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Combined walking outcome measures identify clinically meaningful response to prolonged-release fampridine

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Abstract

Background: Gait impairment is common in multiple sclerosis (MS) and negatively impacts patients' health-related quality of life (HRQoL). Prolonged-release fampridine (PR-fam) improves walking speed, but it is unclear which walking measures are the most suitable for identifying treatment response. Our aim was to assess the effect of PR-fam and the outcome measures that best identify short- and long-term clinically meaningful response.

Methods: We conducted a prospective study in 32 MS patients treated with PR-fam for a year. The assessments at 2 weeks, 3, 6 and 12 months included: timed 25-foot walk (T25FW), 6-minute walk test (6MWT), MS Walking Scale-12 (MSWS-12), a five-level version of the EuroQoL-5 dimensions, and accelerometry. PR-fam response was defined as an improvement in T25FW $\geqslant$20%.

Results: Twenty-five (78%) patients were considered responders after 2 weeks of PR-fam and improved significantly in all measures. Responders to T25FW and MSWS-12 ($n = 19$) showed a significant improvement in HRQoL and accelerometer data compared with responders only to T25FW ($n = 6$). At 1 year, 15/20 (75%) patients remained responders, but only those with permanent response to T25FW and MSWS-12 ($n = 8$; 53%) showed a significant improvement in 6MWT and HRQoL.

Conclusion: The combination of T25FW and MSWS-12 identify better those patients with a clinically significant benefit of PR-fam.

Keywords: accelerometer, minimal clinical difference, multiple sclerosis, patient-reported outcome, PR-fampridine, quality of life

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Introduction

Gait impairment is a frequent manifestation along the course of multiple sclerosis (MS) and has a negative impact on patients' health-related quality of life (HRQoL).[1,2] Prolonged-release fampridine (PR-fam) (Fampyra®; Biogen Idec, Maidenhead, Berkshire, UK) is a voltage-dependent potassium channel blocker that improves conduction in demyelinated nerves.[3] In two phase III double-blind clinical trials (MS-F203 and MS-F204) PR-fam improved the timed 25-foot walk (T25FW) walking speed and this change was associated with patient-rated walking perception.[4,5] Previous reports support an increase of $\geqslant$20% of T25FW as a minimal clinically important difference (MCID),[6–8] but it is unclear if this outcome best identifies short- and long-term clinically meaningful response to PR-fam in the setting of real clinical practice. Moreover, extension studies from clinical trials suggested that longer walking tests might be more relevant for assessing the clinical benefit of PR-fam.[9,10] Free-living accelerometry, especially three-dimensional accelerometers, provides information about walking behavior in the real environment, and daily walking activity (DWA) correlates with disability measures.[11,12] Hence, DWA could be a suitable outcome measure for pharmacological and rehabilitation intervention. Although multiple

outcomes exist for measuring walking in MS,[13] there is no consensus on which tests are more suitable for identifying those patients who actually benefit from therapy.

To address the question of which assessment best identifies patients benefiting from PR-fam, in this study, we aimed to (a) assess the effect of PR-fam using different walking tests and functional measures, and (b) determine the outcome measures that best identify short- and long-term clinically meaningful response to PR-fam.

Methods

Patients

We conducted this prospective study by including all consecutive MS patients with walking impairment followed at the MS unit of the Hospital Clinic of Barcelona that met the approved criteria to be treated with PR-fam:[3] (a) clinically definite MS according to the 2010 McDonald criteria;[14] (b) Expanded Disability Status Scale (EDSS) score between 4.0 and 7.0;[15] (c) no relapses within 60 days; and (d) adequate renal function and no previous history of seizures or cardiac arrhythmia. Patients meeting these criteria were invited to participate in the study. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the protocol approved by the Ethical Committee of the Hospital Clinic of Barcelona (HCB/2015/0045). All subjects had voluntarily given written informed consent prior to their participation.

Study design

Patients were assessed according to the approval of the European Medicines Agency that includes the evaluation of PR-fam response 15 days after treatment initiation.[16] An extra visit was performed one week before to PR-fam initiation to confirm that patients met the inclusion criteria and to register DWA measured through a commercial accelerometer (Actigraph GT3X from Actigraph LLC, Pensacola-FL (USA)) in basal conditions. All clinical visits were performed at the same time of day to minimize variability and the possible effect of other symptoms such as fatigue. PR-fam response was defined as $\geq$20% improvement of T25FW speed after 2 weeks of PR-fam treatment.[6] PR-fam responder patients continued treatment if they agreed and were further assessed at 3 and 6 months, and 1 year. Patients who did not meet the defined response criteria stopped the treatment and were reevaluated at 1 year.

Measures and procedures

Disability was evaluated by scores on the EDSS[15] and the Multiple Sclerosis Functional Composite (MSFC).[17] Three walking measures were obtained: the T25FW test, the 6-min walk test (6MWT),[18] and the 12-item MS Walking Scale (MSWS-12) questionnaire.[19] Two functional measures were also evaluated: the International Physical Activity Questionnaire (IPAQ),[20] and DWA assessed by a portable triaxial accelerometer (Actigraph GT3X, steps/day) for 7 days during waking hours (excluding bathing or swimming) doing their usual routine.[21] Accelerometer data (steps/day and counts/day) were averaged if 3 or more days out of the 7-day period showed $\geq$10 h of accelerometer wearing without any period of $\geq$60 min of no accelerometer data (continuous zeros). HRQoL was measured with the five-level version of the EuroQoL-5 dimensions (EQ-5D-5L) instrument. The EQ index value is divided into five dimensions (mobility, self-care, usual activities, pain/complaints, and anxiety/depression) and the visual analog score (EQ-VAS) estimates the overall health state.[22]

Statistics

Changes in average walking tests (T25FW, 6MWT) and DWA on treatment were reported as percentage of change from average pretreatment value. We considered the MCID change as an improvement of 20% in T25FW test and 6MWT.[6,8,23] The MSWS-12 total score ranges from 12 to 60 and it was transformed to 0–100 by the following formula: [(observed score − 12)/60 − 12] × 100. Negative MSWS-12 change scores imply subject-perceived improvement in walking ability during treatment, and we considered a meaningful clinical change a difference of $\geq$6 points from baseline.[4,5,24] IPAQ questionnaire was expressed as MET-min per week by the following formula: [3.3 METs·min·day (walking) + 4.0 METs·min·day (moderate activity) + 8.0 METs·min·day (vigorous activity)]. EQ index value ranged from 0 (death) to 1 (full health) and we considered a MCID a difference of 0.05.[25] EQ-VAS ranges from 0 (worst quality of life) to 100 (best quality of life). Descriptive analyses (means, ranges, and standard deviations) and the significance of group differences (p values, 95% confidence intervals) from baseline to on-treatment visit

Table 1. Demographic and disease characteristics of the multiple sclerosis population at baseline.

	MS patients ($n = 35$)
Age in years, mean (SD)	50 (20.8)
Sex, women *n* (%)	22 (62.9)
CMI in kg/m^2, mean (SD)	24.8 (4.2)
MS subtype, *n* (%)	
Relapsing–remitting MS	9 (25.7)
Secondary–progressive MS	14 (40)
Primary–progressive MS	12 (34.3)
Disease duration from onset in years, mean (SD)	19 (10)
EDSS score, median (range)	5.5 (4.0–6.5)
T25FW speed in m/s; *n* (%)	
$<$6 s	3 (8.6)
6–7.99 s	8 (22.9)
$\geqslant$8 s	24 (68.6)
MSWS-12 score in %, mean (SD)	81.2 (20)
MS symptoms, *n* (%)	
Fatigue	5 (14.3)
Imbalance	7 (20)
Lower-limb weakness	10 (28.6)
Lower-limb spasticity	11 (31.4)
Lower-limb loss of sensation	2 (5.7)

CMI, corporal mass index; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; MSWS-12, Multiple Sclerosis Walking Scale; SD, standard deviation; T25FW, timed 25-foot walk test.

were evaluated using a Student's paired *t* test and nonparametric Wilcoxon signed rank, otherwise. *t* test and Mann–Whitney *U* test were applied for group comparison. Statistical significance was defined as $p \leqslant 0.05$ and all analyses were performed using SPSS version 20.0 (SPSS Inc, Chicago, IL, USA) software.

Results

Patient demographics and clinical characteristics

A total of 35 consecutive MS patients were included in the study from June 2014 to January 2017. Most of them (74%) had a progressive form of MS and a median EDSS score of 5.5 (range, 4.0–6.5). The demographic and clinical characteristics are shown in Table 1. Patients' major complaint about walking was lower-limb spasticity (31%), lower-limb weakness (29%) and imbalance (20%).

Baseline prolonged-release fampridine safety

Three female patients withdrew from the study before completing baseline evaluation due to adverse events: a syncope that required hospitalization, persistent nausea, and severe dizziness, respectively. Finally, 32 patients completed the baseline evaluation, and 14 (44%) experienced

Table 2. Response to prolonged-release fampridine for the different outcomes categorized by response to the timed 25-foot walk test.

	Responders ($n = 25$)	**Non-responders ($n = 7$)**
Response to different walking tests, *n* (%)		
T25FW, 6MWT and MSWS-12	15 (46.9)	–
T25FWT and 6MWT	6 (18.8)	–
T25FWT and MSWS-12	4 (12.5)	–
MSWS-12	–	3 (9.4)
None	–	4 (12.5)
% of change in T25FW, mean (SD)	51.2 (21.6)**	4.5 (15.1)
% of change in MSWS-12, mean (SD)	−26.2 (16.3)**	−6.6 (16.2)
% of change in 6MWT, mean (SD)	44.5 (58.1)**	5.2 (11.8)
% of change in DWA steps/day, mean (SD)	7 (14.6)*	3.6 (14.4)
IPAQ score in MET-min/week, mean (SD)		
EQ-5D-5L, mean (SD)	1034.2 (3430.1)*	−673.6 (1855.9)
EQ index value	0.1 (0.2)*	0.1 (0.1)*
EQ-VAS	12.1 (13)**	0.8 (19.6)
EDSS score, median (range)		
MSFC, mean (SD)	0 (−0.5–0.0)*	0 (0)
Total *Z* score	0.3 (0.2)**	0.1 (0.2)
9HPT *Z* score	0.3 (0.4)*	0.2 (0.3)
PASAT *Z* score	0.2 (0.7)	0.04 (0.4)

PR-fampridine response was defined as the improvement in speed of ⩾20% in the T25FW. Comparisons were assessed with paired *t* test;
*$p < 0.05$, **$p < 0.01$.
6MWT, 6-minute walk test; 9HPT, nine-hole peg test; DWA, daily walking activity; EDSS, Expanded Disability Status Scale; EQ-5D-5L, five-level version of the EuroQoL-5 dimensions; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent of task; MSFC, Multiple Sclerosis Functional Composite; MSWS-12, Multiple Sclerosis Walking Scale; PASAT, Paced Auditory Serial Addition Test; PR-fampridine, prolonged-release fampridine; SD, standard deviation; T25FW, timed 25-foot walk test; VAS, Visual Analog Scale.

mild and transitory adverse events, the most frequent being: dizziness (18.8%), insomnia (12.5%), and headache (12.5%).

Baseline prolonged-release fampridine response

Twenty-five (78%) patients were considered PR-fam responders. No baseline differences were observed between responder patients and nonresponder patients in walking measures, and global IPAQ (data not shown). PR-fam responder patients had a significant improvement in all walking outcomes (T25FW, 6MWT, MSWS-12), and functional measures (IPAQ, DWA) (Table 2). Responder patients also showed a statistically significant improvement in HRQoL (EQ index value and EQ-VAS), while nonresponder patients only improved in EQ index value (Table 2). Significant changes were found in MSFC *Z* score (mean

Table 3. Response to prolonged-release fampridine for the clinical outcomes categorized by response to timed 25-foot walk test (T25FW) test and Multiple Sclerosis Walking Scale-12 items or T25FW only.

	Responders ($n = 25$)	
	Response to T25FW and MSWS-12 ($n = 19$)	**Response to T25FW only ($n = 6$)**
% of change in T25FW, mean (SD)	51 (21–4)**	51.7 (24.2)*
% of change in MSWS-12, mean (SD)	–33.7 (10.2)**	–2.4 (1.6)*
% of change in 6MWT, mean (SD)	47.4 (66.6)**	35.2 (8.1)*
% of change in DWA steps/day, mean (SD)	11.1 (13.5)*	–6.1 (9.8)
IPAQ score in MET-min/week, mean (SD)	921.5 (3698.6)	1391.3 (2651.3)
EQ-5D-5L, mean (SD)		
EQ index value	0.2 (0.1)*	0.01 (0.2)
EQ-VAS	16.5 (11.1)**	–1.7 (8.2)
EDSS score, median (range)	0 (–0.5–0.5)*	0 (–0.5–0.0)
MSFC, mean (SD)		
Total *Z* score	0.3 (0.2)**	0.4 (0.3)*
9HPT *Z* score	0.4 (0.4)*	0.05 (0.3)
PASAT *Z* score	–0.01 (0.6)	0.7 (0.8)

PR-fampridine response to T25FW was defined as an improvement in speed of ⩾20% in the T25FW and response to the Multiple Sclerosis Walking Scale (MSWS-12) as an improvement of ⩾6 points. Comparisons were assessed with paired *t* test;
*$p < 0.05$, **$p < 0.01$.
6MWT, 6-minute walk test; 9HPT, nine-hole peg test; DWA, daily walking activity; EDSS, Expanded Disability Status Scale; EQ-5D-5L, five-level version of the EuroQoL-5 dimensions; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent of task; MSFC, Multiple Sclerosis Functional Composite; PASAT, Paced Auditory Serial Addition Test; PR-fampridine, prolonged-release fampridine; SD, standard deviation; T25FW, timed 25-foot walk test; VAS, Visual Analog Scale.

difference = 0.3; $p < 0.001$) and hand dexterity in nine-hole peg test (9HPT) *Z* score (mean difference = 0.3; $p = 0.002$) in responder patients (Table 2).

Among responder patients to T25FW test, 15 (60%) patients also improved the 6MWT and MSWS-12; 6 (24%) in the 6MWT only, and 4 (16%) in the MSWS-12 only. The mean improvement in the T25FW test was similar among the three groups of patients (50.3 ± 23.9, 51.7 ± 24.2 and 53.7 ± 7.9, respectively, $p = 0.99$). Patients with response to T25FW test and MSWS-12 ($n = 19$) showed a significant improvement in the percentage of change in DWA, HRQoL (EQ index value and EQ-VAS) and 9HPT *Z* score (Table 3) in contrast to patients who only responded to T25FW test ($n = 6$).

In correlation analysis, the percentage of change in DWA correlated with global MSWS-12 score ($r = −0.49$, $p = 0.01$), and individual aspects of the scale such as the ability to climb up and down stairs ($r = −0.4$, $p = 0.03$), to standing when doing things ($r = −0.4$, $p = 0.03$), balance ($r = −0.5$, $p = 0.02$), the need to use support when walking outdoors ($r = −0.5$, $p = 0.02$) and walking smoothly ($r = −0.4$; $p = 0.04$). The percentage of change in MSWS-12 also correlated with the mean difference of HRQoL (EQ-VAS, $r = −0.4$; $p = 0.03$).

Long-term prolonged-release fampridine response

A total of 20 (80%) of the 25 responder patients were available for longitudinal evaluation (4

Table 4. Longitudinal changes based on the permanent response to T25FW test and MSWS-12.

	Permanent response to T25FW and MSWS-12 ($n = 8$)	Permanent response to T25FW ($n = 7$)
3 months		
% of change in T25FW, mean (SD)	55 (16.8)*	61.2 (26.5)*
% of change in MSWS-12, mean (SD)	−34.4 (14.9)*	−14 (23.7)
% of change in 6MWT, mean (SD)	29.3 (23.6)	39.7 (18)*
% of change in DWA steps/day, mean (SD)	12.5 (25)	−1.3 (6.4)
EQ-5D-5L, mean (SD)		
EQ index value	0.2 (0.2)*	0 (0.2)
EQ-VAS	25 (14.9)*	1.4 (3.8)
EDSS score, median (range)	0 (−0.5–0.0)	0 (−0.5–0.0)
MSFC, mean (SD)		
Total *Z* score	0.3 (0.2)*	0.4 (0.5)
9HPT *Z* score	0.3 (0.5)	0.3 (0.2)*
PASAT *Z* score	0.3 (0.5)	0.3 (1.2)
6 months		
% of change in T25FW, mean (SD)	58.8 (24)*	56.4 (23.4)*
% of change in MSWS-12, mean (SD)	−27.6 (8)*	−0.3 (12.8)
% of change in 6MWT, mean (SD)	31.8 (23.4)*	17.9 (25)
% of change in DWA steps/day, mean (SD)	27.6 (65.4)	−13.6 (51.7)
EQ-5D-5L, mean (SD)		
EQ index value	0.2 (0.1)*	0.1 (0.1)
EQ-VAS	21.9 (16.2)*	−2.5 (4.2)
EDSS score, median (range)	0 (−0.5–0.0)	0 (−0.5–0.0)
MSFC, mean (SD)		
Total *Z* score	0.2 (0.2)	0.4 (0.4)*
9HPT *Z* score	0.2 (0.5)	0.2 (0.4)
PASAT *Z* score	0 (0.4)	0.3 (0.7)
12 months		
% of change in T25FW, mean (SD)	57.5 (26.2)*	43.6 (26)*
% of change in MSWS-12, mean (SD)	−28.4 (11.9)*	8.9 (10.5)*
% of change in 6MWT, mean (SD)	28.2 (11.9)*	1.9 (15.5)

Table 4. (Continued)

	Permanent response to T25FW and MSWS-12 ($n = 8$)	Permanent response to T25FW ($n = 7$)
% of change in DWA steps/day, mean (SD)	19.4 (43.5)	−14.2 (37.1)
EQ-5D-5L, mean (SD)		
EQ index value	0.2 (0.1)*	0 (0.1)
EQ-VAS	21.3 (16.6)*	−7.9 (10.8)
EDSS score, median (range)	0 (−0.5–0.5)	0 (−0.5–0.0)
MSFC, mean (SD)		
Total *Z* score	0.3 (0.2)*	0.3 (0.4)
9HPT *Z* score	0.3 (0.4)	0.04 (0.5)
PASAT *Z* score	0.2 (0.3)	0.5 (0.7)

Permanent response was defined as an improvement in speed of ⩾20% in timed 25-foot walk (T25FW) and an improvement of ⩾6 points in multiple sclerosis walking scale (MSWS-12) in all visits. Comparisons were assessed with paired *t* test;
*$p < 0.05$, **$p < 0.01$.
6MWT, 6-minute walk test; 9HPT, nine-hole peg test; DWA, daily walking activity; EDSS, Expanded Disability Status Scale; EQ-5D-5L, five-level version of the EuroQoL-5 dimensions; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent of task; MSFC, Multiple Sclerosis Functional Composite; MSWS-12, Multiple Sclerosis Walking Scale; PASAT, Paced Auditory Serial Addition Test; SD, standard deviation; VAS, visual analog scale.

patients were excluded because they did not return for all visits, and one decided to discontinue PR-fam because lack of perceived effectiveness). No patient had relapses or changed the disease-modifying therapies or the symptomatic treatment during the study. Eighteen (90%) patients remained as responder patients at 3 months, 17 (85 %) at 6 months and 15 (75%) at 12 months. The longitudinal changes in PR-fam responder patients and nonresponder patients at each timepoint are shown in Supplementary Table 1. At 1 year, 8 out of 15 (53%) responder patients showed permanent response to T25FW test and MSWS-12 during all timepoints of evaluation. This subgroup of patients had a significant improvement in the 6MWT and HRQoL (EQ index value and EQ-VAS) considered clinically meaningful that was not observed in patients with permanent response only to T25FW test (Table 4). Responder patients to both tests had an improvement in DWA that ranged from 12.5% to 27.6%, while responder patients to T25FW test alone had a worsening from −1.3 to −14.2%, despite the difference not reaching statistical significance.

In correlation analysis, changes in HRQoL correlated with changes in MSWS-12 over time (3 months: EQ index value, $r = -0.6$, $p = 0.007$ and EQ-VAS, $r = -0.4$, $p = 0.09$; 6 months: EQ index value, $r = -0.6$, $p = 0.007$ and EQ-VAS, $r = -0.8$, $p < 0.001$; 1 year: EQ index value, $r = -0.8$, $p < 0.001$ and EQ-VAS, $r = -0.7$, $p = 0.002$).

Reevaluation of nonresponder patients at long term

Four out of five patients lost their response to PR-fam and they were retested. Two of them were considered responders, one patient to T25FW test and one to T25FW and MSW-12. The responder to both tests clinically improved in 6MWT (35%), walking mobility (steps/day = 27.6%) and HRQoL (EQ index value = 0.4 and EQ-VAS = 20%) in contrast to the responder to the T25FW test only (6MWT = 0%, DWA = 0.3, EQ index value = 0.03, EQ-VAS = −4).

Evolution of baseline nonresponder patients

Baseline nonresponder patients ($n = 5$) were assessed 1 year after baseline PR-fam evaluation. No significant changes were observed in disability measures (EDSS score and MSFC *Z* score) but they showed a decrease in speed (T25FW test,

mean % of change = −4.4, $p = 0.9$), endurance (6MWT, mean % of change = −13.5, $p = 0.1$), and self-perception (MSWS-12, mean difference = 5.4, $p = 0.7$). Patients also had a decrease in DWA measured by steps (% of change, mean = −12.8, $p = 0.04$) and HRQoL (EQ index value, mean difference = −0.2, $p = 0.04$).

