2019-01

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10.1007/s40263-018-0586-5
CNS Drugs
Springer Verlag

Assessment of Clinically Meaningful Improvements in Self-reported Walking Ability in ~~People~~ Participants with Multiple Sclerosis: Results from the Randomized, Double-blind, Phase III ENHANCE Trial of Prolonged-release Fampridine

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Running head: ~~Clinically Meaningful~~PR-Fampridine-Associated Improvements in ~~Self-reported~~ Walking ~~in MS: Results from the ENHANCE Study~~

Acknowledgements

This study was funded by Biogen. ~~Biogen provided funding for medical writing support in the development of this paper; Malcolm Darkes and Juliet Bell from Excel Scientific Solutions wrote the first draft of the manuscript based on input from authors, and Kristen DeYoung of Excel Scientific Solutions copyedited and styled the manuscript per journal requirements. Biogen reviewed and provided feedback on the paper to the authors. The authors had full editorial control of the paper, and provided their final approval of all content.~~

Main text word count: 6006 words [word count of 4000 words provided as guide; Editor indicated in her comments that longer articles are acceptable]

Abstract [count: 442/500]

Background Walking impairment is a hallmark of multiple sclerosis (MS). It affects >90% of individuals over time reducing independence and negatively impacts health-related quality of life, productivity, and daily activities. Walking impairment is consistently reported as one of the most distressing impairments by individuals with MS. Prolonged-release (PR)-fampridine improves has previously been shown to improve objectively measured walking speed in walking-impaired adults with multiple sclerosis (MS). The impact of PR-fampridine from the perspective of the individual with MS warrants full and detailed examination.

Objective Evaluate whether PR-fampridine has a clinically meaningful effect on self-reported walking ability in walking-impaired people participants with MS (PwMS).

Methods ENHANCE was a phase III, randomized, double-blind, placebo-controlled study of PR-fampridine 10 mg twice daily in PwMS walking-impaired individuals age 18–70 years with either relapsing or progressive forms of MS and an (age 18–70 years; Expanded Disability Status Scale score of 4.0–7.0) at screening. Participants were stratified by EDSS score [≤ 6.0 or 6.5–7.0] at randomization to ensure a balanced level of disability in the treatment groups. Primary endpoint was proportion of participants with mean improvement in Multiple Sclerosis Walking Scale (MSWS-12) score exceeding the predefined threshold for clinically meaningful improvement (≥ 8 points) over 24 weeks. Secondary endpoints included proportion with ≥ 15% improvement in Timed Up and Go (TUG) speed, and mean changes in MS Impact Scale physical impact subscale (MSIS-29 PHYS), Berg Balance Scale (BBS), and ABILHAND scores over 24 weeks.

Results 636 PwMS participants with MS were randomized (PR-fampridine, n = 317; placebo, n = 319; modified intention-to-treat sample: PR-fampridine, n = 315; placebo, n = 318). At baseline in the PR-fampridine and placebo groups, 46% and 51% had a progressive form of MS, median [range] EDSS scores were 6.0 [4.0–7.0], and 5.5 [4.0–7.0], mean [range]

MSWS-12 scores were 63.6 [0–100] and 65.4 [0–100], and mean [range] TUG speed was 0.38 [0.0–1.0] and 0.38 [0.0–1.2] ft/sec, respectively. A significantly higher percentage of PR-fampridine–treated participants [136/315 (43.2%)] had clinically meaningful improvement in MSWS-12 score over 24 weeks vs. placebo [107/318 (33.6%); odds ratio 1.61 (95% confidence interval 1.15 to 2.26); $p = 0.006$]. For PR-fampridine vs. placebo, significantly more participants had a ≥ 15% improvement in TUG speed, and there was significantly greater mean improvement in MSIS-29 PHYS score ($p < 0.05$); numerical improvements that were not statistically significant were observed in BBS/ABILHAND. ~~Safety was consistent with PR-fampridine's established~~ AEs that were more common in the PR-fampridine group than placebo group (difference ≥ 3%) by MedDRA Preferred Term were urinary tract infection and insomnia~~profile~~. There were no seizures reported.

Conclusions PR-fampridine treatment resulted in sustained, clinically meaningful improvements over 24 weeks in self-reported walking and functional ability in walking-disabled ~~PwMS~~participants with MS.

ClinicalTrials.gov identifier NCT02219932.

Key Points

- Findings from the multi-national ENHANCE study in walking-disabled ~~people~~ participants with MS [Expanded Disability Status Scale (EDSS) score 4.0–7.0] ~~demonstrate~~ showed that participants treated ~~treatment~~ with prolonged-release (PR)-fampridine 10 mg twice daily were more likely than those treated with placebo to achieve ~~results in sustained and~~ clinically meaningful improvements in self-reported walking ability over 24 weeks.
- PR-fampridine also was associated with benefits in objectively measured mobility and self-reported physical functioning.

- Additional research is required to better understand the pathophysiologic differences in individuals who do and do not respond to PR-fampridine and ~~evaluation~~ to evaluate the impact of PR-fampridine ~~in people with an EDSS score > 7.0 to assess~~ on manual function, cognition, and fatigue in individuals with an EDSS score > 7.0.

1 Introduction

Impaired walking is a hallmark of multiple sclerosis (MS); 93% of ~~people~~ individuals with MS are walking impaired within 10 years after diagnosis [1]. Impaired walking and mobility have profoundly deleterious effects on independence, health-related quality of life, daytime functioning, and productivity [1, 2]. Maintaining mobility is a high priority for ~~people~~ individuals with MS, irrespective of disease duration and disability level [2, 3].

Prolonged-release (PR)-fampridine (dalfampridine extended-release tablets in the United States), a PR formulation of 4-aminopyridine, is a twice-daily oral treatment indicated to improve walking in ~~people~~ individuals with MS [4]. PR-fampridine is thought to improve conduction in demyelinated pathways by blocking voltage-dependent potassium channels [5]. Two pivotal phase III studies of PR-fampridine ~~(any MS disease course) reported clinically meaningful improvements in~~showed that walking speed, as measured by the Timed 25-Foot Walk (T25FW), improved in PR-fampridine responders (defined as participants with faster walking speed for at least three of four visits during the on-treatment period vs. the maximum speed from five off-drug visits) over 14 weeks [6] and 9 weeks [7] of treatment ~~among responders (faster walking speed for at least three of four visits during the treatment period vs. the maximum speed from five off-drug visits)~~. These trials included individuals with clinically definite MS of any disease course who had objectively measured deficits in walking speed (i.e., T25FW time between 8–45 seconds) [6, 7]. Although these pivotal data were the foundation for the approval of PR-fampridine in the US and European Union,[4, 8] they were limited in terms of demonstrating the duration of effect and offered the opportunity to further build on the clinical meaningfulness of PR-fampridine. Subsequent studies, including the 12-month ENABLE and 6-month MOBILE studies [9, 10], showed that PR-fampridine also had beneficial effects on a broad range of other clinical and self-reported

outcome assessments, including walking, balance, and aspects of life quality over longer treatment periods [9-13].

ENABLE was a single arm, open-label study that showed that PR-fampridine was associated with statistically significant long-term improvements in self-perceived physical functioning and psychological health over time.[9] The exploratory randomized, double-blind, placebo-controlled MOBILE study was designed to further assess the effects of PR-fampridine beyond the 14-week period evaluated in the longest pivotal study, evaluate self-reported walking ability, and identify a clinically meaningful change threshold in the 12-item Multiple Sclerosis Walking Scale (MSWS-12) [10]. At entry to the study, MOBILE participants had a clinical diagnosis of MS of any course for at least 3 months duration with EDSS scores of 4.0–7.0 [10]. The T25FW test was not used as a screening measure in MOBILE, because this was considered covered by previous studies and has implications for study design. Thus, MOBILE participants could have had any walking speed [10].~~The~~ Results from MOBILE demonstrated that treatment with PR-fampridine resulted in early improvements in mobility and balance compared with placebo ~~treatment period was~~ that were sustained over the 6~~- months~~month treatment period~~,~~ .[10] ~~and a~~Additionally, data from the MOBILE study were used to estimate the threshold for a patient-level clinically meaningful improvement in MSWS-12 score ~~was estimated as a~~(i.e., ≥ 8-point mean score reduction) [14]. This threshold of improvement was then used as the primary endpoint for ENHANCE.

The novelty of ENHANCE over previous clinical studies of PR-fampridine is that it was designed to assess the effect of pharmacotherapy on the proportion of participants achieving a criterion for clinically meaningful change in walking using a self-reported outcome measure. The MSWS-12 assesses aspects of walking not capture by objective assessments [15]. While previous studies have shown benefits of PR-fampridine on self-reported outcomes, including walking ability [9, 10], ENHANCE was the first study that

included formal statistical hypothesis testing in the setting of a rigorous study design (i.e., randomized, double-blind, placebo-controlled) to evaluate clinically meaningful improvement on a self-reported outcome. Furthermore, another objective of ENHANCE was to evaluate some of the broader effects of PR-fampridine that have been reported by patients in MS clinics using an expanded range of clinical outcome assessments over a longer treatment period. ~~It is notable that ENHANCE was one of the first studies to use a previously defined criterion of clinically meaningful change on a self-reported outcome as its primary endpoint~~. The main objective of the ENHANCE study was to determine whether PR-fampridine 10 mg twice daily has a clinically meaningful effect on self-reported walking ability when compared with placebo over 6 months of treatment.

2 Methods

2.1 Study Design

ENHANCE was a multi-center, randomized, double-blind, placebo-controlled, parallel-group, phase III study of PR-fampridine vs. placebo in participants ~~people~~ with MS who had walking impairment. The study consisted of a 2-week screening period, a 24-week double-blind treatment period, and a 2-week post-dosing follow-up visit and was carried out at 92 centers in 11 countries (Fig. S1 and Table S1 in ~~Online Resource 1~~Supplementary Material). Independent ethics committees or institutional review boards approved the study protocol and all amendments. The trial was registered with ClinicalTrials.gov (NCT02219932). The first participant was treated on September 29, 2014 and the last participant's last visit was February 11, 2016.

Participants were randomized (1:1) to PR-fampridine 10 mg twice daily or matched placebo for 24 weeks, and were stratified by Expanded Disability Status Scale (EDSS) score (≤ 6.0 or 6.5–7.0) according to a pre-defined randomization list to ensure a balanced level of

disability. There was no placebo run-in phase. The protocol was amended ~~3 months after the study started~~on December 3, 2014 to add stratification by prior aminopyridine use (yes/no) because of concerns regarding potential bias. Enrollment caps were added based on stratification factors: enrollment of participants with prior aminopyridine use was limited to ~ 10% of the overall study population; enrollment of participants with an EDSS score > 6.0 was limited to ~ 35% of the overall study population. All participants, investigators, site personnel, and funder personnel were masked to treatment assignment.

Requests for the data supporting this manuscript should be submitted to the Biogen Clinical Data Request Portal (www.biogenclinicaldatarequest.com).

2.2 Participants

Participant eligibility was assessed by a treating neurologist during a 14-day screening period. Key inclusion criteria were: age 18–70 years, diagnosis of MS (any subtype), ~~and~~ EDSS score of 4.0–7.0, and investigator-assessed walking impairment. Key exclusion criteria were: recent exacerbation of MS (within 60 days of screening visit), recent initiation/change in the dosing of approved immunomodulatory therapies, and any history of seizure, epilepsy, or other convulsive disorder. ~~Online Resource 1~~The Supplementary Material reports full inclusion and exclusion criteria in the Methods section. Concomitant use of approved disease-modifying therapies and medications for fatigue or spasticity were allowed if the drug and dose remained stable throughout the study; physiotherapy and rehabilitation therapy were also allowed.

2.3 Assessments and Endpoints

Measurements of walking ability, physical impact of MS, balance, and manual ability were collected prospectively with widely used self-reported questionnaires [MSWS-12 [16],

Multiple Sclerosis Impact Scale physical subscale (MSIS-29 PHYS) [17], and 56-item ABILHAND for manual ability [18]], performance measures [Timed Up and Go (TUG) speed [19]], and clinician-reported outcomes [Berg Balance Scale (BBS) [20, 21]]. Participants completed questionnaires up to ten times and had at least ten clinic visits during the 26-week study. The MSWS-12, TUG, and MSIS-29 PHYS were evaluated at Screening, Day 1, and Weeks 2, 4, 8, 12, 16, 20, and 24 during the 24-week double-blind treatment period. The BBS was collected at Screening, Day 1 and Weeks 2, 12, and 24. The ABILHAND was collected at Day 1 and Weeks 2, 8, and 20. The MSWS-12 and TUG were also evaluated at the 2-week post-dose follow up (Table 1). Translated questionnaires were provided by licensees where available (MSIS-29 PHYS and MSWS-12: Plymouth University, Plymouth, UK; TUG: American College of Rheumatology, Atlanta, Georgia, USA; ABILHAND: Catholic University of Louvain, Louvain-la-Neuve, Belgium).

The primary endpoint was the proportion of participants ~~people~~ with a mean improvement in MSWS-12 score of ≥ 8 points [14] from baseline over 24 weeks, where improvement was defined as a decrease in score [14]. Clinically meaningful improvement in MSWS-12 score was previously estimated as an ≥ 8-point mean score reduction at the level of the individual based on triangulation of values obtained from both anchor- and distribution-based analyses using data from the MOBILE study [14]. Mean improvement in MSWS-12 was determined by calculating the mean change (i.e., mean on-treatment score over weeks 2–24 minus mean baseline score). MSWS-12 scores were transformed to a 0–100 scale.

Secondary endpoints were assessed over 24 weeks and rank ordered into two groups as a hierarchical testing approach. ~~Group~~ Rank group 1 secondary endpoints were the proportion of participants ~~people~~ with a mean improvement in TUG speed of ≥ 15% from baseline, and mean change from baseline in MSIS-29 PHYS score (range 0–100). The

threshold for a clinically important change in TUG speed was determined using data from the MOBILE study [10] and methods similar to that used in determining the threshold for a clinically important change for the MSWS-12 [14]. Both anchor- and distribution-based methods were used to determine what percentage improvement was clinically meaningful on the TUG speed at the level of the individual. Improvement on the Patient Global Impression of Change (PGIC) and an ≥8-point improvement on the MSWS-12 were used as anchors. The median percentage change in TUG speed in MOBILE study participants who had had ≥1 visit where they reported a score of "slightly improved" on the PGIC was 16.83% (n=81). The median percentage of change in TUG speed in MOBILE study participants who had a ≥8-point improvement in the MSWS-12 was 17.53% (n=54). The distribution-based estimate, which uses estimates of measurement error based on within and between participant variability, was calculated using the standard error of measurement (SEM) = SD√ (1-Reliability) and was 10.0. The average of the three estimates was 15% and was used as the threshold for determining a clinically meaningful improvement in TUG speed in ENHANCE. Rank group 2 endpoints were the mean changes in BBS score (range 0–56) and ABILHAND score (range 0–100).

TUG speed, a performance mobility measure, was included, as it complements the self-reported MSWS-12, correlates with the T25FW (r = 0.85) [22], and detects changes in moderately impaired ~~people~~ individuals with some precision [22, 23]. An exploratory analysis of TUG time was performed. The self-reported 20-item MSIS-29 PHYS assessed the physical impact of MS, the clinician-reported 14-item BBS measured static and dynamic balance, and the self-reported 56-item ABILHAND evaluated manual ability. Table ~~S2~~ 1 ~~in Online Resource 1~~ provides an overview of the questionnaires and estimated clinically important ~~differences~~changes.

Subgroup analyses of MSWS-12 scores included assessment of PR-fampridine efficacy vs. placebo in participants ~~people~~ with lower (baseline EDSS score ≤ 6.0) or greater (EDSS score 6.5, 7.0) disability. Post-hoc analyses evaluated ABILHAND data in participants ~~people~~ with normal (≥ 80) [24] or abnormal (< 80) scores at baseline; results were compared between treatment groups.

Post-hoc analyses of all outcomes were also conducted for those who responded to PR-fampridine as measured by MSWS-12 score (vs. PR-fampridine non-responders and placebo) to determine if these participants ~~people~~ responded in other measurement domains. A PR-fampridine MSWS-12 responder was defined as an ~~person~~ participant with a ≥ 8-point mean improvement in MSWS-12 score from baseline over 24 weeks (see Methods section in~~Online Resource 1~~Supplementary Material for additional details).

Safety was evaluated via physical examination, electrocardiograms, vital signs, clinical laboratory tests, and adverse event (AE) reporting. A treatment-emergent AE was defined as any AE with an onset date on or after the first dose of study treatment, or any pre-existing condition that worsened in severity after the first dose of study treatment. A serious AE was any untoward medical occurrence that resulted in death/risk of death, hospitalization or prolonged hospitalization, persistent or significant disability/incapacity, or resulted in a congenital anomaly/birth defect. AEs were spontaneously reported by participants and recorded using a specific AE collection form within the case report form. Serious AEs had to be reported to the sponsor within 24 hours of the study staff becoming aware of the event. All AEs were recorded using Medical Dictionary for Regulatory Activities (MedDRA; version 18.1) terms. Confirmatory urinary tract infection cultures were evaluated wherever possible to rule out infection or confirm bacterial infection. Compliance with dosing of study drug was calculated based on the number of days study drug was taken (number of tablets dispensed

minus the number returned divided by 2) divided by the number of days of exposure multiplied by 100.

2.4 Statistical Analysis

Efficacy analyses were based on the modified intention-to-treat (mITT) sample, which comprised randomized participants who received at least one dose of study drug and had at least one post-baseline efficacy assessment. The planned sample size of 590 randomized participants was to provide ≥ 90% power at a two-sided 5% significance level and detect a minimum of 14.5% absolute improvement in the on-treatment response rate (i.e., ≥ 8-point mean improvement in MSWS-12 score over 24 weeks) for the PR-fampridine vs. placebo groups, with an assumed 15% dropout rate. Data from one site that enrolled 10 participants ~~people~~ were deemed unreliable due to serious Good Clinical Practice non-compliance and were excluded from the analyses before unblinding. Pre-specified sensitivity analyses were conducted to compare the results with and without the data from these 10 participants, which revealed no appreciable differences across all endpoints.

The pre-specified hypothesis test of the primary endpoint, PR-fampridine treatment effect (proportion of participants ~~people~~ with a clinically significant ≥ 8-point mean improvement in MSWS-12 score), was based on a logistic regression model with treatment group as the classification variable and baseline MSWS-12 score, baseline TUG speed, age, screening EDSS score, and prior aminopyridine use as covariates (to increase the precision of the analysis and provide an unbiased estimate of treatment effect). A multiple imputation method [25] (50 times) was used to impute missing individual post-baseline MSWS-12 scores before deriving the primary endpoint. The electronic device used to administer the MSWS-12 did not allow component questions to go unanswered, so imputation was not required for ~~There were no cases where any~~ individual MSWS-12 item scores ~~were missing~~

~~at any one time point; .~~ ~~therefore~~Therefore, imputation was only performed on assessments that were completely missing for the time point. The reasons for missing MSWS-12 data were: participant did not attend a study visit, participant was lost to follow up or prematurely discontinued from the study, or participant attended the visit but responded "cannot walk at all" on the MSWS-12~~,~~ or the MSWS-12 was not performed or missing because of technical difficulties at the site. Baseline was defined as the mean score over screening and day 1.

A hierarchical testing approach was used to protect the overall type I error rate for the four secondary endpoints. ~~The proportion of people who achieved a ≥ 15% mean improvement in TUG speed from baseline and the change from baseline over the 24-week treatment period in MSIS-29 PHYS score were pre-specified as~~Secondary endpoints were pre-specified as rank group 1~~. The changes from baseline over 24 weeks in BBS and ABILHAND scores were specified as~~ or rank group 2 as described in Section 2.3. Within each rank group, the statistical test was performed using the Hochberg procedure. Statistical tests for rank group 2 could only have been conducted if the tests for rank group 1 reached an overall *p* value threshold of 0.05 with the Hochberg adjustment.

The proportion of participants ~~people~~ with ≥ 15% mean improvement in TUG speed ~~(≥ 15% mean improvement)~~ was analyzed similarly to the primary endpoint. The changes from baseline over 24 weeks in MSIS-29 PHYS, BBS, and ABILHAND scores were analyzed using a mixed-effects model for repeated measures, with treatment group as the classification variable. Covariates in the model were: baseline values for each measure, visit-by-treatment interaction, screening EDSS score, and prior aminopyridine use. Missing values were imputed using the multiple imputation method (50 times).

Subgroup analyses were performed using a similar model for each level of subgroup. Analyses of PR-fampridine MSWS-12 responders (vs. PR-fampridine MSWS-12 non-responders and placebo) used a similar model for each endpoint, except the responder group

(PR-fampridine MSWS-12 responders, PR-fampridine MSWS-12 non-responders, and placebo) was specified in the model as a classification variable instead of a treatment group. A separate analysis was conducted on each endpoint for PR-fampridine MSWS-12 responders vs. placebo MSWS-12 responders and PR-fampridine MSWS-12 non-responders vs. placebo MSWS-12 non-responders (see ~~Supplementary~~ Methods section in ~~Online Resource 1~~Supplementary Material). Raw mean [standard deviation (SD)] scores and floor and ceiling effects were calculated, along with Cohen's effect size (evaluated using both mean change from baseline divided by pre-treatment SD and mean change from baseline divided by pooled SD) and standardized response mean (mean change from baseline divided by SD change from baseline). These scores were presented by treatment group and for PR-fampridine MSWS-12 responders and PR-fampridine MSWS-12 non-responders.

Safety analyses were based on the safety sample (i.e., all participants ~~people~~ randomized and exposed to study drug), excluding participants ~~people~~ from one site for the reasons above. Any AE with a missing onset date and a resolution date after the first dose of study treatment was considered treatment emergent.

Statistical software (SAS® 9.4; SAS Institute Inc.; Cary, North Carolina, USA) generated all summaries and statistical analyses.

3 Results

3.1 Participant Characteristics

Seven hundred fifty-eight participants ~~people~~ were screened and 636 randomized (Fig. 1). One participant ~~person~~ randomized to PR-fampridine did not receive treatment. Of the 635 participants ~~people~~ (safety sample), 633 completed at least one on-treatment efficacy assessment and were included in the mITT analyses (PR-fampridine, *n* = 315; placebo, *n* =

318). Most participants completed 24 weeks of treatment [PR-fampridine, 271/317 (85%); placebo, 258/319 (81%)].

Baseline characteristics were similar between groups (Table ~~1~~2); the most commonly used immunomodulatory medications were glatiramer acetate, fingolimod, interferon beta-1a, and natalizumab. At baseline, the treatment groups were balanced with respect to EDSS scores, distance walked, and MS-related symptoms that potentially affect walking ability (Table ~~1~~2). Mean baseline EDSS scores implied disability severe enough to preclude full daily activities. Baseline MSWS-12 scores and TUG speed indicated moderately poor mobility. Concomitant medication and non-drug therapy use during the study was similar in the PR-fampridine and placebo groups, including anti-spasmodics and physiotherapy (Table ~~S3~~ S2 in ~~Online Resource 1~~Supplementary Material).

Based on the mITT sample (N=633), the following level of post-baseline data were missing and were imputed for efficacy outcomes: MSWS-12 score: 12% [PR-fampridine, 10%; placebo, 14%]; TUG speed: 9% [PR-fampridine, 7%; placebo, 12%]; MSIS-29 PHYS score: 9% [PR-fampridine, 7%; placebo, 11%]; BBS score: 9% [PR-fampridine, 8%; placebo, 11%]; ABILHAND score: 9% [PR-fampridine, 8%; placebo, 11%].

3.2 Primary Efficacy Analyses

~~The~~ A significantly ~~PR-fampridine group had a significantly~~ greater proportion of participants ~~people~~ in the PR-fampridine group (43.2%) versus the placebo group (33.6%) ~~with~~ had a clinically meaningful improvement in mean MSWS-12 score [odds ratio 1.61 (95% confidence interval 1.15 to 2.26); p=0.006], which was the primary end point of the study ~~vs. placebo~~ (Table ~~2~~3). Analysis of the primary endpoint using observed data without imputation provided similar findings. Fig. 2 shows the cumulative proportion of MSWS-12 responders, which plots the proportion of responders for a range of responder threshold definitions. For every integer of MSWS-12 score point change from 0–10, the PR-fampridine

group had a higher proportion of MSWS-12 responders. MSWS-12 score improvement ≥ 10 points was achieved by 38% of PR-fampridine and 27% of placebo-treated participants ~~people~~ (p = 0.003). This implied a consistent treatment benefit with PR-fampridine regardless of responder definition. Fig. 3 shows least squares mean (LSM) changes from baseline in MSWS-12 score per visit, ~~again demonstrating~~ showing ~~the benefit of PR-fampridine vs. placebo~~improvements in MSWS-12 scores observed as early as 2 weeks after treatment initiation with benefits compared with placebo across the 24-week treatment period. Within 2 weeks of stopping PR-fampridine treatment, the effects of PR-fampridine on the MSWS-12 dissipated (Fig. 3). Participants in the PR-fampridine group had a LSM improvement in MSWS-12 score from baseline over the 24-week double-blind treatment period of 6.73 points versus an improvement of 2.59 points in the placebo group, a treatment difference that was statistically significant [LSM improvement vs placebo 4.14 (95% confidence interval −6.22 to −2.06); p<0.001; Table 3].

3.3 Secondary and Other Clinical Efficacy Analyses

~~The PR-fampridine group had a~~A significantly higher proportion of participants ~~people with~~ in the PR-fampridine group (43.5%) versus the placebo group (34.3%) had a clinically meaningful ~~TUG speed~~ improvement~~s~~ in TUG speed (≥ 15% mean increase from baseline [odds ratio 1.46 (95% confidence interval 1.04 to 2.07); p=0.03~~), ~~]). ~~significantly greater~~ TUG speed improved from baseline over 24 weeks by a LSM ~~improvements in~~of 0.05 feet/second in the PR-fampridine group compared with 0.03 feet/second in the placebo group [LSM treatment difference 0.02 (95% confidence interval 0.01 to 0.03); p<0.001; Table 3). ~~TUG speed, and s~~The PR-fampridine group also demonstrated significantly greater LSM improvements from baseline in MSIS-29 PHYS score (8.00 points) vs. placebo (4.68 points) over 24 weeks [LSM improvement vs placebo 3.31 (95% CI −5.13 to −1.50); p<0.001; Table

~~2~~3). These results demonstrated significant improvements in both objective and subjective measures of functioning.

~~Table 2 also shows~~The rank 2 secondary endpoints of change in BBS and ABILHAND scores from baseline over 24 weeks were not statistically significant, although ~~greater~~ there were numerically greater improvements in both ~~BBS and ABILHAND~~assessments ~~scores for~~in the PR-fampridine group compared with the placebo group (Table 3). BBS scores improved from baseline over 24 weeks by an LSM of 1.75 points in the PR-fampridine group versus 1.34 in the placebo group, although the LSM treatment difference was not statistically significant [0.41 (95% confidence interval −0.13 to 0.95); *p*=0.141; Table 3]. Similarly, ABILHAND scores improved from baseline by a LSM of 1.49 points in the PR-fampridine group and by 0.75 points in the placebo group over 24 weeks, which resulted in a non-significant LSM treatment difference of 0.74 (95% confidence interval −0.38 to 1.86; *p*=0.197; Table 3). ~~The differences were numerically small and not significant. However, the baseline participant score distributions for both scales were skewed towards better functioning (Table 1), which could have influenced their ability to measure change.~~

Fig. 4 shows the pre-specified analyses of percentage change in TUG speed per visit. The LSM percentage change from baseline over 24 weeks in TUG speed was greater with PR-fampridine than placebo [15.9% vs. 11.8%; LSM difference 4.17 (95% confidence interval 0.43 to 7.91); p = 0.029]. LSM TUG time decreased from baseline over 24 weeks by −3.3 seconds in the PR-fampridine group and by −1.94 seconds in the placebo group [LSM treatment difference −1.36 (95% confidence interval −2.85 to 0.12); p=0.073]. Similar to what was observed on the MSWS-12, improvements in TUG speed subside when treatment with PR-fampridine was stopped (Fig. 4).

Table ~~S4~~ S3 in ~~Online Resource 1~~Supplementary Material shows the distributional statistics of the PR-fampridine and placebo groups for all the reported efficacy outcomes in the mITT groups at baseline and on treatment, and change from baseline scores. Two effect size calculations (standardized change scores) are also reported. These calculations quantify the magnitude of the treatment effect contextualized by variance at baseline (Cohen's effect size), or the variance of change (standardized response mean). Standardizing the change scores enables a meaningful comparison across different clinical outcome assessments with varying measurement processes. Both effect sizes were interpreted using Cohen's widely used criteria [26], which are thresholds for small (> 0.20), moderate (> 0.50), and large (> 0.80) clinical change. Effect sizes were consistently greater for the PR-fampridine group vs. placebo, with differences implying a clinically small to moderate change.

3.4 Efficacy Subgroup Analyses

Table ~~3~~ 4 shows a pre-specified subgroup analysis of ABILHAND, including the LSM change stratified by disability level (EDSS score ≤ 6.0 vs. 6.5 and 7.0). While the ~~numerical~~ differences between the PR-fampridine and placebo groups were ~~small~~not statistically significant, there were small numerical improvements that were larger ~~,~~ in the more disabled ~~people~~participants ~~showed greater changes~~. Further post-hoc subgroup analyses examined improvements in manual ability, stratified by baseline ABILHAND score: 'normal' was ≥ 80; 'abnormal' was < 80. As predicted clinically, greater numerical improvements were observed in participants ~~people~~ with abnormal manual ability. Formal significance testing was not undertaken for subgroup analyses.

3.5 MSWS-12 Responder Efficacy Analyses

Table ~~4~~ 5 ~~and Table S4 (Online Resource 1)~~ compares outcomes of the post-hoc PR-fampridine MSWS-12 responders with PR-fampridine non-responders and the placebo group. Here, an MSWS-12 responder was defined as an individual from the PR-fampridine group with an improvement (decrease) in MSWS-12 score of ≥ 8 points from baseline. PR-fampridine MSWS-12 responders had greater benefits than PR-fampridine MSWS-12 non-responders and the placebo group across all the efficacy outcome measures. The size of the numerical differences between the PR-fampridine MSWS-12 responder, MSWS-12 non-responder, and placebo groups varied (Table ~~4~~5). Because the MSWS-12 responder analyses were conducted in non-randomized groups, significance testing was not undertaken.

Table ~~S4~~ S3 in ~~Online Resource 1~~Supplementary Material shows the effect sizes for PR-fampridine MSWS-12 responders and non-responders. PR-fampridine MSWS-12 responders had clinically large improvements in MSWS-12 and MSIS-29 PHYS scores, and clinically small to moderate improvements in BBS and ABILHAND scores. Improvements observed in PR-fampridine MSWS-12 responders exceeded ~~notably~~ those of PR-fampridine MSWS-12 non-responders and placebo, except for TUG time. These findings indicate a ~~notable~~ clinical effect across a range of mobility and non-mobility parameters.

Table ~~S5~~ S4 in Supplementary Material~~Online Resource 1~~ shows additional post-hoc analyses of both the PR-fampridine and placebo groups based on MSWS-12 response. These results demonstrated benefits for PR-fampridine MSWS-12 responders across the main mobility outcome measures. PR-fampridine MSWS-12 responders showed higher numerical improvements across all the reported efficacy endpoints compared with other treatment groups. Significance testing was not performed on these MSWS-12 responder analyses.

3.6 Safety Results

Table ~~5~~ 6 shows that treatment-emergent AEs, serious treatment-emergent AEs, and AEs leading to treatment discontinuation were similar in the PR-fampridine and placebo groups. AEs that were more common in PR-fampridine–treated participants (difference vs. placebo ≥ 3%) by MedDRA Preferred Term were urinary tract infection (13% vs 9%) and insomnia (4% vs. <1%). ~~A greater incidence of the MedDRA Preferred Term urinary tract infections was reported for PR-fampridine than placebo; however~~Urine culture was performed in 53 participants in the PR-fampridine group and 33 in the placebo group; culture-positive urinary tract infections were reported in similar proportions of participants in each group (PR-fampridine: 8 [15%]; placebo: 4 [12%]). ~~culture-positive urinary tract infections were reported in similar proportions [15% (8/53) and 12% (4/33), respectively] when tested~~ Among participants who reported an AE within the category of urinary tract infections (PR-fampridine, n=56; placebo, n=37, see Table 6), 28 participants in the PR-fampridine group and 15 participants in the placebo group had a urine culture performed and 8 and 4 were positive, respectively. ~~(cultures were taken wherever possible to rule out infection or confirm bacterial infection).~~

~~AEs that were notably more common in PR-fampridine–treated people (difference vs. placebo ≥ 3%) by MedDRA System Organ Class were urinary tract infection and insomnia~~.

No seizures or convulsions were reported. There were four deaths. One death occurred in each treatment group during the 2-week study follow-up period and was a result of coronary artery stenosis in the PR-fampridine group and acute myocardial infarction in the placebo group~~;~~. ~~these~~ These deaths were considered unrelated to study treatment by the investigators. One death also occurred in each treatment group ≥ 20 days after the last dose of study treatment. The death in the PR-fampridine group was a result of lung cancer with liver and

brain metastasis and the death in the placebo group was a result of ovarian endometrioid carcinoma; ~~and~~ both were ~~also~~ considered unrelated to study treatment by the investigators.

Mean (SD) compliance with dosing of study drug was 98.7% (3.9%) in the PR-fampridine group and 98.4% (4.6%) in the placebo group for the ITT population (N=633). Mean compliance rates were the same as the above for each treatment group in the safety population (N=635).

4 Discussion

ENHANCE was one of the first studies to use a previously defined criterion of clinically meaningful change on a self-reported outcome as its primary endpoint. ~~The novelty of ENHANCE was that it was designed to assess the effect of pharmacotherapy on the proportion of participants achieving a criterion for clinically meaningful change in walking using a self-reported outcome measure [12].[9, 10] Here,~~Results from ENHANCE show that PR-fampridine treatment resulted in a higher proportion of participants ~~people~~ achieving clinically meaningful improvements in self-reported walking ability, clinician-measured mobility, and self-reported physical impact of MS over 24 weeks compared with placebo. These effects of PR-fampridine were statistically significant when compared with placebo. Placebo-treated participants ~~people~~ demonstrated some benefits on efficacy measures, but the magnitude of improvement was consistently greater with PR-fampridine.

Results from ENHANCE not only demonstrate that PR-fampridine has clinically meaningful effects on self-reported walking, balance, and physical functioning in comparison to placebo, but also that a self-reported outcome measure can be used as a sensitive primary endpoint in a controlled clinical trial evaluating treatment effects. Similar to previous studies [10, 13, 27, 28], benefits from PR-fampridine over placebo were apparent as early as 2 weeks after treatment initiation and were sustained over 24 weeks of treatment in ENHANCE ~~[8, 11,~~

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~~24, 25]~~. PR-fampridine's fast action supports the use of the MSWS-12, which is based on the experience of the previous 2 weeks, in this study. Of the multiple studies that have assessed the efficacy of PR-fampridine, ENHANCE was the largest, most geographically diverse trial to date, and ~~≥~~ at least 10 weeks longer than the pivotal phase III trials [6, 7]. Together, these studies provide a consistent body of evidence demonstrating that PR-fampridine is a beneficial treatment for a proportion of ~~people~~ individuals with disabling MS [10, 13, 27, 28].

ENHANCE explored PR-fampridine's effect on manual ability. Improvements in the ABILHAND were small and the treatment difference between PR-fampridine and placebo was not statistically significant. ABILHAND subgroup analyses showed greater numerical benefits for PR-fampridine than placebo in participants ~~people~~ with greater clinician-rated disability (EDSS) and worse self-reported hand function, but formal significant testing was not performed for subgroup analyses. Because deterioration of manual dexterity occurs with increasing disability [29], this could explain why more impaired participants ~~people~~ would have a greater potential to show improvements in ABILHAND scores. Pre-treatment ABILHAND score distributions were skewed towards fewer functional limitations (the scale's 'ceiling'). Therefore, the sample had less potential for measurable change in manual ability, a limitation of the ABILHAND that has been shown previously in individuals with MS [30, 31]. This suboptimal sample-to-scale targeting in less disabled participants ~~people~~ [30, 31] may have contributed to the lack of significant treatment effect in ENHANCE.

Changes in dynamic and static balance (BBS score) in the PR-fampridine and placebo groups were similar over 24 weeks and the treatment difference was not statistically significant, consistent with previous findings [10, 12]. Similar to the ABILHAND, pre-treatment BBS score distributions were skewed towards better balance (the BBS's ceiling) limiting its ability to measure change [32]. Participants ~~People~~ experiencing improved balance with PR-fampridine would have subsequently moved further towards the scale's

ceiling, where the ability to detect change is weakened and the ability to convert 'true' change in dynamic and static balance to a change in BBS score may have been reduced [30-32] ~~(see Supplementary Discussion in Online Resource 1)~~. Additional post-hoc exploration of the BBS is warranted to determine if the results were a true reflection of the impact of PR-fampridine on balance, or an erroneous effect due to limitations of the BBS in this population of walking-disabled participants~~people~~.

There was a significant difference between PR-fampridine and placebo in the analysis of mean change from baseline in TUG speed over 24 weeks, but the treatment group difference was not significant in the analysis of TUG time (Table 3). The best explanation for this discrepancy is that these were exploratory endpoints and the study was not powered to discern a treatment effect.

Results from effect size and standard response mean analyses to determine sample-to-scale targeting for the BBS and ABILHAND scores deserve additional consideration. Pre-treatment mean scores of both clinical outcome assessments were above the scale midpoint. Both distributions were skewed towards better functioning and away from the best point of measurement of the scale. Moreover, PR-fampridine seeks to improve function and move the mean score further to the right, towards the extreme of the scale range where scales are weaker at detecting change. We believe these distributional properties of the data contribute to the smaller change scores and effect sizes demonstrated for the BBS and ABILHAND, and therefore these may have been suboptimal instruments for examining the impact of PR-fampridine in this sample of walking-disabled participants.

Given the impact of balance in the context of walking, the BBS results may have been anomalous, as the effects of PR-fampridine on the BBS were small. While the limited targeting of the BBS to the ENHANCE population may have affected the findings, we believe that internal measurement problems also contributed. A Rasch measurement theory

analysis of BBS data from the PR-fampridine MOBILE study has shown important limitations [33].

The efficacy benefits of PR-fampridine were accompanied by a favorable safety profile, again consistent with other studies [28]. The incidence of positive urine cultures was slightly higher for PR-fampridine than placebo. In contrast, previous findings reported the incidence of laboratory-confirmed urinary tract infections as 2.8% (PR-fampridine) and 4.2% (placebo) [12, 34]. Because PR-fampridine is excreted in urine, bladder irritation may be confounded with bladder infection in some participants~~people~~.

The subgroup analyses of PR-fampridine MSWS-12 responders showed these participants ~~people~~ also had benefits in TUG speed, MSIS-29 PHYS score, and ABILHAND score. Again, these findings allude to MSWS-12 walking responders gaining improvements in other aspects of functioning (non-self-reported functional parameters): walking speed, physical limitations in dynamic and static balance, and manual ability. Although it must be noted that formal statistical testing of the treatment difference was not undertaken in subgroup analyses. The wide range of benefits associated with PR-fampridine is consistent with its proposed mode of action as a blocker of voltage-dependent potassium channels in demyelinated nerve fibers [35]. Results also support the clinical meaningfulness of the MSWS-12 responder definition used in ENHANCE: ≥ 8-point mean improvement [14].

The PR-fampridine MSWS-12 responder effect sizes demonstrated ~~particularly notable~~large improvements in MSWS-12 and MSIS-29 PHYS, clinically small to moderate improvements in BBS score, and small improvements in TUG time and ABILHAND score. Importantly, there is no item overlap between the MSWS-12 and MSIS-29 PHYS, indicating that these scales measure different concepts, despite a strong observed correlation (r = 0.72). Although PR-fampridine MSWS-12 responders improved by ≥ 8 points, the group mean change of > 20 points from baseline, and the associated effect sizes (Cohen's effect size, pre-

treatment SD –1.01, pooled SD –1.94; standardized response mean –1.68) represents striking numerical and clinical improvements. It should be noted that the thresholds used to identify clinically meaningful improvement on the MSWS-12 and TUG speed were based on changes at the level of the individual participant and were not meant to evaluate clinically meaningful change or treatment differences at the group level. The thresholds and criteria for a clinically important change in an assessment identified at the individual level may not be applicable at the group level [36].

The pathophysiological explanation for why only some ~~people~~ individuals with MS respond to PR-fampridine remains unclear. Therefore, it is not yet possible to predict responders a priori, and clinicians need a clinically practical and meaningful responder definition [37]. There is no consensus, and different studies have used different criteria. More labor-intensive definitions are less clinically feasible. For example, the consistent T25FW responder definition of the pivotal phase III studies (faster walking speed for at least three of four treatment visits than the maximum speed of five off-treatment visits) [6, 7] cannot be incorporated easily into clinical practice, despite its scientific advantages.

One possible limitation of this study was that it did not include a conventional objective walking test, such as the T25FW. The T25FW or other longer objective walking test was not included in an effort to limit participant assessment burden and to obtain good quality data on the expanded range of outcome measures in line with patients' reports. The effect of PR-fampridine on T25FW speed already had been demonstrated [6, 7]. While one of the benefits of PR-fampridine is a rapid onset of effects, the converse also is true: when treatment stops the effects of PR-fampridine are lost. This means that patients must be watchful when they discontinue PR-fampridine as their functioning can worsen soon after discontinuation. In addition, this concept provides a mechanism for evaluating ongoing drug benefit in those people who have progressive disease and are therefore, by definition, likely

to worsen over time and in whom it may be difficult to determine whether PR-fampridine is still working. A carefully controlled trial of discontinued treatment – or short drug holiday – can help to determine if PR-fampridine is still beneficial.

ENHANCE was designed with a self-reported primary outcome and thus was planned as large study to overcome the high spontaneous variability associated with subjective measures. The high placebo response observed in this study may be a natural consequence of this variability. Self-reported measures provide unique information on how ~~people~~ individuals feel and function, but there are trade-offs, including problems of stability and interpretability. The broad response categories are open to individual interpretation, based on internal frames of reference that may be influenced by circumstance and mood, and participation in clinical trials is known to be associated with a great deal of expectation [38], with the potential to have greater influence on subjective than objective measures. Learning effects [39, 40] or fatigue [22] may partly explain why mean scores do not return to baseline in the off-treatment period. This study highlights the importance of double-blind, randomized, placebo-controlled clinical trials when self-reported outcomes are the primary endpoints.

5 Conclusions

Results from ENHANCE demonstrate that PR-fampridine was associated with a greater likelihood of walking-impaired participants ~~people~~ with MS experiencing clinically meaningful improvements in self-reported walking ability over 24 weeks vs. placebo. The benefits of PR-fampridine also included improvements in objectively measured mobility and self-reported physical functioning. PR-fampridine has demonstrated clinically meaningful improvements across a range of study types and designs, and in clinical outcome measures that include the MSWS-12, TUG, MSIS-29 PHYS and psychological impact subscales,

T25FW, and 36-Item Short-Form Health Survey physical component summary [6, 7, 9, 10]. Overall, findings from ENHANCE confirm that a self-reported outcome can be used effectively as a primary endpoint in a pharmacotherapy study and provides further evidence demonstrating the favorable risk-benefit profile of PR-fampridine~~, .established through placebo-controlled and real-world studies [5, 6, 24]~~.

Compliance with Ethical Standards

Funding This study was funded by Biogen. Biogen provided funding for medical writing support in the development of this paper; Malcolm Darkes and Juliet Bell from Excel Scientific Solutions wrote the first draft of the manuscript based on input from authors, and Kristen DeYoung of Excel Scientific Solutions copyedited and styled the manuscript per journal requirements. Biogen reviewed and provided feedback on the paper to the authors. The authors had full editorial control of the paper, and provided their final approval of all content. The open access fee was paid by Biogen.

Conflict of interest Jeremy Hobart has received consulting/advisor fees, grants, honoraria, support for clinical service delivery, or research support from Acorda, Biogen, Brickell Biotech, GBT, Merck Serono, MS Society of Great Britain and Northern Ireland, Novartis, Roche, Tigercat, and Vantia; Jeremy Hobart's hospital received a grant from Biogen to assist in the development of clinical service for people with MS and the University received a grant to conduct data analysis, and he received honoraria for attending PR-fampridine advisory boards and payment from Biogen for lectures on MS and PR-fampridine. Tjalf Ziemssen has received grants and personal fees from Bayer, Biogen, Genzyme, Novartis, and Teva; and personal fees from Almirall, GlaxoSmithKline, Merck, and Roche. Peter Feys has received advisory board fees from Biogen; speaker fees from Excemed and Paradigms; and fees for providing educational materials from Neurocompass. Michael Linnebank has received grants to fund a distinct study on PR-fampridine from Biogen, and support for travel and fees payed to his Department for attendance at a PR-fampridine steering board. Andrew D. Goodman has received personal fees from AbbVie, Acorda, Adamas, Atara, Avanir, Bayer, Biogen, Celgene, EMD Serono, Novartis, Roche, Sanofi-Genzyme, Sun, and Teva. His institution (University of Rochester) has received research support for conducting clinical trials from Acorda, Biogen, EMD Serono, Novartis, Ono, Roche, Sanofi-Genzyme, and Teva. Rachel

Farrell has received advisory fees from Biogen; consulting and principal investigator fees from Canbex; and speaker fees from Allergan PLC, GW Pharma, Merck, and Teva. Raymond Hupperts has received grants and honoraria for advisory boards from Biogen, Merck, and Sanofi-Genzyme. Andrew R. Blight was an employee of and holds stock/stock options in Acorda. Veronica Englishby, Manjit McNeill, Ih Chang, and Jacob Elkins are employees of and hold stock/stock options in Biogen. Gabriel Lima was an employee of Biogen at the time the study was conducted and the manuscript drafted; holds stock/stock options in Biogen; current employee of Amgen.

Ethical approval The study was conducted according to the US Code of Federal Regulations Parts 50, 54, 56, and 312 Subpart D; the International Conference on Harmonisation guidelines on Good Clinical Practices (E6); the European Union Clinical Trial Directive 2001/20/EC; the principles of the Declaration of Helsinki; and, where applicable, the European Directives 2001/20 and 2005/28 in relation to conduct of clinical trials and investigational medicinal products. The trial was registered with ClinicalTrials.gov (NCT02219932).

Informed consent Written informed consent was obtained from each individual before study participation.

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Table 1 Questionnaires and clinical tools used to assess walking ability[a]

Instrument	Number of items/ tasks	Score range[b]	Established clinically important change	Threshold used in ENHANCE	Description	Completion dates
MSWS-12	12	100–0	Reduction from baseline score of 6.9 (group comparison) or 8.0 (individual-level comparison) points [14]	Mean 8-point reduction from baseline over 24 weeks	A reliable and accepted self-reported disease-specific measure of mobility limitations owing to MS during the preceding 2 weeks. The 12 questions ask about different aspects of walking: ability and speed of walk; ability to run; ability to climb and descend stairs; balance and smoothness of gait; and support, effort, and concentration required. Participants rate limitations of their mobility due to MS on a Likert 5-point scale (from 1 = not at all to 5 = extremely). Total score ranges from 1–60 and is transformed to a scale of 0–100. A higher MSWS-12 score represents poorer walking ability [10, 14, 16]	Screening, day 1 (before randomization), at weeks 2, 4, 8, 12, 16, 20, and 24 (end of treatment), and 26 (follow-up), or at early termination
TUG speed	1	Continuous	≥15% mean improvement in TUG speed (see Section 2.3).	Mean 15% increase in TUG speed	Objective measure of dynamic balance and mobility [19], which has demonstrated high reliability in individuals with MS; not recommended to predict falls. TUG measures the speed of individuals to move from a seated position to stand up, walk 3 meters, turn, walk 3 meters [21]. In ENHANCE, TUG (ft/s) was performed at the same time (± 3 h) and with the same footwear and	Screening, day 1 (before randomization), at weeks 2, 4, 8, 12, 16, 20, and 24 (end of treatment), and 26 (follow-up)

					walking aids (if required) during each visit to avoid variation. Further research on thresholds of clinically important change for TUG speed is required [23]	
MSIS-29					Psychometrically designed and self-reported disease-specific measure of the impact of MS on physical and psychological health. The MSIS-29 PHYS score is calculated by summing the 20 items and transforming the score to a scale of 0 (no impact of MS) to 100 (extreme impact of MS) [41]	Screening, day 1 (before randomization), at weeks 2, 4, 8, 12, 16, 20, and 24 (end of treatment)
PHYS	20	100–0	≥ 7.5 to 8.0 [17, 42]			
PSYCH	9					
BBS	14	0–56	Falls were frequent with scores > 45[d]		Objective measure of static and dynamic balance, which has demonstrated validity and high test-retest reliability in individuals with MS but possible ceiling effects and variability, with good specificity but low sensitivity. Each task is scored from 0 (unable to perform) to 4 (able to perform independently). A higher BBS score represents better balance; recommended to predict multiple falls once a fall has occurred [20, 21, 43-46]	Screening, day 1 (before randomization), at weeks 2, 12, and 24 (end of treatment)
ABILHAND	56	0–100	TBC for individuals with MS. 0.47–1.89 logits in patients with rheumatoid arthritis [47],		Self-reported measure of manual ability to manage daily activities among chronic stroke patients. Participants estimate the ease or difficulty of performing each upper limb activity using a three-level response scale: impossible (0), difficult (1), and easy (2). A higher ABILHAND	Day 1 (before randomization), at weeks 2, 8, and 20

			and 0.26–0.35 logits in patients with stroke [48]		score represents better manual ability [48, 49]	

MSIS Multiple Sclerosis Impact Scale, MSWS-12 12-item Multiple Sclerosis Walking Scale, MS multiple sclerosis, PHYS Physical Impact subscale, PR prolonged-release, PSYCH, Psychological Impact Subscale, TBC to be confirmed, TUG Timed Up and GO.

[a]When multiple assessments were scheduled at a given visit, they were performed in the following order: MSWS-12, TUG, BBS, MSIS-29, and ABILHAND (followed by any other assessments).

[b]Score ranges are provided as worst score – optimal functioning score.

[c]Not included as a secondary endpoint.

[d]Among older individuals dependent in activities of daily living and living in residential care facilities.

Table ~~1~~ 2 Baseline characteristics of the modified intention-to-treat sample[a]

Characteristic	PR-fampridine (*n* = 315)	Placebo (*n* = 318)
Demographic characteristics		
Age, years	49.0 (9.8)	48.8 (10.5)
Female, *n* (%)	186 (59)	180 (57)
Body mass index, kg/m^2	25.6 (4.8)	25.1 (4.4)
Clinical characteristics		
Disease course, *n* (%)		
Relapsing-remitting	169 (54)	155 (49)
Secondary progressive	95 (30)	99 (31)
Primary progressive	41 (13)	45 (14)
Progressive-relapsing	10 (3)	19 (6)
Median time since diagnosis, years	10.0	10.0
Median time since most recent relapse, years	1.6	1.7
Prior 4-aminopyridine use, *n* (%)	31 (10)	24 (8)
Distance walked, m [*n* (%)][b]		
0	77 (25)	85 (28)
> 0 to < 100	56 (18)	44 (15)
≥ 100 to < 300	81 (27)	82 (27)
≥ 300	90 (30)	91 (30)
MS-related motor symptoms, *n* (%)		
Coordination/balance problems[c]	294 (95)	300 (95)
Fatigue[d]	195 (63)	211 (67)

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Spasticity[d]	276 (88)	265 (84)
Weakness[d]	274 (88)	281 (89)
Clinician-tested outcomes		
EDSS score	5.49 (0.92)	5.48 (0.91)
Median (range)	6.0 (4.0–7.0)	5.5 (4.0–7.0)
EDSS score ≤ 6.0, *n* (%)	246 (78)	246 (77)
EDSS score 6.5 and 7.0, *n* (%)	69 (22)	72 (23)
TUG speed, ft/s	0.38 (0.19)	0.38 (0.20)
Range	0.0–1.0	0.0–1.2
TUG time, s	24.9 (26.6)	27.1 (42.0)
Range	6.3–239.8	0–436.8
BBS score	40.6 (11.6)	40.2 (11.8)
Range	6.0–56.0	4.0–56.0
Self-reported outcomes		
MSWS-12 score	63.6 (21.7)	65.4 (21.9)
Range	0–100	0–100
MSIS-29 PHYS score	52.4 (21.1)	55.3 (21.0)
Range	0.0–98.3	3.3–95.8
ABILHAND score	86.9 (15.8)	84.3 (16.5)
Range	0.9–100.0	26.0–100.0

Data are mean (standard deviation) unless otherwise specified.

BBS Berg Balance Scale, *EDSS* Expanded Disability Status Scale, *MS* multiple sclerosis, *MSIS-29* Multiple Sclerosis Impact Scale, *MSWS-12* 12-item Multiple Sclerosis Walking Scale, *PHYS* physical impact subscale, *PR* prolonged-release, *TUG* Timed Up and Go.

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[a]For most participants, race and ethnicity were not reported because of confidentiality regulations.

[b]Number of participants assessed: PR-fampridine, *n* = 305; placebo, *n* = 302).

[c]Number of participants assessed: PR-fampridine, *n* = 311; placebo, *n* = 316).

[d]Number of participants assessed: PR-fampridine, *n* = 312; placebo, *n* = 315).

Table ~~2~~ 3 Clinical efficacy results in the modified intention-to-treat sample

Endpoint[a]	PR-fampridine (*n* = 315)	Placebo (*n* = 318)	*p* value vs. placebo
Clinically meaningful improvement (≥ 8 points) in MSWS-12 score from baseline over 24 weeks (primary endpoint)			
Participants~~People~~ with improvement, *n* (%)[b,c]	136 (43.2)	107 (33.6)	0.006[d]
Odds ratio vs. placebo (95% CI)[d]	1.61 (1.15 to 2.26)	NA	
Risk difference for adjusted proportions (95% CI)[d]	0.104 (0.030 to 0.178)		
Relative risk (95% CI)[d]	1.38 (1.06 to 1.70)		
MSWS-12 score change from baseline over 24 weeks			
LSM change over 24 weeks (95% CI)[e]	–6.73 (–8.80 to –4.67)	–2.59 (–4.71 to –0.47)	
LSM difference vs. placebo (95% CI)[e]	–4.14 (–6.22 to –2.06)	NA	< 0.001
Clinically meaningful mean improvement (≥ 15%) in TUG speed from baseline over 24 weeks (secondary endpoint: rank group 1)			
Participants ~~People~~ with improvement, *n* (%)[c]	137 (43.5)	110 (34.3)	0.03[d]
Odds ratio vs. placebo (95% CI)[d]	1.46 (1.04 to 2.07)	NA	
Risk difference for adjusted proportions (95% CI)[d]	0.092 (0.009 to 0.175)		

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Relative risk (95% CI)[d]	1.25 (0.99 to 1.51)		
TUG speed change from baseline over 24 weeks, ft/s			
LSM change from baseline (95% CI)[e]	0.05 (0.04 to 0.06)	0.03 (0.02 to 0.04)	
LSM difference from baseline vs. placebo (95% CI)[e]	0.02 (0.01 to 0.03)		< 0.001
TUG time change from baseline over 24 weeks, s			
LSM change from baseline (95% CI)[e]	−3.30 (−4.78 to −1.83)	−1.94 (−3.46 to −0.41)	
LSM difference from baseline vs. placebo (95% CI)[e]	−1.36 (−2.85 to 0.12)		0.073
MSIS-29 PHYS score change from baseline over 24 weeks (secondary endpoint: rank group 1)			
LSM change from baseline (95% CI)[e]	–8.00 (–9.78 to –6.21)	–4.68 (–6.52 to –2.85)	
LSM difference from baseline vs. placebo (95% CI)[e]	–3.31 (–5.13 to –1.50)	NA	< 0.001
BBS score change from baseline over 24 weeks (secondary endpoint: rank group 2)			
LSM change from baseline (95% CI)[e]	1.75 (1.20 to 2.29)	1.34 (0.78 to 1.89)	

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LSM difference from baseline vs. placebo (95% CI)[e]	0.41 (−0.13 to 0.95)		0.141
ABILHAND score change from baseline over 24 weeks (secondary endpoint: rank group 2)			
Participants~~People~~, *n*	312	315	
LSM change from baseline (95% CI)[e]	1.49 (0.36 to 2.61)	0.75 (−0.41 to 1.91)	
LSM difference from baseline vs. placebo (95% CI)[e]	0.74 (−0.38 to 1.86)	NA	0.197

~~Based on 633 people in the modified intention-to-treat sample, the following level of post-baseline data were missing and were imputed for efficacy outcomes: MSWS-12 score: 12% (PR-fampridine, 10%; placebo, 14%); TUG speed: 9% (PR-fampridine, 7%; placebo, 12%); MSIS-29 PHYS score: 9% (PR-fampridine, 7%; placebo, 11%); BBS score: 9% (PR-fampridine, 8%; placebo, 11%); ABILHAND score: 9% (PR-fampridine, 8%; placebo, 11%).~~

BBS Berg Balance Scale, *CI* confidence interval, *LSM* least squares mean. *MSIS-29* Multiple Sclerosis Impact Scale, *MSWS-12* 12-item Multiple Sclerosis Walking Scale, *NA* not applicable, *PHYS* physical impact subscale, *PR* prolonged-release, *TUG* Timed Up and Go.

[a]A complete definition of endpoints is provided in Table ~~S2~~ 1~~in Online Resource 1~~.

[b]Based on seven on-treatment assessments per participant in the modified intention-to-treat sample. The level of missing post-baseline MSWS-12 data was generally similar between treatment groups except for missing data due to discontinuations (PR-fampridine, 5%; placebo, 9%).

[c]Percentage based on binomial proportions.

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[d]Calculated using an adjusted logistic regression model (missing data imputed using multiple imputation).

[e]Based on a mixed-effects model for repeated measures using a common variance/covariance matrix structure.

Table ~~3~~ 4 Subgroup analysis of ABILHAND outcomes with respect to EDSS score and ABILHAND function at baseline

Endpoint[a]	PR-fampridine (*n* = 315)	Placebo (*n* = 318)
ABILHAND score stratified by baseline EDSS score		
EDSS score ≤ 6.0		
Participants~~People~~, *n*	244	244
Mean (SD) on treatment	89.98 (12.96)	88.17 (14.09)
Range	25.5–100.0	30.7–100.0
LSM change from baseline over 24 weeks[b]	1.32	1.22
LSM difference from baseline vs. placebo (95% CI)[b]	0.10 (–1.04 to 1.24)	NA
EDSS score 6.5 and 7.0		
Participants~~People~~, *n*	68	71
Mean (SD) on treatment	83.84 (15.90)	78.30 (17.53)
Range	43.2–100.0	36.2–100.0
LSM change from baseline over 24 weeks[b]	2.10	–0.95
LSM difference from baseline vs. placebo (95% CI)[b]	3.05 (–0.09 to 6.19)	NA
ABILHAND score stratified by normal and abnormal ABILHAND scores at baseline		
Normal (≥ 80) ABILHAND score at baseline		
Participants~~People~~, *n*	234	210
Mean (SD) on treatment	94.56 (6.65)	93.76 (8.23)

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Range	72.5–100.0	45.6–100.0
LSM change from baseline over 24 weeks[b]	–0.44	–1.04
LSM difference from baseline vs. placebo (95% CI)[b]	0.61 (–0.37 to 1.58)	NA
Abnormal (< 80) ABILHAND score at baseline		
Participants~~People~~, *n*	78	105
Mean (SD) on treatment	70.89 (14.72)	70.32 (14.71)
Range	25.5–95.2	30.3–96.4
LSM change from baseline over 24 weeks[b]	5.62	4.81
LSM difference from baseline vs. placebo (95% CI)[b]	0.81 (–2.53 to 4.15)	NA

CI confidence interval, *EDSS* Expanded Disability Status Scale, *LSM* least squares mean, *NA* not applicable, *PR* prolonged-release, *SD* standard deviation.

[a]A positive change in ABILHAND score indicates improvement in manual ability; a complete definition of endpoints is provided in Table ~~S2~~ 1~~in Online Resource 1.~~

[b]Based on a mixed-effect model for repeated measures using a common variance/covariance matrix structure.

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Table 4–5 Mobility outcome measures, with stratification of the PR-fampridine group by MSWS-12 response (≥ 8-point mean improvement)

Endpoint[a]	PR-fampridine responders (*n* = 136)	PR-fampridine non-responders (*n* = 179)	Placebo (*n* = 318)
MSWS-12 score change from baseline[b]			
LSM (SE) change from baseline over 24 weeks	–20.58 (1.18)	2.17 (1.01)	–3.64 (0.91)
LSM difference vs. placebo (95% CI)	–16.94 (–19.21 to –14.68)	5.81 (3.75 to 7.88)	
LSM difference vs. non-responders (95% CI)	–22.76 (–25.25 to –20.26)		
Clinically meaningful improvement (≥ 15%) in TUG speed			
Participants ~~People~~ with improvement, %[c]	52.4	36.6	34.7
Odds ratio vs. placebo (95% CI)[d]	2.28 (1.47 to 3.53)	1.04 (0.69 to 1.57)	
Odds ratio vs. non-responders (95% CI)[d]	2.20 (1.35 to 3.58)		
TUG percentage speed change from baseline[b]			
LSM (SE) change from baseline over 24 weeks	23.83 (2.39)	10.80 (2.09)	12.29 (1.90)
LSM difference vs. placebo (95% CI)	11.54 (6.92 to 16.17)	–1.49 (–5.84 to 2.87)	

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LSM difference vs. non-responders (95% CI)	13.03 (7.91 to 18.15)		
MSIS-29 PHYS score[b]			
LSM (SE) change from baseline over 24 weeks	–17.43 (1.102)	–1.90 (0.95)	–5.31 (0.85)
LSM difference from baseline vs. placebo (95% CI)	–12.12 (–14.22 to –10.01)	3.41 (1.46 to 5.35)	
LSM difference from baseline vs. non-responders (95% CI)	–15.52 (–17.88 to –13.17)		
BBS score[b]			
LSM (SE) change from baseline over 24 weeks	2.57 (0.36)	1.21 (0.32)	1.39 (0.28)
LSM difference from baseline vs. placebo (95% CI)	1.18 (0.49 to 1.87)	–0.18 (–0.82 to 0.45)	
LSM difference from baseline vs. non-responders (95% CI)	1.36 (0.59 to 2.13)		
ABILHAND score[b]	*n* = 133		*n* = 315
LSM (SE) change from baseline over 24 weeks	3.33 (0.76)	0.34 (0.65)	0.89 (0.59)
LSM difference from baseline vs. placebo (95% CI)	2.44 (1.01 to 3.87)	–0.54 (–1.86 to 0.77)	
LSM difference from baseline vs. non-responders (95% CI)	2.98 (1.39 to 4.58)		

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BBS Berg Balance Scale, *CI* confidence interval, *LSM* least squares mean, *MSIS-29* Multiple Sclerosis Impact Scale, *MSWS-12* 12-item Multiple Sclerosis Walking Scale, *PHYS* physical impact subscale, *PR* prolonged-release, *SE* standard error, *TUG* Timed Up and Go.

[a]A complete definition of endpoints is provided in Table ~~S2~~ 1~~in Online Resource 1~~.

[b]LSM, LSM difference, and 95% CI calculated using an adjusted analysis of covariance model (missing data imputed using multiple imputation).

[c]Estimated proportion based on binomial proportions.

[d]Odds ratio and 95% CI calculated using an adjusted logistic regression model (missing data imputed using multiple imputation).

Table ~~5~~ 6 AEs in the safety sample

AE, *n* (%)	**PR-fampridine (*n* = 316)**	**Placebo (*n* = 319)**
Any AE	**207 (66)**	**190 (60)**
Any severe AE	**9 (3)**	**8 (3)**
Any treatment-related AE[a]	**56 (18)**	**43 (13)**
Serious AE	**25 (8)**	**21 (7)**
Serious AE in > 1 participant~~person~~ by MedDRA PT		
MS relapse	14 (4)	10 (3)
Urinary tract infection	2 (< 1)	1 (< 1)
Fall	2 (< 1)	2 (< 1)
Any treatment-related serious AE[a]	**0**	**1 (< 1)**
AE leading to dose interruption	**19 (6)**	**11 (3)**
AE leading to treatment discontinuation	**21 (7)**	**23 (7)**
AE leading to study withdrawal	**22 (7)**	**24 (8)**
Death[b]	**1 (< 1)**	**1 (< 1)**
Most common treatment-emergent AE by MedDRA SOC (≥ 5% in any treatment group)[c]		
Infections and infestations	97 (31)	88 (28)
Nervous system disorders	86 (27)	68 (21)

Musculoskeletal and connective tissue disorders	56 (18)	43 (13)
General disorders and administration site conditions	31 (10)	33 (10)
Injury, poisoning, and procedural complications	36 (11)	29 (9)
Gastrointestinal disorders	43 (14)	27 (8)
Investigations	25 (8)	17 (5)
Psychiatric disorders	23 (7)	11 (3)
Skin and subcutaneous tissue disorders	23 (7)	13 (4)
Renal and urinary disorders	18 (6)	7 (2)
Most common treatment-emergent AEs by MedDRA PT (≥ 5% in any treatment group)[c]		
Urinary tract infection	41 (13)	30 (9)
MS relapse	34 (11)	33 (10)
Fall	24 (8)	19 (6)
Back pain	16 (5)	11 (3)
Headache	15 (5)	15 (5)
Nasopharyngitis	15 (5)	18 (6)
Upper respiratory tract infection	15 (5)	10 (3)
Treatment-emergent AEs of special interest by MedDRA ~~SOC and~~ PT (≥ 1% in any treatment group)[c]		
Urinary tract infections	56 (18)	37 (12)

Urinary tract infection	41 (13)	30 (9)
Cystitis	4 (1)	2 (< 1)
Micturition urgency	4 (1)	0
Cardiovascular disorders	6 (2)	2 (< 1)
Palpitations	4 (1)	1 (< 1)
Serious hypersensitivity	8 (3)	4 (1)
Rash	8 (3)	4 (1)

AE adverse event, *MedDRA* Medical Dictionary of Regulatory Activities, *MS* multiple sclerosis, *PR* prolonged-release, *PT* Preferred Term, *SOC* System Organ Class.

[a]Investigators assessed whether the AE was related to study drug.

[b]Both deaths were considered unrelated to study treatment (coronary artery stenosis and acute myocardial infarction), and occurred after the participant ~~person~~ had completed study treatment but before completing the 2-week post-treatment follow-up.

[c]Listed in descending order of frequency for the PR-fampridine group. Treatment-emergent AEs were defined as AEs that started on or after the first dose of study drug, or pre-existing conditions that worsened in severity after the first dose of study drug; a participant was only counted once within each PT. A serious AE was any untoward medical occurrence that resulted in death/risk of death, hospitalization/prolonged hospitalization, persistent or significant disability/incapacity, or resulted in a congenital anomaly/birth defect. Severe AEs were defined as symptoms causing severe discomfort, incapacitation, or significant impact on daily life.

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Figure legends

Fig. 1 Participant disposition. *AE* adverse event, *BID* twice daily, *PR* prolonged-release.

Fig. 2 Estimated proportion of study participants who met each threshold of mean MSWS-12 score change over 24 weeks in the modified intention-to-treat sample. The MSWS-12 was transformed to a 0–100 scale; higher score = greater walking limitation. Negative change indicates improvement. Estimated percentages were based on binomial proportions. Multiple imputation was used for missing post-baseline data. Nominal *p* values for PR-fampridine vs. placebo are from a logistic regression model adjusted for covariates (see Methods). *MSWS-12* 12-item Multiple Sclerosis Walking Scale, *PR* prolonged-release.

Fig. 3 LSM changes in MSWS-12 score over 24 weeks in the modified intention-to-treat sample. Negative change indicates improvement. Multiple imputation was used for missing post-baseline data except for during follow-up where observed data were used. Error bars indicate SE. *DB* double blind, *LSM* least squares mean, *MSWS-12* 12-item Multiple Sclerosis Walking Scale, *PR* prolonged-release, *SE* standard error.

Fig. 4 LSM percentage change in TUG speed over 24 weeks in the modified intention-to-treat sample. TUG speed is given in ft/s. Positive change indicates improvement. Multiple imputation was used for missing post-baseline data except for during follow-up where observed data were used. Error bars indicate SE. *DB* double blind, *LSM* least squares mean, *PR* prolonged-release, *SE* standard error, *TUG* Timed Up and Go.

Fig 1

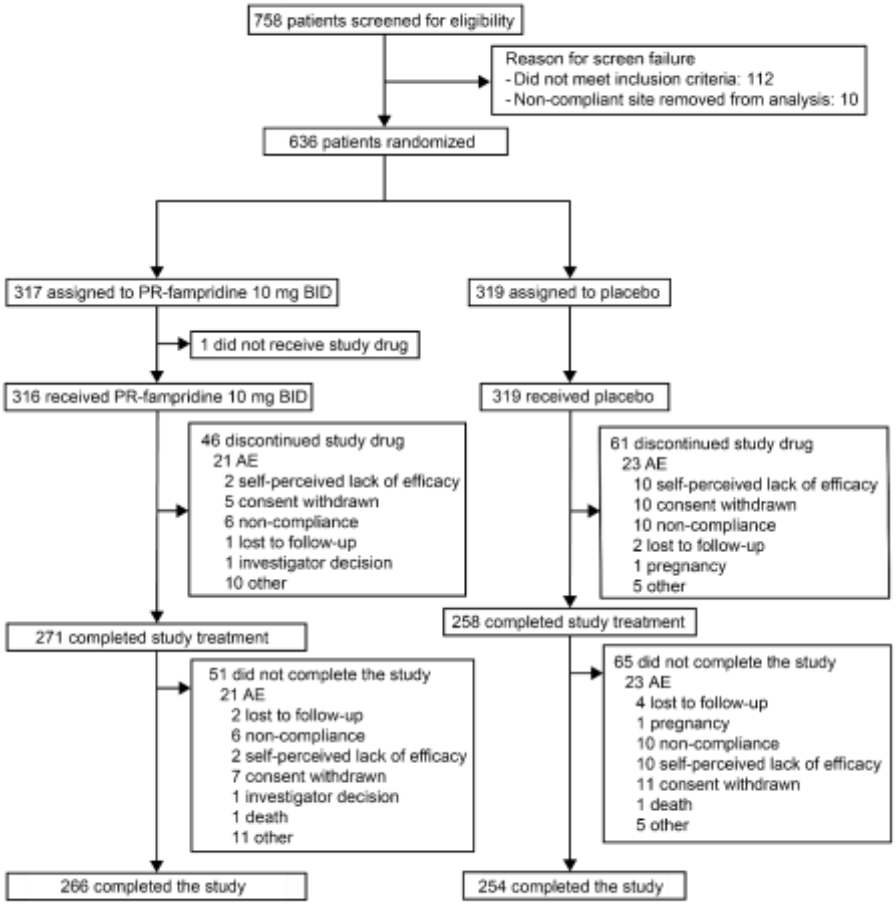

758 patients screened for eligibility
Reason for screen failure
- Did not meet inclusion criteria: 112
- Non-compliant site removed from analysis: 10
636 patients randomized
317 assigned to PR-fampridine 10 mg BID
319 assigned to placebo
1 did not receive study drug
316 received PR-fampridine 10 mg BID
319 received placebo
46 discontinued study drug
21 AE
2 self-perceived lack of efficacy
5 consent withdrawn
6 non-compliance
1 lost to follow-up
1 investigator decision
10 other
61 discontinued study drug
23 AE
10 self-perceived lack of efficacy
10 consent withdrawn
10 non-compliance
2 lost to follow-up
1 pregnancy
5 other
271 completed study treatment
258 completed study treatment
51 did not complete the study
21 AE
2 lost to follow-up
6 non-compliance
2 self-perceived lack of efficacy
7 consent withdrawn
1 investigator decision
1 death
11 other
65 did not complete the study
23 AE
4 lost to follow-up
1 pregnancy
10 non-compliance
10 self-perceived lack of efficacy
11 consent withdrawn
1 death
5 other
266 completed the study
254 completed the study

Fig 2.

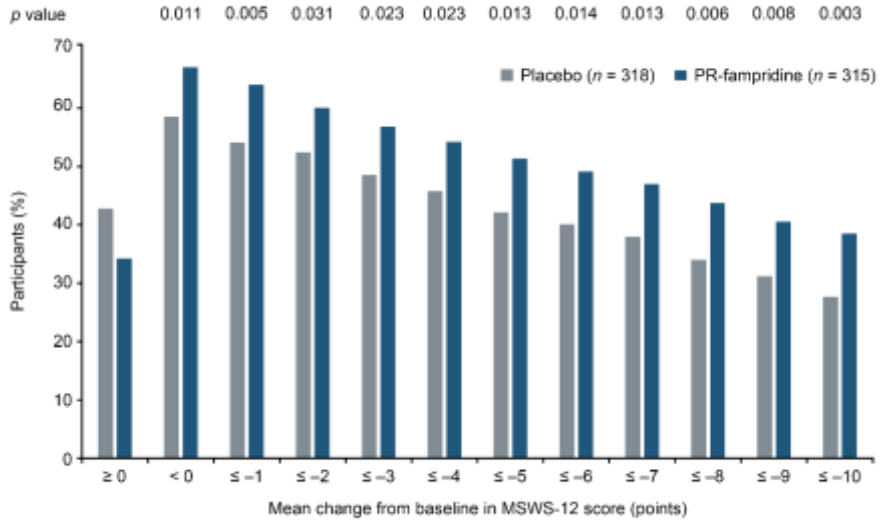
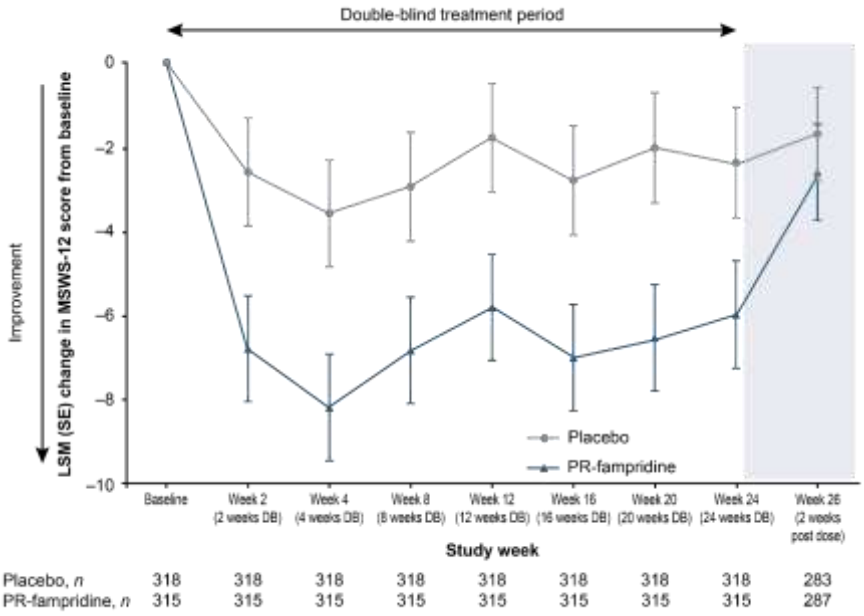
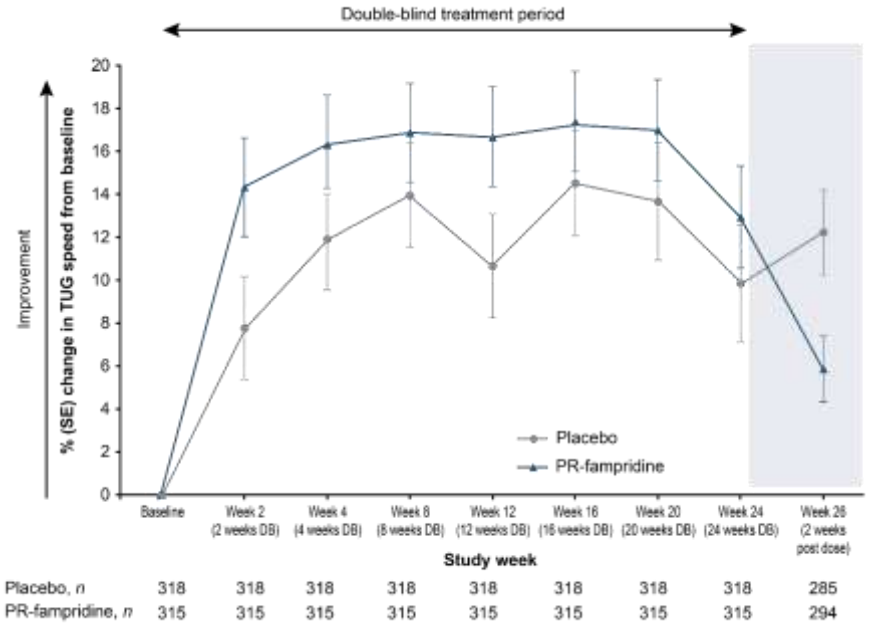

p value
0.011
0.005
0.031
0.023
0.023
0.013
0.014
0.013
0.006
0.008
0.003
Placebo (n = 318)
PR-fampridine (n = 315)
Participants (%)
70
60
50
40
30
20
10
0
≥ 0
< 0
≤ –1
≤ –2
≤ –3
≤ –4
≤ –5
≤ –6
≤ –7
≤ –8
≤ –9
≤ –10
Mean change from baseline in MSWS-12 score (points)

Fig 3.



Placebo, *n*	318	318	318	318	318	318	318	318	283
PR-fampridine, *n*	315	315	315	315	315	315	315	315	287

Fig 4.



Placebo, *n*	318	318	318	318	318	318	318	318	285
PR-fampridine, *n*	315	315	315	315	315	315	315	315	294