National Institute for Health and Care Excellence

Final

Multiple sclerosis in adults: management

[E] Evidence review for pharmacological management of mobility problems

NICE guideline NG220

Evidence reviews underpinning recommendation 1.5.18 and research recommendations in the NICE guideline

June 2022

Final

These evidence reviews were developed by Guideline Development Team NGC

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1.1 Review question

For adults with MS, including people receiving palliative care, what is the clinical and cost effectiveness of pharmacological interventions for mobility?

1.1.1 Introduction

Problems with mobility are commonly experienced by people with MS, affecting an estimated 85% of individuals. Effective management is essential since reduced mobility can significantly affect activities of daily living, vocational and recreational activities, and quality of life. It is possible that pharmacological and non-pharmacological methods may influence different aspects of mobility, and so their combined use may be complementary. This chapter examines the evidence for the use of fampridine for treatment of mobility problems, specifically walking. Fampridine is the only licenced treatment for MS-related walking impairment.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: Adults (≥18 years) with MS, including people receiving palliative care. Exclusion: Children and young people (≤18 years).
Intervention	Fampridine including prolonged release fampridine Synonyms: 4-aminopyridine, 4-pyridinamine, pyridylamine, dalfampridine (generally prescribed as oral, 10 mg/bd or 10mg od for impaired renal function).
Comparisons	• Placebo or no treatment • Usual care which may include rehabilitation and physiotherapy
Outcomes	Measures of walking ability and upper limb mobility/dexterity, for example 6-Minute Walk Test, Timed 25-Foot Walk Test and 9-Hole Peg Test. Health-related quality of life (validated), for example 29-Item MS Impact Scale, EQ-5D and SF-36 Adverse events: • Mortality • Adverse events leading to withdrawal • Urinary tract infections • Confusion • Seizures • Falls • Headache • Fractures

	Changes in validated disability or impairment scales assessing for example: • MS Impact Scale 29 (MSIS-29) • Motor function • Spasticity • Fatigue Follow-up: • At 6 months (if multiple time points are reported, we will only record the closest reported time point up to 6 months) • >6 months - 12 months (data from >12 months follow-up may be included but will be downgraded for indirectness)
Study design	Systematic reviews of RCTs and RCTs Crossover RCTs with a washout period of at least 1 week will be included (a 1-week washout period was considered to be sufficient for fampridine as the elimination half-life is reported to be 6 hours in a European Medicines Agency report, which suggests a washout period of five days to be adequate).

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A search was conducted for randomised trials comparing the effectiveness of fampridine versus placebo, no treatment or usual care for mobility in people with MS.

Fifteen randomised controlled trials (from twenty papers), including eleven parallel trials and four crossover trials with a washout period of at least one week between fampridine and placebo treatment, were included in the review;[3, 6, 8, 9, 11-13, 17-21, 26, 33, 35, 37, 43, 45, 46, 48] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

Apart from two studies where the type of MS was not stated or was unclear, all studies included people with different types of MS rather than limiting to a specific type, including relapsing-remitting, primary progressive, secondary progressive and progressive-relapsing MS. Across studies relapsing-remitting MS usually made up the majority of each study population, with secondary progressive being the most common type in a smaller proportion of studies. The average Expanded Disability Status Scale (EDSS) score at baseline was <6.0 for most studies, with some limiting to scores <6.0 and others including a range that expanded to >6.0 but the majority with a score <6.0. This disability scale is scored on a scale of 0-10, with higher scores indicating increased disability. A score of 6.0 on this scale indicates the need for a walking aid, while scores of <6.0 are associated with increasing walking impairment as scores increase but no need for a walking aid. As scores increase above 6.0, the number of walking aids increases, and the distance people are able to walk with aids reduces. A score of 10.0 represents death due to MS. The proportion of those using concomitant disease-modifying treatments for MS was unclear for most studies. Although some studies excluded those that had recently started a new disease-modifying treatment or had changed dose, they did not appear to exclude their use outright, so it is likely in most studies there were some patients taking these drugs.

All of the included studies used the dose of 10 mg fampridine twice daily as specified in the protocol and the dose stated in the BNF. After reviewing all full-text studies and after discussion with committee members, other studies that used different doses were excluded as it was agreed that there was sufficient evidence from studies using this recommended dose and that it would not be appropriate to include studies using doses other than that specified in the BNF. The duration of treatment varied across studies and was between 2 and 24 weeks, depending on which outcome was being measured. The majority of studies treated patients with fampridine for less than the 6 months specified in the protocol, with only the MOBILE and ENHANCE trials consisting of 24 weeks treatment.

Some studies reported certain outcomes incompletely or in a format that could not be analysed (for example, as medians rather than means). These results are presented in Table 4 below – although risk of bias was assessed a full GRADE assessment could not be performed due to the format that they were reported in.

All outcomes listed in the protocol were reported by at least one study, however outcomes such as fatigue and spasticity were reported by very few studies compared to other outcomes such as walking tests and certain adverse events.

All of the included studies were funded by industry, with either Biogen or Acorda Therapeutics being mentioned as sources of funding.

Inconsistency

For six outcomes heterogeneity was observed that could not be explained by subgrouping strategies. Heterogeneity could not be explained for one of the following reasons: there were

three or fewer studies in each meta-analysis, meaning subgroup analyses could not be performed; all (or all but one) study were in the same category for each subgrouping strategy; or when studies were split into subgroups, heterogeneity remained within the individual subgroups. Random effects analysis was therefore used for these outcomes and downgrading for inconsistency was performed in GRADE.

Indirectness

Two outcomes (Six Spot Step Test change from baseline at 4 weeks and 9-Hole Peg Test at 4 weeks where it was unclear if results were for the dominant or non-dominant hand) were downgraded for indirectness as they were reported by a single study (Jensen 2016) that had used an open-label fampridine treatment phase prior to randomisation to select for fampridine responders that were then included in the randomised trial, meaning the population may not represent the general MS population and had been selected towards those most likely to experience an effect with fampridine. In addition, the population may have represented a population less likely to experience adverse events with fampridine as some participants withdrew from the open-label phase due to adverse events. This was also the case for outcomes reported in another study (Valet 2021)[43]. For the two outcomes that could be meta-analysed with other studies, downgrading for indirectness was not performed as the majority of the evidence, based on weighting in the meta-analysis, did not come from studies with this indirectness issue.

All studies reported outcomes that fell within time-point of 6 months specified in the protocol, with none reporting data for between 6 and 12 months. Of all of the included studies, only two reported outcomes at exactly 6 months of treatment, with the others reporting outcomes at a much shorter time-point than 6 months. For those that did not report outcomes at 6 months, indirectness was considered to be present for those with a follow-up <3 months because for a chronic condition such as MS, it is difficult to determine whether treatments are likely to be effective medium- to long-term if the longest available follow-up is only weeks or one or two months. This approach to downgrading based on time-points was in line with other review protocols in this guideline.

Meta-analysis

Studies reported continuous outcomes in various ways across and within studies. For example, within a single study the same outcome was sometimes reported dichotomously (e.g., >20% improvement in Timed 25-Foot Walk test speed compared to baseline) as well as in a continuous format (e.g., final value or change from baseline in Timed 25-Foot Walk test speed). In these cases, both forms of the outcome have been extracted and pooled with other studies reporting outcomes in the respective format.

Note that caution should be used when interpreting continuous outcomes that have been reported in a dichotomous format, as although it can simplify interpretation, most often there is not a strong enough reason for selecting cut-off points and dichotomisation of the data can lead to reduced statistical power, an increased risk of a false positive result, underestimation of the variation in outcome between groups and it reduces the data to two endpoints rather than representing the full spectrum of data when reported as a continuous measure. For example, when reported as the number achieving a 20% improvement in outcome compared to baseline, participants with improvements of 21% and 19% would be categorised into event and non-event groups, respectively, suggesting large differences between them when there is actually only a 2% difference between these two participants.

Final values and change scores, as well as parallel and crossover trials, have been combined where possible.

Studies not using fampridine specifically for mobility

Two studies[8, 37] were identified that stated to be using fampridine for reasons other than mobility, such as the treatment of cognition. Where this was the case, as long as the appropriate dose was being used (10 mg twice daily), studies were still included if they reported at least one mobility outcome. Where studies had used fampridine for reasons other than mobility in MS but had not reported at least one mobility outcome, they were excluded.

The median EDSS score at baseline in these studies appeared to be lower (4.0 to 4.5 in De Giglio 2019 and 3.5 in Satchidan and 2020) compared with the majority of other studies using fampridine specifically for mobility (most had mean or median EDSS values between 5.0 and 6.0), suggesting reduced impairment in mobility in these two studies. However, they did include some with EDSS scores ≥6.0 and did not explicitly exclude those with mobility impairments. As the inclusion of these two studies did not appear to affect the direction of mobility outcomes overall in meta-analyses, and we did not set a lower limit for EDSS values in terms of inclusion in the review, these studies were retained in the review.

Previously included studies

A number of studies that were included in the previous version of this evidence review were no longer eligible to be included based on the current protocol. The reason that all of these studies were no longer included in this review was that they used a dose other than 10 mg twice daily (or once daily for renal impairment). As sufficient evidence was found from studies using this recommended dose, which was specified in the protocol and is the dose specified in the BNF, it was considered appropriate to exclude these studies: van Diemen 1992[44], Bever 1994[4], Schwid 1997[39], Rossini 2001[36] and Goodman 2007[14].

Three studies (Goodman 2008[11], Goodman 2009[13] and Goodman 2010[12]) from the previous version of this evidence review were retained and meta-analysed where possible with data from studies published since the previous version was completed.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix I.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
All studies were funded by industry, with the majority being supported by Biogen and others being supported by Acorda Therapeutics.				
Brown 2016[6] USA	Fampridine (n=43) Dalfampridine extended release 10mg twice daily	Multiple Sclerosis N = 43 **Age (Mean [SE]):**	Measures of walking ability and upper limb mobility/dexterity at ≤6 months:	Crossover trial – 2-week washout period

Study	Intervention and comparison	Population	Outcomes	Comments
All studies were funded by industry, with the majority being supported by Biogen and others being supported by Acorda Therapeutics.				
	for two weeks (n=22 during the first treatment period, n=21 during the second treatment period) Placebo (n=43) Matched placebo twice daily for two weeks (n=21 during the first treatment period, n=22 during the second treatment period) Concomitant therapy: No additional information	Fampridine first treatment period: 55 (2.5) years Placebo first treatment period: 53.3 (2.2) years **Type of multiple sclerosis:** Primary progressive: 6 Relapsing-remitting: 26 Secondary progressive: 11 **EDSS (mean [SE]):** Fampridine first treatment period: 5.1 (0.3) Placebo first treatment period: 5.3 (0.2) **Disease modifying treatment status:** Not stated/unclear	6-Minute Walk Test Timed Get Up and Go test 12-item Multiple Sclerosis Walking Scale Changes in validated disability or impairment scales at ≤6 months: Physical Activity and Disability Survey-Revised Total Score Physical Activity and Disability Survey – Exercise and Leisure Subscore	Downgraded for indirectness as time-point was <3 months
De Giglio 2019[8] Italy Other publications associated with this study: Prosperini 2020[35]	Fampridine (n=80) Slow-release dalfampridine 10mg twice daily for twelve weeks Placebo (n=40) Matched placebo twice daily for twelve weeks Concomitant therapy: No additional information	Multiple Sclerosis N = 120 **Age (Mean [SD]):** Fampridine: 49.3 (7.8) years Placebo: 46.7 (8.7) years **Type of multiple sclerosis:** Primary progressive: 3 Relapsing-remitting: 103 Secondary progressive: 14 **EDSS (median [range]):** Fampridine: 4 (1-6)	Measures of walking ability and upper limb mobility/dexterity at ≤6 months: 25-Foot Walk Test 9-Hole Peg Test Health-related quality of life at ≤6 months: Multiple Sclerosis Impact Scale 29 Adverse events at ≤6 months: Discontinuation due to adverse events Urinary tract infection Focal seizure Headache	

Study	Intervention and comparison	Population	Outcomes	Comments
All studies were funded by industry, with the majority being supported by Biogen and others being supported by Acorda Therapeutics.				
		Placebo: 4.5 (1.5-5.5) **Disease modifying treatment status:** Not stated/unclear	Fall Changes in validated disability or impairment scales at ≤6 months: Multiple Sclerosis Functional Composite Modified Fatigue Impact Scale – total score Modified Fatigue Impact Scale – physical subscale	
Goodman 2008[11] USA and Canada	Fampridine (n=52) Fampridine 10mg twice daily for fifteen weeks Placebo (n=47) Matched placebo twice daily for fifteen weeks Groups taking fampridine 15mg and 20mg were also included in the study, but were not included in this review as they did not fulfil the inclusion criteria. Concomitant therapy: No additional information	Multiple Sclerosis N = 99 (206 if including the arms excluded from this review) **Age (Mean [SD]):** Fampridine: 49.8 (8.34) years Placebo: 49.0 (8.99) years **Type of multiple sclerosis:** Primary progressive: 24 Relapsing-remitting: 23 Secondary progressive: 52 **EDSS (mean [SD]):** Fampridine: 5.83 (0.9) Placebo: 5.87 (0.97) **Disease modifying treatment status:** Not stated/unclear	Measures of walking ability and upper limb mobility/dexterity at ≤6 months: Timed 25-Foot Walk Test 12-item Multiple Sclerosis Walking Scale 9-Hole Peg Test Adverse events at ≤6 months: Discontinuation due to adverse events Urinary tract infection Fall Headache Changes in validated disability or impairment scales at ≤6 months: Subject Global Impression of Change Multiple Sclerosis Functional Composite Ashworth score	Was included in the previous version of the guideline for this review
Goodman 2009[13]	Fampridine (n=229)	Multiple Sclerosis N = 301	Measures of walking ability and upper limb	Was included in the previous version of

Study	Intervention and comparison	Population	Outcomes	Comments
All studies were funded by industry, with the majority being supported by Biogen and others being supported by Acorda Therapeutics.				
USA and Canada	Sustained-release fampridine 10mg twice daily for fourteen weeks (with a 2-week placebo twice daily run-in phase at the start of the study and a 4 week no treatment phase at the end of the study) Placebo (n=72) Matched placebo twice daily for sixteen weeks (and a 4 week no treatment phase at the end of the study) Concomitant therapy: No additional information	**Age (Mean [SD]):** Fampridine: 51.5 (8.7) years Placebo: 50.9 (8.9) years **Type of multiple sclerosis:** Primary progressive: 45 Relapsing-remitting: 83 Secondary progressive: 160 Progressive-relapsing: 12 **EDSS (mean [SD]):** Fampridine: 5.8 (1.0) Placebo: 5.8 (1.1) **Disease modifying treatment status:** 66.0% in fampridine and 71.0% in placebo groups said to have been receiving concomitant treatment with an interferon or glatiramer acetate	mobility/dexterity at ≤6 months: Timed 25-Foot Walk test Adverse events at ≤6 months: Mortality Withdrawal due to adverse events Urinary tract infection Confusional state Focal seizure Fall Headache Ankle Fracture	the guideline for this review
Goodman 2010[12] USA and Canada	Fampridine (n=120) Extended-release fampridine 10mg twice daily for nine weeks (after a two-week placebo run-in phase) Placebo (n=119) Matched placebo twice daily for eleven weeks	Multiple Sclerosis N = 239 **Age (Mean [SD]):** Fampridine: 51.8 (9.6) years Placebo: 51.7 (9.8) years **Type of multiple sclerosis:** Primary progressive: 31 Relapsing-remitting: 83	Measures of walking ability and upper limb mobility/dexterity at ≤6 months: Timed 25-Foot Walk Test 12-item Multiple Sclerosis Walking Scale Adverse events at ≤6 months: Withdrawal due to adverse events	Was included in the previous version of the guideline for this review Downgraded for indirectness as time-point was <3 months

Study	Intervention and comparison	Population	Outcomes	Comments
All studies were funded by industry, with the majority being supported by Biogen and others being supported by Acorda Therapeutics.				
	Concomitant therapy: No additional information	Secondary progressive: 7 **EDSS (mean [SD]):** Fampridine: 5.8 (1) Placebo: 5.6 (1.2) **Disease modifying treatment status:** 69.2% in fampridine and 69.7% in placebo groups said to have been receiving concomitant immunomodulator treatment with an interferon, glatiramer acetate or natalizumab	Urinary tract infection Complex partial seizure Fall Headache Patella fracture Changes in validated disability or impairment scales at ≤6 months: Ashworth score	
Hobart 2019[17] ENHANCE trial Across 12 different countries, including the UK	Fampridine (n=317) Prolonged-release fampridine 10mg twice daily for twenty-four weeks Placebo (n=319) Matched placebo twice daily for twenty-four weeks Concomitant therapy: 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.	Multiple Sclerosis N = 636 **Age (Mean [SD]):** Fampridine: 49.0 (9.8) years Placebo: 48.8 (10.5) years **Type of multiple sclerosis:** Primary progressive: 86 Relapsing-remitting: 324 Secondary progressive: 194 Progressive-relapsing: 29 EDSS (median [range]): Fampridine: 6.0 (4.0-7.0) Placebo: 5.5 (4.0-7.0)	Measures of walking ability and upper limb mobility/dexterity at ≤6 months: Timed Up and Go test 12-item Multiple Sclerosis Walking Scale ABILHAND score Health-related quality of life at ≤6 months: Multiple Sclerosis Impact Scale 29 – Physical impact subscale Adverse events at ≤6 months: Mortality Withdrawal due to adverse events Urinary tract infection Seizures Fall	ENHANCE trial

Study	Intervention and comparison	Population	Outcomes	Comments
All studies were funded by industry, with the majority being supported by Biogen and others being supported by Acorda Therapeutics.				
	Physiotherapy and rehabilitation were allowed.	**Disease modifying treatment status:** Disease-modifying therapies could be continued if the drug and dose remained stable throughout the study.	Headache Changes in validated disability or impairment scales at ≤6 months: EDSS score	
Hupperts 2016[18] MOBILE trial Across 6 different countries, including the UK Other publications associated with this study: Gasperini 2016[9]	Fampridine (n=68) Prolonged-release fampridine 10mg twice daily for twenty-four weeks Placebo (n=64) Matched placebo twice daily for twenty-four weeks Concomitant therapy: No additional information	Multiple Sclerosis N = 132 **Age (mean):** Fampridine: 49.8 years Placebo: 49.8 years **Type of multiple sclerosis:** Primary progressive: 18 Relapsing-remitting: 44 Secondary progressive: 68 Progressive-relapsing: 2 **EDSS (mean [range]):** Fampridine: 5.6 (4.0-7.0) Placebo: 5.9 (4.0-7.0) **Disease modifying treatment status:** Most stable concomitant therapies for the treatment of MS were permitted.	Measures of walking ability and upper limb mobility/dexterity at ≤6 months: Timed Up and Go Test 12-item Multiple Sclerosis Walking Scale Health-related quality of life at ≤6 months: Multiple Sclerosis Impact Scale 29 – physical Adverse events at ≤6 months: Withdrawal due to adverse events Urinary tract infection Seizures Fall Headache Changes in validated disability or impairment scales at ≤6 months: Patient Global Impression of Change scale	MOBILE trial The study also reports the following outcomes incompletely or as median values meaning they could not be analysed: • Multiple Sclerosis Impact Scale 29 – psychological subscale • EQ-5D The outcome of Patient Global Impression of Change was downgraded for indirectness as the time-point was <3 months
Jacques 2018[19] Canada	Fampridine (n=21) Prolonged-release fampridine 10mg	Multiple Sclerosis N = 41 **Age (mean [SD]):** 52.22 (8.91) years	Measures of walking ability and upper limb mobility/dexterity at ≤6 months:	

Study	Intervention and comparison	Population	Outcomes	Comments
All studies were funded by industry, with the majority being supported by Biogen and others being supported by Acorda Therapeutics.				
	twice daily for fourteen weeks Placebo (n=20) Matched placebo twice daily for fourteen weeks Concomitant therapy: All people underwent rehabilitation as per the NeuroGym EAMT approach, consisting of three sessions of one hour per week for a period of six weeks. This was followed by an eight-week observational period where people kept taking their medication and were encouraged to continue a training program at home.	**Type of multiple sclerosis:** Primary progressive: 9 Relapsing-remitting: 20 Secondary progressive: 12 **EDSS ≥6:** Fampridine: 6 Placebo: 7 **Disease modifying treatment status:** Not stated/unclear	6-Minute Walk test Timed 8-meter walk Adverse events at ≤6 months: Withdrawal due to adverse events	
Jensen 2016[20] Denmark	Fampridine (n=17) Slow-release fampridine 10mg twice daily for four weeks Placebo (n=20) Matched placebo twice daily for four weeks Concomitant therapy: No additional information	Multiple Sclerosis N = 37 **Age (mean [SD]):** Fampridine: 50.8 (6.5) years Placebo: 48.4 (6.4) years **EDSS (mean [SD]):** Fampridine: 5.8 (0.8) Placebo: 5.5 (0.7) **Type of multiple sclerosis:** Not stated/unclear	Measures of walking ability and upper limb mobility/dexterity at ≤6 months: Timed 25-Foot walk Six Spot Step Test 9-Hole Peg Test	The population for the randomised controlled trial consisted of responders to fampridine in a previously conducted open-label enrichment phase and therefore may represent an indirect population. Downgraded for indirectness as time-point was <3 months

Study	Intervention and comparison	Population	Outcomes	Comments
All studies were funded by industry, with the majority being supported by Biogen and others being supported by Acorda Therapeutics.				
		Disease modifying treatment status: Not stated/unclear		
Marion 2020[26] Australia	Fampridine(n=20) Fampridine-modified release 10mg twice daily for eight weeks Placebo (n=20) Matched placebo twice daily for eight weeks Concomitant therapy: No additional information	Multiple Sclerosis N = 40 **Age (median [IQR]):** Fampridine: 53.5 (47.0-64.0) years Placebo: 51.5 (43.5-63.0) years **Type of multiple sclerosis:** Primary progressive: 13 Relapsing-remitting: 9 Secondary progressive: 18 **EDSS:** Mild (0-3), 15% in fampridine and 5% in placebo Moderate (3.5-5.5), 20% in fampridine and 55% in placebo Severe (≥6), 65% in fampridine and 40% in placebo **Disease modifying treatment status:** Not stated/unclear	Adverse events at ≤6 months: Withdrawal due to adverse events Urinary tract infection	Downgraded for indirectness as time-point was <3 months
Pickering 2017[33] Australia	Fampridine (n=25) Fampridine 10mg twice daily for three months Placebo (n=25) Matched placebo twice daily for three months	Multiple Sclerosis N = 25 **Age (mean [SD]):** 54.4 (11) years **Type of multiple sclerosis:** Not stated/unclear **EDSS:**	Measures of walking ability and upper limb mobility/dexterity at ≤6 months: 9-Hole Peg Test 6-Minute Walk Test Timed 25-Foot Walk Test Timed Up and Go test	Crossover trial – 30-day washout phase between treatment periods

Study	Intervention and comparison	Population	Outcomes	Comments
All studies were funded by industry, with the majority being supported by Biogen and others being supported by Acorda Therapeutics.				
	Concomitant therapy: No additional information	0.0-2.0, 32% 2.5-4.0, 44% 4.5-6.0, 24% **Disease modifying treatment status:** Not stated/unclear	Manual ability (ABILHAND score) Locomotion ability (ABILOCO score) Adverse events at ≤6 months: Discontinuation due to adverse events Headache Changes in validated disability or impairment scales at ≤6 months: Disability Sum Score Fatigue Severity Scale	
Satchidanand 2020[37] USA	Fampridine (n=45) Dalfampridine 10mg twice daily for twelve weeks Placebo (n=15) Matched placebo twice daily for twelve weeks Concomitant therapy: No additional information	Multiple Sclerosis N = 60 **Age (mean [SD]):** 49.3 (9.8) years **Type of multiple sclerosis:** Primary progressive: 1 Relapsing-remitting: 49 Secondary progressive: 11 **EDSS score (median [range]):** Fampridine: 3.5 (1.0-6.5) Placebo: 3.5 (1.5-6.5) **Disease modifying treatment status:** Not stated/unclear	Measures of walking ability and upper limb mobility/dexterity at ≤6 months: 6-Minute Walk Test Timed 25-Foot Walk test Adverse events at ≤6 months: Withdrawal due to adverse events Changes in validated disability or impairment scales at ≤6 months: Fatigue Severity Scale	

Study	Intervention and comparison	Population	Outcomes	Comments
All studies were funded by industry, with the majority being supported by Biogen and others being supported by Acorda Therapeutics.				
Valet 2021[43] Belgium	Fampridine (n=24) Received 6-week treatment with 10 mg prolonged-release fampridine twice daily either first or second, with each stage separated by a 2-week washout period Placebo (n=24) Received 6-week treatment with placebo twice daily for 6 weeks either first or second, separated by a 2-week washout period. Concomitant therapy: No additional information	Multiple Sclerosis N = 24 (23 analysed) **Age (mean [SD]):** 46.0 (10.0) years **Type of multiple sclerosis:** Primary progressive: 3 Relapsing-remitting: 8 Secondary progressive: 12 **EDSS score (median [range]):** 4 (4-5) **Disease modifying treatment status:** Majority receiving these treatments (48% interferon, 17% natalizumab, 4% fingolimod and 4% azathioprine)	Measures of walking ability and upper limb mobility/dexterity at ≤6 months: 6-Minute Walk Test Timed 25-Foot Walk Test	The population for the randomised controlled trial consisted of responders to fampridine in a 2-week run-in period where all participants received 10 mg fampridine twice daily and responders were identified, meaning this may represent an indirect population Crossover trial with 2-week washout period between stages Downgraded for indirectness as time-point was <3 months The study also reports the following outcomes incompletely or as median values meaning they could not be analysed: • MS Walking Scale-12 • EMIF – French version of Fatigue Impact Scale (total score and physical sub score) • SEP-59 – French Quality of Life Instrument
Yapundich 2015[46] USA Other publications	Fampridine (n=143) Dalfampridine extended-release 10mg twice daily for four weeks	Multiple Sclerosis N = 286 **Age (mean [SD]):** Fampridine: 53.4 (9.5) years	Measures of walking ability and upper limb mobility/dexterity at ≤6 months: 6-Minute Walk Test	Downgraded for indirectness as time-point was <3 months

Study	Intervention and comparison	Population	Outcomes	Comments
All studies were funded by industry, with the majority being supported by Biogen and others being supported by Acorda Therapeutics.				
associated with this study: Applebee 2015[3] Kantor 2015[21]	Placebo (n=143) Matched placebo twice daily for four weeks An additional group received 5mg of dalfampridine extended-release. This group was not included in the analysis as it did not fulfil the protocol criteria. Concomitant therapy: No additional information	Placebo: 52.2 (9.9) years **Type of multiple sclerosis:** Primary progressive: 23 Relapsing-remitting: 210 Secondary progressive: 44 Progressive-relapsing: 8 **EDSS (mean [SD]):** Fampridine: 4.7 (1.5) Placebo: 4.8 (1.6) **Disease modifying treatment status:** Not stated/unclear	Timed 25-Foot Walk test 12-Item Multiple Sclerosis Walking Scale Adverse events at ≤6 months: Mortality Withdrawal due to adverse events Urinary tract infection Seizures Headache	
Zorner 2016[48] Switzerland Other publications associated with this study: Weller 2020[45]	Fampridine (n=61) Prolonged-release fampridine 10mg twice daily for six weeks Placebo (n=61) Matched placebo twice daily for six weeks Concomitant therapy: No additional information	Multiple Sclerosis N = 61 **Age (Mean [SD]):** 48.6 (9.8) years **Type of multiple sclerosis:** Primary progressive: 5 Relapsing-remitting: 29 Secondary progressive: 21 **EDSS (mean [SD]):** 4.9 (1.3) **Disease modifying treatment status:** 16%, 4%, 38% and 4% had concomitant treatment with an interferon, glatiramer acetate,	Measures of walking ability and upper limb mobility/dexterity at ≤6 months: Timed 25-Foot Walk test Adverse events at ≤6 months: Urinary tract infection Headache Ankle fracture	Crossover trial – 2-week washout period Downgraded for indirectness as time-point was <3 months The study also reports the following outcomes incompletely meaning they could not be analysed: • 6-Minute Walk Test • Timed Up and Go test • 12-Item Walking Scale • Dynamic Gait Index • Motor fatigue • Cognitive fatigue

Study	Intervention and comparison	Population	Outcomes	Comments
All studies were funded by industry, with the majority being supported by Biogen and others being supported by Acorda Therapeutics.				
		natalizumab and fingolimod, respectively.		

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: fampridine versus placebo for mobility in MS

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Fampridine
Measures of walking ability and upper limb mobility/dexterity					
6-Minute Walk Test					
6-Minute walk test improvement at 2 weeks compared to baseline - ≥ 55.06 metre improvement follow up: 2 weeks	100 (1 RCT)	⊕⊕◯◯ LOW[a,b]	RR 3.04 (1.33 to 6.98)	Moderate 122 per 1,000	250 more per 1,000 (40 more to 732 more)
6-Minute walk test improvement at 2 weeks compared to baseline - ≥20% improvement follow up: 2 weeks	100 (1 RCT)	⊕⊕◯◯ LOW[a,b]	RR 3.16 (1.49 to 6.68)	Moderate 143 per 1,000	309 more per 1,000 (70 more to 812 more)
6-Minute Walk Test - mixture of change and final scores at 4-12 weeks - metres (higher is better) follow up: 4-12 weeks	147 (4 RCTs)	⊕◯◯◯ VERY LOW[a,b,c]	-	The mean 6-Minute Walk Test at 4-12 weeks (metres) was not reported for any studies.	MD 14.70 higher (0.08 higher to 29.33 higher)
6-Minute Walk Test at 2 weeks -	100 (1 RCT)	⊕⊕◯◯ LOW[a,b]	-	The mean 6-Minute Walk Test change	MD 86.9 feet higher (24.46 higher to 149.34 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Fampridine
change from baseline - feet (higher is better) follow up: 2 weeks				from baseline at 2 weeks was 41.7 feet.	
6-Minute Walk Test at 14 weeks - % change from baseline (higher is better) follow up: 14 weeks	41 (1 RCT)	⊕◯◯◯ VERY LOW[a,d]	-	The mean 6-Minute Walk Test % change from baseline at 14 weeks was 18.8%	MD 5.87 higher (3.5 lower to 15.24 higher)
Timed 25-Foot Walk Test – speed or time					
Timed 25-Foot Walk test speed improvement of >20% or ≥20% from baseline at 4-14 weeks follow up: 4-14 weeks	369 (2 RCTs)	⊕◯◯◯ VERY LOW[a,b,d]	RR 1.64 (1.20 to 2.25)	Moderate	
				201 per 1,000	129 more per 1,000 (40 more to 252 more)
Timed 25-Foot Walk test speed improvement - faster walking speed for 3/4 on-treatment visits (across 6-14 weeks) compared to max speed during off-treatment visits follow up: 6-14 weeks	588 (3 RCTs)	⊕⊕◯◯ LOW[a,b]	RR 3.77 (2.56 to 5.55)	Moderate	
				88 per 1,000	245 more per 1,000 (138 more to 402 more)
Timed 25-Foot Walk test speed improvement at 12 weeks follow up: 12 weeks	25 (1 RCT)	⊕◯◯◯ VERY LOW[a,d]	OR 1.20 (0.24 to 6.12)	Moderate	
				480 per 1,000	46 more per 1,000 (299 fewer to 370 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Fampridine
Definition of improvement unclear					
Timed 25-Foot Walk Test (speed) at 4-14 weeks - mixture of change and final scores (higher is better) follow up: 4-14 weeks	862 (4 RCTs)	⊕⊕◯◯ LOW[a,b]	-	The mean Timed 25-Foot Walk Test (speed) at 4-14 weeks was 0.1-0.17 for change scores (based on 2 of 3 studies as one did not report the control group value) and not reported for final scores (n=1).	MD 0.15 higher (0.09 higher to 0.21 higher)
Timed 25-Foot Walk Test (time) at 4-12 weeks - mixture of change and final scores (lower is better) follow up: 4-12 weeks	235 (4 RCTs)	⊕◯◯◯ VERY LOW[a,b,c,d]	-	The mean timed 25-Foot Walk Test (time) at 4-12 weeks was 0.3 for change scores (n=1) and 8.0 for final values (based on 1 of 3 studies as two did not report the control group value)	MD 1.16 lower (2.75 lower to 0.44 higher)
Timed 8-Metre Walk Test					
Timed 8-Metre Walk Test (time) at 14 weeks - % change from baseline (lower is better) follow up: 14 weeks	41 (1 RCT)	⊕◯◯◯ VERY LOW[a,d]	-	The mean timed 8-Metre Walk Test (time) % change from baseline at 14 weeks was 2.25%	MD 8.94 lower (20.78 lower to 2.9 higher)
Six Spot Step Test					
Six Spot Step Test (time) change from baseline at 4 weeks (lower is better) follow up: 4 weeks	35 (1 RCT)	⊕◯◯◯ VERY LOW[a,d,e]	-	The mean Six Spot Step Test (time) change from baseline at 4 weeks was 0.6 seconds	MD 3.85 lower (8.03 lower to 0.33 higher)
Timed Up and Go Test – speed or time					

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Fampridine
Timed Up and Go test (time) - change from baseline at 4-24 weeks (lower is better) follow up: 4-24 weeks	675 (2 RCTs)	⊕◯◯◯ VERY LOW[a,b]	-	The mean timed Up and Go test (time) change from baseline at 4-24 weeks was not reported	MD 1.11 lower (1.93 lower to 0.29 lower)
Timed Up and Go test (speed) - change from baseline at 24 weeks (higher is better) follow up: 24 weeks	633 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean timed Up and Go test (speed) change from baseline at 24 weeks was not reported	MD 0.02 higher (0.01 higher to 0.03 higher)
Timed Up and Go test improvement in speed at 24 weeks follow up: 24 weeks ≥15% improvement	764 (2 RCTs)	⊕⊕◯◯ LOW[a,d]	RR 1.30 (1.09 to 1.56)	Moderate	
				324 per 1,000	97 more per 1,000 (29 more to 181 more)
Timed Up and Go test improvement at 12 weeks (unclear whether speed or time but likely time based on baseline value given) follow up: 12 weeks Definition of improvement unclear	25 (1 RCT)	⊕◯◯◯ VERY LOW[a,d]	OR 0.80 (0.15 to 4.14)	Moderate	
				720 per 1,000	47 fewer per 1,000 (442 fewer to 194 more)
12-Item Multiple Sclerosis Walking Scale					
MSWS-12 - change from baseline at 4-24 weeks (lower is better)	1281 (5 RCTs)	⊕⊕⊕◯ MODERATE[a]	-	The mean MSWS-12 - change from baseline at 4-24 weeks was - 3.56 to 0.73	MD 3.12 lower (4.55 lower to 1.68 lower)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Fampridine
Scale from: 0 to 100 follow up: 4-24 weeks				(based on 2 of 5 studies as three did not report the control group value)	
MSWS-12 improvement compared to baseline at 24 weeks follow up: 24 weeks ≥8-point improvement	765 (2 RCTs)	⊕⊕◯◯ LOW[a,d]	RR 1.35 (1.12 to 1.62)	Moderate	
				309 per 1,000	108 more per 1,000 (37 more to 192 more)
9-Hole Peg Test – dominant or non-dominant hand					
9-Hole Peg Test - dominant hand (time) at 12-14 weeks - mix of final values and change scores (lower is better) follow up: 12-14 weeks	217 (2 RCTs)	⊕⊕⊕◯ MODERATE[a]	-	The mean 9-Hole Peg Test - dominant hand (time) at 12-14 weeks was -2.27 seconds for change scores (n=1) and 26.8 seconds for final scores (n=1)	MD 1.79 lower (5.26 lower to 1.68 higher)
9-Hole Peg Test - non-dominant hand (time) at 12-14 weeks - mix of final values and change scores (lower is better) follow up: 12-14 weeks	217 (2 RCTs)	⊕⊕⊕◯ MODERATE[a]	-	The mean 9-Hole Peg Test - non-dominant hand (time) at 12-14 was -0.32 for change scores (n=1) and 31.5 for final scores (n=1)	MD 2.6 lower (5.77 lower to 0.56 higher)
9-Hole Peg Test - unclear if dominant or non-dominant (time) at 4 weeks (lower is better) follow up: 4 weeks	35 (1 RCT)	⊕⊕◯◯ LOW[a,e]	-	The mean 9-Hole Peg Test - unclear if dominant or non-dominant (time) change from baseline at 4 weeks was 0.6 seconds	MD 0.9 lower (3.25 lower to 1.45 higher)
9-Hole Peg Test right-hand improvement	22 (1 RCT)	⊕◯◯◯ VERY LOW[a,d]	OR 0.63 (0.16 to 2.41)	Moderate	
				773 per 1,000	91 fewer per 1,000 (420 fewer to 119 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Fampridine
compared to baseline at 12 weeks follow up: 12 weeks Definition of improvement unclear					
9-Hole Peg Test left-hand improvement compared to baseline at 12 weeks follow up: 12 weeks Definition of improvement unclear	25 (1 RCT)	⨁◯◯◯ VERY LOW[a,d]	OR 1.20 (0.24 to 5.97)	Moderate 600 per 1,000	43 more per 1,000 (335 fewer to 300 more)
Health related quality of life					
Multiple Sclerosis Impact Scale-29					
MSIS-29 - mix of change and final scores at 12-24 weeks (one is clearly physical subscale unclear if other is the same or overall score; lower is better) Scale from: 0 to 100 follow up: 12-24 weeks	753 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	-	The mean MSIS-29 score at 12-24 weeks was not reported for change scores (n=1) and 71.3 for final scores (n=1)	MD 3.31 lower (5.09 lower to 1.52 lower)
MSIS-29 PHYS improvement compared to baseline at 24 weeks follow up: 24 weeks ≥7-point improvement	132 (1 RCT)	⨁◯◯◯ VERY LOW[a,d]	RR 1.54 (0.97 to 2.43)	Moderate 297 per 1,000	160 more per 1,000 (9 fewer to 425 more)
Adverse events					
				Moderate	

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Fampridine
Mortality during treatment period 4-24 weeks follow up: 4-24 weeks	1089 (3 RCTs)	⊕◯◯◯ VERY LOW[a,f]	RD 0.00 (-0.01 to 0.01)	2 per 1,000	0 fewer per 1,000 (10 fewer to 10 more)[g]
Adverse events leading with withdrawal 4-24 weeks follow up: 4-24 weeks	1921 (12 RCTs)	⊕◯◯◯ VERY LOW[a,f,h]	RD 0.02 (0.00 to 0.04)	Moderate	
				23 per 1,000	20 more per 1,000 (0 fewer to 40 more)[g]
Urinary tract infection 4-24 weeks follow up: 4-24 weeks	1902 (9 RCTs)	⊕⊕◯◯ LOW[a,d]	RR 1.18 (0.89 to 1.56)	Moderate	
				100 per 1,000	18 more per 1,000 (11 fewer to 56 more)
Confusional state (reports as reason for 1 withdrawing from study, unclear whether any more minor events occurred) 14 weeks follow up: 14 weeks	283 (1 RCT)	⊕◯◯◯ VERY LOW[a,d]	OR 3.80 (0.04 to 349.30)	Moderate	
				0 per 1,000	5 more per 1,000 (18 fewer to 27 more)[g]
Seizures (definition varies across studies with some only reporting those that led to withdrawal and unclear if any less serious events occurred) 4-24 weeks follow up: 4-24 weeks	1622 (7 RCTs)	⊕◯◯◯ VERY LOW[a,f]	RD 0.00 (-0.01 to 0.01)	Moderate	
				1 per 1,000	0 fewer per 1,000 (10 fewer to 10 more)[g]
Falls 4-24 weeks follow up: 4-24 weeks	1568 (7 RCTs)	⊕◯◯◯ VERY LOW[a,d]	RR 0.98 (0.73 to 1.32)	Moderate	
				125 per 1,000	3 fewer per 1,000 (34 fewer to 40 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Fampridine
Headache 4-24 weeks follow up: 4-24 weeks	1933 (10 RCTs)	⊕◯◯◯ VERY LOW[a,d,h]	RR 1.30 (0.92 to 1.82)	Moderate 79 per 1,000	24 more per 1,000 (6 fewer to 65 more)
Fracture (definition varies across studies and all only report those that led to withdrawal, unclear if any more serious events occurred) 6-14 weeks follow up: 6-14 weeks	577 (3 RCTs)	⊕◯◯◯ VERY LOW[a,b,d]	OR 6.14 (0.58 to 65.26)	Moderate 0 per 1,000	10 more per 1,000 (10 fewer to 30 more)[g]
Disability and impairment scales					
Multiple Sclerosis Functional Composite					
MSFC total score at 12-14 weeks - mix of change and final values (higher is better) follow up: 12-14 weeks Scale unclear	217 (2 RCTs)	⊕◯◯◯ VERY LOW[a,d,i]	-	The mean MSFC total score at 12-14 weeks was 0.08 for change scores (n=1) and for -0.5 final scores (n=1)	MD 0.4 higher (0.61 lower to 1.42 higher)
Physical Activity and Disability Survey-Revised					
PADS-R change from baseline at 4 weeks - Total score (higher is better) follow up: 4 weeks Scale unclear	42 (1 RCT)	⊕◯◯◯ VERY LOW[a,b]	-	The mean PADS-R change from baseline at 4 weeks - Total score was not reported	MD 0.3 higher (0.06 higher to 0.54 higher)
PADS-R change from baseline at 4 weeks - Exercise and Leisure sub score (higher is better)	42 (1 RCT)	⊕◯◯◯ VERY LOW[a,b,d]	-	The mean PADS-R change from baseline at 4 weeks - Exercise and Leisure sub score was not reported	MD 0.3 higher (0.03 higher to 0.57 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Fampridine
follow up: 4 weeks Scale unclear					
Overall Disability Sum Score					
Overall Disability Sum Score improvement compared to baseline at 12 weeks follow up: 12 weeks Definition of improvement unclear	25 (1 RCT)	⊕◯◯◯ VERY LOW[a,d]	OR 0.70 (0.11 to 4.59)	Moderate 720 per 1,000	77 fewer per 1,000 (500 fewer to 202 more)
Subject/Patient Global Impression of Change					
Subject Global Impression of Change - change from baseline at 14 weeks (higher is better) Scale from: 1 to 7 follow up: 14 weeks	96 (1 RCT)	⊕◯◯◯ VERY LOW[a,d]	-	The mean subject Global Impression of Change - change from baseline at 14 weeks was -0.2	MD 0.2 higher (0.25 lower to 0.65 higher)
Patient Global Impression of Change improvement compared to baseline at 2 weeks follow up: 2 weeks Definition of improvement unclear	132 (1 RCT)	⊕◯◯◯ VERY LOW[a,b.d]	RR 1.82 (1.11 to 3.00)	Moderate 250 per 1,000	205 more per 1,000 (28 more to 500 more)
ABILHAND or ABILOCO questionnaires					
ABILHAND at 12-24 weeks - mix of change and final scores (higher is	652 (2 RCTs)	⊕⊕◯◯ LOW[a,i]	-	The mean ABILHAND score at 12-24 weeks was not reported for change scores	MD 0.07 lower (2.1 lower to 1.96 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Fampridine
better) Scale from: 0 to 100 follow up: 12-24 weeks				(n=1) or final scores (n=1)	
ABILOCO at 12 weeks (higher is better) follow up: 12 weeks	25 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean ABILOCO score at 12 weeks was not reported	MD 0.3 lower (0.89 lower to 0.29 higher)
Spasticity					
Ashworth score change from baseline at 9-14 weeks (lower is better) Scale from: 0 to 4 follow up: 9-14 weeks	334 (2 RCTs)	⊕◯◯◯ VERY LOW[a,b,i]	-	The mean Ashworth score change from baseline at 9-14 weeks was -0.06 to -0.11	MD 0.04 lower (0.22 lower to 0.15 higher)
Fatigue					
Fatigue Severity Scale improvement compared to baseline at 12 weeks follow up: 12 weeks Definition of improvement unclear	25 (1 RCT)	⊕◯◯◯ VERY LOW[a,d]	OR 0.80 (0.16 to 4.03)	Moderate 360 per 1,000	50 fewer per 1,000 (277 fewer to 334 more)
Fatigue Severity Scale at 12 weeks (lower is better) Scale from: 9 to 63 follow up: 12 weeks	57 (1 RCT)	⊕◯◯◯ VERY LOW[a,d]	-	The mean fatigue Severity Scale at 12 weeks was not reported	MD 0.05 higher (0.05 lower to 0.15 higher)
Modified Fatigue Impact Scale change from baseline at 12 weeks - Total score (lower is	120 (1 RCT)	⊕⊕◯◯ LOW[a,d]	-	The mean modified Fatigue Impact Scale change from baseline at 12 weeks - Total score was -0.20	MD 7.60 lower (13.86 lower to 1.34 lower)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Fampridine
better) Scale from: 0 to 84 follow up: 12 weeks					
Modified Fatigue Impact Scale change from baseline at 12 weeks - Physical subscale (lower is better) Scale from: 0 to 36 follow up: 12 weeks	120 (1 RCT)	⊕⊕◯◯ LOW[a,d]	-	The mean modified Fatigue Impact Scale change from baseline at 12 weeks - Physical subscale was -0.2	MD 2.4 lower (5.51 lower to 0.71 higher)
Modified Fatigue Impact Scale change from baseline at 12 weeks – Cognitive subscale (lower is better) Scale from: 0 to 40 follow up: 12 weeks	120 (1 RCT)	⊕⊕◯◯ LOW[a,d]	-	The mean modified Fatigue Impact Scale change from baseline at 12 weeks – Cognitive subscale was 0.2	MD 4.80 lower (7.71 lower to 1.89 lower)
Modified Fatigue Impact Scale change from baseline at 12 weeks – Psychosocial subscale (lower is better) Scale from: 0 to 8 follow up: 12 weeks	120 (1 RCT)	⊕⊕◯◯ LOW[a,d]	-	The mean modified Fatigue Impact Scale change from baseline at 12 weeks – Psychosocial subscale was 0.18	MD 0.76 lower (1.67 lower to 10.15 higher)

a. Downgraded by 1 increment if there were some concerns about the majority of the evidence, and downgraded by 2 increments if the majority of the evidence was at high risk of bias

b. Downgraded by 1 increment as the majority of the evidence reports the outcome at a time-point <3 months

c. Downgraded by 1 increment due to unexplained heterogeneity based on point estimates differing between the studies. Although all four studies have the same direction of effect the size of the difference varies.

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. For specific MIDs used for continuous outcomes, see footnotes in GRADE tables in Appendix F of this evidence review.

e. Population randomised was selected from people identified as fampridine responders in a previous open-label phase and may not represent the general population interested in

f. Downgraded by 2 increments as imprecision was considered to be very serious based on an OIS of <80%. Imprecision was assessed based on calculated OIS value due to zero events in both arms of some studies.

g. Absolute effect calculated manually using risk difference due to zero events in one or both arms of at least one study.

h. Publication bias not assessed as evidence already graded very low quality

i. Downgraded by 1 increment due to unexplained heterogeneity based on point estimates differing in direction and a high I2 value.

See Appendix F for full GRADE tables.

Table 4: Fampridine versus placebo for mobility in MS – outcomes that could not be analysed with GRADE due to incomplete reporting or reporting as median values

Study	Outcome definition	Results	Fampridine group (n analysed)	Placebo group (n analysed)	Risk of bias
Measures of walking ability and upper limb mobility/dexterity					
6-Minute Walk Test, distance					
Zorner 2016[48] Crossover trial	% change from baseline in 6-MWT distance at 6 weeks	Results were only reported in the form of a graph and a statement that 6-MWT distance was significantly increased under fampridine treatment compared to placebo (P<0.0001), with a 4% change from baseline in the fampridine group. The percentage change from baseline in the placebo group was not explicitly reported, but from the graph appeared to be ~-4%.	N=55	N=55	High Indirectness as reported at time-point <3 months
Timed 25-Foot Walk Test, speed					
Goodman 2008[11] Parallel trial	% change from baseline in T25FW test speed at 14 weeks	Results were only reported in the form of a graph with the mean % change in the 10 mg fampridine group appearing to be >2 times higher than in the placebo group.	N=51	N=46	High
Zorner 2016[48] Crossover trial	% change from baseline in T25FW test speed at 6 weeks	Only mean values under each treatment were reported: • Fampridine: 9% change from baseline • Placebo: 2% change from baseline	N=55	N=55	High Indirectness as reported at time-point <3 months

Study	Outcome definition	Results	Fampridine group (n analysed)	Placebo group (n analysed)	Risk of bias
		Graph also provided and statement in text that the percentage change from baseline under fampridine was significantly higher compared to under placebo (P<0.0001).			
Timed Up and Go Test, speed					
Hupperts 2016 (MOBILE trial)[18] Parallel trial	% change from baseline in TUG test speed at 24 weeks	Results were only reported in the form of a graph and a statement that fampridine treatment resulted in a greater median improvement from baseline in TUG speed compared to placebo.	N=68	N=63	High
Timed Up and Go Test, time					
Zorner 2016[48] Crossover trial	TUG test time, final values at 6 weeks	Results were only reported in the form of a graph and a statement that no significant changes on this test were identified under fampridine treatment.	N=55	N=55	High Indirectness as reported at time-point <3 months
12-Item Multiple Sclerosis Walking Scale					
Hupperts 2016 (MOBILE trial)[18] Parallel trial	Change from baseline on MSWS-12 at 24 weeks	Results were only reported in the form of a graph and a statement that fampridine treatment resulted in a greater median improvement from baseline in MSWS-12 compared to placebo.	N=68	N=64	High
Valet 2021[43] Crossover trial	Score in fampridine group relative to placebo after 6-week treatment periods.	Appear to be median values with interquartile range (or possibly 95% CI) as this is how they were reported at baseline and no SE reported for the results: 1.7 (-10.0 to 11.3) in fampridine vs. placebo after 6-week treatment periods separated by 2-week washout period	N=23	N=23	Some concerns Indirectness as reported at time-point <3 months
Zorner 2016[48] Crossover trial	Change from baseline on 12-Item Walking	Results were only reported in the form of a graph and a statement that no significant changes on this test were identified under fampridine treatment.	N=55	N=55	High Indirectness as reported at

Study	Outcome definition	Results	Fampridine group (n analysed)	Placebo group (n analysed)	Risk of bias
	Scale at 6 weeks				time-point <3 months
Dynamic Gait Index					
Zorner 2016[48] Crossover trial	Dynamic Gait Index, final values at 6 weeks	Results were only reported in the form of a graph and a statement that no significant changes on this test were identified under fampridine treatment.	N=55	N=55	High Indirectness as reported at time-point <3 months
Health related quality of life					
Multiple Sclerosis Impact Scale-29, Physical subscale					
Hupperts 2016[18] and Gasperini 2016[9] (MOBILE trial) Parallel trial	Change from baseline on MSIS-29 Physical subscale at 24 weeks	Results were only reported in the form of a graph and a statement that fampridine treatment resulted in a greater median improvement from baseline in MSIS-29 Physical score compared to placebo. The second paper also reported that at week 24 there was an 89% difference between fampridine and placebo groups in terms of mean change from baseline.	N=68	N=64	High
Multiple Sclerosis Impact Scale-29, Psychological subscale					
Hupperts 2016[18] and Gasperini 2016[9] (MOBILE trial) Parallel trial	Change from baseline on MSIS-29 Psychological subscale at 24 weeks	The second paper provided results only in a graph and stated that at week 24 there was a 148% difference between fampridine and placebo groups in terms of mean change from baseline.	N=68	N=64	High
EQ-5D-5L Visual Analogue Scale					
Hupperts 2016 (MOBILE trial)[18] Parallel trial	EQ-5D-5L VAS, difference between groups at 24 weeks	Reported in the paper as the median treatment difference (95% CI) between groups: • 0.00 (-4.17 to 4.67)	N=68	N=64	High
EQ-5D-5L Utility Score					
Hupperts 2016 (MOBILE trial)[18]	EQ-5D-5L Utility, difference between	Reported in the paper as the median treatment difference (95% CI) between groups: • 0.00 (–0.04, 0.04)	N=68	N=64	High

Study	Outcome definition	Results	Fampridine group (n analysed)	Placebo group (n analysed)	Risk of bias
Parallel trial	groups at 24 weeks				
SEP-59 – French quality of life instrument (scale 0-100)					
Valet 2021[43] Crossover trial	Score in fampridine group relative to placebo after 6-week treatment periods.	Appear to be median values with interquartile range (or possibly 95% CI) as this is how they were reported at baseline and no SE reported for the results: -2.2 (-10.3 to 5.9) in fampridine vs. placebo after 6-week treatment periods separated by 2-week washout period	N=23	N=23	Some concerns Indirectness as reported at time-point <3 months
Disability and impairment scales					
Motor fatigue - Wurzburg Fatigue Inventory for Multiple Sclerosis					
Zorner 2016[48] Crossover trial	Change from baseline in motor fatigue (WEIMuS scale) at 6 weeks	Results were only reported in the form of a graph and a statement that no significant changes on this test were identified under fampridine treatment.	N=55	N=55	High Indirectness as reported at time-point <3 months
Cognitive fatigue - Wurzburg Fatigue Inventory for Multiple Sclerosis					
Zorner 2016[48] Crossover trial	Change from baseline in cognitive fatigue (WEIMuS scale) at 6 weeks	Results were only reported in the form of a graph and a statement that no significant changes on this test were identified under fampridine treatment.	N=55	N=55	High Indirectness as reported at time-point <3 months
Fatigue – total score and physical sub score on French version of Fatigue Impact Scale (scale 0-100)					
Valet 2021[43] Crossover trial	Score in fampridine group relative to placebo after 6-week treatment periods.	Appear to be median values with interquartile range (or possibly 95% CI) as this is how they were reported at baseline and no SE reported for the results: <u>Total score:</u> -1.7 (-12.9 to 9.5) in fampridine vs. placebo after 6-week treatment periods separated by 2-week washout period <u>Physical sub score</u> -2.1 (-17.6 to 13.3) in fampridine vs. placebo after	N=23	N=23	Some concerns (for total score and physical sub score) Indirectness as reported at time-point <3 months

Study	Outcome definition	Results	Fampridine group (n analysed)	Placebo group (n analysed)	Risk of bias
		6-week treatment periods separated by 2-week washout period			

1.1.7 Economic evidence

1.1.7.1 Included studies

Three health economic studies with the relevant comparison were included in this review[1, 28, 40, 41].

These are summarised in the health economic evidence profile below (**Table 5**) and the health economic evidence tables in Appendix H.

1.1.7.2 Excluded studies

One relevant health economic study was excluded due to assessment of limited applicability and methodological limitations[47]. Of note, All Wales Medicines Strategy Group also conducted a health economic analysis of fampridine upon which a decision to recommend the drug using a patient access scheme was made.[2] However due to confidentiality, all results are redacted and so this study was excluded prior to assessment of applicability and methodological quality.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Summary of included economic evidence

Table 5: Health economic evidence profile: Fampridine versus usual care

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Scottish Medicines Consortium 2020[41] Scottish Medicines Consortium 2018[40] (Scotland)	Partially applicable [(a)]	Potentially serious limitations [(b)]	• Decision tree and Markov model • Cost-utility analysis (QALYs) • Population: Adults with MS with walking disability (EDSS scores 4-7) • Comparators: 1. Best supportive care (BSC) 2. Fampridine treatment (10mg orally twice daily for 24 weeks) • Follow-up: 5 years Base case analysis for 2020 SMC submission included a patient access scheme (commercial in confidence). 2018 submission included results using fampridine list price.	£2,105[(c)]	0.16	£13,156[(d)]	Probability fampridine treatment cost effective (£20/30k threshold): Not report (NR) Uncertainty: Results were most sensitive to the assumption that utility values persisted between week 24 to the 5-year time horizon and the withdrawal rate of BSC, when varying by 95% confidence intervals. Scenario analyses with the greatest upward impact on the ICER were the use of utility values derived from EQ-5D-3L data from the ENHANCE study or where treatment-specific utility differences were removed from the model. A prior submission of this economic model to the SMC in 2018 reported the ICER using the list price for (instead of with a PAS).

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
							The ICER was £44,739 when the MOBILE utility data was used (EQ5D-5L, not mapped to EQ5D-3L) and £149,659 when the ENHANCE utility data was used (EQ5D-3L). They included a number of other scenarios, including using the MOBILE EQ5D-5L mapped to EQ5D-3L, the ICER was £92,961.
National Institute for Health and Care Excellence, P.188, 2014[28] (UK)	Partially Applicable[e]	Potentially serious limitations [f]	• Simple cost-utility analysis (QALYs) based on an RCT included in the clinical review of NICE CG186: Goodman et al. (2010) • Population: Adults with MS who have responded to treatment with fampridine. • Comparators: 1. No fampridine 2. Fampridine treatment (10mg orally twice daily) • Time horizon: one year.	£4,719 [g]	0.029	£160,884	Probability fampridine treatment cost effective (£20/30k threshold): NR Threshold analysis: change in incremental EQ-5D-3L for the ICER to decrease to £20,000/QALY is 0.236. Assuming baseline MSWS-12 scores and MSWS-12 score at 9 weeks in placebo group are unchanged, this corresponds to a decrease in the MSWS-12 score in the fampridine responders' group by of 52.11 (compared to the 6.04 reported in the study).
Acosta 2021[1] (Sweden)	Partially applicable[h]	Potentially serious limitations[i]	• Markov model • Cost-utility analysis (QALYs)	£1,249 [j]	0.12	£10,411	Probability fampridine treatment cost effective (£20/30k threshold): NR

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			• Population: Adults with MS with walking disability (EDSS scores 4-7) • Comparators: 1.Best supportive care (BSC) 2.Fampridine treatment (10mg orally twice daily for 24 weeks) • Time horizon: 20 years				Results were most sensitive to the T25FW score at baseline, the utility value to responders at week 24 and carried forward, the cost of professional care, PR-fampridine withdrawal rate and the cost of a day off work. Results from sensitivity analyses were generally insensitive to variations in patients' baseline characteristics. Scenario analyses with the greatest upward impact on the ICER were the use of utility values from the PR-fampridine responders at baseline for the BSC group. Using EQ-5D-5L values from MOBILE or the pooled utility data from the combined ENHANCE and MOBILE trials decreased the ICER. A societal perspective scenario analysis decreased the ICER.

Abbreviations: BSC = Best supportive care; ICER = incremental cost-effectiveness ratio; MS = multiple sclerosis; NA = not applicable; NR = not reported; QALYs= quality-adjusted life years. SMC = Scottish Medical Consortium. T25FW = Timed 25-foot walk.

(a) Utility estimates were derived from the EQ-5D-5L (MOBILE) and mapped to the EQ-5D-3L using an algorithm. No discounting reported.

(b) Intervention effects and outcomes were obtained from several RCTs. The reason for selecting certain outcomes from certain trials was not provided and so it was difficult to assess the extent to which bias may have been introduced without referring to primary studies. The analysis was based on two out of the 14 studies included in the

clinical review and has not used meta-analysed results in its analysis and so may not reflect the full body of clinical evidence available. Only the cost of treatment differed; all other resources were assumed the same for both treatment arms. The cost of fampridine and therefore total costs were withheld from the report due to commercial sensitivity. Total and incremental costs were not reported; incremental costs were back calculated given incremental QALYs and ICER. Deterministic scenario analysis was completed, and results were reported. Probabilistic sensitivity analyses were not conducted/reported. SMC authors did not include a declaration of conflicts of interest, though presumably this is publicly available through their website.

(c) 2020 and 2018 UK pounds for 2020 and 2018 SMC submissions respectively. Cost components incorporated: Medicine acquisition, monitoring and response assessment for fampridine, background resource use (GP and outpatient visits, inpatient days and emergency hospital visits), and adverse events.

(d) The base-case ICER was £13,156 when the list price was adjusted using a Patient access scheme (PAS).

(e) Difference in QALY calculated as the incremental change in EQ-5D-3L score between baseline and follow-up using an algorithm that mapped MSWS-12 scores to EQ-5D-3L scores. The improvement in EQ-5D was assumed to be constant over a year.

(f) Analysis based on a single RCT (Goodman 2009) and therefore is not representative of full body of available evidence. Utilities were estimated through a mapping function which is associated with limitations. Only fampridine costs included. Costs for identification of responders (non-responder costs), monitoring and adverse event costs have not been included.

(g) 2014 UK pounds. Cost of drug treatment only.

(h) Swedish health care perspective; may not reflect UK NHS current practice. Discounted costs and outcomes at an annual rate of 3% (3.5% is the preferred rate stated in the NICE reference case).

(i) Due to the lack of long-term clinical trial or resource use data for 12-item MS walking scale (MSWS-12) that was used to measure treatment response, disease progression was defined using a different measure (T25FW). Long-term treatment effect had to be extrapolated as the T25FW Data collected in extension studies was only available up to 5 years following the end of the original Phase III trials. Long-term utilities were estimated by carrying the last observed value (week 24) forward to 20 years, creating uncertainty towards the degree to which these values reflect utility in the patient population in the long run. The values used for resource use data were not specific to the Swedish market. Probabilistic sensitivity analysis (PSA) only provided for societal not healthcare perspective. The PSA did not account for the possible pairwise correlations between relevant inputs and may therefore overestimate the variability of the probabilistic results displayed in the cost-effectiveness plane.

(j) 2018 Swedish Krona converted to UK pounds[32]. Cost of fampridine is lower in Sweden compared to the UK list price (£109 versus £362 per 56-pack (28-day supply)). Cost components incorporated: Both direct (PR-fampridine drug cost, monitoring and assessment costs, healthcare professionals, hospitalizations, treatment of AEs, cost of care and modifications/aids) and indirect (absence from work) costs were estimated in the base-case analysis to reflect the societal perspective. Societal costs included and presented here as a scenario analysis only.

Please note, the incremental QALYs are different between the three studies above (NICE 2014, SMC 2020 and Acosta 2021) due to the economic analyses adopting different time horizons (1 year, 5 years and 20 years) and the use of different clinical evidence to estimate QALYs (Goodman 2009:[13] MSWS-12 scores mapped to EQ5D-3L, MOBILE RCT:[18] EQ5D-5L mapped to 3L and ENHANCE RCT:[16] EQ5D-3L). In addition, both Acosta and the SMC analyses applied baseline utilities that differed between comparators, accounting for the higher QALY gain. The SMC has the highest QALY gain due to applying MOBILE utility data and treatment response rates, which were more favourable to fampridine compared to estimates from ENHANCE, which Acosta used for the base case.

The SMC summarised the following as the main weaknesses with the analysis:

- The ICER results are upwardly sensitive to using the EQ-5D-3L from ENHANCE (£25,690/QALY) versus the EQ-5D (3L or 5L) data from MOBILE. The company asserted that the EQ-5D-3L is not sensitive enough to capture changes in quality of life in patients treated with fampridine due to the limited number of response categories in the questionnaire. It remains uncertain whether the EQ-5D-3L, or EQ-5D-5L mapped to the EQ-5D-3L predicts a more reliable estimate of utility outcomes or whether differences in utility data are in part due to the MOBILE study having a better response than the ENHANCE study.
- Utility values are modelled separately for responders and non-responders in each treatment arm. The submitting company justified this assumption with recourse to trial data showing not just more responders with fampridine than BSC but also that there is a greater absolute difference from baseline in the MSWS-12 between fampridine responders and BSC responders. While this is noted, it remains an area of uncertainty and leads to increased ICERs when applying the same utility values by treatment arm for responders and non-responders.
- Beyond week 24 in the model, the company estimated long-term utilities by carrying the last observed value (week 24) forward and assuming these utility values apply for the remainder of the five-year time horizon. This approach is not aligned with the modelled time-horizon, which is longer than the observation period, therefore the degree to which this approach reflects utility in the patient population beyond 24 weeks is uncertain. The ICER is sensitive to the EQ-5D data time point applied over the model time horizon.
- The model combines a range of data sources and the compatibility of these data sources in terms of outcome measures (using MSWS-12 for efficacy and T25FW for progression) and patient characteristics is uncertain.
- There is some imbalance in the treatment and control groups at baseline in the key data source for the base case utility weights (the MOBILE study). The mean time since diagnosis was 12.4 years in the control (BSC) group and 10.9 years in the treatment (fampridine) group. This could lead to bias with patients perhaps being healthier, with less time to progression, in the fampridine arm than BSC.

1.1.9 Economic model

Although a number of health economic studies have been identified in the literature, these studies either include a reduced price which is not reflective of the current list price for fampridine[1, 41] or do not include all of the available quality of life evidence from the latest trials of fampridine (ENHANCE and MOBILE)[28]. As a result, in this guideline update, the cost-effectiveness of fampridine was one of the areas which was prioritised for original health economic modelling. The analysis was also undertaken to address the limitations of the previous models, with a primary focus on finding the best approach to pool and extrapolate the utility data from ENHANCE[16] and MOBILE trials[24]. As the committee were aware that the cost of fampridine remained high and therefore unlikely to be cost-effective, the aim of the analysis was also to identify the price at which fampridine would be considered a cost-effective treatment.

Model methods

A technical report for this analysis including full details of all methods and model inputs is available in a separate PDF: ‘Appendix A Health economic model write-up’.

A cost–utility analysis was undertaken to compare fampridine (10mg twice daily) plus best supportive care (fampridine) to best supportive care alone (BSC) in adults with multiple sclerosis as defined in the revised McDonald criteria for at least three months, investigator-assessed walking impairment and an expanded disability status scale (EDSS) score of 4 to 7. This analysis took a current UK NHS and personal social services perspective. A Markov model was constructed in order to calculate costs and QALYs over a 5-year time horizon, using 4-week cycles. Of note, the reason for choosing a 5-year time horizon rather than a lifetime horizon was twofold: firstly, fampridine is not associated with a reduced or increased risk of death, negating the need for a lifetime horizon. Secondly, the model applies EQ-5D utility as the mean change over the 24-week trial period collected from the fampridine and placebo arms, which was then carried forward over the remainder of the 5-year time horizon. It would be difficult to justify that week 24 utility values would continue to be representative for a period longer than 5 years. The committee considered that extrapolating to 5 years was appropriate as published evidence suggests that fampridine responders sustained an improved walking speed over 5 years compared with non-responders, with walking speed decreasing over time[10]. Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance. An incremental analysis was undertaken.

The clinical outcomes incorporated in the model were: quality of life (EQ-5D-3L), fampridine treatment response assessed using the 12-item Multiple Sclerosis Walking Scale (MSWS-12), walking ability progression over time using the Timed 25-foot walk (T25FW), non-serious adverse events (AEs) of interventions and death due background mortality (adjusted for an MS population).

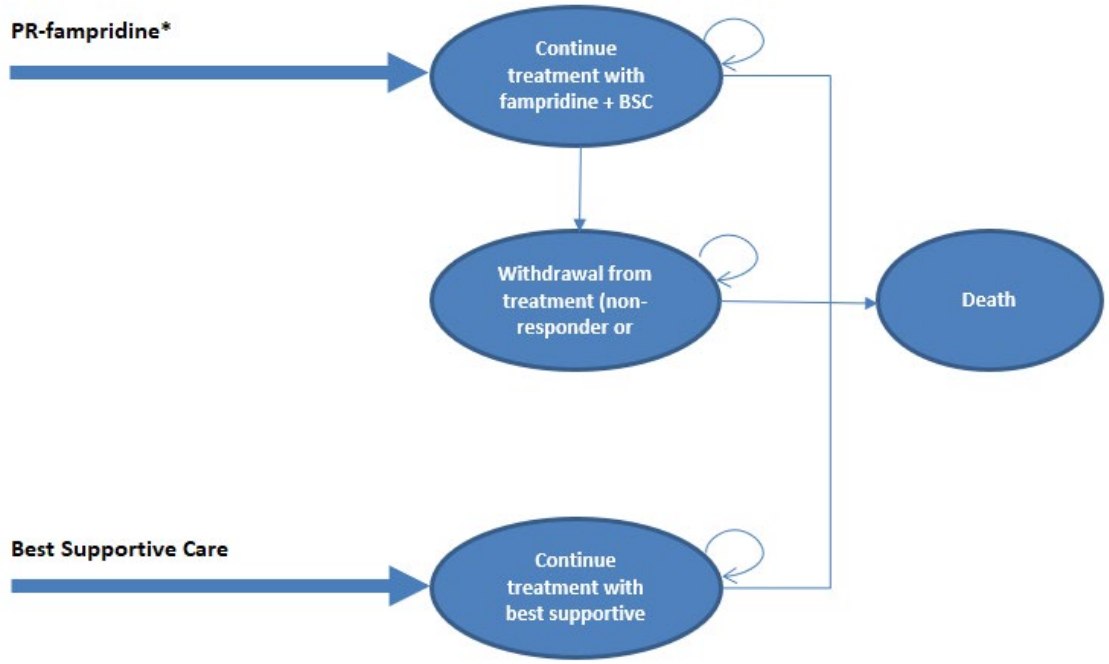
The model captured the impact of fampridine in two ways: improvement in quality of life and slower rate of decline in walking speed over time. The latter in turn would reduce healthcare and personal social services (PSS) resource use, as people with slower walking speeds can incur considerable costs associated with poorer health outcomes and the provision of mobility aids, home/workplace adaptations, and the requirement for both formal and informal care in order to achieve activities of daily living (ADLs). Long-term natural progression of walking speed decline was estimated using T25FW scores due to the absence of long-term clinical data for MSWS-12 (12-item MS walking scale).[22, 10] Data from an Adelphi study [34] which provided a correlation between T25FW and resource use was used to then estimate total healthcare and PSS resource use for fampridine compared to BSC-treated individuals. It was assumed that once people were classed as fampridine non-responders or withdrew from fampridine treatment, they would have the same natural progression of walking speed decline as BSC-treated individuals.

The Markov model was comprised of four health states (Figure 1). For those receiving BSC alone, they enter the model in the ‘continue treatment with BSC’ health state. People receiving fampridine incurred the drug and response assessment costs until the end of the responder-identification period, which is set at four weeks (one cycle) post treatment initiation. Response was defined as any participant who achieved a mean improvement from baseline of at least eight points on the twelve-item multiple sclerosis waking scale (MSWS-12) score over 24-weeks. It was deemed appropriate to use the 24-week mean improvement in MSWS-12 for the 4-week responder-identification as the improvement over placebo reported in ENHANCE was observed from two weeks and maintained over the 24 weeks. This approach was also taken in the previous health economic models. The fampridine summary of product characteristics’ therapeutic indication for a responder assessment at two to four weeks was based in part upon this evidence.[17] If they are classified as non-responders, they enter the ‘withdrawal from treatment’ health state. If they are classified as responders, they would then enter the ‘continue treatment with fampridine and BSC’ health state. At each cycle there is a probability that those who are in the ‘continue treatment with fampridine and BSC’ health state enter the ‘withdrawal from treatment’ health state due to any reason including lack of response to treatment, AEs or other reasons. Once people withdraw from fampridine treatment they are assumed to incur costs equal to those in the

'continue treatment with BSC' health state, reflecting clinical practice. Utilities for the BSC were calculated by applying the pooled change from baseline of the placebo arms of the MOBILE and ENHANCE trials to the pooled baseline placebo utilities. Utilities for people in the 'continue treatment with fampridine and BSC' and 'withdraw from treatment' health states were calculated by applying the mean difference in change from baseline taken from the pooled 'fampridine responders' and 'non-responders' arms of the MOBILE and ENHANCE trials, respectively. Death was an absorbing state in the model, and patients could transition from any health state to the death state at any cycle in the model. Of note, the utility values were taken from post hoc responder analyses of ENHANCE and MOBILE. As these were post hoc responder analyses, they did not meet the clinical review protocol and so were not included in clinical review above but are presented in the full model write up (Appendix A).

Despite evidence suggesting an observed walking speed improvement following the re-initiation of fampridine[10] it was conservatively assumed that those who enter the 'withdrawal from treatment' health state cannot transition back to the 'continue treatment with fampridine and BSC' health state and all treatment effects is lost.

Figure 1: Model structure



Abbreviations: BSC, best supportive care; PR, prolonged-release
** In the first cycle, participants in the fampridine group incurred treatment costs and assessment costs for both health states to account for response evaluation*

The probability of non-serious adverse events for fampridine and BSC were included in the analysis and were applied in each cycle for each health state. These were taken from the ENHANCE study and the evidence identified in the clinical review. MS relapses were assumed to be unrelated to fampridine treatment and associated with inflammatory disease activity and were therefore excluded from the model. Only adverse events occurring in ≥ 5% of patients were included in the analysis. As only non-serious adverse events occurred in ≥ 5% of patients these were the only AEs incorporated in the model.

Model inputs are described in full in the separate technical report, an overview of some of the model inputs is reported in Table 6. Note, healthcare resource use and PSS resource use and associated costs by T25FW are not reported in this summary table.

Of note, the health economic model only uses a subset of the RCT evidence reported in the clinical review above. In terms of estimating the probability of fampridine response and quality of life, ENHANCE and MOBILE RCTs were included as they were the only two RCTs that reported the MSWS-12 improvement compared to baseline at 24 weeks and both studies were alone in undertaking post-hoc analyses that collected EQ-5D data.

Table 6: Overview of parameters used in the model

Input	Data	Source
Comparators	Fampridine BSC	ENHANCE Study 2019[17]
Population	Adults with MS with walking disability (EDSS 4 to 7)	Biogen 2018
Perspective	UK NHS & PSS	NICE reference case[27]
Discount rate	Costs: 3.5% Outcomes: 3.5%	
Time horizon	5 years	SMC 2020, AWMSG 2019[2, 41]
Cohort settings		
Age, years	48.9	ENHANCE 2019[17]
Female, n (%)	72%	Public Health England 2020[42]
Baseline probabilities		
Baseline T25FW (feet per second)	2.10 (SE: 0.2)	Baseline values from MS-F203[13] and MS-F204[12] trials
Age and MS adjusted general population mortality rate	Variable	ONS English life tables 2017-19[31] and MS specific SMRs from Manouchehrinia 2016[25]
Treatment effects		
Probability of response to fampridine treatment	0.432	Pooled analysis of ENHANCE (2019)[17] and MOBILE (2016)[18]
4-weekly probability of treatment withdrawal	0.007 (95% CI 0.0 to 0.01)	Pooled analysis of long-term extension studies of MSF203 and MS-F204[38]
Adverse events (AEs)		
Non-serious AE probability – fampridine	0.09 (95% CI 0.06 to 0.12)	ENHANCE[17]
Non-serious AE probability – BSC	0.06 (95% CI 0.04 to 0.09)	
Utilities		
BSC	[redacted]	Pooled estimates from ENHANCE and MOBILE (mean over 24 weeks, adjusted to pooled BSC at baseline)
Fampridine non-responder	[redacted]	
Fampridine responders	[redacted]	
AE disutility	[redacted]	Acosta 2021[1]

Costs		
28-day supply of Fampyra 10mg modified-release tablets (Biogen Idec Ltd)	£362	BNF, NHS indicative price: 56 tables (Hospital only)[5]
Responder assessment at 4 weeks	£38.33	PSSRU 2020[7], 30 min appointment with hospital- based Band 6 physiotherapist and a 5-minute Neurologist visit. Qualification costs included (excluding individual and productivity costs).
AE costs		
UTI	£36.99	PSSRU 2020[7], Assumes band 6 nurse, assume 30-minute surgery appointment (Surgery consultation time by a clinical nurse specialist from PSSRU 2015), as well as the average cost of two antibiotics commonly prescribed and urine testing (NHS 2018/2019[30]; Little 2009[23]).
Fall	n/a	No cost to NHS as these were described as non-serious adverse events in the clinical trial and would therefore not necessitate medical intervention from a health care professional.
Headache	n/a	
Nasopharyngitis	n/a	
Back pain	£34.89	Calculated assuming 50% visit a GP while the other 50% visit a community physiotherapist, Band 6 (assume 40 min appointment). PSSRU 2020[7], Qualification costs included (excluding individual and productivity costs).
Upper respiratory tract infection	£3.78	Calculated assuming 10% visit a GP and get amoxicillin prescription (Amoxicillin 500mg three times daily, 5 days). Dose and unit cost from BNF accessed June 2021. PSSRU 2020[7], Qualification costs included (excluding individual and productivity costs). Assumes 9.22 min consultation.
Cardiovascular disorders (palpitations, tachycardia, arrhythmia)	£36.55	PSSRU 2020[7], Qualification costs included (excluding individual and productivity costs). Assumes 9.22 min GP consultation.
Rash	£15.25	PSSRU 2020[7], Qualification costs included (excluding individual and productivity costs). Assumes 9.22 min consultation.

Abbreviations: AWMSG = All Wales Medicines Strategy Group, BNF = British national formulary, EDSS = Expanded disability status score, PSSRU = Personal social services research unit, SMC = Scottish Medicines Consortium, SMR = Standardised mortality ratio, T25FW = Timed-25-foot walk.

**AE unit costs were fixed but were made probabilistic using estimates of uncertainty for each of the AE rates reported in ENHANCE or clinical review meta-analyses which were used to weight the unit costs of each AE to estimate an average AE cost for BSC and fampridine.*

The model was built probabilistically to account for the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 5,000 times for the base-case analysis and 5,000 times for each sensitivity analysis – and results were summarised in terms of mean costs and QALYs, and the percentage of time each comparator was the most cost-effective strategy at a threshold of £20,000/£30,000 per QALY gained. In addition, various sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed, and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

Results

Base case results and the threshold analysis results on the cost of fampridine using the base case inputs are presented in Table 7. Fampridine was associated with higher costs and higher QALYs. The incremental cost effectiveness ratio (ICER) for the probabilistic analysis was £82,099 per QALY gained which is significantly higher than the NICE threshold of £20,000, and therefore fampridine would be not considered cost effective. The probability of fampridine being cost effective was very low, 7%. The main driver of the results was high cost of fampridine for a marginal benefit over the 5-year time horizon. The probabilistic threshold analysis found that fampridine would be considered cost-effective by NICE if the drug cost was £202 per 4-week supply instead of the current list price of £362.

A number of sensitivity analyses (SAs) were conducted and are described in detail in the full report. Best supportive care remained cost effective in all sensitivity analyses. Changes that did not significantly impact the results were including the proportion of females from the ENHANCE trial (SA1), applying a 1.5% discount rate for cost and outcomes (SA2), applying pooled utility estimates to the baseline placebo value from ENHANCE (SA3), excluding AE disutility (SA9) and increasing the cost of the responder assessment to include a full appointment time with a neurologist (SA10).

SA5, which replicated the base case approach from the SMC[41] submission (minus the patient access scheme), had the lowest ICER (£[redacted]). This is unsurprising considering that this scenario used MOBILE EQ-5D-3L utility data and treatment response rates alone, rather than the pooled estimates with ENHANCE. MOBILE reported a higher proportion of fampridine responders and greater benefits in terms of quality of life than the ENHANCE RCT, but when these two studies are pooled in the base case, the larger ENHANCE trial carries more weight. Treatment-specific utilities were also not adjusted in this scenario; considering that fampridine responders had the highest baseline utility in the MOBILE trial, this would have further benefited fampridine in the results. A similar outcome was seen in SA6 which produced an ICER of £30,603 from applying the same approach as SA5 but using EQ-5D-5L values from MOBILE instead of EQ-5D-3L.

Removing the benefit of fampridine in terms of reduced healthcare and PSS resource use linked to better walking ability had the most significant impact on the results and created the largest ICERs (SA11 and SA12).

Applying a societal perspective to the analysis, including non-professional care costs associated with changes in T25FW speed (in addition to healthcare and PSS costs included in the base case), was not sufficient to produce a cost-effective result for fampridine, as the ICER was only reduced to £66,052 per QALY.

The threshold price that would allow fampridine to be cost-effective (£20,000/QALY) for each of the SAs was estimated. The prices were overall similar to the cost identified for the base case, ranging between £183 and £228. The exceptions were when the MOBILE EQ5D-3L and 5L utilities (unadjusted for baseline differences) were used, this resulted in fampridine costs of £323 and £285 respectively. These higher costs reflect the more favourable MOBILE trial EQ5D data being used. The other exceptions were when the healthcare resource use and healthcare and PSS resource use were not included in the analyses, this results in fampridine costs of £51 and £53 respectively. Thus, reflecting the lower of value of fampridine when the reduction in resource use from a slower decline in walking speed is removed from the model.

Table 7: Probabilistic Base case results

Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	Incr. Costs	Incr. QALYs	ICER fampridine vs BSC	NMB @£20K	Rank @£20K	Probability CE @£20K	NMB @£30K	Rank @£30K
Base-case results: Fampridine vs best supportive care (a)														
Fampridine	£56,646	£51,807	4.91	4.51	3.06	2.81	£4,662	0.06	£82,099	£4,357	2	0.07	£32,438	2
BSC	£51,685	£47,145	4.91	4.51	3.00	2.75	n/a	n/a	n/a	£7,883	1	0.93	£35,397	1
Threshold analysis on cost of fampridine in combination with base case (28-day supply fampridine cost of £202 creates £20,000 ICER)														
Fampridine	£53,227	£48,633	4.91	4.51	3.06	2.81	£1,141	0.06	£19,746	£7,551	2	0.48	£35,644	1
BSC	£52,071	£47,493	4.91	4.51	3.00	2.75	n/a	n/a	n/a	£7,537	1	0.52	£35,051	2

Abbreviations: BSC: best supportive care, CE: cost effective, LYs: life years, NMB: net monetary benefit, QALYs: quality adjusted life years, £20k: £20,000 per QALY gained, £30K: £30,000 per QALY gained.

(a) Fampridine list price cost for 28-day supply (4 weeks): £362

Limitations

The model was limited in terms of the data source that could be included as a treatment effect, as utility values were taken from post-hoc analyses that were only available up to week 24. The mean utility over 24 weeks reported in the trial was applied in the model for this time as well as up to 5 years. Alongside this, due to the lack of long-term clinical trial or resource use data for 12-item MS walking scale (MSWS-12) that was used to measure treatment response, disease progression was defined using a different measure (T25FW). There was also uncertainty around the relationship between the resource use (and therefore costs) and the treatment effect; the values used for resource use data were obtained from data from 5 European countries (albeit including the UK), with data regarding T25FW scores only reported in <10% of respondents. Furthermore, several assumptions had to be made in order to estimate unit costs and resource use.

Conclusion

In conclusion, the base case and all sensitivity analyses found that fampridine at its current list price was not the cost-effective option at a threshold of £20,000 per QALY (probability of being most cost effective 7% in base case).

All results and a full discussion of limitations and interpretation of the analysis are included in the full technical report for this analysis available in a separate document 'Appendix A Health economic model write-up'. The committee's discussion and interpretation are summarised in '1.11.12 The committee's discussion and interpretation of the evidence'.

1.1.10 Unit costs

Relevant annual unit cost of fampridine is provided below to aid consideration of cost effectiveness.

Resource	Unit costs	Source
Fampridine (10mg twice daily, cost per year)	£4,719	NHS indicative price, BNF 2020

1.1.11 Evidence statements

Effectiveness

For evidence that could be assessed using GRADE, see summary of evidence in Table 3.

See Table 4 for details of evidence that could not be analysed using GRADE.

Economic

- Two cost–utility analyses found that fampridine was cost effective compared to best supportive care for the management of mobility symptoms in people with MS (EDSS 4-7), due to either a Patient Access Scheme (PAS) in place (ICER: £13,156 per QALY gained) or the inclusion of a drug cost that was more than a third of the UK list price (£109 versus £362)(£10,411 per QALY respectively). These analyses were assessed as partially applicable with potentially serious limitations.
- Another cost–utility analysis found that fampridine was not cost effective compared to no fampridine for the management of mobility symptoms in people with MS who have responded to fampridine treatment (ICER: £160,884 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.

- One original cost–utility analysis found that fampridine was not cost effective compared to best supportive care for the management of mobility symptoms in people with MS (EDSS 4-7) (ICER: £82,099 per QALY gained). This analysis was assessed as directly applicable with potentially serious limitations.

1.11.12 The committee's discussion and interpretation of the evidence

1.11.12.1 The outcomes that matter most

All outcomes listed in the protocol were considered to be equally important for decision-making demonstrating the impact of the management of mobility in people with MS. The outcomes included in the protocol fell into four key areas: Measures of walking ability and upper limb mobility/dexterity; health-related quality of life (validated); adverse events; and changes in validated disability or impairment scales assessing overall impact of MS, motor function, spasticity and fatigue.

The preferred format of continuous outcomes (in a continuous format, such as mean and standard deviation, or a dichotomous format, for example where the number of people experiencing a certain level of improvement is reported rather than mean and standard deviation) was not specified in the protocol and any format these outcomes were reported in were therefore extracted. For some studies this meant that a dichotomous and continuous version of the same outcome were extracted (for example, final values on the Timed 25-Foot Walk Test at the end of the treatment period as a continuous measure and the proportion in each group that achieved ≥20% improvement on the Timed 25-Foot Walk Test at the end of treatment compared to baseline as the dichotomous measure), while others only reported the outcome in a continuous format and others only in a dichotomous format. Caution was noted when interpreting continuous outcomes that had been reported in a dichotomous format as there are various limitations associated with this.

Similarly, for outcomes reported continuously, the format these were reported in differed across studies, with some reporting final values at the end of treatment, some reporting the absolute change from baseline at the end of treatment and others reporting the % change from baseline at the end of treatment.

Although two different time-points for outcome-reporting were prespecified in the protocol (at 6 months and between 6 and 12 months), all evidence identified was reported at ≤6 months, with no studies reporting data for the 6–12-month time-point. Overall, most studies reported outcomes at <6 months rather than at 6 months, with only two studies (ENHANCE and MOBILE) reporting at exactly 6 months and the others reporting at a much shorter time-point. For those that did not report outcomes at 6 months, indirectness was considered to be present for those with a follow-up <3 months because for a chronic condition such as MS, it is difficult to determine whether treatments are likely to be effective medium- to long-term if the longest available follow-up is only weeks or one or two months. This approach to downgrading based on time-points was in line with other review protocols in this guideline.

Although response to treatment was an important component in the health economic model, this was not included as an outcome in the clinical review. In terms of mobility outcomes, the clinical review focused on scores on specific mobility scales rather than the dichotomous outcome of whether or not each person responded to treatment, the definition of which might vary between studies and be defined post-hoc in some cases. The clinical review did however allow inclusion of results detailing the number of people experiencing a certain level of improvement for outcomes.

<u>Measures of walking ability and upper limb mobility/dexterity</u>

An exhaustive list of scales and tests that would be relevant for inclusion was not specified in the protocol and instead the following list of examples of those that would be relevant and most likely to be reported was provided: Walking distance as measured by the 6-Minute Walk Test (2-Minute Walk Test if not available); walking speed measured on the Timed 25-Foot Walk Test (10-Minute Walk Test if not available); Get Up and Go Test; 12-Item Multiple Sclerosis Walking Scale; and 9-Hole Peg Test.

As these were examples only, any other measure of walking ability or upper limb mobility/dexterity reported in studies that appeared to be relevant were also extracted, which included the Timed 8-Metre Walk Test and Six Spot Step Test, which were reported by one study each.

The five example tests specified in the protocol were well reported across studies; however, meta-analyses were often limited to three or fewer studies due to the varying nature in which studies reported the outcomes (for example, dichotomous vs. continuous data or speed vs. time reported for particular outcomes).

These outcomes of walking ability and upper limb mobility/dexterity were important measures in order to assess the effect of fampridine on walking ability/upper limb mobility, which was the aim of the review question. Upper limb mobility outcomes were included to assess the potential effect fampridine might have in those that are confined to a wheelchair, as walking tests would not be applicable to this subpopulation.

Although other outcomes such as muscle strength and balance outcomes that may be linked to walking ability and/or upper limb mobility were identified in the studies included in the evidence review, these were not extracted as they were not considered to be direct measures of walking ability/upper limb mobility.

Health-related quality of life (validated)

An exhaustive list of scales that would be relevant for inclusion was not specified in the protocol and instead the following list of examples of those that would be relevant and most likely to be reported was provided: MS Impact Scale-29; EQ-5D; and SF-36.

As these were examples only, any other scale reported in studies that appeared to be relevant were also extracted, which included the Subject/Patient Global Impression of Change (reported in two studies), ABILHAND questionnaire (measure of manual ability; reported in two studies) and ABILOCO questionnaire (measure of locomotion ability; reported in one study). Although it was agreed these were less commonly used currently, these outcomes were included in the review as there was limited evidence for the examples given in the protocol, with only three studies providing data for the MS Impact Scale-29, one study reporting EQ-5D as median treatment difference which could therefore not be analysed by GRADE and no data for the SF-36 scale.

Outcomes covering health-related quality of life were important measures as patient-reported quality of life is very important when considering the effects of interventions and is also important in the development of economic models.

Adverse events

The following adverse events were listed in the protocol, to be reported separately: Mortality; adverse events leading to withdrawal; urinary tract infections; confusion; seizures; falls; headache; and fractures.

All of these adverse events were reported by at least one study, but the most well-reported outcomes were adverse events leading to withdrawal (twelve studies), headache (ten studies), urinary tract infection (nine studies), seizures (seven studies) and falls (seven studies). Mortality, confusion and fractures were less well-reported, with three, one and three studies reporting these outcomes, respectively. For confusion and fracture outcomes, and for some studies that reported the seizure outcome, only events leading to withdrawal were reported and there was no information as to whether any more minor events may have occurred that did not lead to withdrawal.

Adverse events were an important measure for this review to give insight into any adverse events that may be associated with fampridine treatment to balance against any effects observed on mobility outcomes, quality of life and changes in disability and impairment scales when deciding whether or not it should be recommended for use.

Changes in validated disability or impairment scales

An exhaustive list of scales that would be relevant for inclusion was not specified in the protocol and instead the following list of examples of those that would be relevant was provided:

- MS Impact Scale-29 (MSIS-29)
- Motor function, for example: Expanded Disability Status Scale (EDSS); Multiple Sclerosis Functional Composite (MSFC), Cambridge Multiple Sclerosis Basic Score (CAMBS); Functional Assessment of Multiple Sclerosis (FAMS); and National Fatigue Index (NFI).
- Spasticity, for example: Modified Ashworth Scale; Tardieu Scale; Penn Spasm Frequency Scale (PSFS), Muscle Elastography MS Scale (MEMSs); Fugl Meter Scale (FMS); Numeric Rating Scale for Spasticity (NRS-S); MS Spasticity Scale-88 (MSSS); and Patient-reported Impact of Spasticity Measure (PRISM)
- Fatigue, for example: National Fatigue Index (NFI); Fatigue Severity Scale (FSS); and Modified Fatigue Impact Scale (MFIS)

As these were examples only, any other scale reported in studies that appeared to be relevant were also extracted, which included the Physical Activity and Disability Survey-Revised (PADS-R) scale and Overall Disability Sum Score (ODSS), reported by one study each. Although it was agreed these were less commonly used currently, these outcomes were included in the review as there was limited evidence for the examples given in the protocol, with only three studies providing data for the MSIS-29, two studies reporting data for the MSFC (motor function), two studies providing results for the Ashworth scale (spasticity) and three studies providing information for the fatigue outcome (two measured using Fatigue Severity Scale and one study reporting the Modified Fatigue Impact Scale).

These outcomes covering disability and impairment scales were important measures for inclusion in the review to give insight into possible effects of fampridine across MS symptoms in general, rather than on specific walking tests. Spasticity and fatigue were considered important to include as they often co-exist with mobility impairment and overlap with/affect mobility and its treatment.

1.11.12.2 The quality of the evidence

A total of fifteen randomised controlled trials were included in this review, all comparing 10 mg fampridine twice daily to placebo. This included eleven parallel trials and four crossover trials with at least a 1-week washout period (a 1-week washout period was considered to be sufficient for fampridine when used in crossover trials as the elimination half-life is reported to be 6 hours in a European Medicines Agency report, which suggests a washout period of five days to be adequate).

The quality of the evidence as assessed by GRADE ranged from very low to moderate, with the majority being of low or very low quality. Across all outcomes, downgrading was primarily due to imprecision, indirectness based on a time-point <3 months and/or risk of bias. Within risk of bias ratings, the most common reasons contributing to a rating of ‘some concerns’ or

'high' risk of bias for an outcome were a lack of information about allocation concealment, concerns about the degree of missing data and selective reporting of results.

A number of outcomes were also downgraded for inconsistency as there was heterogeneity present in the meta-analyses that could not be explained by prespecified subgrouping strategies. Heterogeneity could not be explained for one of the following reasons: there were three or fewer studies in each meta-analysis, meaning subgroup analyses could not be performed; all (or all but one) study were in the same category for each subgrouping strategy; or when studies were split into subgroups, heterogeneity remained within the individual subgroups. A random effects analysis was used for these outcomes and downgrading for inconsistency performed as part of the GRADE quality rating.

Two outcomes (Six Spot Step Test change from baseline at 4 weeks and 9-Hole Peg Test at 4 weeks where it was unclear if results were for the dominant or non-dominant hand) were downgraded for indirectness as they were reported by a single study that had used an open-label fampridine treatment phase prior to randomisation to select for fampridine responders that were then included in the randomised trial, meaning the population may not represent the general MS population and had been selected towards those most likely to experience an effect with fampridine. In addition, the population may have represented a population less likely to experience adverse events with fampridine as some participants withdrew from the open-label phase due to adverse events. This was also the case for outcomes reported in another study – for the two outcomes that could be meta-analysed with other studies, downgrading for indirectness was not performed as the majority of the evidence, based on weighting in the meta-analysis, did not come from studies with this indirectness issue.

All studies reported outcomes that fell within time-point of 6 months specified in the protocol, with none reporting data for between 6 and 12 months. Of all of the included studies, only two reported outcomes at exactly 6 months of treatment, with the others reporting outcomes at a much shorter time-point than 6 months. For those that did not report outcomes at 6 months, indirectness was considered to be present for those with a follow-up <3 months because for a chronic condition such as MS, it is difficult to determine whether treatments are likely to be effective medium- to long-term if the longest available follow-up is only weeks or one or two months. This approach to downgrading based on time-points was in line with other review protocols in this guideline.

Although two meta-analyses included at least ten studies and would have been eligible for assessment of publication bias, these outcomes were already graded very low quality even before publication bias was considered and publication bias was therefore not assessed as it would not have led to a change in the quality rating for these outcomes.

It is noted that all studies included in the review were funded by industry, with the majority being supported by Biogen and the remaining studies being supported by Acorda Therapeutics.

The most well-reported outcomes across studies were measures of walking ability and adverse events, with health-related quality of life outcomes and the different categories of validated disability or impairment scales being reported by only two or three studies each. Upper limb mobility reported on the 9-Hole Peg Test was also not as well reported as measures of walking ability. However, despite walking ability being reported by fourteen of the fifteen included studies, meta-analyses were often limited to three or fewer studies due to difference across studies in terms of the test performed and reported (6-Minute Walk Test or Timed 25-Foot Walk Test) and the way different studies reported results for the same test (for example, as a continuous measure or as a dichotomous outcome reporting the number that reached a specific threshold of improvement compared to baseline). There was also variation within adverse events as to how well-reported they were, with withdrawal due to adverse events and headache being reported by twelve and ten studies, respectively, and outcomes of confusion and fracture being reported for one and three studies, respectively.

1.1.12.3 Benefits and harms

As outlined in the outcomes section there are four main categories of outcomes and within these there are multiple measures, meaning meta-analyses were often limited to only a few studies. Added to this were the difficulties in the generalisation of the data given only two studies reported data at the 6-month time-point specified as ideal in the protocol. The 6-month time-point was specified as for chronic conditions such as MS, it is difficult to determine whether treatments are likely to be effective medium- to long-term if the longest available follow-up is only weeks or one or two months. The limitation of studies with a shorter follow-up, meaning it is difficult to assess the medium-term effect of fampridine from these studies and to therefore draw conclusions, was noted and taken into account alongside the committee's clinical experience, which included the knowledge that fampridine may not lead to improvement in many patients but that there is a small percentage that that do seem to experience an important difference to walking ability.

The outcomes are explained and summarised below.

Measures of walking ability and upper limb mobility/dexterity

6-Minute Walk Test: across five different variations of reporting for this outcome (including two dichotomous versions and three continuous versions), based on the point estimate a possible benefit of fampridine was identified for all. However, for all but one of these, there was uncertainty in this conclusion as confidence intervals suggested uncertainty in direction and/or size of the effect. For the version where there was no uncertainty, this was a single study reporting change from baseline at 2 weeks in feet, graded moderate quality with 100 people included. Four other studies reported similar data (final values or change scores across three studies for this test at 4-12 weeks) but could not be combined with this study as they reported results in metres rather than feet. Quality across these variations ranged from very low to moderate, with all but one being from a single study. For the one where meta-analysis was possible, 147 people were included and quality was low based on GRADE. Other variations of this outcome included 41 to 100 people in the analysis.

Timed 25-Foot Walk Test – speed or time:

Speed: four variations of Timed 25-Foot Walk Test speed were reported across studies (including three dichotomous versions and one continuous version). Point estimates for two of the three dichotomous versions suggested a possible benefit of fampridine for this outcome, with the absolute effect indicating at least 100 more people per 1000 experiencing improvement compared to baseline higher than the threshold used in the definition (at least 20%, reported by two studies, or faster compared to baseline on three of four on-treatment visits, reported by three studies) compared to the placebo group. For the definition that involved faster walking speed compared to baseline on three of four on-treatment visits, confidence intervals were also consistent with this conclusion, while the definition using a 20% improvement threshold had more uncertainty as the lower confidence interval did not reach 100 per 1000. For the third dichotomous version, which was reported by a single study of 25 people and assessed as very low quality based on GRADE, the definition of 'improvement' was not clear and may have included any improvement compared to baseline; the results for this version suggested no difference as the point estimate for the absolute effect was much lower than 100 per 1000 and confidence intervals also suggested uncertainty in the direction of the effect. For the continuous version of this outcome, four studies reported either change or final scores, and the point estimate and confidence intervals suggested a possible benefit of fampridine. Quality ranged from very low to moderate across the four variations and for three of the four variations analyses included two to four studies with 369 to 862 people analysed.

Time: four studies reported time on this outcome measure as a continuous outcome, with some reporting change scores and others final scores. Quality was very low based on GRADE and included 235 people in the analysis. The point estimate suggested a possible benefit of fampridine as the time taken was lower in this group, however, there was some uncertainty in this result given the confidence intervals crossed the null line

Timed 8-Metre Walk Test – time: A single study of 41 people reported this outcome as % change from baseline at 14 weeks. The quality was very low based on GRADE and the point estimate suggested a possible benefit of fampridine compared to the control group, though confidence intervals indicated uncertainty in the size and direction of the effect.

Six Spot Step Test – time: A single study of 35 people reported this outcome as a change from baseline score at 4 weeks. The quality was very low based on GRADE and the point estimate suggested a possible benefit of fampridine compared to the control group, though confidence intervals indicated uncertainty in the size and direction of the effect.

Timed Up and Go Test – speed or time:

Speed: two variations of Timed Up and Go Test speed were reported across studies (including one dichotomous version and one continuous version). Point estimates for both versions suggested no difference between the fampridine and placebo groups for this outcome, with the absolute effect for the dichotomous version being just below 100 more per 1000 experiencing improvement of at least 15% compared to baseline and the change from baseline value in the intervention group appearing to be small for the continuous version. Quality was moderate and low, respectively, for the dichotomous and continuous versions, with 764 people analysed (two studies) for the dichotomous version and 633 people analysed (one study) for the continuous version.

Time: two studies (675 people analysed) reported time on this outcome measure as a continuous outcome, with both reporting change scores. Quality was low based on GRADE and the point estimate suggested a possible benefit of fampridine as the time taken was lower in this group, however, there was some uncertainty in this result given the lower confidence interval was a much smaller difference based on the units of seconds being used.

Unclear if speed or time: one further study (including 25 people) reported this outcome but did not define whether the results were for speed or time on this test. It was reported as a dichotomous measure, with the proportion with improvement on the Timed Up and Go Test being reported, and the definition or threshold used for improvement also being unclear. The quality was very low based on GRADE and the point estimate for the absolute effect suggested no difference between the two groups.

12-Item Multiple Sclerosis Walking Scale: across two different variations of reporting for this outcome (including one dichotomous version and one continuous version), based on the point estimate a possible benefit of fampridine was identified in both cases. However, there was uncertainty in this conclusion for both variations as confidence intervals suggested uncertainty in the size of the effect. Quality was moderate for the continuous version measured as a change from baseline (five studies with 1281 people analysed) and low for the dichotomous version using at least an 8-point improvement compared to baseline as the threshold for improvement (two studies with 765 people analysed).

9-Hole Peg Test – dominant or non-dominant hand - time:

Dominant/right-hand: two studies reported the outcome for dominant hand as a continuous measure (mix of final and change scores, 217 people analysed, moderate quality) and another study (22 people analysed, very low quality) reported results as a dichotomous measure, reporting the proportion with improvement for the right hand with the threshold used unclear. Point estimates suggested either a possible benefit of fampridine (continuous version) or no difference between the two groups (dichotomous version). However, for both versions the confidence intervals indicated uncertainty in the size and direction of the effect.

Non-dominant/left-hand: two studies reported the outcome for non-dominant hand as a continuous measure (mix of final and change scores, 217 people analysed, moderate quality) and another study (25 people analysed, very low quality) reported results as a dichotomous measure, reporting the proportion with improvement for the left hand with the threshold used unclear. Point estimates suggested either a possible benefit of fampridine (continuous version) or no difference between the two groups (dichotomous version). However, for both versions the confidence intervals indicated uncertainty in the size and direction of the effect.

Unclear if dominant or non-dominant hand: a further study reported a continuous measure for this outcome, though it was unclear whether the results were for the dominant or non-dominant hand meaning it could not be pooled with other similar studies (35 people analysed, low quality). The point estimate suggested a possible benefit of fampridine compared to placebo, however the confidence intervals indicated uncertainty in the size and direction of the effect.

Overall summary of measures of walking ability and upper limb mobility/dexterity

The committee concluded that despite limitations of the evidence, including uncertainty for most outcomes based on confidence intervals, varied reporting of similar outcomes across studies, the fact that most studies included were small and funded by industry and only two studies reporting at the time-point of 6 months, the point estimates did suggest possible benefits of fampridine for measures of walking ability and upper limb mobility/dexterity and agreed that fampridine may have an important effect on mobility in some people with MS.

Health-related quality of life and patient-reported outcomes

Multiple Sclerosis Impact Scale-29: two studies reported the outcome as a continuous measure (mix of final and change scores, 753 people analysed, moderate quality) and another study (132 people analysed, very low quality) reported results as a dichotomous measure, reporting the proportion with at least a 7-point improvement compared to baseline. Point estimates for both suggested a possible benefit of fampridine compared to placebo. However, for both versions the confidence intervals indicated uncertainty in the direction and/or size of the effect.

Multiple Sclerosis Functional Composite: two studies (217 people analysed) reported this outcome measure as a continuous outcome (mix of change and final scores reported). Quality was very low based on GRADE and the point estimate suggested a possible benefit of fampridine compared to placebo, though uncertainty in the size and direction of the effect was present based on confidence intervals.

Physical Activity and Disability Survey-Revised: one study (42 people analysed) reported this outcome measure as a continuous change from baseline measure. The results for the total score and exercise and leisure sub score indicated a possible benefit of fampridine based on the point estimate, though the confidence intervals for both suggested uncertainty

in the size of the effect. Quality was low (total score) or very low (exercise and leisure subdomain) based on GRADE.

Overall Disability Sum Score: one study (25 people analysed, very low quality) reported this outcome measure as a dichotomous outcome of improvement compared to baseline, with the threshold for improvement not defined. The point estimate suggested no difference between the two groups, with confidence intervals also suggesting uncertainty in the size and direction of the effect.

Subject/Patient Global Impression of Change: two studies reported this outcome, either as a continuous measure (one study, 96 people analysed, very low quality) or a dichotomous measure (one study, 132 people analysed, very low quality), with the threshold used for improvement in the dichotomous outcome not reported. Point estimates for both suggested a possible benefit of fampridine compared to placebo. However, for both versions the confidence intervals indicated uncertainty in the direction and/or size of the effect.

ABILHAND or ABILOCO questionnaires:

ABILHAND: two studies (652 people analysed) reported this outcome measure as a continuous outcome (mix of change and final scores reported). Quality was low based on GRADE and the point estimate suggested no difference between the two groups, with uncertainty in the size and direction of the effect also being present based on confidence intervals.

ABILOCO: one study (25 people analysed) reported this outcome measure as a continuous outcome in the form of final values. Quality was moderate based on GRADE and the point estimate suggested no difference between the two groups, with uncertainty in the size and direction of the effect also being present based on confidence intervals.

Spasticity: two studies (334 people analysed, very low quality) reported this outcome using the Ashworth score as a continuous change from baseline measure. The point estimate suggested a possible benefit of fampridine compared to placebo. However, the confidence intervals indicated uncertainty in the size and direction of the effect.

Fatigue: three studies reported this outcome (two as a continuous measure and one as a dichotomous measure). Those reporting continuous measures reported fatigue using different scales (one used Fatigue Severity Scale and the other used Modified Fatigue Impact Scale, reporting total score as well as the score for the physical, cognitive and psychosocial subscales), meaning data could not be pooled for any studies. For the five continuous measures reported, the point estimate for one (Fatigue Severity Scale, 57 people analysed, very low quality) suggested no difference between the two groups, while for the other four (total, and physical, cognitive and psychosocial subscale scores on Modified Fatigue Impact Scale, 120 people analysed, low quality) the point estimate suggested a possible benefit of fampridine compared to placebo. However, for three of these outcomes (total score, physical sub score and psychosocial sub score) there was uncertainty in the direction and/or size of the effect based on confidence intervals. For the dichotomous outcome (one study, 25 people analysed, very low quality), which was defined as an improvement on Fatigue Severity Scale compared to baseline with the threshold not being specified, the point estimate also suggested no difference between the two groups, with uncertainty in the size and direction of effect indicated based on confidence intervals.

Overall summary of health-related quality of life and patient reported outcomes

The committee agreed that limitations as described above for mobility measures also applied to evidence for health-related quality of life and patient-reported outcomes. In addition, these outcomes in general were less well-reported across studies, with only one or two studies

reporting them in most cases. However, it was noted that the point estimates for most did suggest possible benefits of fampridine for these measures.

Adverse events

Adverse events reported across studies for this comparison included mortality (three studies, 1089 people analysed, very low quality), adverse events leading to withdrawal (twelve studies, 1921 people analysed, very low quality), urinary tract infection (nine studies, 1902 people analysed, low quality), confusional state (one study, 283 people analysed, very low quality), seizures (seven studies, 1622 people analysed, very low quality), falls (seven studies, 1568 people analysed, very low quality), headache (ten studies, 1933 people analysed, very low quality) and fracture (three studies, 577 people analysed, very low quality).

Although point estimates for adverse events leading to withdrawal, urinary tract infection, confusional state, headache and fracture suggested increased events in the fampridine group compared to placebo, and for falls there were fewer events in the fampridine group compared to placebo, none of the outcomes reached the threshold used for adverse events of 50 more or fewer events per 1000, meaning the point estimates were considered to indicate no difference between the two groups. For all outcomes there was uncertainty in the direction of effect based on confidence intervals and for many outcomes, the outcome was only experienced by a small number of participants, depending on the study.

Overall summary of adverse events

The committee agreed that limitations in terms of the number of studies reporting at a time-point of 6 months, uncertainty in the direction and size of the effect for outcomes and the fact that most studies included were small and funded by industry also applied to evidence for adverse events. Adverse events were generally well-reported across studies, with most individual adverse events being reported by at least seven studies, with the exceptions being mortality, confusion and fracture. An additional limitation associated with adverse events was the often small number of events that occurred making it difficult to determine any difference. The committee agreed that overall, despite increased events in the fampridine group compared to placebo for some outcomes, the point estimate for the absolute risk difference suggested no clinically important difference between the two groups for any adverse event, with differences not crossing the 50 per 1000 threshold for any outcome.

Overall summary of all outcomes

Across all the outcomes included for the single comparison covered in this review, point estimates suggested either possible benefits of fampridine 10 mg twice daily treatment compared to placebo or no difference between the two groups; for those suggesting a benefit, in most cases there was uncertainty in this conclusion based on the confidence intervals as the direction and/or size of the effect was uncertain.

After reviewing the evidence presented, the committee noted that although there was uncertainty for most outcomes based on confidence intervals and most studies included were small and funded by industry, the point estimates did suggest possible benefits of fampridine for measures of walking ability and upper limb mobility/dexterity and most quality of life or patient-reported outcome measures, and the results for all reported adverse events suggested no clinically important increase in the incidence of these events in the fampridine group.

The committee agreed that for people with walking impairment, even small improvements in walking can be extremely beneficial for people with MS, for example a small improvement

may mean they can perform daily activities they could not before, such as walking around the home for longer or walking around the supermarket, allowing more independence. In addition, it was noted that impact on walking style, not just speed, can be important to people with MS. From their experience, the committee were aware that fampridine does not always have a large effect in patients but noted that in a small percentage it can make an important difference to walking ability. However, it was noted that currently it is not possible to predict which patients are likely to respond to fampridine without a trial period, after which fampridine is discontinued if no effect on mobility is observed.

Based on a discussion of the clinical and cost-effectiveness evidence and clinical experience, although the committee noted that the use of fampridine is a clinically effective treatment for some people, a recommendation not to offer fampridine to treat mobility problems in people with MS was made, as it is not cost-effective at the current list price.

1.1.12.4 Cost effectiveness and resource use

The economic evidence review identified four relevant published economic evaluations. Original economic modelling was also undertaken. Three of the published studies were cost-utility analyses that were submitted by the manufacturers for the approval of fampridine in Scotland and Sweden, respectively. The final economic evaluation that was included was conducted by the NGC as part of the previous MS guideline. Of note, the manufacturers had also conducted an economic analysis of fampridine as part of a submission to the All-Wales Medicines Strategy Group (AWMSG).[2] As this analysis reported no results due to commercial in confidence figures, it was not included in this evidence review, nor was it assessed for applicability of methodological quality.

The first study included was published by the Scottish Medicine's consortium (SMC)[41], where fampridine was approved in Scotland following the appraisal of the manufacturing company's submission. This included a cost-utility analysis; using an initial decision tree, fampridine responder and non-responder status for each participant were determined at four weeks, followed by a cohort Markov model over the time horizon of five years. Utility estimates were derived from the EQ-5D-5L data collected within the MOBILE study[18] (n = 132) and mapped to the EQ-5D-3L using an algorithm. Utility values were modelled separately for responders and non-responders in each treatment arm (with the EQ-5Ddata in the placebo arm of the MOBILE study used as a proxy for the best supportive care (BSC) alone comparator), no adjustments for differences in baseline utilities was done. The base-case ICER was £13,156 when the list price was adjusted using a Patient access scheme (PAS). The results were most sensitive to the assumption that utility values persisted between week 24 to the 5-year time horizon and the withdrawal rate of BSC. Scenario analyses with the greatest upward impact on the ICER were the use of utility values derived from EQ-5D-3L data from the ENHANCE study[17] (n = 636) or where treatment-specific utility differences were removed from the model. A prior submission of this economic model to the SMC in 2018 was also included in the evidence review, which reported the ICER using the list price for fampridine (instead of with a PAS). The ICER was £44,739 when the MOBILE utility data was used (EQ5D-5L, not mapped to EQ5D-3L) and £149,659 when the ENHANCE utility data was used (EQ5D-3L). They included several other scenarios, including using the MOBILE EQ5D-5L mapped to EQ5D-3L, the ICER was £92,961. The SMC did not approve the use of fampridine based on the 2018 submission as the submitting company did not present a sufficiently robust economic analysis to gain acceptance.

For this review, both studies were deemed partially applicable as the utility estimates were derived from the EQ-5D-5L and mapped to the EQ-5D-3L using an algorithm and did not pool the ENHANCE and MOBILE quality of life data. The submitting company asserted that the EQ-5D-3L is not sensitive enough to capture changes in quality of life in people treated with fampridine due to the limited number of response categories in the questionnaire.

However, given that a robust rationale was not presented for this assertion, the committee view was that it remains uncertain whether the EQ-5D-3L, or EQ-5D-5L mapped to the EQ-5D-3L predicts a more reliable estimate of utility outcomes, or, whether differences in utility data are in part due to the MOBILE study having a better response than the ENHANCE study. The NICE position statement does not recommend using the EQ-5D-5L value set for England and prefers that any institution preparing evidence submissions for NICE should use the 3L value set for reference-case analyses[29] The study was assessed as having potentially serious limitations such as intervention effects and outcomes were obtained from several RCTs. The reason for selecting certain outcomes from certain trials was not provided, which meant that the committee found it difficult to assess the extent to which bias may have been introduced without referring to primary studies. There was also some imbalance in the treatment and control groups at baseline in the key data source for the base case utility weights (the MOBILE study). The mean time since diagnosis was 12.4 years in the control (BSC) group and 10.9 years in the treatment (fampridine) group.

The third study was by Acosta (2021)[1] which was a cost-utility analysis developed for the approval of fampridine in Sweden. The analysis included a Markov model that was developed to model responders and non-responders after a four-week evaluation period, where the fampridine group moved to either ‘continue with fampridine and BSC' health state, ‘withdrawal from treatment’ or ‘death’ health states over a 20-year time horizon. Unlike the SMC submissions, utility data incorporated into the model was taken from ENHANCE, which collected EQ-5D-3L only, and the same utility was applied for placebo, non-responders and those who withdrew. Baseline utilities still differed between comparators (Fampridine responders versus BSC group), however. The analysis took a Swedish societal perspective; however, costs and results were presented in this review through a healthcare payer perspective as this will better reflect a UK NHS context. The results from a societal perspective were reported as a scenario analysis.

The base-case ICER was £10,411 for a healthcare payer perspective, however, it is important to note that the cost of fampridine is lower in Sweden compared to the UK list price, as a 28-day supply/56-pack is £109 in Sweden versus £362 according to the BNF. Results in the one-way sensitivity analysis (OWSA) were most sensitive to the T25FW score at baseline, the utility value to responders at week 24 and carried forward, the cost of professional care, PR-fampridine withdrawal rate and the cost of a day off work. Aside from the T25FW score at baseline, the OWSA and PSA results were overall insensitive to variations in patients’ baseline characteristics. Three scenario analyses were conducted due to the sensitivity of carrying forward Week 24 utility values from ENHANCE only. The first used EQ-5D-5L values from MOBILE, which increased the incremental QALY to 0.44 and decreased the ICER to £2,839/QALY. The second applied pooled utility data from the combined ENHANCE and MOBILE trials, which increased the incremental QALY to 0.15 and decreased the ICER to £8,329/QALY. The third scenario analysis assigned the same utility values for BSC and PR-fampridine responders at baseline, which decreased the incremental QALY to 0.04 and increased the ICER to £31,232/QALY.

The study was deemed partially applicable as the Swedish health care perspective does not fully reflect UK NHS current practice, alongside the use of an annual discount rate of 3% for costs and outcomes (3.5% is the preferred rate stated in the NICE reference case). This analysis was also found to have potentially serious limitations, including: defining long-term disease progression using a different measure than what was used to measure treatment response; extrapolating the long-term treatment effect as the Timed 25-foot walk data collected in extension studies was only available up to 5 years following the end of the original Phase III trials; estimating long-term utilities by carrying the carrying the last observed value (week 24) forward to 20 years and using resource use data that was not specific to the Swedish market but is related UK resource use.

The fourth study included was a de novo analysis taken from the 2014 MS guideline[28]. This was the only economic study included as part of previous guideline evidence review as no

relevant economic evaluations comparing fampridine with usual care were identified. This was a simple cost utility analysis with a one-year time horizon where no one was assumed to have died. The analysis was based on RCT by Goodman et al. (2008, 2010)[11, 12], which compared EQ-5D-3L improvement of adults with MS who were given fampridine for 9 weeks to a control group receiving a placebo. A systematic search of quality of life (QoL) studies was conducted and a study (Hawton et al. (2012)[15]) provided a mapping function to estimate EQ-5D scores from MSWS-12 scores. QALY gain with fampridine was estimated assuming the effectiveness throughout the year is similar to the effectiveness observed at 9 weeks Only drug costs were incorporated into the analysis as the number of assessments is uncertain and could be equal to that number of visits in an untreated population. This meant that if more visits are required for patients undergoing treatment, the cost of fampridine in the analysis could potentially be an underestimate. Downstream costs were not included in the analysis as no data was available from the RCTs on the impact of fampridine on healthcare utilisation. The previous GDG considered that fampridine may result in plausible downstream savings due to delayed deterioration of mobility and accounted for this when interpreting results.

The base case results found fampridine to have an ICER of £160,884 and was therefore not considered to be cost-effective at a threshold of £20,000 per QALY. Based on these results, fampridine would be even less cost-effective for a group of patients who have not had the trial yet. A threshold analysis found that with the cost of treatment being constant, the change in incremental EQ-5D scores required for the ICER to decrease to £20,000/QALY was 0.236. This study was deemed partially applicable as it was a simple cost-utility analysis with a short-term time horizon. The study was limited as the base case relied on a single RCT with a limited number of participants, where all limitations of the clinical data also would apply to the economic analysis. Direct EQ-5D data measuring treatment effect on health-related quality of life was also not available, compelling the use of a mapping function a condition-specific measure to a generic quality of life measure. The MSWS-12 does not assess the other domains of EQ-5D, which are self-care, usual activities, pain/discomfort and anxiety and depression. The mapping function had also not been validated. Lastly, only the cost of treatment was considered when comparing interventions. The committee agreed that to sufficiently assess of the cost-effectiveness of fampridine, monitoring and adverse event costs should be incorporated into the analysis.

Of note, the incremental QALYs are different between the three studies above (NICE 2014, SMC 2020 and Acosta 2021) due to the economic analyses adopting different time horizons (1 year, 5 years and 20 years) and the use of different clinical evidence to estimate QALYs (Goodman 2009:[13] MSWS-12 scores mapped to EQ5D-3L, MOBILE RCT:[18] EQ5D-5L mapped to 3L and ENHANCE RCT:[16] EQ5D-3L). In addition, both Acosta and the SMC analyses applied baseline utilities that differed between comparators, accounting for the higher QALY gain. The SMC has the highest QALY gain due to applying MOBILE utility data and treatment response rates, which were more favourable to fampridine compared to estimates from ENHANCE, which Acosta used for the base case.

Although a number of health economic studies were identified in the literature, these studies either include a reduced price which is not reflective of the current list price for fampridine or do not include all of the available quality of life evidence from the latest trials of fampridine (ENHANCE and MOBILE). As a result, in this guideline update, the cost-effectiveness of fampridine was one of the areas which was prioritised for original health economic modelling. The analysis was also undertaken to address the limitations of the previous models, with a primary focus on finding the best approach to pool and extrapolate the utility data from ENHANCE and MOBILE trials. As the committee were aware that the cost of fampridine remained high and therefore unlikely to be cost-effective, the aim of the analysis was also to identify the price at which fampridine would be considered a cost-effective treatment.

The analysis was a cost-utility analysis using a 5-year time horizon comparing fampridine plus best supportive care to best supportive care only. Threshold analyses were also conducted to identify the price at which fampridine would be considered a cost-effective treatment for the base case and scenario analyses.

Clinical data concerning treatment response and quality-of-life improvements were taken from pooled estimates of the ENHANCE and MOBILE trials (post-hoc analyses [16] [24] were used for quality of life estimates). This was agreed upon by the committee as it would allow the model to include the largest evidence base possible and address critiques highlighted in the published studies for either using the smaller (and more favourable to fampridine) clinical trial in the case of MOBILE as well as addressing the potential insensitivity of EQ-5D-3L estimates as was suggested in the ENHANCE trial. The EQ-5D change scores (i.e., change from baseline in the fampridine and usual care groups from each study) were meta-analysed as this was deemed to be the most precise way of using the data from the trials as it would remove treatment-specific baseline utility differences from the model. Intervention costs associated with providing fampridine included drug costs and a responder-assessment cost at 4 weeks. Adverse event costs were calculated using the probability of each AE for those treated with fampridine or placebo in ENHANCE which were then used as weights to find the average unit cost of an AE for fampridine, except for UTIs, falls and headaches, which were based on risk ratios calculated from meta-analyses of studies reporting these AE rates in the clinical review. Resource use over the time horizon was informed was by relationship between healthcare resource consumption (HCRU) and walking speed (measured by T25FW) from an Adelphi study.[34]

Both the deterministic and probabilistic base case results found fampridine plus BSC to not be cost-effective compared to BSC alone (probabilistic analysis was £82,099 per QALY gained and £82,847 in the deterministic analysis). The probabilistic analysis found there would be a 7% probability of fampridine being cost-effective at a threshold of £20,000 per QALY gained, and through a threshold analysis, determined that for fampridine to be considered cost-effective, the drug cost would have to fall to £202 (from £362 as listed in the BNF. [5]

To address the uncertainty towards the cohort settings, treatment effects (primarily in terms of quality of life inputs) and resource use costs incorporated into the model, several scenario analyses were performed. Threshold analyses were also undertaken for each of these scenarios to estimate the maximum price fampridine could be set to and achieve an ICER of £20,000 per QALY. The overall conclusion was robust to all sensitivity analyses tested.

The committee discussed the limitations of the analysis. This included how the model was limited in terms of the data source that could be included as a treatment effect, as utility values were taken from post-hoc analyses that were only available up to week 24 and were therefore extrapolated beyond trial period to 5 years. Alongside this, due to the lack of long-term clinical trial or resource use data for 12-item MS walking scale (MSWS-12) that was used to measure treatment response, disease progression was defined using a different measure (T25FW). There was also uncertainty around the relationship between the resource use (and therefore costs) and the treatment effect; the values used for resource use data were obtained from data from 5 European countries (albeit including the UK), with data regarding T25FW scores only reported in <10% of respondents. The validity of this Adelphi data was a concern for the committee. Furthermore, several assumptions had to be made to estimate unit costs and resource use.

The committee raised concerns over the removal of all clinical benefit for non-responders, however acknowledged the lack of clinical evidence to support a sustained effect of fampridine following treatment.

The model does not account for any potential differences in fampridine response by gender as the studies do not report treatment effects by gender. The proportion of females in the model cohort was based on data from Public health England[40] which reports that 72% of MS

diagnoses were in women. The committee noted it is not known whether a difference exists. Of note, in the model, the gender split only impacts the mortality rate as a gender specific MS standardised mortality rate was included in the model. This will not affect the conclusions of the model, as the mortality rate is applied equally in both treatment arms. The costs of treatment were incurred for responders and non-responders up to four weeks and then only for responders but with 4 weekly probability applied to not responding hence forward.

The committee discussed the clinical and economic evidence, although the use of fampridine can be clinically effective at improving mobility and quality of life for responders, a recommendation was made to not offer fampridine to treat mobility problems in people with MS was made, as it is not cost-effective at the current list price.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendation 1.5.18 and the research recommendation on mobility.

1.1.14 References

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Appendices

Appendix A – Review protocols

Review protocol for pharmacological management of mobility in MS

ID	Field	Content
0.	PROSPERO registration number	CRD42020224189
1.	Review title	Pharmacological management of mobility
2.	Review question	For adults with MS, including people receiving palliative care, what is the clinical and cost effectiveness of pharmacological interventions for mobility?
3.	Objective	This review will aim to determine the clinical effectiveness of pharmacological treatment for improving mobility in people with MS. Treatment is mainly using fampridine and therefore the review will focus on the evidence for this drug only.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • Date limitations: databased will be searched from 2014 onwards (last search conducted for CG186) • English language studies

		• Human studies • Validated study filters for systematic reviews and RCTs The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details). Key studies: **ENHANCE Trial.** Hobart 2019,. Assessment of Clinically Meaningful Improvements in Self-Reported Walking Ability in Participants with Multiple Sclerosis: Results from the Randomized, Double-Blind, Phase III ENHANCE Trial of Prolonged-Release Fampridine **MOBILE trial.** Hupperts 2016. Prolonged-release fampridine and walking and balance in MS: randomised controlled MOBILE trial
5.	Condition or domain being studied	Multiple sclerosis
6.	Population	Inclusion: Adults (≥18 years) with MS, including people receiving palliative care. Exclusion: Children and young people (≤18 years).

7.	Intervention	**Pharmacological interventions:** Fampridine including prolonged release fampridine • Synonyms: 4-aminopyridine, 4-pyridinamine, pyridylamine, dalfampridine (generally prescribed as oral, 10 mg/bd or 10mg od for impaired renal function. Other doses may be included but will need to check with the GC)
8.	Comparator	• Placebo or no treatment • Usual care which may include rehabilitation and physiotherapy
9.	Types of study to be included	Systematic reviews of RCTs and RCTs will be considered for inclusion. For a systematic review to be included it must be conducted to the same methodological standard as NICE guideline reviews. If sufficient details are not provided to include a relevant systematic review, the review will only be used for citation searching. Cross-over trials will also be considered for inclusion if they have an appropriate washout period of at least 1 week. We consider RCT data to be the best evidence for reviews of interventions. In addition, the surveillance review and GC have highlighted the existence of relevant RCTs in this area. Therefore, if no RCT data is available observational data will not be considered due to the risk of confounding variables influencing the study results, reducing our confidence in the overall results of the review. Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	• 3,4-diaminopyridine (used to treat other neuromuscular diseases but not MS). • Dosing studies /studies comparing different doses of fampridine to each other • Non-English language studies.

		• Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study. • Non randomised studies / observational studies
11.	Context	This review will inform the update of the following recommendation in CG 186: 1.5.10 Do not use fampridine to treat lack of mobility in people with MS because it is not a cost-effective treatment.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical. **Measures of walking ability and upper limb mobility/dexterity for example:** • Walking distance measured by the 6-minute walk test (6MWT) (if not available the 2-minute walk test (2MWT) can be extracted if reported instead) • Walking speed measured by the 25-foot walk (T25FW) (if not available the 10-minute walk test (10MWT) can be extracted if reported instead) • 'Get up and go test' • 12-item Multiple Sclerosis Walking Scale (MSWS-12) • 9-hole peg test (upper limb mobility/dexterity outcome as walk tests, are not applicable to people in wheelchairs). **Health-related quality of life (Validated) for example:** • MS Impact Scale 29 (MSIS-29) • EQ-5D, SF-36, **Adverse events:** • Mortality

		• Adverse events leading to withdrawal • Urinary tract infections • confusion • seizures • falls • headache • fractures Composite adverse events outcomes will be extracted if none of the above adverse events are reported. **Changes in validated disability or impairment scales assessing for example:** • MS Impact Scale 29 (MSIS-29) • **Motor function** (e.g., Expanded Disability Status Scale (EDSS), the Multiple Sclerosis Functional Composite (MSFC), the Cambridge Multiple Sclerosis Basic Score (CAMBS), the Functional Assessment of Multiple Sclerosis (FAMS), the National Fatigue Index (NFI)) • **Spasticity** (e.g., Modified Ashworth scale, Tardieu Scale, Penn Spasm Frequency Scale (PSFS), Muscle Elastography MS Scale (MEMSs), Fugl Meyer Scale (FMS), Numeric Rating Scale for Spasticity (NRS-S), MS Spasticity Scale-88 (MSSS), Patient-reported Impact of Spasticity Measure (PRISM) • **Fatigue** (e.g., National Fatigue Index (NFI), fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS)) Follow-up: - At 6 months (if multiple time points are reported, we will only record the closest reported time point up to 6 months) • >6 months - 12 months (data from > 12 months follow up may be included but will be downgraded)

13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. The following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)
15.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate

		risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. To maximise the amount of data for meta-analysis, where multiple scales have been used for an outcome such as mobility, fatigue or spasticity, the most commonly reported ones across studies will be extracted and meta-analysed with priority given to those included in CG 186. Where available, outcome data from new studies will be meta-analysed with corresponding data included in CG 186. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. If sufficient data is available, meta-regression or NMA-meta-regression will be conducted. WinBUGS will be used for network meta-analysis, if possible, given the data identified.

16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS). • According to disability (EDSS <6 and EDSS ≥6). • Disease modifying treatment status (currently using and not currently using).		
17.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date	October 2020		
21.	Anticipated completion date	July 2022		
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	x	☐

		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
23.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail MultipleSclerosisUpdate@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
24.	Review team members	From the National Guideline Centre: Dr Sharon Swain [Guideline lead] Dr Saoussen Ftouh [Senior systematic reviewer] Nicole Downes [Systematic reviewer] Sophia Kemmis Betty [Senior health economist]		

		Emma Carter [Health economist] Lina Gulhane [Information specialist] Emma Clegg [Information specialist]
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
28.	Other registration details	
29.	Reference/URL for published protocol	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts

		• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	Multiple sclerosis, mobility, fampridine, physiotherapy, exercise, fatigue, spasticity	
32.	Details of existing review of same topic by same authors	None	
33.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34..	Additional information		
35.	Details of final publication	www.nice.org.uk	

Table 8: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence.

	• Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. For questions being updated, the search will be run from 2014, which was the cut-off date for the searches conducted for NICE guideline CG186.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2005 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[27] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

	The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2005 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'. • Studies published before 2005 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

This literature search strategy was used for the following review:

- The clinical and cost effectiveness of pharmacological interventions for mobility for adults with MS, including people receiving palliative care.

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[27]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 9: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	01 January 2014 – 08 September 2021	None Exclusions (animal studies, letters, comments, children)
Embase (OVID)	01 January 2014 – 08 September 2021	None Exclusions (animal studies, letters, comments, conference abstracts, children)
The Cochrane Library (Wiley)	Cochrane Reviews 2014 to 2021 Issue 9 of 12 CENTRAL 2014 to 2021 Issue 9 of 12	None Exclusions (conference abstracts & clinical trials)
Epistemonikos (The Epistemonikos Foundation)	01 January 2014 – 08 September 2021	Systematic Reviews Exclusions (Cochrane Reviews)

Medline (Ovid) search terms

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	Myelitis, Transverse/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	Demyelinating Diseases/
9.	Demyelinating Autoimmune Diseases, CNS/

10.	(Demyelinat* adj2 (syndrome* or disease* or autoimmune)).ti,ab.
11.	Chronic Cerebrospinal Venous Insufficiency.ti,ab.
12.	Venous Insufficiency/cf, co, di, dg, et [Cerebrospinal Fluid, Complications, Diagnosis, Diagnostic Imaging, Etiology]
13.	(Devic* adj (disease or syndrome)).ti,ab.
14.	(clinical* isolat* adj syndrome*).ti,ab.
15.	exp Optic Neuritis/
16.	Neuromyelitis Optica.ti,ab.
17.	(NMO spectrum adj (disease* or disorder*)).ti,ab.
18.	or/1-17
19.	letter/
20.	editorial/
21.	news/
22.	exp historical article/
23.	Anecdotes as Topic/
24.	comment/
25.	case report/
26.	(letter or comment*).ti.
27.	or/19-26
28.	randomized controlled trial/ or random*.ti,ab.
29.	27 not 28
30.	animals/ not humans/
31.	exp Animals, Laboratory/
32.	exp Animal Experimentation/
33.	exp Models, Animal/
34.	exp Rodentia/
35.	(rat or rats or mouse or mice).ti.
36.	or/29-35
37.	18 not 36
38.	limit 37 to English language
39.	*Aminopyridines/
40.	exp 4-Aminopyridine/
41.	(fampridine* or dalfampridine* or aminopyridine* or ampyra or "el 970" or "el970" or fampyra or neurelan or pymadin* or pyridine* or "4-pyridinamine*" or amifampridine*).ti,ab.
42.	(1003-40-3 or 504-24-5).rn.
43.	or/39-42
44.	38 and 43
45.	exp Rehabilitation/
46.	exp Physical Therapy Modalities/
47.	Self care/
48.	Self efficacy/
49.	Patient Care Team/
50.	Ambulatory care/
51.	rehab*.ti,ab.
52.	(physiotherapy or neurophysiotherapy).ti,ab.

53.	(interdisciplinary or multidisciplinary or inter disciplinary or multi disciplinary or MDT or home based or ambulatory care or non pharmacological or non pharma).ti,ab.
54.	((self or own or personal or alone) adj3 (efficacy or treatment* or programme* or program* or technique* or manag* or intervention* or therap* or train* or strateg* or method* or counsel* or care* or caring or course*)).ti,ab.
55.	((treatment* or therap* or intervention* or fatigue or energy) adj2 (strateg* or method* or programme* or program* or technique* or manag* or train* or course*)).ti,ab.
56.	((energ* or fatigue* or tired*) adj2 (effectiv* or conserv* or level* or physical)).ti,ab.
57.	Transcutaneous Electrical Nerve Stimulation/
58.	(TENS or electroanalgesi* or electro analgesi*).ti,ab.
59.	(electric* nerve adj2 stimulation adj2 (transcutaneous or percutaneous or analgesi*)).ti,ab.
60.	(electrostimulation adj2 (transcutaneous or percutaneous or analgesi*)).ti,ab.
61.	FACETS.ti,ab.
62.	Exercise therapies/
63.	Muscle Stretching Exercises/
64.	Physical endurance/
65.	Physical fitness/
66.	exp "Physical Education and Training"/
67.	Exercise Movement Techniques/
68.	(exercising or exercise*).ti,ab.
69.	((physical or muscle* or muscular) adj2 (endurance or fitness or exertion or stretch* or stand* or splinting or flexibl* or train*)).ti,ab.
70.	((fitness or aerobic or resistance) adj2 (technic* or technique* or train*)).ti,ab.
71.	Bicycling/ or Walking/
72.	(cycling or cycle or bicycling or bicycle or treadmill* or walk*).ti,ab.
73.	Yoga/ or Tai ji/
74.	(tai ji or tai chi or taichi or taiji or taijiquan).ti,ab.
75.	(gym or calisthenics or pilates or yoga*).ti,ab.
76.	Clothing/ or Shoes/
77.	(lycra or balancewear).ti,ab.
78.	((cooling or temperature balanc*) adj2 (device* or clothing or clothes or cloth or garment*)).ti,ab.
79.	or/45-78
80.	Mobility limitation/ or Movement/ or Locomotion/ or Postural Balance/
81.	(mobil* or balanc* or move* or moving or movement* or motion or locomotion* or locomotor or ambulat*).ti,ab.
82.	80 or 81
83.	38 and 79 and 82
84.	44 or 83

Embase (Ovid) search terms

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	myelitis/
6.	transverse myelitis.ti,ab.

7.	or/1-6
8.	demyelinating disease/
9.	(Demyelinat* adj2 (syndrome* or disease* or autoimmune)).ti,ab.
10.	Chronic Cerebrospinal Venous Insufficiency.ti,ab.
11.	vein insufficiency/co, di, et [Complication, Diagnosis, Etiology]
12.	(Devic* adj (disease or syndrome)).ti,ab.
13.	(clinical* isolat* adj syndrome*).ti,ab.
14.	exp optic neuritis/
15.	Neuromyelitis Optica.ti,ab.
16.	(NMO spectrum adj (disease* or disorder*)).ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	case report/ or case study/
22.	(letter or comment*).ti.
23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental Animal/
30.	animal model/
31.	exp Rodent/
32.	(rat or rats or rodent* or mouse or mice).ti.
33.	or/25-32
34.	17 not 33
35.	limit 34 to English language
36.	*aminopyridine derivative/
37.	fampridine/
38.	(fampridine* or dalfampridine* or aminopyridine* or ampyra or "el 970" or "el970" or fampyra or neurelan or pymadin* or pyridine* or "4-pyridinamine*" or amifampridine*).ti,ab.
39.	(1003-40-3 or 504-24-5).rn.
40.	or/36-39
41.	35 and 40
42.	exp *Rehabilitation/
43.	*Self care/
44.	*Patient Care/
45.	Ambulatory care/
46.	rehab*.ti,ab.
47.	(physiotherapy or neurophysiotherapy).ti,ab.
48.	(interdisciplinary or multidisciplinary or inter disciplinary or multi disciplinary or MDT or home based or ambulatory care or non pharmacological or non pharma).ti,ab.

49.	((self or own or personal or alone) adj3 (efficacy or treatment* or programme* or program* or technique* or manag* or intervention* or therap* or train* or strateg* or method* or counsel* or care* or caring or course*)).ti,ab.
50.	((treatment* or therap* or intervention* or fatigue or energy) adj2 (strateg* or method* or programme* or program* or technique* or manag* or train* or course*)).ti,ab.
51.	((energ* or fatigue* or tired*) adj2 (effectiv* or conserv* or level* or physical)).ti,ab.
52.	*Transcutaneous Nerve Stimulation/
53.	(TENS or electroanalgesi* or electro analgesi*).ti,ab.
54.	(electric* Nerve adj2 stimulation adj2 (transcutaneous or percutaneous or analgesi*)).ti,ab.
55.	(electrostimulation adj2 (transcutaneous or percutaneous or analgesi*)).ti,ab.
56.	FACETS.ti,ab.
57.	*Alternative therapies/
58.	*Physical medicine/
59.	exp *kinesiotherapy/
60.	*Muscle stretching/
61.	*Stretching Exercises/
62.	*Endurance training/
63.	*Fitness/
64.	exp *Physical Education/
65.	*Movement Therapy/
66.	*Muscle training/
67.	*Exercise/
68.	(exercising or exercise*).ti,ab.
69.	((physical or muscle* or muscular) adj2 (endurance or fitness or exertion or stretch* or stand* or splinting or flexibl* or train*)).ti,ab.
70.	((fitness or aerobic or resistance) adj2 (technic* or technique* or train*)).ti,ab.
71.	Bicycling/ or Walking/
72.	(cycling or cycle or bicycling or bicycle or treadmill* or walk*).ti,ab.
73.	*Yoga/ or *Tai ji/
74.	(tai ji or tai chi or taichi or taiji or taijiquan).ti,ab.
75.	(gym or calisthenics or pilates or yoga*).ti,ab.
76.	*Clothing/
77.	(lycra or balancewear).ti,ab.
78.	((cooling or temperature balanc*) adj2 (device* or clothing or clothes or cloth or garment*)).ti,ab.
79.	or/42-78
80.	*Walking difficulty/ or *Locomotion/
81.	(mobil* or balanc* or move* or moving or movement* or motion or locomotion* or locomotor or ambulat*).ti,ab.
82.	80 or 81
83.	35 and 79 and 82
84.	41 or 83

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Multiple Sclerosis] explode all trees
#2.	((multiple or disseminated) NEAR/2 scleros*):ti,ab
#3.	encephalomyelitis disseminata:ti,ab

#4.	MS:ti
#5.	MeSH descriptor: [Myelitis, Transverse] this term only
#6.	transverse myelitis:ti,ab
#7.	(OR #1-#6)
#8.	MeSH descriptor: [Demyelinating Diseases] this term only
#9.	(Demyelinat* NEAR/2 (syndrome* or disease* or autoimmune)):ti,ab
#10.	Chronic Cerebrospinal Venous Insufficiency:ti,ab
#11.	MeSH descriptor: [Venous Insufficiency] this term only and with qualifier(s): [diagnostic imaging - DG, cerebrospinal fluid - CF, complications - CO, diagnosis - DI, etiology - ET]
#12.	(Devic* NEXT (disease or syndrome)):ti,ab
#13.	((clinical* NEXT isolat*) NEXT syndrome*):ti,ab
#14.	MeSH descriptor: [Optic Neuritis] explode all trees
#15.	Neuromyelitis Optica:ti,ab
#16.	(NMO spectrum NEXT (disease* or disorder*)):ti,ab
#17.	(OR #1-#16)
#18.	MeSH descriptor: [Aminopyridines] this term only
#19.	MeSH descriptor: [4-Aminopyridine] explode all trees
#20.	(fampridine* or dalfampridine* or aminopyridine* or ampyra or "el 970" or "el970" or fampyra or neurelan or pymadin* or pyridine* or "4-pyridinamine*" or amifampridine*):ti,ab
#21.	(OR #18-#20)
#22.	#17 AND #21
#23.	MeSH descriptor: [Rehabilitation] explode all trees
#24.	MeSH descriptor: [Physical Therapy Modalities] explode all trees
#25.	MeSH descriptor: [Self Care] explode all trees
#26.	MeSH descriptor: [Self Efficacy] explode all trees
#27.	MeSH descriptor: [Patient Care Team] explode all trees
#28.	MeSH descriptor: [Ambulatory Care] explode all trees
#29.	rehab*:ti,ab
#30.	(physiotherapy or neurophysiotherapy):ti,ab
#31.	(interdisciplinary or multidisciplinary or inter disciplinary or multi disciplinary or MDT or home based or ambulatory care or non pharmacological or non pharma):ti,ab
#32.	((self or own or personal or alone) near/3 (efficacy or treatment* or programme* or program* or technique* or manag* or intervention* or therap* or train* or strateg* or method* or counsel* or care* or caring or course*)):ti,ab
#33.	((treatment* or therap* or intervention* or fatigue or energy) near/2 (strateg* or method* or programme* or program* or technique* or manag* or train* or course*)):ti,ab
#34.	((energ* or fatigue* or tired) near/2 (effectiv* or conserv* or level* or physical)):ti,ab
#35.	MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] explode all trees
#36.	(TENS or electroanalgesi* or electro analgesi*):ti,ab
#37.	(electric* nerve near/2 stimulation near/2 (transcutaneous or percutaneous or analgesi*)):ti,ab
#38.	(electrostimulation near/2 (transcutaneous or percutaneous or analgesi*)):ti,ab
#39.	FACETS:ti,ab
#40.	MeSH descriptor: [Exercise Therapy] explode all trees
#41.	MeSH descriptor: [Muscle Stretching Exercises] explode all trees
#42.	MeSH descriptor: [Physical Endurance] explode all trees

#43.	MeSH descriptor: [Physical Fitness] explode all trees
#44.	MeSH descriptor: [Physical Education and Training] explode all trees
#45.	MeSH descriptor: [Exercise Movement Techniques] explode all trees
#46.	(exercising or exercise*):ti,ab
#47.	((physical or muscle* or muscular) near/2 (endurance or fitness or exertion or stretch* or stand* or splinting or flexibl* or train*)):ti,ab
#48.	(fitness or aerobic or resistance) adj2 (technic* or technique* or train*):ti,ab
#49.	MeSH descriptor: [Bicycling] explode all trees
#50.	MeSH descriptor: [Walking] explode all trees
#51.	(cycling or cycle or bicycling or bicycle or treadmill* or walk*):ti,ab
#52.	MeSH descriptor: [Yoga] explode all trees
#53.	MeSH descriptor: [Tai Ji] explode all trees
#54.	(tai ji or tai chi or taichi or taiji or taijiquan):ti,ab
#55.	(gym or calisthenics or pilates or yoga*):ti,ab
#56.	MeSH descriptor: [Clothing] explode all trees
#57.	MeSH descriptor: [Shoes] explode all trees
#58.	(lycra or balancewear):ti,ab
#59.	((cooling or temperature balanc*) near/2 (device* or clothing or clothes or cloth or garment*)):ti,ab
#60.	(OR #23-#59)
#61.	MeSH descriptor: [Mobility Limitation] explode all trees
#62.	MeSH descriptor: [Movement] explode all trees
#63.	MeSH descriptor: [Locomotion] explode all trees
#64.	MeSH descriptor: [Postural Balance] 2 tree(s) exploded
#65.	(mobil* or balanc* or move* or moving or movement* or motion or locomotion* or locomotor or ambulat*):ti,ab
#66.	(OR #61-#65)
#67.	#17 and #60 and #66
#68.	#22 or #67

Epistemonikos search terms

1.	((advanced_title_en:(multiple sclerosis) OR advanced_abstract_en:(multiple sclerosis)) AND (advanced_title_en:(mobility) OR advanced_abstract_en:(mobility)) OR (advanced_title_en:((rehab* OR neurorehab*)) OR advanced_abstract_en:((rehab* OR neurorehab*)) OR (advanced_title_en:((fampridine* OR dalfampridine* OR aminopyridine* OR ampyra OR "el 970" OR "el970" OR fampyra OR neurelan OR pymadin* OR pyridine* OR "4-pyridinamine*" OR amifampridine*)) OR advanced_abstract_en:((fampridine* OR dalfampridine* OR aminopyridine* OR ampyra OR "el 970" OR "el970" OR fampyra OR neurelan OR pymadin* OR pyridine* OR "4-pyridinamine*" OR amifampridine*))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search with the Multiple Sclerosis population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics. Searches for quality of life studies were run for general information.

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 07 September 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, children)
Embase	01 January 2014 – 07 September 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, conference abstracts, children)
Centre for Research and Dissemination (CRD)	HTA – 01 January 2014 – 31 March 2018 NHSEED – 01 January 2014 – March 2015	None
The International Network of Agencies for Health Technology Assessment (INAHTA)	01 January 2018 – 07 September 2021	None

Medline (Ovid) search terms

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	Myelitis, Transverse/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	*Demyelinating Diseases/
9.	*Demyelinating Autoimmune Diseases, CNS/
10.	(Demyelinat* adj2 (syndrome* or disease* or autoimmun*)).ti,ab.
11.	(Chronic Cerebrospinal Venous Insufficiency or CCSVI).ti,ab.
12.	Venous Insufficiency/cf, co, di, dg, et [Cerebrospinal Fluid, Complications, Diagnosis, Diagnostic Imaging, Etiology]
13.	(Devic* adj (disease or syndrome)).ti,ab.
14.	((clinical* isolat* or radiological* isolat*) adj2 syndrome*).ti,ab.
15.	exp Optic Neuritis/
16.	((neuromyelitis or neuritis or neuropapillitis) adj2 (retrobulbar or optic*)).ti,ab.
17.	(NMO or NMOSD).ti,ab.
18.	or/1-17
19.	letter/
20.	editorial/
21.	news/
22.	exp historical article/
23.	Anecdotes as Topic/

24.	comment/
25.	case report/
26.	(letter or comment*).ti.
27.	or/19-26
28.	randomized controlled trial/ or random*.ti,ab.
29.	27 not 28
30.	animals/ not humans/
31.	exp Animals, Laboratory/
32.	exp Animal Experimentation/
33.	exp Models, Animal/
34.	exp Rodentia/
35.	(rat or rats or rodent* or mouse or mice).ti.
36.	or/29-35
37.	18 not 36
38.	limit 37 to English language
39.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
40.	38 not 39
41.	Economics/
42.	Value of life/
43.	exp "Costs and Cost Analysis"/
44.	exp Economics, Hospital/
45.	exp Economics, Medical/
46.	Economics, Nursing/
47.	Economics, Pharmaceutical/
48.	exp "Fees and Charges"/
49.	exp Budgets/
50.	budget*.ti,ab.
51.	cost*.ti.
52.	(economic* or pharmaco?economic*).ti.
53.	(price* or pricing*).ti,ab.
54.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
55.	(financ* or fee or fees).ti,ab.
56.	(value adj2 (money or monetary)).ti,ab.
57.	or/41-56
58.	quality-adjusted life years/
59.	sickness impact profile/
60.	(quality adj2 (wellbeing or well being)).ti,ab.
61.	sickness impact profile.ti,ab.
62.	disability adjusted life.ti,ab.

63.	(qal* or qtime* or qwb* or daly*).ti,ab.
64.	(euroqol* or eq5d* or eq 5*).ti,ab.
65.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
66.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
67.	(hui or hui1 or hui2 or hui3).ti,ab.
68.	(health* year* equivalent* or hye or hyes).ti,ab.
69.	discrete choice*.ti,ab.
70.	rosser.ti,ab.
71.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
72.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
73.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
74.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
75.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
76.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
77.	or/58-76
78.	40 and 57
79.	40 and 77
80.	78 or 79

Embase (Ovid) search terms

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	myelitis/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	demyelinating disease/
9.	(Demyelinat* adj2 (syndrome* or disease* or autoimmun*)).ti,ab.
10.	(Chronic Cerebrospinal Venous Insufficiency or CCSVI).ti,ab.
11.	vein insufficiency/co, di, et [Complication, Diagnosis, Etiology]
12.	(Devic* adj (disease or syndrome)).ti,ab.
13.	((clinical* isolat* or radiological* isolat*) adj2 syndrome*).ti,ab.
14.	exp optic neuritis/
15.	((neuromyelitis or neuritis or neuropapillitis) adj2 (retrobulbar or optic*)).ti,ab.
16.	(NMO or NMOSD).ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	(conference abstract or conference paper).pt.
22.	case report/ or case study/

23.	(letter or comment*).ti.
24.	or/18-23
25.	randomized controlled trial/ or random*.ti,ab.
26.	24 not 25
27.	animal/ not human/
28.	nonhuman/
29.	exp Animal Experiment/
30.	exp Experimental Animal/
31.	animal model/
32.	exp Rodent/
33.	(rat or rats or rodent* or mouse or mice).ti.
34.	or/26-33
35.	17 not 34
36.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
37.	35 not 36
38.	limit 37 to English language
39.	health economics/
40.	exp economic evaluation/
41.	exp health care cost/
42.	exp fee/
43.	budget/
44.	funding/
45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.
52.	or/39-51
53.	quality adjusted life year/
54.	"quality of life index"/
55.	short form 12/ or short form 20/ or short form 36/ or short form 8/
56.	sickness impact profile/
57.	(quality adj2 (wellbeing or well being)).ti,ab.
58.	sickness impact profile.ti,ab.
59.	disability adjusted life.ti,ab.
60.	(qal* or qtime* or qwb* or daly*).ti,ab.
61.	(euroqol* or eq5d* or eq 5*).ti,ab.
62.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
63.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
64.	(hui or hui1 or hui2 or hui3).ti,ab.
65.	(health* year* equivalent* or hye or hyes).ti,ab.
66.	discrete choice*.ti,ab.

67.	rosser.ti,ab.
68.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
69.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
70.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
71.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
72.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
73.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
74.	or/53-73
75.	38 and 52
76.	38 and 74
77.	75 or 76

NHS EED and HTA (CRD) search terms

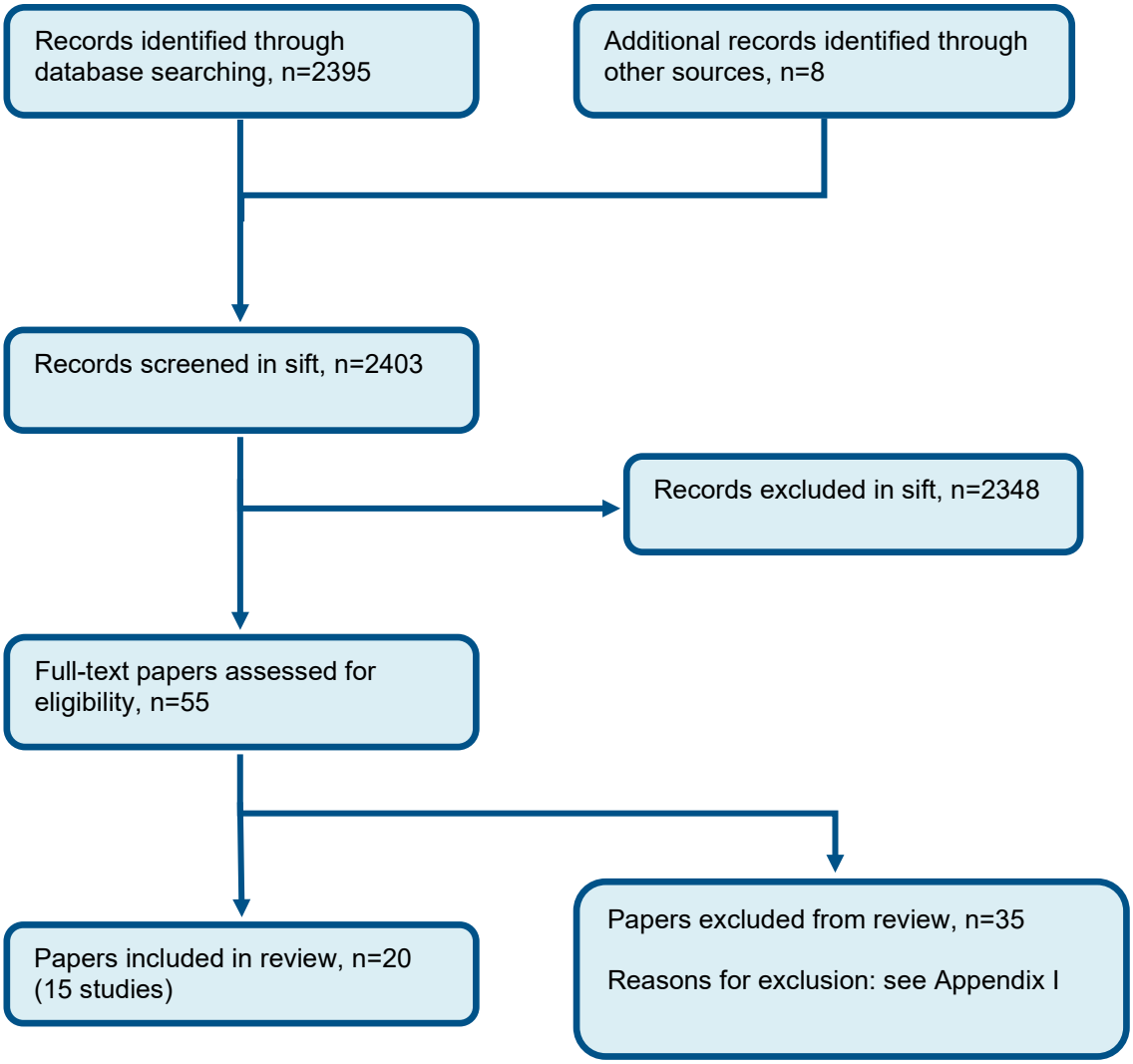
#1.	MeSH DESCRIPTOR Multiple Sclerosis EXPLODE ALL TREES
#2.	(((multiple or disseminated) adj2 scleros*))
#3.	(encephalomyelitis disseminata)
#4.	(MS)
#5.	MeSH DESCRIPTOR Myelitis, Transverse EXPLODE ALL TREES
#6.	(transverse myelitis)
#7.	MeSH DESCRIPTOR Demyelinating Diseases EXPLODE ALL TREES
#8.	((Demyelinat* adj2 (syndrome or disease)))
#9.	(Chronic Cerebrospinal Venous Insufficiency)
#10.	MeSH DESCRIPTOR Venous Insufficiency
#11.	(((Devic or "devic's") adj (disease or syndrome)))
#12.	(((clinically isolated or radiologically isolated) adj syndrome))
#13.	MeSH DESCRIPTOR Optic Neuritis EXPLODE ALL TREES
#14.	(Neuromyelitis Optica)
#15.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

INAHTA search terms

1.	(multiple sclerosis)[mh] OR (((multiple or disseminated) adj2 scleros*)) OR (encephalomyelitis disseminata) OR (MS)[Title] OR (Myelitis, Transverse)[mh] OR (transverse myelitis) OR (Demyelinating Diseases)[mh] OR (Demyelinating Autoimmune Diseases, CNS)[mh] OR ((Demyelinat* adj2 (syndrome* or disease* or autoimmun*))) OR ((Chronic Cerebrospinal Venous Insufficiency or CCSVI)) OR (venous insufficiency)[mh] OR ((Devic* adj (disease or syndrome))) OR (((clinical* isolat* or radiological* isolat*) adj2 syndrome*)) OR (optic neuritis)[mh] OR (((neuromyelitis or neuritis or neuropapillitis) adj2 (retrobulbar or optic*))) OR ((NMO or NMOSD))

Appendix C – Effectiveness evidence study selection

Figure 2: Flow chart of clinical study selection for the review of pharmacological management of mobility in MS



Appendix D – Effectiveness evidence

Applebee, 2015

Bibliographic Reference	Applebee, A.; Goodman, A. D.; Mayadev, A. S.; Bethoux, F.; Goldman, M. D.; Klingler, M.; Blight, A. R.; Carrazana, E. J.; Effects of Dalfampridine Extended-release Tablets on 6-minute Walk Distance in Patients With Multiple Sclerosis: A Post Hoc Analysis of a Double-blind, Placebo-controlled Trial; Clinical Therapeutics; 2015; vol. 37 (no. 12); 2780-7

Study details

Secondary publication of another included study- see primary study for details	Primary study: Yapundich, R.; Applebee, A.; Bethoux, F.; Goldman, M. D.; Hutton, G. J.; Mass, M.; Pardo, G.; Klingler, M.; Henney, H. R., 3rd; Blight, A. R.; Carrazana, E. J.; Evaluation of Dalfampridine Extended Release 5 and 10 mg in Multiple Sclerosis: A Randomized Controlled Trial; International Journal of Ms Care; 2015; vol. 17 (no. 3); 138-45 Study provides more detailed information on one of the outcomes measures reported in the primary study (6-MWT) - data from this secondary paper has been extracted where appropriate into the evidence table for the primary study.
Other publications associated with this study included in review	• Kantor, D.; Chancellor, M. B.; Snell, C. W.; Henney, H. R., 3rd; Rabinowicz, A. L.; Assessment of confirmed urinary tract infection in patients treated with dalfampridine for multiple sclerosis; Postgraduate Medicine; 2015; vol. 127 (no. 2); 218-22

Brown, 2016

Bibliographic Reference	Brown, T. R.; Simnad, V. I.; A Randomized Crossover Trial of Dalfampridine Extended Release for Effect on Ambulatory Activity in People with Multiple Sclerosis; International Journal of Ms Care; 2016; vol. 18 (no. 4); 170-6

Study details

Trial name / registration number	Not reported
Study location	USA
Study setting	From Multiple Sclerosis centre at a single hospital medical centre in the USA - outpatients?
Study dates	Not reported
Sources of funding	One author has worked as a consultant for and received speaking honoraria from Acorda Therapeutics (company that provided the drugs and placebo for the study).
Inclusion criteria	Confirmed diagnosis of MS based on the McDonald criteria; aged 18-75 years; a screening 6-Minute Walk Test distance of 50-500 m; and an EDSS score of 0-6.5.
Exclusion criteria	Contraindication to dalfampridine extended release; use of any aminopyridine product or mitoxantrone in the past 6 months; or conditions that would not allow a 6-Minute Walk Test to be performed.
Recruitment / selection of participants	Not reported
Intervention(s)	Dalfampridine extended release. Patients were randomised to receive dalfampridine during the first (n=22) or second treatment period (n=21). Dalfampridine treatment was for 4 weeks (10 mg twice daily), separated from the placebo treatment by a 2-week off-treatment washout period. Active and placebo drugs appeared identical and were provided by Acorda Therapeutics. Patients were instructed to take one blinded tablet every 12 hours during the treatment periods. There is missing data and it is unclear whether all patients completed both treatment periods.
Comparator	Patients were randomised to receive placebo during the first (n=21) or second treatment period (n=22). Placebo treatment was for 4 weeks (twice daily), separated from the dalfampridine treatment by a 2-week off-treatment washout period. Active and placebo drugs appeared identical and were provided by Acorda Therapeutics. Patients were instructed to take one blinded tablet every 12 hours during the treatment periods. There is missing data, and it is unclear whether all patients completed both treatment periods.
Number of participants	43 randomised, though there is missing data, and it is unclear how many completed both treatment periods

Duration of follow-up	Treatment duration of 4 weeks for each treatment period
Additional comments	Continuous outcomes appear to have been provided in a format suitable for analysis in crossover trials, but insufficient detail provided for most dichotomous outcomes to analyse correctly. Dichotomous outcomes therefore extracted by treating groups as a parallel study. All but 2 patients in each group were taking disease-modifying therapies.

Study arms

Dalfampridine extended release (N = 43)

Patients were randomised to receive dalfampridine during the first (n=22) or second treatment period (n=21). Dalfampridine treatment was for 4 weeks (10 mg twice daily), separated from the placebo treatment by a 2-week off-treatment washout period. Active and placebo drugs appeared identical and were provided by Acorda Therapeutics. Patients were instructed to take one blinded tablet every 12 hours during the treatment periods. There is missing data, and it is unclear whether all patients completed both treatment periods.

Placebo (N = 43)

Patients were randomised to receive placebo during the first (n=21) or second treatment period (n=22). Placebo treatment was for 4 weeks (twice daily), separated from the dalfampridine treatment by a 2-week off-treatment washout period. Active and placebo drugs appeared identical and were provided by Acorda Therapeutics. Patients were instructed to take one blinded tablet every 12 hours during the treatment periods. There is missing data, and it is unclear whether all patients completed both treatment periods.

Characteristics

Arm-level characteristics

Characteristic	Dalfampridine extended release (N = 43)	Placebo (N = 43)
% Female Sample size	n = 19 ; % = 86.4	n = 11 ; % = 52.4
Mean age (SD) (years) Mean (SE)	55 (2.5)	53.3 (2.2)
White Sample size	n = 21 ; % = 95.5	n = 21 ; % = 100
Black Sample size	n = 1 ; % = 4.5	n = 0 ; % = 0
Comorbidities Text	Not reported	Not reported
MS duration (years) Mean (SE)	13.3 (1.7)	13.5 (1.5)
Primary progressive Sample size	n = 4 ; % = 18.2	n = 2 ; % = 9.5
Relapsing-remitting Sample size	n = 13 ; % = 59.1	n = 13 ; % = 61.9

Characteristic	Dalfampridine extended release (N = 43)	Placebo (N = 43)
Secondary progressive Sample size	n = 5 ; % = 22.7	n = 6 ; % = 28.6
EDSS score Expanded Disability Status Scale Mean (SE)	5.1 (0.3)	5.3 (0.2)
PAI at baseline (strides/min) Peak activity index Mean (SE)	28.6 (1.8)	28.1 (1.7)
6MWT at baseline (metres) 6-Minute Walk Test Mean (SE)	260.1 (22)	271.9 (16.4)
TUG test time (seconds) Timed Up and Go test Mean (SE)	12.1 (1.4)	11.9 (1.2)
PADS-R (total score) at baseline Physical Activity and Disability Surgery-Revised. Total score. Mean (SE)	0.06 (0.27)	0.48 (0.21)
MSWS-12 score at baseline 12-item Multiple Sclerosis Walking Scale. Mean (SE)	63.5 (4.3)	64.5 (2.6)
Steps per day	5229.8 (591.1)	5920.3 (505.9)

Characteristic	Dalfampridine extended release (N = 43)	Placebo (N = 43)
Mean (SE)		
Percentage of day inactive Mean (SE)	82 (1.4)	78.8 (1.3)

Patient characteristics are reported according to the groups they were randomised to (dalfampridine followed by placebo or placebo followed by dalfampridine, n=22 and n=21, respectively)

Outcomes

Study timepoints

- Baseline
- 3 week (Accelerometery outcomes were measured for 1 week during the third week of each treatment period (4 weeks treatment with each). Matches 6-month time-point in protocol though is indirect as is 3-week treatment rather than 6 months.)
- 4 week (Non-accelerometery outcomes were measured at the end of each study period (4 weeks treatment with each). Matches 6-month time-point in protocol though is indirect as is 4-week treatment rather than 6 months.)

Results - raw data (analysed as a parallel trial)

Outcome	Dalfampridine extended release, Baseline, N = 43	Dalfampridine extended release, 3-week, N = 43	Dalfampridine extended release, 4-week, N = 43	Placebo, Baseline, N = 43	Placebo, 3-week, N = 43	Placebo, 4-week, N = 43
Adverse event leading to treatment discontinuation	n = NA ; % = NA	n = NA ; % = NA	n = 1 ; % = 2.3	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0

Outcome	Dalfampridine extended release, Baseline, N = 43	Dalfampridine extended release, 3-week, N = 43	Dalfampridine extended release, 4-week, N = 43	Placebo, Baseline, N = 43	Placebo, 3-week, N = 43	Placebo, 4-week, N = 43
Due to weakness, fatigue and nausea in 1 patient No of events						
Seizures No of events	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0
Falls No of events	n = NA ; % = NA	n = NA ; % = NA	n = 6 ; % = 14	n = NA ; % = NA	n = NA ; % = NA	n = 7 ; % = 16.3
Headache No of events	n = NA ; % = NA	n = NA ; % = NA	n = 5 ; % = 11.6	n = NA ; % = NA	n = NA ; % = NA	n = 4 ; % = 9.3

Insufficient detail has been provided to report dichotomous outcomes in the preferred way in crossover trials (as paired within-patient data) and they have therefore been analysed by treating the two treatments as a parallel randomised trial comparing dalfampridine with placebo, with n=43 in each arm (those that took at least one dose of any study medication, note that n=2 withdrew from the study before it was complete - 1 due to an adverse event and 1 withdrew consent).

Results - difference in change score from baseline between treatments

Outcome	Dalfampridine extended release vs Placebo, 3-week vs Baseline , N2 = 42, N1 = 42	Dalfampridine extended-release vs Placebo, 4-week vs Baseline, N2 = 42, N1 = 42
6MWT (metres) 6-Minute Walk Test. Mean (SE) baseline values were reported to be 260.1 (22.0) vs. 271.9 (16.4) for those randomised to dalfampridine or placebo first,	NR	0.981

Outcome	Dalfampridine extended release vs Placebo, 3-week vs Baseline , N2 = 42, N1 = 42	Dalfampridine extended-release vs Placebo, 4-week vs Baseline, N2 = 42, N1 = 42
respectively. Mean (SD) baseline value for the whole population at baseline was calculated to be 265.9 (90.78, n=43). P-value		
6MWT (metres) 6-Minute Walk Test. Mean (SE) baseline values were reported to be 260.1 (22.0) vs. 271.9 (16.4) for those randomised to dalfampridine or placebo first, respectively. Mean (SD) baseline value for the whole population at baseline was calculated to be 265.9 (90.78, n=43). Mean (SE)	NR (NR)	0.3 (13.61)
Timed Get Up and Go test (seconds) Time rather than speed. Mean (SE) baseline values were reported to be 12.1 (1.4) vs. 11.9 (1.2) for those randomised to dalfampridine or placebo first, respectively. Mean (SD) baseline value for the whole population at baseline was calculated to be 12.0 (6.07, n=43). P-value	NR	0.042
Timed Get Up and Go test (seconds) Time rather than speed. Mean (SE) baseline values were reported to be 12.1 (1.4) vs. 11.9 (1.2) for those randomised to dalfampridine or placebo first, respectively. Mean (SD) baseline value for the whole population at baseline was calculated to be 12.0 (6.07, n=43). Mean (SE)	NR (NR)	-1 (0.5)
MSWS-12 score 12-item Multiple Sclerosis Walking Scale. Scale is usually 0-100 but not clear	NR	0.796

Outcome	Dalfampridine extended release vs Placebo, 3-week vs Baseline , N2 = 42, N1 = 42	Dalfampridine extended-release vs Placebo, 4-week vs Baseline, N2 = 42, N1 = 42
in this study (assumed to be 0-100). Forest plot label suggests result favours dalfampridine but the result suggests otherwise based on the fact lower scores indicate better outcome on this scale - assumed graph label is wrong. Mean (SE) baseline values were reported to be 63.5 (4.3) vs. 64.5 (2.6) for those randomised to dalfampridine or placebo first, respectively. Mean (SD) baseline value for the whole population at baseline was calculated to be 63.99 (16.66, n=43). P-value		
MSWS-12 score 12-item Multiple Sclerosis Walking Scale. Scale is usually 0-100 but not clear in this study (assumed to be 0-100). Forest plot label suggests result favours dalfampridine but the result suggests otherwise based on the fact lower scores indicate better outcome on this scale - assumed graph label is wrong. Mean (SE) baseline values were reported to be 63.5 (4.3) vs. 64.5 (2.6) for those randomised to dalfampridine or placebo first, respectively. Mean (SD) baseline value for the whole population at baseline was calculated to be 63.99 (16.66, n=43). Mean (SE)	NR (NR)	0.5 (2.1)
PADS-R Total score Physical Activity and Disability Survey-Revised. Scale unclear. Limited information in the study but based on information from elsewhere this appears to be a patient-reported outcome measure of their level of activity in the preceding week, with 0.0 being the mean score and negative and positive values indicating low or high activity relative to others with neurological conditions. Mean (SE) baseline values were reported to be 0.06 (0.27) vs. 0.48 (0.21) for those randomised to dalfampridine or placebo first, respectively.	NR	0.021

Outcome	Dalfampridine extended release vs Placebo, 3-week vs Baseline , N2 = 42, N1 = 42	Dalfampridine extended-release vs Placebo, 4-week vs Baseline, N2 = 42, N1 = 42
Mean (SD) baseline value for the whole population at baseline was calculated to be 0.265 (1.148, n=43). P-value		
PADS-R Total score Physical Activity and Disability Survey-Revised. Scale unclear. Limited information in the study but based on information from elsewhere this appears to be a patient-reported outcome measure of their level of activity in the preceding week, with 0.0 being the mean score and negative and positive values indicating low or high activity relative to others with neurological conditions. Mean (SE) baseline values were reported to be 0.06 (0.27) vs. 0.48 (0.21) for those randomised to dalfampridine or placebo first, respectively. Mean (SD) baseline value for the whole population at baseline was calculated to be 0.265 (1.148, n=43). Mean (SE)	NR (NR)	0.3 (0.12)
PADS-R Exercise and Leisure subscore One domain of the Physical Activity and Disability Survey-Revised. Scale unclear. Limited information in the study but based on information from elsewhere this appears to be a patient-reported outcome measure of their level of activity in the preceding week, with 0.0 being the mean score and negative and positive values indicating low or high activity relative to others with neurological conditions. This survey is made up of multiple domains but only one is reported here. Baseline values not reported for this subscale. P-value	NR	0.058
PADS-R Exercise and Leisure subscore One domain of the Physical Activity and Disability Survey-Revised. Scale	NR (NR)	0.3 (0.14)

Outcome	Dalfampridine extended release vs Placebo, 3-week vs Baseline , N2 = 42, N1 = 42	Dalfampridine extended-release vs Placebo, 4-week vs Baseline, N2 = 42, N1 = 42
unclear. Limited information in the study but based on information from elsewhere this appears to be a patient-reported outcome measure of their level of activity in the preceding week, with 0.0 being the mean score and negative and positive values indicating low or high activity relative to others with neurological conditions. This survey is made up of multiple domains but only one is reported here. Baseline values not reported for this subscale. Mean (SE)		

6MWT - Polarity - Higher values are better

Timed Get Up and Go test - Polarity - Lower values are better

MSWS-12 score - Polarity - Lower values are better

PADS-R Total score - Polarity - Higher values are better

PADS-R Exercise and Leisure sub score - Polarity - Higher values are better

Results are provided as the difference in change from baseline score for dalfampridine relative to placebo treatment. CONSORT diagram suggests n=42 patients were included in this analysis, though there may be missing data for some patients, and it unclear how this was addressed. Number included in analyses is not well reported elsewhere.

Compares difference in intra-participant changes from baseline from the period that they were taking dalfampridine relative to the period in which they took placebo. Statistical results were based on a mixed-effects repeated-measures model using maximum likelihood, with change from baseline as the response variable. The model included sequence (dalfampridine or placebo first or second), treatment period (1 or 2) and treatment (dalfampridine or placebo) as fixed effects.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial (Pharma)

Adverse event leading to treatment discontinuation_4-week treatment

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear method of randomisation and unclear if allocation sequence was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High *(Missing data rate could be up to 12% within the study and there is a low event rate)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Seizures_4-week treatment

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear method of randomisation and unclear if allocation sequence was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High *(Missing data rate could be up to 14% within the study and there is a low event rate)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Falls_4-week treatment

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear method of randomisation and unclear if allocation sequence was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High *(Missing data rate could be up to 14% within the study)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(No data for paired within-patient analyses to be extracted)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Headache_4-week treatment

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear method of randomisation and*

Section	Question	Answer
		unclear if allocation sequence was concealed)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High *(Missing data rate could be up to 14% within the study)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(No data for paired within-patient analyses to be extracted)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Change in 6MWT from baseline relative to placebo_4 weeks treatment

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear method of randomisation and unclear if allocation sequence was concealed)*

Section	Question	Answer
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High *(Missing data rate could be up to 14% within the study)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Change in Timed Get Up and Go test from baseline relative to placebo_4 weeks treatment

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear method of randomisation and unclear if allocation sequence was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High *(Missing data rate could be up to 14% within the study)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Change in MSWS-12 score from baseline relative to placebo_4 weeks treatment

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear method of randomisation and unclear if allocation sequence was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High *(Missing data rate could be up to 14% within the study)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Other patient-reported outcomes measured but not reported fully)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Change in PADS-R Total score from baseline relative to placebo_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear method of randomisation and unclear if allocation sequence was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High *(Missing data rate could be up to 14% within the study)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Reports total score and only one of the subdomains of the survey based on significance. Also, another patient-reported outcome measured but not reported fully)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Change in PADS-R Exercise and Leisure sub score from baseline relative to placebo_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear method of randomisation and unclear if allocation sequence was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High *(Missing data rate could be up to 14% within the study)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Reports total score and only one of the subdomains of the survey based on significance. Also, another patient-reported outcome measured but not reported fully)*

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

De Giglio, 2019

Bibliographic Reference	De Giglio, L.; De Luca, F.; Gurreri, F.; Ferrante, I.; Prosperini, L.; Borriello, G.; Quartuccio, E.; Gasperini, C.; Pozzilli, C.; Effect of dalfampridine on information processing speed impairment in multiple sclerosis; Neurology; 2019; vol. 93 (no. 8); e733-e746

Study details

Other publications associated with this study included in review	• Prosperini, L.; Castelli, L.; De Giglio, L.; Bonanno, V.; Gasperini, C.; Pozzilli, C.; Dalfampridine to Improve Balance in Multiple Sclerosis: Substudy from a Randomized Placebo-Controlled Trial; Neurotherapeutics; 2020; vol. 17 (no. 2); 704-709
Trial name / registration number	EU Clinical Trials Register: 2013-002558-64
Study location	Italy
Study setting	2 regional referral MS centres in Rome
Study dates	Patients were enrolled from February 2015 to June 2016

Sources of funding	Sponsored by an investigator-initiated trial grant from Biogen - funder provided financial resources to perform the study and dalfampridine but had no role in the study design, data collection, data analysis, data interpretation or writing of the report. Various authors report receiving travel grants, consulting fees, lecture fees or research funding from industry (including Biogen, Genzyme, Teva, Novartis, Merck, Almirall, Roche and Bayer). One author also reported research funding from Federazione Italiana Sclerosi Multipla.
Inclusion criteria	Diagnosis of MS according to revised McDonald criteria; aged 18-65 years (inclusive); and a score on Symbol Digit Modalities Test below the 10th percentile of normative values of the Italian population. Patients were referred to the trial in the clinics based on cognitive complaints.
Exclusion criteria	Clinical relapse in the previous 60 days; history of major depression or psychosis; severe or moderate depression according to Beck Depression Inventory II (with a cut-off score of 19); history of seizures; any condition that would interfere with study conduction; and introduction or modification of any medication including medication for mood, fatigue or cognition in the previous month.
Recruitment / selection of participants	Patients were referred to the trial in the clinics based on cognitive complaints. Patients were screened during routine visits at MS centres. If meeting all inclusion criteria and no exclusion criteria, screening procedures with the SDMT with the psychologist were performed. No indication as to whether this was consecutive patients. Enrolment was between February 2015 and June 2016.
Intervention(s)	Slow-release dalfampridine. N=80. Randomised to take slow-release dalfampridine (10 mg twice daily) for 12 consecutive weeks. After 12 weeks patients returned to the centre to repeat tests and fill out questionnaires. Adherence was checked by physicians by calculating the percentage of tablets assumed of those prescribed. All evaluations were repeated after a 4-week washout period. Packages and tablets for dalfampridine and placebo were identical and only identifiable by a code. Details about coding was saved in a closed envelope only opened at the end of the trial. Adherence to medication was >97%. 71 patients completed the 12 weeks of treatment and 9 were lost to follow-up (5 presented with an adverse event and 4 refused to complete the cognitive assessment at the end of treatment). One further patient refused to complete the 4-week follow-up assessment after treatment had finished, meaning 70 patients completed the whole study in this group.
Comparator	Placebo. N=40. Randomised to take placebo (twice daily) for 12 consecutive weeks. After 12 weeks patients returned to the centre to repeat tests and fill out questionnaires. Adherence was checked by physicians by calculating the percentage of tablets assumed of those prescribed. All evaluations were repeated after a 4-week washout period. Packages and tablets for dalfampridine and placebo were identical and only identifiable by a code. Details about coding was saved in a closed envelope only opened at the end of the trial. 38 patients completed the 12 weeks of treatment

	and 2 dropped out (1 presented an adverse event and 1 refused to complete the cognitive assessment at the end of treatment). One further patient refused to complete the 4-week follow-up assessment after treatment had finished, meaning 37 patients completed the whole study in this group.
Number of participants	120 randomised (n=80 randomised to dalfampridine and n=40 randomised to placebo). 2.1 randomisation. Data from all randomised patients was included in the intention to treat analyses but data was imputed for those with missing data (drop-out rate was 9.2% up to end of treatment period and 10.8% at the 4-week off-treatment follow-up).
Duration of follow-up	12 weeks on treatment and follow-up at 4 weeks after the end of the treatment period
Additional comments	Extracted results at end of 12 weeks treatment period and not 4-week follow-up following the last dose as interested in the effect while on treatment not after it has been discontinued

Study arms

Slow-release dalfampridine (N = 80)

Randomised to take slow-release dalfampridine (10 mg twice daily) for 12 consecutive weeks. After 12 weeks patients returned to the centre to repeat tests and fill out questionnaires. Adherence was checked by physicians by calculating the percentage of tablets assumed of those prescribed. All evaluations were repeated after a 4-week washout period. Packages and tablets for dalfampridine and placebo were identical and only identifiable by a code. Details about coding was saved in a closed envelope only opened at the end of the trial.

Placebo (N = 40)

Randomised to take placebo (twice daily) for 12 consecutive weeks. After 12 weeks patients returned to the centre to repeat tests and fill out questionnaires. Adherence was checked by physicians by calculating the percentage of tablets assumed of those prescribed. All evaluations were repeated after a 4-week washout period. Packages and tablets for dalfampridine and placebo

were identical and only identifiable by a code. Details about coding was saved in a closed envelope only opened at the end of the trial.

Characteristics

Arm-level characteristics

Characteristic	Slow-release dalfampridine (N = 80)	Placebo (N = 40)
% Female Sample size	n = 50 ; % = 63	n = 24 ; % = 60
Mean age (SD) Mean (SD)	49.3 (7.8)	46.7 (8.7)
Ethnicity Text	Not reported	Not reported
Mild depression Based on cut-off of 14 on Beck Depression Inventory Sample size	n = 30 ; % = 37.5	n = 20 ; % = 50
Disease duration (years) Mean (SD)	14.7 (9)	17.2 (8.5)
EDSS score Expanded Disability Status Scale Median (range)	4 (1-6)	4.5 (1.5-5.5)

Characteristic	Slow-release dalfampridine (N = 80)	Placebo (N = 40)
Relapsing-remitting Sample size	n = 72 ; % = 90	n = 31 ; % = 77.5
Secondary progressive Sample size	n = 7 ; % = 8.75	n = 7 ; % = 17.5
Primary progressive Sample size	n = 1 ; % = 1.25	n = 2 ; % = 5
BDI score Beck Depression Inventory Mean (SD)	10.7 (5.5)	12.27 (5.8)
MFIS score Modified Fatigue Impact Scale Mean (SD)	19.8 (9.6)	21.7 (8.1)
Fatigued patients Based on cut-off of 38 on Modified Fatigue Impact Scale Sample size	n = 46 ; % = 57.5	n = 26 ; % = 65
Cognitive impairment Defined as failure on at least 2 of the cognitive tests used in the study Sample size	n = 71 ; % = 88.8	n = 37 ; % = 92.5
Cognitive Impairment Index score Mean (SD)	18.3 (5.7)	18.6 (5.9)

Characteristic	Slow-release dalfampridine (N = 80)	Placebo (N = 40)
MSIS-29 score Multiple Sclerosis Impact Scale Mean (SD)	73.9 (26.4)	76.2 (22.8)
MSFC score Multiple Sclerosis Functional Composite Mean (SD)	0.2 (2)	-0.2 (2.6)
25-FWT Timed 25-Foot Walk Test Mean (SD)	7.3 (2.4)	8.2 (4.9)
Dominant hand Mean (SD)	26.2 (11.3)	29.4 (15.4)
Non-dominant hand Mean (SD)	28 (9.8)	31.5 (17.1)

Outcomes

Study timepoints

- Baseline
- 12 week (Results reported at the end of the 12-week treatment period. Slightly indirect to 6-month time-point in protocol as only at 3 months rather than 6 months.)

Results – raw data

Outcome	Slow-release dalfampridine, Baseline, N = 80	Slow-release dalfampridine, 12-week, N = 80	Placebo, Baseline, N = 40	Placebo, 12-week, N = 40
25FWT (seconds) Timed 25-Foot Walk Test Mean (SE)	7.4 (0.3)	6.5 (0.4)	8.3 (0.8)	8 (0.7)
Relapsing-remitting subgroup only N=72 in dalfampridine group and N=31 in placebo group (90% and 77.5% of original groups, respectively). Does not appear to have stratified for this strategy prior to the study, so may have broken randomisation, particularly given differences in proportion that had relapsing-remitting MS in the original groups. To be used only if heterogeneity in meta-analyses. Mean (SE)	7.3 (0.3)	6.5 (0.3)	7.4 (0.7)	7.2 (0.6)
Dominant hand - whole study population Mean (SE)	26.2 (1.27)	25 (1.5)	29.4 (2.43)	26.8 (1.6)
Non-dominant hand - whole study population Mean (SE)	28 (1.1)	26.7 (1.1)	31.5 (2.68)	31.5 (3)
Dominant hand - relapsing remitting subgroup only N=72 in dalfampridine group and N=31 in placebo group (90% and 77.5% of original groups, respectively). Does not appear to have stratified for this strategy prior to the study, so may have broken randomisation, particularly given differences in proportion that had relapsing-remitting MS in the original groups. To be used only if heterogeneity in meta-analyses.	25.9 (1.4)	24.8 (1.5)	27.3 (2.8)	24.2 (1.6)

Outcome	Slow-release dalfampridine, Baseline, N = 80	Slow-release dalfampridine, 12-week, N = 80	Placebo, Baseline, N = 40	Placebo, 12-week, N = 40
Mean (SE)				
Non-dominant hand - relapsing-remitting subgroup only N=72 in dalfampridine group and N=31 in placebo group (90% and 77.5% of original groups, respectively). Does not appear to have stratified for this strategy prior to the study, so may have broken randomisation, particularly given differences in proportion that had relapsing-remitting MS in the original groups. To be used only if heterogeneity in meta-analyses. Mean (SE)	27.5 (1.1)	26.2 (1.4)	29.1 (2.9)	28.7 (3.4)
MSIS-29 score Multiple Sclerosis Impact Scale. Scale not reported in this study but is usually 0-100. Mean (SE)	73.7 (3)	68 (3.1)	76.2 (3.6)	71.3 (3.5)
Relapsing-remitting subgroup only N=72 in dalfampridine group and N=31 in placebo group (90% and 77.5% of original groups, respectively). Does not appear to have stratified for this strategy prior to the study, so may have broken randomisation, particularly given differences in proportion that had relapsing-remitting MS in the original groups. To be used only if heterogeneity in meta-analyses. Mean (SE)	74 (3.2)	68 (3.4)	74.9 (3.6)	70.3 (3.4)
Discontinuation due to adverse events Dalfampridine: n=2 postural instability, n=1 sleeplessness, n=1 focal seizure and n=1 palpitation and postural instability; placebo: n=1 postural instability and subsequent fall. Focal seizure and fall	n = NA ; % = NA	n = 5 ; % = 6.25	n = NA ; % = NA	n = 1 ; % = 2.5

Outcome	Slow-release dalfampridine, Baseline, N = 80	Slow-release dalfampridine, 12-week, N = 80	Placebo, Baseline, N = 40	Placebo, 12-week, N = 40
considered serious events as they resulted in brief visits to emergency department even if there were no long-term consequences. No of events				
Urinary tract infection No of events	n = NA ; % = NA	n = 7 ; % = 9	n = NA ; % = NA	n = 4 ; % = 10
Focal seizure 1 considered a serious event as resulted in a brief emergency department visit, unclear if all seizures occurring in study reported or just those considered serious. No of events	n = NA ; % = NA	n = 1 ; % = 1.25	n = NA ; % = NA	n = 0 ; % = 0
Headache No of events	n = NA ; % = NA	n = 6 ; % = 7.5	n = NA ; % = NA	n = 4 ; % = 10
Fall No of events	n = NA ; % = NA	n = 4 ; % = 5	n = NA ; % = NA	n = 2 ; % = 5
MSFC total score Multiple Sclerosis Functional Composite. Scale not reported. Appears to suggest higher score is better. Mean (SE)	0.1 (0.2)	0.6 (0.3)	-0.2 (0.4)	-0.5 (0.5)
Relapsing-remitting subgroup only N=72 in dalfampridine group and N=31 in placebo group (90% and 77.5% of original groups, respectively). Does not appear to have	0.3 (0.2)	0.7 (0.3)	0.16 (0.4)	-0.1 (0.4)

Outcome	Slow-release dalfampridine, Baseline, N = 80	Slow-release dalfampridine, 12-week, N = 80	Placebo, Baseline, N = 40	Placebo, 12-week, N = 40
stratified for this strategy prior to the study, so may have broken randomisation, particularly given differences in proportion that had relapsing-remitting MS in the original groups. Mean (SE)				

25FWT - Polarity - Lower values are better

9-HPT - Polarity - Lower values are better

MSIS-29 score - Polarity - Lower values are better

MSFC total score - Polarity - Higher values are better

Note that there was missing data for some patients in each group as n=9 and n=2 in the dalfampridine and placebo groups, respectively, did not complete the 12-week assessment. However, for continuous outcomes missing data has been imputed and analysed as intention to treat with n=80 and n=40 in the dalfampridine and placebo groups, respectively. For dichotomous outcomes, the missing data for each outcome was unclear and so the randomised numbers have been used as denominators.

Results - change from baseline

Outcome	Slow-release dalfampridine, 12-week vs Baseline, N = 80	Placebo, 12-week vs Baseline, N = 40
MFIS total score Modified Fatigue Impact Scale. Scale not reported in paper but found elsewhere to be 0-84. Mean (95% CI)	-7.84 (-11.7 to -3.9)	-0.2 (-4.6 to 4.9)

Outcome	Slow-release dalfampridine, 12-week vs Baseline, N = 80	Placebo, 12-week vs Baseline, N = 40
MFIS physical subscale Modified Fatigue Impact Scale. Scale not reported but found elsewhere to be 0-36. Mean (95% CI)	-2.6 (-4.8 to -0.4)	-0.2 (-2.5 to 2.1)
MFIS cognitive score Modified Fatigue Impact Scale. Scale not reported but found elsewhere to be 0-40. Mean (95% CI)	-4.6 (-6.5 to -2.8)	0.2 (-2.1 to 2.5)
MFIS psychosocial score Modified Fatigue Impact Scale. Scale not reported but found elsewhere to be 0-8. Mean (95% CI)	-0.58 (-1.1 to -0.02)	0.18 (-0.6 to 1)

MFIS total score - Polarity - Lower values are better

MFIS physical subscale - Polarity - Lower values are better

MFIS cognitive score - Polarity - Lower values are better

MFIS psychosocial score - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (Pharma)

25FWT_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(possible issue with allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

25FWT_12 weeks_relapsing-remitting subgroup

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(no stratification for this group before randomisation and baseline characteristics not reported)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(no information to inform missing data assessment in this subgroup and may have differed compared to the whole study population)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

9-HPT_dominant hand_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(possible issue with allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

9-HPT_non-dominant hand_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(possible issue with allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

9-HPT_12 weeks_dominant hand_relapsing-remitting subgroup

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(no stratification for this group before randomisation and baseline characteristics not reported)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(no information to inform missing data assessment in this subgroup and may have differed compared to the whole study population)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

9-HPT_12 weeks_non-dominant hand_relapsing-remitting subgroup

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(no stratification for this group before randomisation and baseline characteristics not reported)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(no information to inform missing data assessment in this subgroup and may have differed compared to the whole study population)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

MSIS-29 score_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(possible issue with allocation concealment)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

MSIS-29 score_12 weeks_relapsing-remitting subgroup

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(no stratification for this group before randomisation and baseline characteristics not reported)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(no information to inform missing data assessment in this subgroup and may have differed compared to the whole study population)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Discontinuation due to adverse events_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(possible issue with allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Urinary tract infection_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(possible issue with allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(proportion missing for this outcome unclear but proportion for whole study is similar to event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Focal seizure_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(possible issue with allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(proportion missing for this outcome unclear but proportion for whole study is higher than event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(unclear whether other seizures may have occurred but not led to withdrawal and therefore not included here)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Headache_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(possible issue with allocation concealment)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(proportion missing for this outcome unclear but proportion for whole study is higher than event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Fall_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(possible issue with allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(proportion missing for this outcome unclear but proportion for whole study is higher than event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

MSFC total score_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(possible issue with allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

MSFC total score_12 weeks_relapsing-remitting subgroup

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(no stratification for this group before randomisation and baseline characteristics not reported)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(no information to inform missing data assessment in this subgroup and may have differed compared to the whole study population)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

MFIS total score_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(possible issue with allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

MFIS physical subscale_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(possible issue with allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

MFIS cognitive subscale_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(possible issue with allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

MFIS psychosocial subscale_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(possible issue with allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Gasperini, 2016

Bibliographic Reference	Gasperini, C.; Hupperts, R.; Lycke, J.; Short, C.; McNeill, M.; Zhong, J.; Mehta, L. R.; Prolonged-release fampridine treatment improved subject-reported impact of multiple sclerosis: Item-level analysis of the MSIS-29; Journal of the Neurological Sciences; 2016; vol. 370; 123-131

Study details

Secondary publication of another included study- see primary study for details	Primary study: • Hupperts, R.; Lycke, J.; Short, C.; Gasperini, C.; McNeill, M.; Medori, R.; Tofil-Kaluza, A.; Hovenden, M.; Mehta, L. R.; Elkins, J.; Prolonged-release fampridine and walking and balance in MS: randomised controlled MOBILE trial; Multiple Sclerosis; 2016; vol. 22 (no. 2); 212-21 Study reports further information for some outcomes reported in the primary study and this information has been extracted into the tables for the primary study.

Goodman, 2008

Bibliographic Reference	Goodman, A. D.; Brown, T. R.; Cohen, J. A.; Krupp, L. B.; Schapiro, R.; Schwid, S. R.; Cohen, R.; Marinucci, L. N.; Blight, A. R.; Fampridine, M. S. F. Study Group; Dose comparison trial of sustained-release fampridine in multiple sclerosis; Neurology; 2008; vol. 71 (no. 15); 1134-41

Study details

Trial name / registration number	NCT00053417
Study location	24 sites across the USA (n=22 sites) and Canada (n=2 sites)
Study setting	Outpatient?
Study dates	The first participant visit was on 27th February 2003 and the last participant visit was on 18th December 2003.
Sources of funding	Appears to be supported by Acorda Therapeutics
Inclusion criteria	Adulted aged 18-70 years; diagnosis of MS as defined by McDonald criteria; ability to complete two trials of the T25FW test in an average of 8-60 seconds at screening
Exclusion criteria	Recent MS relapse; and recent changes in medication. Possibly others but not well reported.
Recruitment / selection of participants	Not reported.
Intervention(s)	Fampridine 10 mg. N=52. Two-week single-blind placebo run-in phase in all groups. Randomised to receive 10 mg fampridine twice daily (also a 15 mg and 20 mg dose group included but not relevant to our protocol). Patients were instructed to take one tablet every 12 hours. Appears to be 15 weeks treatment (2-week dose escalation for higher fampridine dose groups which did not apply to this group, followed by a 12-week stable dose treatment period and dose reduction from higher doses over a 1-week period, which did not apply to the 10 mg group). N=2 discontinued the intervention (n=1 lost to follow-up and n=1 withdrew consent). N=51 were analysed in intention to treat analyses (all randomized participants who had at least one efficacy measurement during the double-blind treatment period), with n=1 excluded due to there being no post-treatment measurement. N=52 were analysed in safety sample analyses. Across study compliance with medication was >96% and comparable across groups.
Comparator	Two-week single-blind placebo run-in phase in all groups. Randomised to receive placebo twice daily. Patients were instructed to take one tablet every 12 hours. Appears to be 15 weeks treatment. N=2 discontinued the intervention (n=1 lost to follow-up and n=1 adverse event). N=47 were included in analyses as the intention to treat population (all randomized participants who had at least one efficacy measurement during the double-blind treatment period). Across study compliance with medication was >96% and comparable across groups.

Number of participants	N=206 randomised (n=99 relevant to our protocol as two other arms of higher fampridine dose were not relevant). N=52 and N=47 randomised to fampridine 10 mg and placebo groups, respectively.
Duration of follow-up	Follow-up up to end of 15-week treatment period and additional follow-up assessment after 2-week washout period.

Study arms

Fampridine 10 mg (N = 52)

Two-week single-blind placebo run-in phase in all groups. Randomised to receive 10 mg fampridine twice daily (also a 15 mg and 20 mg dose group included but not relevant to our protocol). Patients were instructed to take one tablet every 12 hours. Appears to be 15 weeks treatment (2-week dose escalation for higher fampridine dose groups which did not apply to this group, followed by a 12-week stable dose treatment period and dose reduction from higher doses over a 1-week period, which did not apply to the 10 mg group).

Placebo (N = 47)

Two-week single-blind placebo run-in phase in all groups. Randomised to receive placebo twice daily. Patients were instructed to take one tablet every 12 hours. Appears to be 15 weeks treatment.

Characteristics

Arm-level characteristics

Characteristic	Fampridine 10 mg (N = 52)	Placebo (N = 47)
% Female Sample size	n = 36 ; % = 69	n = 27 ; % = 57
Mean age (SD) (years) Range	28 to 69	28 to 69
Mean age (SD) (years) Mean (SD)	49.8 (8.34)	49 (8.99)
Caucasian Sample size	n = 50 ; % = 96	n = 44 ; % = 94
Black Sample size	n = 2 ; % = 3.8	n = 2 ; % = 4
Hispanic Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Other Sample size	n = 0 ; % = 0	n = 1 ; % = 2.1
Comorbidities	Not reported	Not reported

Characteristic	Fampridine 10 mg (N = 52)	Placebo (N = 47)
Text		
Relapsing-remitting Sample size	n = 10 ; % = 19	n = 13 ; % = 28
Primary progressive Sample size	n = 12 ; % = 23	n = 12 ; % = 26
Secondary progressive Sample size	n = 30 ; % = 58	n = 22 ; % = 47
MS disease duration (years) Range	0.1 to 32	1.9 to 37
MS disease duration (years) Mean (SD)	10.7 (7.15)	13.9 (8.82)
EDSS score Expanded Disability Status Scale Range	3 to 6.5	2.5 to 6.5
EDSS score Expanded Disability Status Scale Mean (SD)	5.83 (0.9)	5.87 (0.97)
T25FW (feet/second) Timed 25-Foot Walk Test. Mean (SD)	1.94 (0.87)	1.87 (0.9)

Characteristic	Fampridine 10 mg (N = 52)	Placebo (N = 47)
Dominant hand Mean (SD)	35.7 (28.4)	33.9 (23.8)
Non-dominant hand Mean (SD)	30.6 (13.1)	35.7 (23.5)
MSFC composite Multiple Sclerosis Functional Composite Mean (SD)	0.04 (0.75)	-0.1 (0.67)
Ashworth Score Measure of spasticity Mean (SD)	0.88 (0.77)	1.2 (0.78)
MSWS-12 score 12-Item Multiple Sclerosis Walking Scale. Mean (SD)	76.3 (16.2)	75.7 (16.6)
Subject Global Impression score Patient-reported outcome measure of change in disease Mean (SD)	4.32 (0.1)	4.38 (0.79)

Intention to treat population includes 51 participants in fampridine 10 mg twice daily group for analysis of main efficacy variables and 52 randomized participants for demographics and disease characteristics. Unclear whether this applies to all efficacy measures listed below or only specific ones.

Outcomes

Study timepoints

- Baseline
- 14 week (Results reported at the end of a 14-week treatment period (reported as 12-week stable dose but before this there was two weeks treatment at the same dose for the 10 mg group - only the 15 and 20 mg groups had titration during the first two weeks and were not extracted). Matches 6-month time-point in our protocol but indirectness as 14 weeks rather than 6 months.)

Results - raw data

Outcome	Fampridine 10 mg, Baseline, N = 52	Fampridine 10 mg, 14-week, N = 52	Placebo, Baseline, N = 47	Placebo, 14-week, N = 47
T25FW test improvement >20% compared to baseline Timed 25-Foot Walk Test. Baseline values were 1.94 (0.87) and 1.87 (0.90) in fampridine and placebo groups, respectively. No of events	n = NA ; % = NA	n = 12 ; % = 23.5	n = NA ; % = NA	n = 6 ; % = 12.8
T25FW test improvement >20% compared to baseline Timed 25-Foot Walk Test. Baseline values were 1.94 (0.87) and 1.87 (0.90) in fampridine and placebo groups, respectively. Sample size	n = NA	n = 51	n = NA	n = 46
Discontinuation due to adverse events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 1 ; % = 2.13

Outcome	Fampridine 10 mg, Baseline, N = 52	Fampridine 10 mg, 14-week, N = 52	Placebo, Baseline, N = 47	Placebo, 14-week, N = 47
No of events				
Urinary tract infection No of events	n = NA ; % = NA	n = 6 ; % = 12	n = NA ; % = NA	n = 2 ; % = 4
Fall No of events	n = NA ; % = NA	n = 10 ; % = 19	n = NA ; % = NA	n = 5 ; % = 11
Headache No of events	n = NA ; % = NA	n = 6 ; % = 12	n = NA ; % = NA	n = 4 ; % = 9

All of those randomised received at least one dose of study drug and were included in safety analyses for adverse event outcomes. For T25FW test, not all of those randomised had data available, as indicated in the table below.

Results - change or % change from baseline

Outcome	Fampridine 10 mg, 14-week vs Baseline, N = 51	Placebo, 14-week vs Baseline, N = 47
T25FW test % change from baseline (feet/second) Timed 25-Foot Walk Test. Baseline values were 1.94 (0.87) and 1.87 (0.90) in fampridine and placebo groups, respectively. Values not reported in the text so could not be analysed. Sample size	n = 51	n = 46
T25FW test % change from baseline (feet/second) Timed 25-Foot Walk Test. Baseline values were 1.94 (0.87) and 1.87 (0.90) in fampridine and placebo groups, respectively. Values not reported in the text so could not be analysed.	NR (NR)	NR (NR)

Outcome	Fampridine 10 mg, 14-week vs Baseline, N = 51	Placebo, 14-week vs Baseline, N = 47
Mean (SE)		
MSWS-12 change from baseline 12-Item Multiple Sclerosis Walking Scale. Scale not reported but usually 0-100? Baseline values were 76.3 (16.2) and 75.7 (16.6) for fampridine and placebo groups, respectively. Sample size	n = 51	n = 46
MSWS-12 change from baseline 12-Item Multiple Sclerosis Walking Scale. Scale not reported but usually 0-100? Baseline values were 76.3 (16.2) and 75.7 (16.6) for fampridine and placebo groups, respectively. Mean (SD)	-5.33 (16.15)	-3.56 (14.55)
9-HPT change from baseline - dominant hand (seconds) 9-Hole Peg Test. Baseline values were 35.7 (28.4) and 33.9 (23.8) for fampridine and placebo groups, respectively. Sample size	n = 51	n = 46
9-HPT change from baseline - dominant hand (seconds) 9-Hole Peg Test. Baseline values were 35.7 (28.4) and 33.9 (23.8) for fampridine and placebo groups, respectively. Mean (SD)	-4.03 (17.2)	-2.27 (12.12)
9-HPT change from baseline - non-dominant hand (seconds) 9-Hole Peg Test. Baseline values were 30.6 (13.1) and 35.7 (23.5) for fampridine and placebo groups, respectively. Sample size	n = 51	n = 46

Outcome	Fampridine 10 mg, 14-week vs Baseline, N = 51	Placebo, 14-week vs Baseline, N = 47
9-HPT change from baseline - non-dominant hand (seconds) 9-Hole Peg Test. Baseline values were 30.6 (13.1) and 35.7 (23.5) for fampridine and placebo groups, respectively. Mean (SD)	-2.17 (5.32)	-0.32 (11.64)
SGI score change from baseline Subject Global Impression of Change. Scale 1-7. Patient-reported effect of study medication on their health status on previous week. Baseline values were 4.32 (0.10) and 4.38 (0.79) for fampridine and placebo groups, respectively. Sample size	n = 50	n = 46
SGI score change from baseline Subject Global Impression of Change. Scale 1-7. Patient-reported effect of study medication on their health status on previous week. Baseline values were 4.32 (0.10) and 4.38 (0.79) for fampridine and placebo groups, respectively. Mean (SD)	0 (1.27)	-0.2 (0.96)
MSFC composite change from baseline Multiple Sclerosis Functional Composite. Scale unclear. Baseline values were 0.04 (0.75) and -0.10 (0.67) for fampridine and placebo groups, respectively. Sample size	n = 51	n = 46
MSFC composite change from baseline Multiple Sclerosis Functional Composite. Scale unclear. Baseline values were 0.04 (0.75) and -0.10 (0.67) for fampridine and placebo groups, respectively. Mean (SD)	0.1 (0.31)	0.08 (0.2)

Outcome	Fampridine 10 mg, 14-week vs Baseline, N = 51	Placebo, 14-week vs Baseline, N = 47
Ashworth score change from baseline. Measure of spasticity. Scale not reported but usually 0-4? Baseline values were 0.88 (0.77) and 1.20 (0.78) for fampridine and placebo groups, respectively. Sample size	n = 51	n = 46
Ashworth score change from baseline. Measure of spasticity. Scale not reported but usually 0-4? Baseline values were 0.88 (0.77) and 1.20 (0.78) for fampridine and placebo groups, respectively. Mean (SD)	-0.04 (0.45)	-0.11 (0.38)

T25FW test % change from baseline - Polarity - Higher values are better

MSWS-12 change from baseline - Polarity - Lower values are better

9-HPT change from baseline - dominant hand - Polarity - Lower values are better

9-HPT change from baseline - non-dominant hand - Polarity - Lower values are better

SGI score change from baseline - Polarity - Higher values are better

MSFC composite change from baseline - Polarity - Higher values are better

Ashworth score change from baseline. - Polarity - Lower values are better

Modified intention to treat population was used for analysis, with n=1 that did not receive at least one post-baseline visit being excluded in the fampridine group. Additional missing data was present for specific outcomes and is indicated in the table below.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (Pharma)

T25FW test improvement >20% compared to baseline_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and allocation concealment unclear)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Missing data for group relevant to protocol unclear and overall rate is >10%)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Discontinuation due to adverse events_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and allocation concealment unclear)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Dropout across the two arms is higher than event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Urinary tract infection_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and allocation concealment unclear)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Fall_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and allocation concealment unclear)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Headache_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and allocation concealment unclear)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

T25FW test % change from baseline_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and allocation concealment unclear)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Missing data for group relevant to protocol unclear and overall rate is >10%)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

MSWS-12 change from baseline_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and allocation concealment unclear)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

9-HPT dominant hand change from baseline_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and allocation concealment unclear)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

9-HPT non-dominant hand change from baseline_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and allocation concealment unclear - larger difference at baseline for this outcome)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SGI score change from baseline_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and allocation concealment unclear)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

MSFC composite score change from baseline_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and allocation concealment unclear - larger difference at baseline for this outcome)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Ashworth score change from baseline_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and allocation concealment unclear - larger difference at baseline for this outcome)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Goodman, 2010

Bibliographic Reference	Goodman, A. D.; Brown, T. R.; Edwards, K. R.; Krupp, L. B.; Schapiro, R. T.; Cohen, R.; Marinucci, L. N.; Blight, A. R.; Investigators, M. S. F.; A phase 3 trial of extended release oral dalfampridine in multiple sclerosis; Ann Neurol; 2010; vol. 68 (no. 4); 494-502

Study details

Trial name / registration number	NCT00483652
Study location	39 centres across the USA and Canada
Study setting	Outpatient?
Study dates	Not reported
Sources of funding	Study funded by Acorda Therapeutics, Inc. and supported by a grant from the Stony Brook Research Foundation. Three authors were employed by Acorda Therapeutics, Inc. and held stocks in the company. Four other authors received funds from Acorda Therapeutics, Inc. Another author had received honoraria and travel reimbursements for various companies.

Inclusion criteria	Aged 18-70 years; clinically defined MS; and had a T25FW test time between 8 and 45 seconds.
Exclusion criteria	Prior exposure to dalfampridine; MS exacerbation within 60 days; history of seizures; evidence of epileptiform activity on an electroencephalogram; and any condition that would interfere with study conduct. Additional restrictions on changes in concomitant medications were designed to avoid possible related changes in MS symptoms.
Recruitment / selection of participants	Patients were selected from 39 centres in the United States and Canada. Patients underwent screening and eligible patients returned 1 week later to start the trial.
Intervention(s)	Extended-release fampridine. N=120 randomised. 1-week after screening, patients entered a 2-week single-blind placebo run-in phase (1 tablet taken every 12 hours). Patients subsequently randomised to take extended-release fampridine (10 mg twice daily) for 9 weeks. Patients were asked to time their last dose of medication so that at the final visit assessments could be made ~10-12 hours after this last dose had been taken. A follow-up assessment was also performed at 2 weeks after the final dose. Analysis was performed in the modified intention to treat population (all randomised patients who had at least 1 efficacy evaluation during the double-blind treatment period), which was n=119 in this group (n=1 discontinued due sponsor decision before completing any of the scheduled walking speed assessments) . The safety population was used to analyse adverse events and included all 120 patients in this group as all received at least one dose. Only 1 patient in this group was said to be non-compliant. Overall, n=7 discontinued the treatment before the end of the study (n=4 due to adverse events, n=2 due to protocol non-compliance and n=1 due to sponsor decision prior to them taking any dose of the drug).
Comparator	Placebo. N=119 randomised. 1-week after screening, patients entered a 2-week single-blind placebo run-in phase (1 tablet taken every 12 hours). Patients subsequently randomised to take placebo twice daily for 9 weeks. Patients were asked to time their last dose of medication so that at the final visit assessments could be made ~10-12 hours after this last dose had been taken. A follow-up assessment was also performed at 2 weeks after the final dose. Analysis was performed in the modified intention to treat population (all randomised patients who had at least 1 efficacy evaluation during the double-blind treatment period), which was n=118 in this group (n=1 discontinued due to an adverse events before completing any of the scheduled walking speed assessments) . The safety population was used to analyse adverse events and included all 119 patients in this group as all received at least one dose. Only 1 patient in this group was said to be non-compliant. Overall, n=5 discontinued the treatment before the end of the study (n=4 due to adverse events and n=1 due to protocol non-compliance).
Number of participants	N=239 randomised (n=120 to fampridine and n=119 to placebo). Modified intention to treat population used for most analyses (all randomised patients who had at least 1 efficacy evaluation during the double-blind treatment period), which was n=119 in fampridine and n=118 in placebo groups. Safety analyses were used to analyses of adverse events and included all patients in each group as they all received at least one dose of drug/placebo.

Duration of follow-up	Up to the end of the 9-week treatment period and an additional follow-up 2 weeks following the last dose.

Study arms

Extended-release fampridine (N = 120)

Randomised to receive extended-release fampridine (10 mg twice daily) for 9 weeks.

Placebo (N = 119)

Randomised to receive placebo twice daily for 9 weeks.