Discussion

The objective of this study was to assess PR-fam response by using different walking tests and functional measures, and determine the most suitable outcome measures to identify short- and long-term clinically meaningful response to PR-fam in the setting of real clinical practice. Our study shows that at 2 weeks after therapy initiation, most patients (78%) are PR-fam responder patients but only those with a combined response to T25FW test and MSWS-12 had a significant and clinically meaningful improvement in HRQoL and DWA. Moreover, this study provides new information on the usefulness of combined outcomes measures, suggesting that patients with permanent response to both tests at 1 year were those who remained with a clinically significant effect in endurance and HRQoL. The observed strong correlation between the change in measures of HRQoL and patient-reported outcome (MSWS-12) emphasizes the clinical relevance of the results and contributes to build on the existing real-world experience with this drug.

In this study, we used as criteria of PR-fam response the most accepted MCID of ⩾20% in the T25FW test because this threshold represents a clinically meaningful change in walking performance.[6,26,27] Using this definition, up to 75% of the PR-fam responder patients at short term remained as responder patients at 1 year. However, a significant persistent efficacy over a period of 2 years using other established criteria of response has also been reported.[28] The study showed that 80% of the patients with ⩾10% of improvement (T25FW test) at short term maintained a similar degree of responsiveness after long-term therapy. Moreover, more than one third of patients with none or poor initial response improved their walking function when they were tested again after 2 years.[28] Our results agree with previous results because two out of the four patients who lost the criteria of response over the period of study exhibited responsiveness once again. Overall, these data reinforce the importance of a further reevaluation of the efficacy in patients with poor initial response but also in those who lose the efficacy over time. Conversely, monitoring the efficacy on a regular basis is important because its loss may be related to progression of the disease not revealed by a change in the EDSS score, such as we observed in the evolution of our cohort of nonresponder patients at baseline.

Our study has several limitations. We do not know whether the clinically meaningful outcome observed in our study could have been reached with lower thresholds of T25FW test or using other response criteria defined in previous clinical trials. In fact, it has been suggested that the use of a different anchor might result in a different threshold for a clinically meaningful change in the T25FW test.[7] Moreover, the T25FW test has a ceiling effect in patients with mild disability.[13] In our study, for example, responder patients who scored the T25FW test in less than 6 sec had a mean percentage of change of 21%, but it rose to 55% in those who scored in more than 8 sec. Another limitation of the study was the small sample size that might have influenced the statistical significance of some outcomes. For example, the significant improvement in DWA at short term was lost at long term; however, at 1 year, we found a DWA increase in responder patients to the T25FW test and MSWS-12 (12.5–27.6%), whereas those responder patients to T25FW only had a decrease DWA (−1.3 to −14.2%). The fact that we observed a good correlation between improvement of DWA and MSWS-12 suggests an additional benefit effect may be clinically meaningful in the real-life setting. Additional studies, however, are needed to confirm these data. Finally, safety findings were according to pivotal studies, and no new adverse events were observed with PR-fam long-term therapy.

In conclusion, our study confirms long-term beneficial effect of PR-fam on walking function in real clinical practice, and suggests that the combination of objective measures (T25FW test) and patient-reported outcomes (MSWS-12) in the definition of PR-fam responder patients best identifies those patients with clinically meaningful improvement.

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Conflict of interest statement

NSV received compensation for consulting services and speaker honoraria from Genzyme and Bayer-Schering.
YB received speaker honoraria from Biogen, Novartis and Genzyme.
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EHM-L is a researcher in the OCTIMS Study, an observational study (which involves no specific drugs) to validate SD-OCT as a biomarker for multiple sclerosis, sponsored by Novartis. She has received speaking honoraria from Biogen and Genzyme and travel reimbursement from Genzyme, Roche, for international and national meetings over the last 3 years. She is a member of the working committee of the International Multiple Sclerosis Visual System (IMSVISUAL) Consortium.
IZ has received travel reimbursement from Genzyme, Biogen, Merck for national and international meetings over the last 3 years.
IP received travel funding from Roche Spain and Sanofi-Aventis, European Academy of Neurology, and European Committee for Treatment and Research in Multiple Sclerosis; holds a patent for an affordable eye tracking system to measure eye movement in neurologic diseases; and holds stock options in Aura Innovative Robotics.
CM declared no conflicts of interest.
PV received consultation fees from Roche, Novartis, Neurotech Pharma and hold stocks of Bionure Farma, Mint-Labs, Spire Bioventures and Health Engineering. He is currently an employee of Genentech, but this work was done before joining the company as part of his academic activities.
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