BID	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 316 (7.91%)	21 / 319 (6.58%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 316 (0.32%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 316 (0.32%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian endometrioid carcinoma			
subjects affected / exposed	0 / 316 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			

subjects affected / exposed	1 / 316 (0.32%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 316 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 316 (0.63%)	2 / 319 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 316 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 316 (0.32%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 316 (0.32%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	1 / 316 (0.32%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 316 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Atrioventricular block second degree			
subjects affected / exposed	0 / 316 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 316 (0.32%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 316 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			
subjects affected / exposed	14 / 316 (4.43%)	10 / 319 (3.13%)	
occurrences causally related to treatment / all	0 / 16	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 316 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 316 (0.32%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 316 (0.32%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Endometrial atrophy			
subjects affected / exposed	0 / 316 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	0 / 316 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 316 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	0 / 316 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 316 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 316 (0.32%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder empyema			
subjects affected / exposed	1 / 316 (0.32%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site infection			

subjects affected / exposed	0 / 316 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 316 (0.63%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Fampridine 10mg BID	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	100 / 316 (31.65%)	93 / 319 (29.15%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	22 / 316 (6.96%)	17 / 319 (5.33%)	
occurrences (all)	39	26	
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	31 / 316 (9.81%)	31 / 319 (9.72%)	
occurrences (all)	34	35	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	16 / 316 (5.06%)	11 / 319 (3.45%)	
occurrences (all)	16	11	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 316 (4.75%)	18 / 319 (5.64%)	
occurrences (all)	15	19	
Urinary tract infection			
subjects affected / exposed	40 / 316 (12.66%)	29 / 319 (9.09%)	
occurrences (all)	53	32	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2014	- In response to questions by the Committee for Medicinal Products for Human Use about potential biases that might be introduced based on prior AP use, stratification at randomization was added for prior use (yes or no) of any AP (including fampridine/4-AP and 3,4-DAP in any formulation) to help achieve balance in the numbers of subjects with prior use in each treatment group. - Enrollment caps were added based on stratification factors, as follows: - Enrollment of subjects with prior AP use was limited to approximately 10% of the overall study population. This cap was added to mitigate the risk of potential unblinding due to prior treatment. - Enrollment of subjects with an EDSS score >6 was limited to approximately 35% of the overall study population. This cap was added to ensure that the study would generate data across the range of EDSS scores (4 to 7) and to allow a distribution of EDSS scores among enrolled subjects that is representative of the actual MS patient population treated with prolonged-release fampridine. - A statement was added that TUG and BBS assessments could not be performed by the same study site personnel. - The required sequence for multiple tests and assessments at a visit was updated to facilitate the capture of the endpoints in a hierarchical manner. - Permissible and exclusionary prior and concomitant medications were clarified with respect to alemtuzumab, dimethyl fumarate, and botulinum toxin. - Clarification was added to contraception requirements and the definitions of childbearing potential, effective contraception (for males and females), and abstinence.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported