Long-term effects of prolonged-release fampridine in cognitive function, fatigue, mood and quality of life of MS patients: the IGNITE study

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Abstract

Background: Studies have reported conflicting results regarding the potential benefit of prolonged release (PR) fampridine in other domains besides walking. Moreover, only a small number of studies have explored long- term effects of PR fampridine. The aim of this study was to assess cognitive function, quality of life, mood and fatigue in MS patients treated with fampridine after 6 and 12 months of treatment.

Methods: IGNITE was an observational, open label study**.** Subjects were examined with the timed 25-foot walk (T25FW) and the BICAMS battery and were asked to complete the Multiple Sclerosis Impact Scale (MSIS-29), Modified Fatigue Impact Scale (MFIS), Beck Depression Inventory-II (BDI-II) and MS International Quality-of-Life questionnaire (MUSIQOL) at baseline and at weeks 24 and 48. Patients were sub-grouped into responders (n:40) and non-responders (n:20) according to T25FW performance after 2 weeks on treatment.

Results: After 6 months, statistically significant improvement was observed on T25FW ($p<0.001$), SDMT ($p<0.001$) and MSIS29 ($p<0.001$), for responders. After 1 year on treatment, statistically significant improvement was observed in T25FW ($p <0.001$), MSIS29 ($p=0.004$), SDMT ($p<0.001$) and MUSIQOL ($p=0.03$) for responders. There were no statistically significant improvements for the non-responders.

Conclusions: PR Fampridine may have a beneficial effect on information processing speed though not on memory. Study data provide some evidence that fampridine treatment may reduce the impact of MS on daily activities and improve quality of life but has no effect on subjective fatigue and mood.

Keywords: fampridine, cognition, fatigue, quality of life, BICAMS

1.Introduction

Multiple sclerosis (MS) is one of the most common disabling diseases of the Central Nervous System (CNS) especially during early adult life [1].Walking difficulties occur often during the course of the disease and interfere with daily activities of people with MS (PwMS).[2,3]Walking impairment is considered one of the most disabling symptoms of the disease, according to PwMS ,[4] while there is increasing evidence that deterioration of gait in the absence of active inflammatory processes might be one of the symptoms signaling the transition from relapsing-remitting to secondary progressive MS[5]. Cognitive impairment occurs in about half of PwMS, [6] fatigue is the most commonly reported symptom [7] and mood disturbances are frequently observed [8]. These all have a negative impact on patients' everyday functioning, ability to work and quality of life. [9]

Fampridine is a potassium channel blocker that improves the impaired axonal conduction associated with CNS demyelination [10] and has been approved as a symptomatic treatment, for the improvement of walking in adult PwMS with walking disability (EDSS 4-7). According to phase III studies, [11,12] 38% of patients presented an average 25% improvement in the ttimed 25 Foot Walk (T25FW), while post marketing studies have suggested that the percentage of responders may be higher. [13-15]. The long-term impact of prolonged release (PR) fampridine in walking has also been studied and findings suggest a sustained beneficial effect in walking ability [16,17] In addition, several studies explored the potential benefits of PR fampridine in cognition, fatigue and quality of life of PwMS with conflicting results [18-22].

The aim of this investigator initiated, observational study (an **I**nvestigator Initiated Observational Study to Evaluate the Lon**g**-Term Effects of Prolo**n**ged-release Fampr**i**dine on Cogni**t**ive Performance, Fatigu**e**, Depression and Quality of Life in MS Patients. 'IGNITE') was to assess cognitive function, quality of life, depression and fatigue in adult PwMS, after 6 months and 1 year on treatment with PR fampridine. Together with the identified need for real life data regarding the use of PR fampridine in the everyday clinical setting, the results from this study may provide additional information regarding the selection of appropriate candidates for PR fampridine treatment.

2.Materials and methods

2.1 Study population

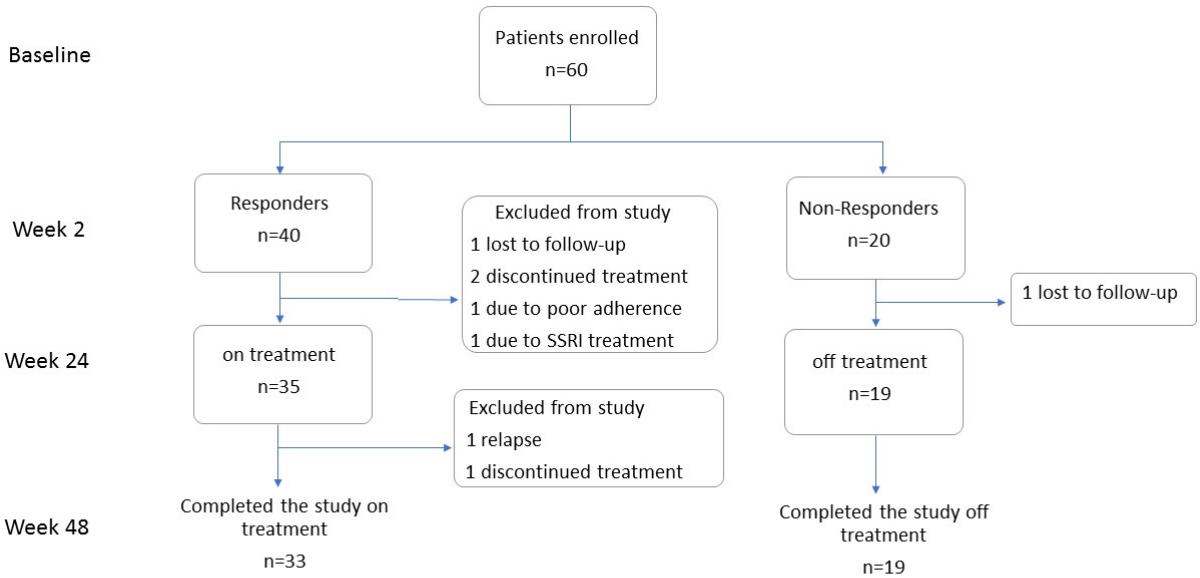
Sixty adult MS patients (31 females; age 51 ± 9.4) fulfilling the Greek prescription guidelines for PR fampridine were recruited to this investigator initiated, open label, prospective study. Testing was conducted in the Multiple Sclerosis Center of AHEPA University Hospital, was approved by the ethical committee of Aristotle University of Thessaloniki and was performed in accordance with the ethical standards of the

Helsinki Declaration. Patients included in the study had to be free of relapses or disease progression for at least 3 months and not been exposed to fampridine in the past. Since concomitant symptomatic treatment for fatigue and mood could interact with study results, we recruited patients not willing to receive antidepressants, stimulants, anxiolytics or a psychotherapeutic intervention of any kind. All patients provided written informed consent prior to participation in the study.

2.2 Study Design

Patients were evaluated regarding their disability status and walking speed by an experienced neurologist. Cognitive assessment was performed by a trained neuropsychologist in a quiet room with no distractions. In addition, all patients were asked to complete self-administered questionnaires about quality of life (QoL), impact of MS in daily activities, fatigue and mood. Visits were performed at baseline and after 6 and 12 months. After 2 weeks on treatment with PR fampridine, patients were re-evaluated regarding walking ability and sub grouped into responders and non-responders depending on their walking performance as measured by T25FW. An improvement of at least 20% in T25FW performance was used to designate responders in most of the patients; for those with a baseline performance less or equal to 8 seconds, an improvement of at least 15% was considered indicative of a responder [21]. Non-responders discontinued PR fampridine but were assessed in the same follow ups as responders. Detailed records of any adverse events were kept and adherence to treatment was also taken into account. The study flow chart is presented in **figure 1**.

Figure 1. *Study flow chart.*



2.3 Assessment tools

Patients' disability was assessed on the Expanded Disability Status Scale (EDSS) and walking ability was evaluated using the T25FW. Patients' cognitive function was assessed using the Greek validated version of the BICAMS battery. [23,24] This comprised the Symbol Digit Modality Test (SDMT, information processing speed) [25], Greek Verbal Learning Test (GVLT, verbal memory) [26] and Brief Visuospatial Memory Test Revised (BVMT-R, visual memory) [27]. The total number of words and items across learning trials was used for scoring the GVLT and BVMT-R tests. Alternate forms were used for each visit in order to avoid practice effects. Patients were also asked to complete the Modified Fatigue Impact Scale (MFIS) [28],

the Beck Depression Inventory -II (BDI-II) [29], the Multiple Sclerosis Impact Scale [30] (MSIS-29) and the MS International Quality-of-Life questionnaire (MusiQoL) [31].

2.4 Statistical analysis

To conduct the statistical analysis, IBM SPSS Statistics Version 23 was used. First, descriptive statistics were calculated and data were tested for their normality with Shapiro-Wilk Test. Paired Samples t-test and non-parametric Wilcoxon Signed Rank test were implemented for normal and not normal distributed data respectively, to evaluate the impact of the drug administration on patient's scores on the tests that were conducted in the different visits. Results with p-values lower than 0.05 were considered significant.

3. Results

Overall, 33 (82.5%) responders and 19 (95%) non-responders completed all visits. Patients' demographics and disease characteristics are presented in table 1. Subgroup demographics were comparable in some extent, regarding age p:0.19 and disease duration p:0.87. Among the responders, the percentages of patients according to the type of their disease were: Relapsing Remitting MS (RRMS) 27,5%, Primary Progressive (PPMS) 35% and Secondary Progressive (SPMS) 37,5%. Alternatively, 61% of RRMS, 82,3% of PPMS and 60% of SPMS responded to treatment. Moreover, baseline assessments were similar between responders and non-responders, besides lower baseline MSIS-29 and T25FW performance in the responders' group. Detailed data regarding the performance of both groups in all visits are presented in table 2.

Table 1. *patients' demographics and disease characteristics at baseline, after 2, 24 and 48 weeks. (R: responders, NR: non-responders, RR: relapsing-remitting, PP: primary progressive, SP: secondary progressive)*

Timepoint	**baseline**	**Week 2**		**Week 24**		**Week 48**	
	All patients	**R**	**NR**	**R**	**NR**	**R**	**NR**
Number of patients (n)	**60**	**40**	**20**	**35**	**19**	**33**	**19**
Females (%)	**31 (51,6%)**	**19(47.5%)**	**12(60%)**	**17(48.5%)**	**11(57.8%)**	**15(45.4%)**	**11(57.8%)**
Mean (median) age	**51 (51)**	**52.5 (51.5)**	**48 (50)**	**52.4(52)**	**48(51)**	**52.5(53)**	**48(51)**
Mean (median) years from diagnosis	**13.7(13)**	**14(14)**	**12.9 (10)**	**14.4(14)**	**13.2(12)**	**14.1(14)**	**13.2(12)**
Mean (median) EDSS score	**5.5 (6.0)**	**5.3(5.5)**	**5.4 (5.5)**	**5.3(5.5)**	**5.9(6.0)**	**5.3(5.5)**	**5.9(6.0)**
Type of MS (RR-PP-SP)	**18-17-25**	**11-14-15**	**7-3-10**	**11-11-13**	**7-2-10**	**9-11-13**	**7-2-10**

Table 2: Performance of both groups in baseline, week 24 and week 48. All p values correspond to group comparisons regarding baseline performance. Statistically significant probability values are presented in italics. Total number of items recalled across the learning trials was used for scoring GVLT and BVMT-R. Results are presented as mean (SD). R: responders, NR: non-responders.

Measures	**Baseline**		**Week 24**				**Week 48**			
	R	NR	R	p value	NR	p value	R	p value	NR	p value
Number (n)	35	19	35		19		33		19	
EDSS	5.4(0.8)	5.8 (0.7)	5.3(0.9)	0.22	5.9(0.7)	0.74	5.3(0.9)	0.73	6.0 (0.6)	0.37
T25FW	15.6(9.5)	21.7(15.9)	12.3(7.9)	*<0.001*	25.3(19.9)	0.54	12.8 (8.2)	*<0.001*	25.6(18.6)	0.49
BICAMS										
SDMT	32.0(13.6)	33.7(14.6)	35.6(14.6)	*<0.001*	33.6(14.7)	0.98	34.7(14.3)	*<0.001*	34.8(14.2)	0.82
GVLT	49.6(13.5)	50(6.9)	51.0(11.8)	0.09	50(6.5)	1.00	50(11.5)	0.8	51.4(6.5)	0.52
BVMT-R	14.1(6.2)	13 (6.2)	14.3(6.1)	0.66	13.6(5.9)	0.75	14.8 (6.6)	0.28	13.1(6.6)	0.9
MFIS total	43.9(14.4)	43.3(13.8)	42.7(13.7)	0.33	43.6(13)	0.82	41.2(13.2)	0.08	41.2(14.6)	0.09
Cognitive	14.8 (8.8)	13.1(7.2)	14.2(7.9)	0.55	13.1(5.8)	1.00	12.9(7.2)	0.15	11.2(7)	0.15
Physical	24.2 (6.1)	24.3 (7)	24.5 (6.3)	0.68	25.7 (6.6)	0.33	23.8 (6.4)	0.71	24.8(7.6)	0.70
Psychosocial	4.6(1.6)	5.3 (1.8)	4.8(1.9)	0.48	4.8 (1.4)	0.15	4.6(1.6)	0.92	5.1(1.5)	0.63
BDI-II	12.1(6.4)	14.1(6.8)	12.4(7.1)	0.66	12.5(4.4)	0.40	11.5(4.9)	0.67	12.2(5.1)	0.35
MSIS-29	71.6 (14.4)	76.5(17.4)	65.2(13.4)	*<0.001*	74.5(13.3)	0.33	64.8(13.9)	*0.04*	75.6(13.1)	0.66
MusiQoL	59.6 (10.5)	56.9 (12.2)	61.8 (8.0)	0.10	57.8(12.8)	0.73	64.4 (13.1)	*0.03*	57.5(12.9)	0.81

EDSS: Expanded Disability Status Scale, T25FW: Timed 25 Foot Walk, BICAMS: Brief International Cognitive Assessment in MS, SDMT: Symbol Digit Modalities Test, GVLT: Greek Verbal Learning Test, BVMT-R: Brief Visuospatial Memory Test Revised, MFIS: Modified Fatigue Impact Scale, BDI-II: Beck Depression Inventory-II, MSIS-29: Multiple Sclerosis Impact Scale, MusiQoL: MS International Quality-of-Life questionnaire.

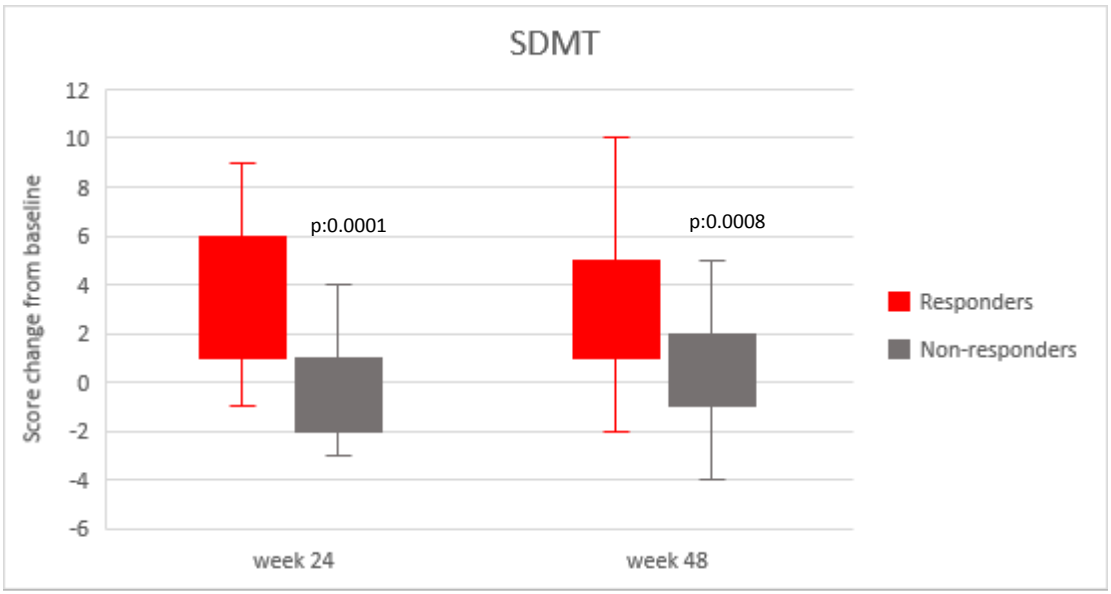
3.1 Disability status and walking ability

Regarding disability status as measured by EDSS, no statistically significant change was observed by weeks 24 or 48 in both groups (responders p=0.22, p=0.73 respectively, non-responders p=0.74, p=0.37 respectively). However, there was some individual variation. Six responders demonstrated a 0.5-1-point improvement in EDSS score after fampridine treatment due to change in their ambulation score. Four responders and seven non-responders had a higher EDSS compared to baseline by the end of the study. Walking ability, as expected, improved with statistical significance for the responders group at both week 24 and 48, but not in the non-responders group, when compared to baseline. (responders week 24 p<0.001; week 48 p<0.001).

3.2 Cognitive function

Both groups were assessed with the BICAMS battery at baseline, 6 and 12 months, using alternate forms at each visit. Regarding cognitive processing speed, statistically significant improvement in SDMT performance was observed in the responders group at both week 24 (p<0.001) and 48 (p<0.001), but not in the non-responders group (p =0.98, p=0.82 respectively). At week 24, responders demonstrated a mean change of 3.63 ± 3.18 points in SDMT performance, compared to -0.11 ± 1.97 for non-responders (p=0.0001). By week 48, responders presented a mean change of 3.12 ± 2.89, compared to 1.05 ± 2.07 for non-responders (p=0.0008) (**figure 2)**.

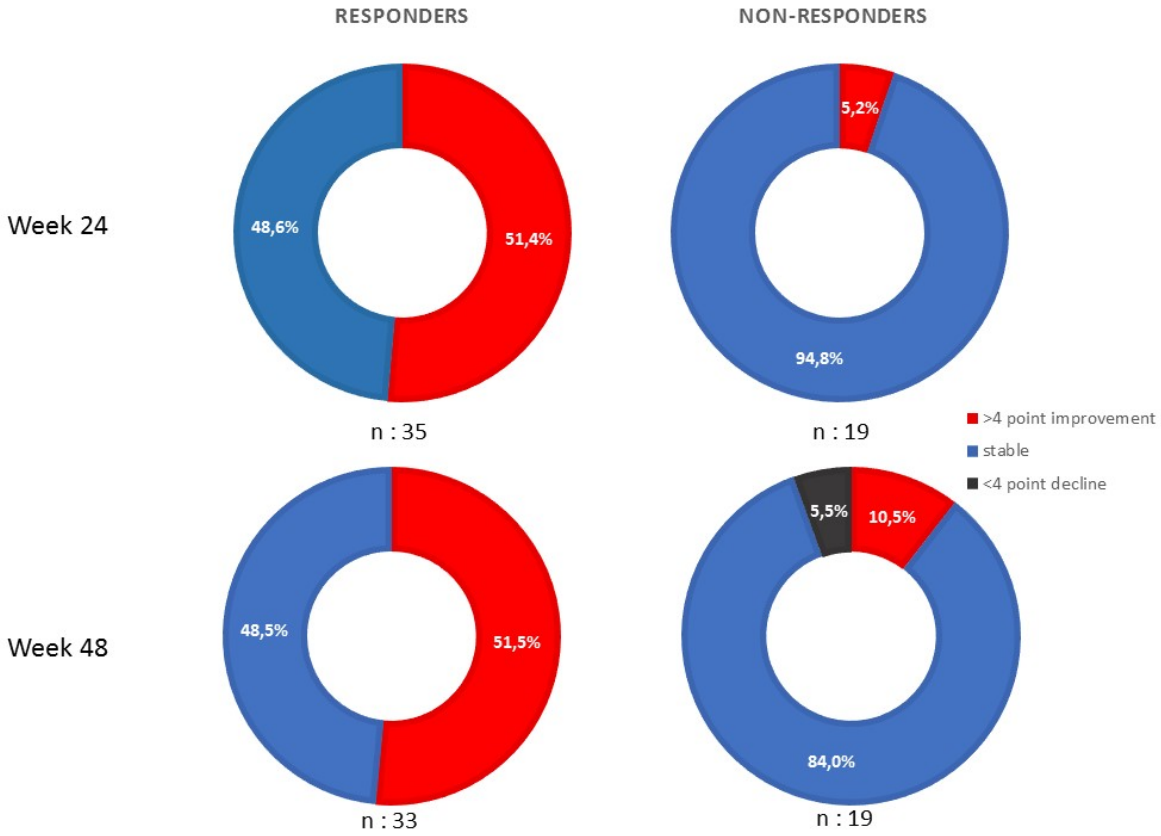
Figure 2. Performance of both groups in Symbol Digit Modalities Test (SDMT).



n	35	33
n	19	19

To investigate the clinical significance of the SDMT results, the criterion of 4-points change was applied [32,33]. In the responders group, in week 24, 18/35 (51,4%) demonstrated a 4-point improvement, while the rest presented changes less or equal to ±3 points and thus were classified as stable. In week 48, 17/33 (51.5%) of responders presented at least a 4-point improvement in SDMT performance and the rest remained stable. No patient in the responder group presented a decline in the performance by more than 4 points. In the non-responders group, in week 24, a 4-point improvement was observed in 1/19 (5.2%), while in week 48 2/19 (10.5%) patients demonstrated a 4 -point improvement and 1/19 (5.5%) patient presented a 4-point decline on SDMT performance **(figure 3).** There were no significant changes in verbal or visual memory function, for either group, at either time point (table 2).

Figure 3. Percentage of patients with clinically meaningful change in Symbol Digit Modalities Test performance in week 24 and week 48, compared to baseline.



3.3 Fatigue, Mood and Quality of Life

There were also no significant changes in fatigue or mood for either group, at either time point (table 2). However, there was a significant improvement in MSIS-29 for the responders at both time points, compared to baseline (week 24, $p<0.001$; week 48, $p=0.04$). There was no improvement in MS impact for the non-responders at either time point (figure 4). Responders also reported improvement in quality of life by the end of the study (week 24 $p=0.1$; week 48 $p=0.03$). Once again, there was no improvement in quality of life for the non-responders at either time point (figure 5).

Figure 4: Subjects' score in MSIS-29 questionnaire. * p=0.05, ** p<0.001.

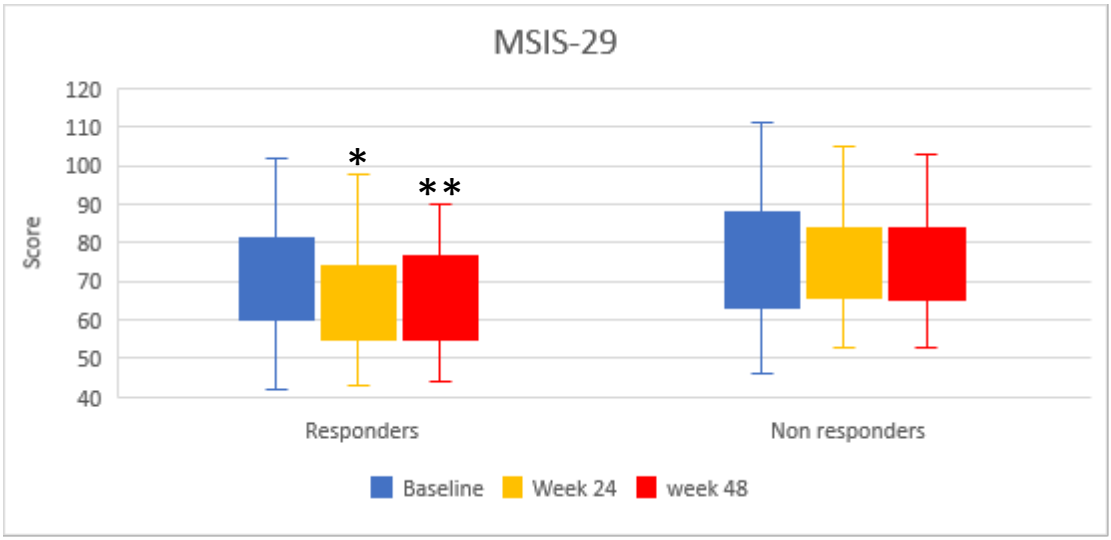
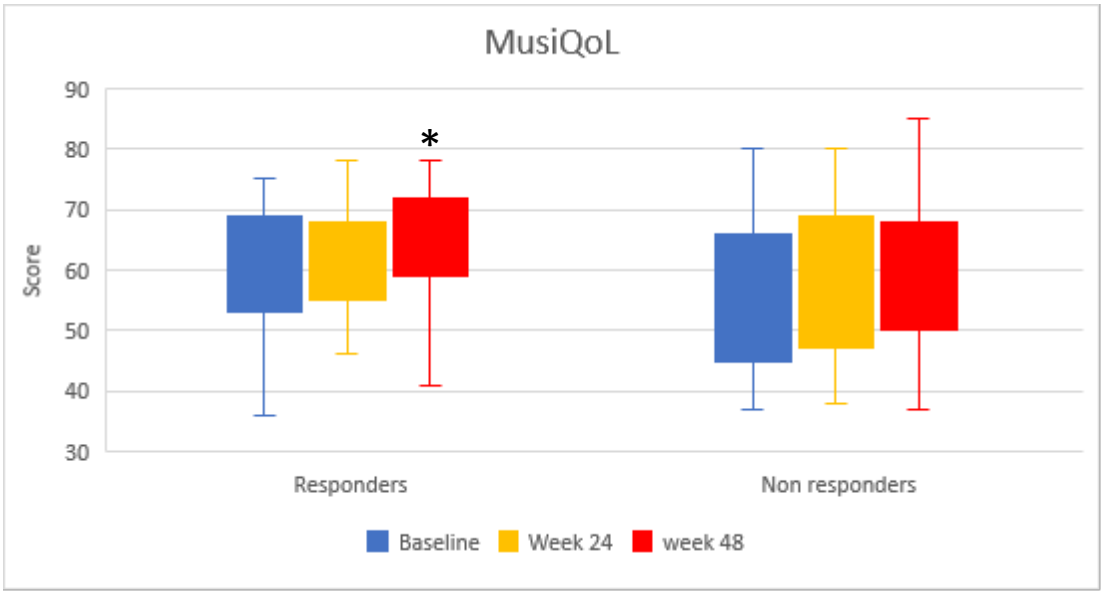


Figure 5. Subjects' score in MusiQoL questionnaire. * p=0.05



3.5 Safety

Overall, adverse events possibly related to treatment were mild and the majority of them occurred during the first two weeks. Gastrointestinal disturbances and dizziness were the two most frequently reported events. Both were mild and self -limited. One patient reported a urinary tract infection which resolved with antibiotics. All other adverse events resolved without the need for any action. All adverse events possibly related to treatment are presented in **table 3.** Regarding adverse events non-related to treatment, a patient experienced a severe relapse and therefore left the study. Also, one patient presented Grade II lymphopenia due to concomitant disease modifying treatment (DMT).

Table 3: Adverse events possibly related to treatment, during study duration.

Adverse event	***Number of events***	***% of patients***
Gastrointenstinal disturbances	2	3.3
Diziness	2	3.3
Back pain	1	1.6
Headache	1	1.6
Itching	1	1.6
Urinary tract infection	1	1.6

4. Discussion

The potential benefits of PR fampridine on other functions besides walking ability have been studied before, however few studies have investigated the effect of fampridine

treatment in the longer term. Improvements in walking ability over a year or more have frequently been reported in responders [17,18,34]. The effect we reported of improved walking reducing EDSS scores for responders on fampridine has been previously noted [34]. Our study has reported significant improvements for responders at 6 and 12 months on information processing speed, measured by the SDMT, but not on verbal or visual memory. About 50% of MS patients treated with fampridine presented a clinically meaningful improvement in SDMT scores after both 6 and 12 months.

These findings are in accordance with previous studies that used SDMT as an outcome measure. In particular, Jensen et al. reported improvement in SDMT scores after 1 month of fampridine treatment [19]. In a small study with 10 PPMS patients, improvement in SDMT scores was observed after 6 months on treatment. [35] More recently, in a study with 134 patients and 77 healthy controls, improvement in information processing speed was demonstrated after 6 months on fampridine treatment. [36]

A previous fampridine study showed significant improvement for information processing speed, as measured by the PASAT, after 9-12 months of treatment [18]. Another study with four weeks' fampridine treatment in a crossover design reported no treatment effect for information processing speed, again measured on the PASAT [37]. An even shorter study with 14 days' Dalfampridine treatment failed to show a treatment effect on the PASAT [34].

Impaired information processing speed in MS has been attributed to a 'disconnection syndrome' [38]; transmission of high speed signals may be weakened in demyelinated axons. Fampridine penetrates the blood-brain barrier [39] and improves impaired axonal conduction by selectively blocking potassium channels [40], therefore an improvement of conduction in cognitive circuits could explain our study results. However, this potential mechanism should further be explored with experimental research. Interestingly, although preclinical studies have suggested a role for specific potassium channels in learning and memory [41], in this study no beneficial effects of PR fampridine were observed regarding memory. Impairment in memory is often observed in MS and is attributed to delayed retrieval due to the mechanisms described above but may also require the integrity of specific areas involved in memory storage. [42,43].

Patient reported outcomes regarding the impact of MS in everyday functioning and quality of life may provide important additional information to clinicians regarding response to treatment [44,45]. In this study, a sustained improvement regarding the impact of MS in daily instrumental activities, as measured by MSIS-29, was observed. An overall improvement of quality of life was also reported after one year on fampridine treatment and these findings might reflect the improvement in walking ability and cognitive processing speed also observed in the responders group. Our results are consistent with previous findings. An improvement in MSIS-29 scores was observed after 6 months treatment with fampridine in a previous double-blind study.

[46] The large, open label ENABLE study's participants demonstrated significant improvement in health-related quality of life, measured by the SF-36. [13] and patients treated with fampridine have also reported improvement in working ability and social life [47].

In this study there was a trend towards improvement in fatigue among responders, but this did not reach statistical significance. A recent double-blind, placebo-controlled study with 32 MS patients reported improvement in physical fatigue after 2-years of fampridine treatment. [20] A treatment effect on fatigue after only 14 days' Dalfampridine treatment has been reported [34]. The four-week treatment crossover trial of fampridine reported a significant treatment effect on cognitive fatigue, determined by comparing performance on early and late PASAT items [37]. We found no significant change in mood.

Interestingly enough, the vast majority of the PPMS patients were responders, despite the general though not evidence – based impression for the contrary. However, in the long-term efficacy studies of fampridine in MS [16,17] no valid correlation was detected between patient's responsiveness to fampridine and the specific type of MS, whereas PPMS patients exhibited significant positive effects.

This open label observational study provided data to support the potential benefits of fampridine treatment in various domains besides walking ability. However, there are several limitations of this study, such as the small sample size. The impact of DMTs and physiotherapy were not taken into consideration as possible confounding factors. However, none of the patients switched DMT 6 months prior to the study and during the study duration. In addition, subjects with the progressive forms of the disease were over represented in this study. We also selected patients who were not taking symptomatic medications. Since this was a non-interventional study, the non-responder group did not continue on the medication. However, these patients might have responded in certain cognitive aspects apart from their response to walking. Large scale, double blind studies could further explore the long-term impact of PR fampridine in various domains and provide more robust findings.

5. Conclusions

The IGNITE study demonstrated a significant improvement in cognitive processing speed and impact of MS in daily activities after fampridine treatment. Study data have provided some evidence that fampridine treatment may have a longer term beneficial effect on quality of life, but not on mood and fatigue. The mechanism that explains why some patients respond to treatment whilst others do not, remains to be explored in future studies. Further investigation regarding brain and cognitive reserve may provide additional information regarding response to treatment.

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