Characteristics

Arm-level characteristics

Characteristic	Extended-release fampridine (N = 120)	Placebo (N = 119)
% Female Sample size	n = 88 ; % = 73.3	n = 74 ; % = 62.2
Mean age (SD) (years) Range	25 to 73	24 to 70

Characteristic	Extended-release fampridine (N = 120)	Placebo (N = 119)
Mean age (SD) (years) Mean (SD)	51.8 (9.6)	51.7 (9.8)
White Sample size	n = 113 ; % = 94.2	n = 105 ; % = 88.2
Black Sample size	n = 3 ; % = 2.5	n = 9 ; % = 7.6
Hispanic Sample size	n = 2 ; % = 1.7	n = 2 ; % = 1.7
American Indian/Alaskan Native Sample size	n = 0 ; % = 0	n = 1 ; % = 0.8
Other Sample size	n = 2 ; % = 1.7	n = 2 ; % = 1.7
Comorbidities Text	Not reported	Not reported
Relapsing-remitting Sample size	n = 43 ; % = 35.8	n = 40 ; % = 33.6
Primary progressive Sample size	n = 10 ; % = 8.3	n = 21 ; % = 17.6

Characteristic	Extended-release fampridine (N = 120)	Placebo (N = 119)
Secondary progressive Sample size	n = 62 ; % = 51.7	n = 56 ; % = 47.1
Progressive-relapsing Sample size	n = 5 ; % = 4.2	n = 2 ; % = 1.7
Immunomodulator treatment Concomitant treatment with an interferon, glatiramer acetate or natalizumab Sample size	n = 83 ; % = 69.2	n = 83 ; % = 69.7
Disease duration (years) Range	0.5 to 45.6	0.1 to 34.1
Disease duration (years) Mean (SD)	14.4 (9.5)	13.1 (8.7)
EDSS score Expanded Disability Status Scale. Range	2.5 to 6.5	1.5 to 7
EDSS score Expanded Disability Status Scale. Mean (SD)	5.8 (1)	5.6 (1.2)
T25FW speed (feet/second) Timed 25-Foot Walk Test. Sample size	n = 119	n = 118

Characteristic	Extended-release fampridine (N = 120)	Placebo (N = 119)
T25FW speed (feet/second) Timed 25-Foot Walk Test. Mean (SD)	2.1 (0.8)	2.2 (0.7)
Ashworth score Measure of spasticity Sample size	n = 119	n = 118
Ashworth score Measure of spasticity Mean (SD)	0.9 (0.6)	0.8 (0.7)
MSWS-12 score 12-Item Multiple Sclerosis Walking Scale. Sample size	n = 119	n = 118
MSWS-12 score 12-Item Multiple Sclerosis Walking Scale. Mean (SD)	73.8 (17.8)	67.7 (22.6)
SGI score Subject Global Impression score. Sample size	n = 119	n = 118
SGI score Subject Global Impression score. Mean (SD)	4.3 (0.9)	4.4 (0.8)

Baseline characteristics and demographics are provided for the as randomised population and efficacy measures at baseline are provided for the analysed modified intention to treat population, with n=119 and n=118 in fampridine and placebo groups, respectively, as indicated in the table.

Outcomes

Study timepoints

- Baseline
- 9 week (For efficacy measures and continuous outcomes, the average value of all follow-up assessments during the 9-week treatment period are reported. Adverse events reported across the 9-week treatment period. Matches 6-month time-point in protocol but indirect as 9 weeks rather than 6 months.)

Results - raw data

Outcome	Extended-release fampridine, Baseline, N = 120	Extended-release fampridine, 9-week, N = 120	Placebo, Baseline, N = 119	Placebo, 9-week, N = 119
T25FW responder Timed 25-Foot Walk test. Responder defined as patient with faster walking speed for at least 3 of the first 4 visits during the double-blind treatment period compared with the maximum speed for any of the 5 off-drug visits (baseline and after drug discontinuation). No of events	n = NA ; % = NA	n = 51 ; % = 42.86	n = NA ; % = NA	n = 11 ; % = 9.32
T25FW responder Timed 25-Foot Walk test. Responder defined as patient with faster walking speed for at least 3 of the first 4 visits during the double-blind	n = NA ; % = NA	n = 119	n = NA ; % = NA	n = 118

Outcome	Extended-release fampridine, Baseline, N = 120	Extended-release fampridine, 9-week, N = 120	Placebo, Baseline, N = 119	Placebo, 9-week, N = 119
treatment period compared with the maximum speed for any of the 5 off-drug visits (baseline and after drug discontinuation). Sample size				
Withdrawal due to adverse events Fampridine (n=1 each of hypotension, headache, patella fracture and neurological symptoms); placebo (n=1 each of ventricular extrasystoles, coordination abnormal, complex partial seizure and gastro-oesophageal reflux disease). No of events	n = NA ; % = NA	n = 4 ; % = 3.3	n = NA ; % = NA	n = 4 ; % = 3.4
Urinary tract infection No of events	n = NA ; % = NA	n = 21 ; % = 17.5	n = NA ; % = NA	n = 10 ; % = 8.4
Complex partial seizure Reports that one of those that withdrew from the study was due to a complex partial seizure - unclear whether other more minor versions of seizure occurred but were not reported, as only the most common or serious adverse events are reported. No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 1 ; % = 0.84
Fall No of events	n = NA ; % = NA	n = 14 ; % = 11.7	n = NA ; % = NA	n = 20 ; % = 16.8
Headache No of events	n = NA ; % = NA	n = 11 ; % = 9.2	n = NA ; % = NA	n = 1 ; % = 0.8

Outcome	Extended-release fampridine, Baseline, N = 120	Extended-release fampridine, 9-week, N = 120	Placebo, Baseline, N = 119	Placebo, 9-week, N = 119
Patella fracture Reports that one of those that withdrew from the study was due to a patella fracture - unclear whether other more minor versions of fracture occurred but were not reported, as only the most common or serious adverse events are reported. No of events	n = NA ; % = NA	n = 1 ; % = 0.83	n = NA ; % = NA	n = 0 ; % = 0

Numbers analysed in each group are given according to the safety population, defined as those that were randomised and received at least one dose of investigational drug, which was all of those originally randomised. Note that the denominators differ for the efficacy outcomes as the modified intention to treat population was used (all of those randomised and had at least 1 efficacy assessment during double-blind treatment period), as indicated in the table.

Results - change from baseline

Outcome	Extended-release fampridine, 9-week vs Baseline, N = 119	Placebo, 9-week vs Baseline, N = 118
T25FW average change from baseline across double-blind period (feet/second) Timed 25-Foot Walk test. Baseline values were 2.1 (0.8) and 2.2 (0.7) in the fampridine and placebo groups, respectively. Paper reported mean and 95% CIs for fampridine responders and non-responders separately, which were combined to calculate mean and SD for the fampridine group as a whole so that it could be compared to placebo. Data reported in the paper: fampridine responders, 0.51 feet/second (95% CI, 0.43 to 0.59 feet/second); fampridine non-responders, 0.12 feet/second (95% CI, 0.05 to 0.19 feet/second); and placebo, 0.17 feet/second (95% CI, 0.10 to 0.23) feet/second). Mean (SD)	0.29 (0.35)	0.17 (0.36)

Outcome	Extended-release fampridine, 9-week vs Baseline, N = 119	Placebo, 9-week vs Baseline, N = 118
MSWS-12 average change from baseline across double-blind period 12-Item Multiple Sclerosis Walking Scale. Scale usually 0-100. Baseline values were 73.8 (17.8) and 67.7 (22.6) in the fampridine and placebo groups, respectively. Only mean values reported so no assessment of variability (P-value of 0.021 for comparison between the two groups). Mean (SD)	-2.62 (NR)	0.73 (NR)
Ashworth score average change from baseline across double-blind period Measure of spasticity. Scale usually 0-4. Baseline values were 0.9 (0.6) and 0.8 (0.7) in the fampridine and placebo groups, respectively. Only mean values reported so no assessment of variability (P-value of 0.015 for comparison between the two groups). Mean (SD)	-0.18 (NR)	-0.06 (NR)

T25FW average change from baseline across double-blind period - Polarity - Higher values are better

MSWS-12 average change from baseline across double-blind period - Polarity - Lower values are better

Ashworth score average change from baseline across double-blind period - Polarity - Lower values are better

Numbers analysed in each group are given according to the modified intention to treat population (all of those randomised and had at least 1 efficacy assessment during double-blind treatment period).

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (Pharma)

T25FW responder_9-week average

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information on allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Withdrawal due to adverse events_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information on allocation concealment)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Urinary tract infection_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information on allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Complex partial seizure_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information on allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Fall_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information on allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Headache_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information on allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Patella fracture_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information on allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	**Overall Directness**	**Indirectly applicable *(time-point <3 months)***

T25FW average change from baseline across double-blind period_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information on allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

MSWS-12 average change from baseline across double-blind period_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information on allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Ashworth score average change from baseline across double-blind period_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information on allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Goodman, 2009

Bibliographic Reference	Goodman, A. D.; Brown, T. R.; Krupp, L. B.; Schapiro, R. T.; Schwid, S. R.; Cohen, R.; Marinucci, L. N.; Blight, A. R.; Fampridine, M. S. F. Investigators; Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial; Lancet; 2009; vol. 373 (no. 9665); 732-8

Study details

Other publications associated with this study included in review	• Limone, B. L.; Sidovar, M. F.; Coleman, C. I.; Estimation of the effect of dalfampridine-ER on health utility by mapping the MSWS-12 to the EQ-5D in multiple sclerosis patients; Health & Quality of Life Outcomes; 2013; vol. 11; 105
Trial name / registration number	NCT00127530
Study location	33 centres across the USA and Canada
Study setting	Outpatient?
Study dates	Not reported
Sources of funding	Funded by Acorda Therapeutics Inc. The sponsor was responsible for data collection and statistical analysis, and collaborated with the authors in study design, data interpretation, writing of the report and decision to publish the final report.
Inclusion criteria	Aged 18-70 years; clinically defined MS; and ability to complete two trials of T25FW test in an average time of 8-45 seconds at screening.
Exclusion criteria	Onset of MS exacerbation within 60 days prior to the screening; history of seizures or evidence of epileptiform activity on a screening electroencephalogram; and any condition that would interfere with the conduct or interpretation of the study. Additional restrictions on changes in concomitant medications to avoid related changes in MS symptoms during the trial were also set.

Recruitment / selection of participants	Not reported
Intervention(s)	Sustained-release fampridine. N=229 randomised. Initial 2-week single-blind placebo run-in phase with one tablet taken every 12 hours (twice daily). Randomly assigned to receive fampridine (10 mg twice daily) for a 14-week treatment period. This was followed by a 4-week no treatment period. Of those randomised, n=1 did not receive the allocated intervention. A further n=17 discontinued the intervention (n=11 due to adverse events, n=4 withdrew consent and n=2 due to other reasons). A total of n=224 were included in the analysis for this group (excluded: n=1 did not receive the intervention, n=3 discontinued due to non-treatment emergent adverse events and n=1 withdrew consent, before completing any double-blind walking speed and MSWS-12 assessments). Analyses were based on the intention to treat population (all randomised patients who had at least one efficacy assessment of T25FW and MSWS-12 during the double-blind treatment period). Compliance with study medication was >97%.
Comparator	Placebo. N=72 randomised. Initial 2-week single-blind placebo run-in phase with one tablet taken every 12 hours (twice daily). Randomly assigned to receive placebo twice daily for a 14-week treatment period. This was followed by a 4-week no treatment period. All of those randomised received the allocated placebo. N=1 discontinued the placebo (lost to follow-up). All n=72 patients randomised to this group were included in the analysis for this group. Analyses were based on the intention to treat population (all randomised patients who had at least one efficacy assessment of T25FW and MSWS-12 during the double-blind treatment period). Compliance with study medication was >97%.
Number of participants	N=301 randomised (n=229 to fampridine and n=72 to placebo). 3.1 ratio. N=296 analysed as part of the intention to treat population (all randomised patients who had at least one efficacy assessment of T25FW and MSWS-12 during the double-blind treatment period), with n=224 in the fampridine group and n=72 in the placebo group. Safety sample (those randomised and receiving at least one dose of study drug) was used to assess adverse events (n=228 in fampridine and n=72 in placebo).
Duration of follow-up	Follow-up up to end of 14-week treatment period and an additional follow-up at 4 weeks after treatment discontinuation.

Study arms

Sustained-release fampridine (N = 229)

Initial 2-week single-blind placebo run-in phase with one tablet taken every 12 hours (twice daily). Randomly assigned to receive fampridine (10 mg twice daily) for a 14-week treatment period. This was followed by a 4-week no treatment period.

Placebo (N = 72)

Initial 2-week single-blind placebo run-in phase with one tablet taken every 12 hours (twice daily). Randomly assigned to receive placebo twice daily for a 14-week treatment period. This was followed by a 4-week no treatment period.

Characteristics

Arm-level characteristics

Characteristic	Sustained-release fampridine (N = 229)	Placebo (N = 72)
% Female number/analysed (%)	162/228 (71%)	43/72 (60%)
Mean age (SD) (years) Range	26 to 70	34 to 69
Mean age (SD) (years) Sample size	n = 228	n = 72
Mean age (SD) (years) Mean (SD)	51.5 (8.7)	50.9 (8.9)
White number/analysed (%)	211/228 (93%)	67/72 (93%)
Black	10/228 (4%)	3/72 (4%)3

Characteristic	Sustained-release fampridine (N = 229)	Placebo (N = 72)
number/analysed (%)		
Hispanic number/analysed (%)	3/228 (1%)	1/72 (1%)
Asian/Pacific islander number/analysed (%)	3/228 (1%)	1/72 (1%)
Other number/analysed (%)	1/228 (0.4%)	0/72 (0%)
Comorbidities Text	Not reported	Not reported
Relapsing-remitting number/analysed (%)	62/228 (27%)	21/72 (29%)
Primary progressive number/analysed (%)	31/228 (14%)	14/72 (19%)
Secondary progressive number/analysed (%)	125/228 (55%)	35/72 (49%)
Progressive-relapsing number/analysed (%)	10/228 (4%)	2/72 (3%)
Immunomodulator treatment Concomitant treatment with an interferon or glatiramer acetate	151/228 (66%)	51/72 (71%)

Characteristic	Sustained-release fampridine (N = 229)	Placebo (N = 72)
number/analysed (%)		
MS duration (years) Range	0.4 to 41.7	1.4 to 37.7
MS duration (years) Sample size	n = 228	n = 72
MS duration (years) Mean (SD)	13.4 (8.29)	12.7 (8.21)
EDSS score Expanded Disability Status Scale Range	2.5 to 7	2.5 to 6.5
EDSS score Expanded Disability Status Scale Sample size	n = 228	n = 72
EDSS score Expanded Disability Status Scale Mean (SD)	5.8 (1)	5.8 (1.1)
T25FW (feet/second) Timed 25-Foot Walk Test Sample size	n = 228	n = 72

Characteristic	Sustained-release fampridine (N = 229)	Placebo (N = 72)
T25FW (feet/second) Timed 25-Foot Walk Test Mean (SD)	2.1 (0.7)	2.1 (0.7)
Ashworth score Measure of spasticity Sample size	n = 228	n = 72
Ashworth score Measure of spasticity Mean (SD)	1 (0.7)	1 (0.7)
MSWS-12 score 12-Item Multiple Sclerosis Walking Scale Sample size	n = 228	n = 72
MSWS-12 score 12-Item Multiple Sclerosis Walking Scale Mean (SD)	70.7 (18.6)	68.5 (22.3)
SGI score Subject Global Impression score. Sample size	n = 226	n = 72
SGI score Subject Global Impression score. Mean (SD)	4.6 (0.9)	4.7 (0.9)

Note that baseline characteristics are given for n=228 in the fampridine group and n=72 in the placebo group, based on the intention to treat population (all randomised patients who had at least one efficacy assessment of T25FW and MSWS-12 during the double-blind treatment period), as indicated in the table. There was also some further missing data for the SGI measure at baseline and is indicated in the table.

Outcomes

Study timepoints

- Baseline
- 14 week (Most outcomes only reported as an average of all the follow-up visits during the on-treatment period, rather than specifically at the 14-week follow-up assessment.)

Results - raw data

Outcome	Sustained-release fampridine, Baseline, N = 229	Sustained-release fampridine, 14-week, N = 228	Placebo, Baseline, N = 72	Placebo, 14-week, N = 72
T25FW improvement on treatment Timed 25-Foot Walk test. A timed walk responder was defined as a patient with a faster walking speed for at least 3 of 4 visits during the double-blind treatment period compared with the maximum speed for any of the first 5 off-drug visits (4 prior to double-blind treatment and 1 at 2 weeks after discontinuation of treatment). Missed assessments were assumed to fall within the off-treatment range (no imputation). number/analysed (%)	NA	78/224 (35%)	NA	6/72 (8%)

Outcome	Sustained-release fampridine, Baseline, N = 229	Sustained-release fampridine, 14-week, N = 228	Placebo, Baseline, N = 72	Placebo, 14-week, N = 72
Mortality No deaths during treatment. Note there was n=1 death in the fampridine group at 5 weeks after the final dose (ischaemic and hypertensive heart disease). No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Mortality No deaths during treatment. Note there was n=1 death in the fampridine group at 5 weeks after the final dose (ischaemic and hypertensive heart disease). Sample size	n = NA ; % = NA	n = 211	n = NA ; % = NA	n = 71
Withdrawal due to adverse events In n=8 patients adverse events began during the double-blind treatment and a further n=3 had events that occurred before the double-blind period. No of events	n = NA ; % = NA	n = 11 ; % = 5	n = NA ; % = NA	n = 0 ; % = 0
Withdrawal due to adverse events In n=8 patients adverse events began during the double-blind treatment and a further n=3 had events that occurred before the double-blind period. Sample size	n = NA ; % = NA	n = 222	n = NA ; % = NA	n = 71
Urinary tract infection No of events	n = NA ; % = NA	n = 31 ; % = 14	n = NA ; % = NA	n = 10 ; % = 14

Outcome	Sustained-release fampridine, Baseline, N = 229	Sustained-release fampridine, 14-week, N = 228	Placebo, Baseline, N = 72	Placebo, 14-week, N = 72
Confusional state Reports that one of those that withdrew from the study was due to confusional state - unclear whether other more minor versions of confusion occurred but were not reported, as only the most common or serious adverse events are reported. No of events	n = NA ; % = NA	n = 1 ; % = 0.44	n = NA ; % = NA	n = 0 ; % = 0
Confusional state Reports that one of those that withdrew from the study was due to confusional state - unclear whether other more minor versions of confusion occurred but were not reported, as only the most common or serious adverse events are reported. Sample size	n = NA ; % = NA	n = 212	n = NA ; % = NA	n = 71
Focal seizure Reports that one of those one of the serious adverse events observed under fampridine included a focal seizure - unclear whether other more minor versions of seizures occurred but were not reported, as only the most common or serious adverse events are reported. No of events	n = NA ; % = NA	n = 1 ; % = 0.44	n = NA ; % = NA	n = 0 ; % = 0
Focal seizure Reports that one of those one of the serious adverse events observed under fampridine included a focal seizure - unclear whether other more minor versions of seizures occurred but were not reported, as only the most common or serious adverse events are reported. Sample size	n = NA ; % = NA	n = 212	n = NA ; % = NA	n = 71

Outcome	Sustained-release fampridine, Baseline, N = 229	Sustained-release fampridine, 14-week, N = 228	Placebo, Baseline, N = 72	Placebo, 14-week, N = 72
Fall No of events	n = NA ; % = NA	n = 36 ; % = 16	n = NA ; % = NA	n = 11 ; % = 15
Headache No of events	n = NA ; % = NA	n = 13 ; % = 6	n = NA ; % = NA	n = 4 ; % = 6
Ankle fracture Reports that one of those that withdrew from the study was due to an ankle fracture - unclear whether other more minor versions of fracture occurred but were not reported, as only the most common or serious adverse events are reported. No of events	n = NA ; % = NA	n = 1 ; % = 0.44	n = NA ; % = NA	n = 0 ; % = 0
Ankle fracture Reports that one of those that withdrew from the study was due to an ankle fracture - unclear whether other more minor versions of fracture occurred but were not reported, as only the most common or serious adverse events are reported. Sample size	n = NA ; % = NA	n = 212	n = NA ; % = NA	n = 71

Total number analysed for each group is given for the safety sample in which adverse events were analysed, including all of those randomised that had at least one dose of study drug (n=228 in fampridine and n=72 in placebo). Available case analyses with appropriate denominators have been extracted where possible, as indicated in the table.

Results - average change from baseline

Outcome	Sustained-release fampridine, 14-week vs Baseline, N = 224	Placebo, 14-week vs Baseline, N = 72
Average change in T25FW test across double-blind period (feet/second) Timed 25-Foot Walk test. Paper reported mean and 95% CIs for fampridine responders and non-responders separately, which were combined to calculate mean and SD for the fampridine group as a whole so that it could be compared to placebo. Data reported in the paper: fampridine responders, 0.51 feet/second (95% CI, 0.41 to 0.61 feet/second); fampridine non-responders, 0.16 feet/second (95% CI, 0.11 to 0.21 feet/second); and placebo, 0.10 feet/second (95% CI, 0.03 to 0.17 feet/second). Mean (SD)	0.28 (0.4)	0.1 (0.3)

Average change in T25FW test across double-blind period - Polarity - Higher values are better

Number analysed in each group was based on the intention to treat population, defined as those randomised who had at least one efficacy assessment of T25FW and MSWS-12 during the double-blind treatment period.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (Pharma)

T25FW test improvement compared to off-drug visits_14-week average

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information about allocation concealment)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Mortality_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(dropout higher than event rate and differed between groups, with most withdrawals due to adverse events)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Withdrawal due to adverse events_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Urinary tract infection_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Confusional state_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(dropout higher than event rate and differed between groups, with most withdrawals due to adverse events)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Focal seizure_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(dropout higher than event rate and differed between groups, with most withdrawals due to adverse events)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Fall_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Headache_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information about allocation concealment)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(dropout similar to event rate and differed between groups, with most withdrawals due to adverse events)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Ankle fracture_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(dropout higher than event rate and differed between groups, with most withdrawals due to adverse events)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Average change in T25FW test compared to baseline_14-week average

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of information about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Hobart, 2019

Bibliographic Reference	Hobart, J.; Ziemssen, T.; Feys, P.; Linnebank, M.; Goodman, A. D.; Farrell, R.; Hupperts, R.; Blight, A. R.; Englishby, V.; McNeill, M.; Chang, I.; Lima, G.; Elkins, J.; investigators, Enhance study; Assessment of Clinically Meaningful Improvements in Self-Reported Walking Ability in Participants with Multiple Sclerosis: Results from the Randomized, Double-Blind, Phase III ENHANCE Trial of Prolonged-Release Fampridine; CNS Drugs; 2019; vol. 33 (no. 1); 61-79

Study details

Trial name / registration number	ENHANCE trial. Registration number: NCT02219932.
Study type	Randomised controlled trial (RCT) Parallel RCT

Study location	Performed across 92 centres in 12 different countries: Bulgaria, Czech Republic, Finland, Italy, Lithuania, The Netherlands, Poland, Russia, Serbia, Switzerland, UK and USA.
Study setting	Outpatient.
Study dates	The first participant was treated on 29th September 2014 and the last participant's final visit was 11th February 2016.
Sources of funding	Study funded by Biogen. Biogen funded medical writing support in the development of the paper. Excel Scientific Solutions wrote the first draft of the manuscript based on input from authors and edited in line with journal requirements. Biogen reviewed and provided feedback on the paper to the authors. Authors had full editorial control of the paper and provided final approval of all content. Open access fee paid by Biogen.
Inclusion criteria	Participant eligibility was assessed by a treating neurologist during a 14-day screening period. Inclusion criteria were: age 18-70 years; diagnosis of MS (any subtype); EDSS score 4.0-7.0; an investigator-assessed walking impairment; ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information in accordance with national and local patient privacy regulations; negative pregnancy test at screening and on day 1 in females of childbearing potential and agreement to practice effective contraception; and ability to understand and comply with the protocol requirements.
Exclusion criteria	History of human immunodeficiency virus; presence of acute or chronic hepatitis; known allergy to fampridine, pyridine-containing substances or any of the inactive ingredients in the prolonged-release fampridine tablet; any history of seizure, epilepsy or other convulsive disorder (except febrile seizures in childhood); creatinine clearance <80 ml/min; history of malignant disease within 5 years prior to the screening visit, including solid tumours and haematological (apart from basal cell and squamous cell carcinomas of the skin that were completely excised and considered cured); onset of MS exacerbation within 60 days prior to the screening visit; history of any major surgical intervention (other than skin biopsy) within 30 days prior to screening or day 1; any non-MS-related condition or factor likely to interfere with walking ability, such as major surgery of the foot, leg or hip, any significant trauma or known peripheral neuropathy of the lower limb; pulmonary disease that could affect the participant's daily activities; psychiatric disorder likely to affect participation in the study; uncontrolled hypertension at screening visit; history of any clinical significant cardiac, endocrinological, haematological, immunological, metabolic, urological, neurological (other than MS), dermatological or other major disease; clinically significant abnormal laboratory values; body mass index ≥40 kg/m^2; history of severe anaphylactic reactions; use of off-label MS treatment including rituximab, daclizumab or antibody (except natalizumab) within 3 months prior to screening visit, during screening period or scheduled for use during study participation; use of mitoxantrone or cyclophosphamide within 3 months before screening, during screening period or scheduled for use during study; initiation of natalizumab or alemtuzumab treatment or any change in existing dosing of these drugs within 3 months prior to screening or during the screening visit; initiation or change in existing dose of interferon beta-1b, interferon beta-1a, fingolimod, teriflunomide, glatiramer acetate or dimethyl fumarate within 30 days prior to screening

	visit or during screening period; pulsed steroid treatment within 60 days prior to screening visit or during screening period; change in medication dose or regimen for treatment of fatigue or depression within 30 days of screening visit or during screening period; any change in prophylactic treatment for pain with antidepressants or anticonvulsants within 30 days of screening visit or during screening period; any change in dose or regimen of anti-spastic agents within 7 days prior to screening visit or during screening period; treatment with an investigational drug within 30 days before screening visit or during screening period; treatment with any aminopyridine within 30 days before screening visit or during the screening period; treatment with organic cation transporter 2 inhibitors within 5 half-lives prior to screening visit or during screening period; history of drug or alcohol abuse within 2 year of screening visit; female participants currently pregnant or considering pregnancy while participating in the study; female participants currently breastfeeding; inability to comply with study requirements; those planning to take part in another clinical study (including observational) during the current study; and other unspecified reasons that in the opinion of the investigator or Biogen made the participant unsuitable for enrolment.
Recruitment / selection of participants	Patients with MS that had a walking impairment. Stratified by EDSS score (≤6.0 or 6.5-7.0) according to predefined randomisation list to ensure balanced level of disability. Protocol amended December 2014 to also stratify by prior aminopyridine use (yes/no) due to concerns about potential bias (after some patients had started being treated). Enrolment caps based on stratification factors were added: enrolment of those with prior aminopyridine use was limited to ~10% of the overall study population and enrolment of participants with EDSS >6.0 was limited to ~35% of the overall population. Participants were randomised using an interactive voice/web response system.
Intervention(s)	**Prolonged-release fampridine:** taken at a dose of 10 mg twice daily (bid) for 24 weeks. There was no placebo run-in phase. 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 were also allowed. 2-week post-dosing follow-up visit was performed. 87% were on any concomitant medication, including Baclofen (21%), colecalciferol (15%), tizanidine (11%), ibuprofen (10%), methylprednisolone (11%) and paracetamol (10%). 14% received any concomitant non-drug therapy, including physiotherapy (5%), bladder catheterisation (0%) and rehabilitation therapy (<1%). 317 were randomised to this group but only 315 analysed in the modified intention to treat population. 271/317 randomised (85%) completed 24 weeks of treatment.
Comparator	**Placebo:** matched placebo twice daily (bid) for 24 weeks. 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 were also allowed. 2-week post-dosing follow-up visit was performed. 90% were on any concomitant medication, including Baclofen (20%), colecalciferol (15%), tizanidine (12%), ibuprofen (10%), methylprednisolone (9%) and paracetamol (9%). 16% received any concomitant non-drug therapy, including physiotherapy (6%), bladder catheterisation (3%) and rehabilitation therapy (2%). 319 were randomised to this group

	but only 318 analysed in the modified intention to treat population. 258/319 randomised (81%) completed 24 weeks of treatment.
Number of participants	636 randomised (633 completed at least one on-treatment efficacy assessment and were included in modified intention to treat analyses; 635 participants completed had at least one dose of the study drug and were included in the safety sample analyses for adverse events)
Duration of follow-up	2 weeks following the final dose of the 24-week treatment period
Additional comments	Study consisted of a 2-week screening period, a 24-week double-blind treatment period and a 2-week post-dosing follow-up visit. All participants, investigators, site personnel and funder personnel were masked to treatment assignment.

Study arms

Prolonged-release fampridine (N = 317)

Dose was 10 mg twice daily for 24 weeks. No placebo run-in phase. 315 analysed in this arm in modified intention to treat analyses (those randomised that received at least one dose of study drug and had at least one post-baseline efficacy assessment). 271/317 randomised completed 24 weeks of treatment (85%). The safety sample (those randomised and that were exposed to study drug) was used to analyse adverse events and included 316 in this arm (1 randomised to this group did not receive treatment).

Placebo (N = 319)

Matched placebo for 24 weeks. 318 analysed in this arm in modified intention-to-treat analyses (those randomised that received at least one dose of study drug and had at least one post-baseline efficacy assessment). 258/319 randomised completed 24 weeks of treatment (81%). The safety sample (those randomised and that were exposed to study drug) was used to analyse adverse events and included 319 in this arm (all of those randomised to this group received treatment).

Characteristics

Arm-level characteristics

Characteristic	Prolonged-release fampridine (N = 317)	Placebo (N = 319)
% Female n/total analysed (%)	186/315 (59%)	180/318 (57%)
Mean age (SD) Sample size	n = 315	n = 318
Mean age (SD) Mean (SD)	49 (9.8)	48.8 (10.5)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Body mass index Sample size	n = 315	n = 318
Body mass index Mean (SD)	25.6 (4.8)	25.1 (4.4)
Relapsing-remitting n/total analysed (%)	169/315 (54%)	155/318 (49%)

Characteristic	Prolonged-release fampridine (N = 317)	Placebo (N = 319)
Secondary progressive n/total analysed (%)	95/315 (30%)	99/318 (31%)
Primary progressive n/total analysed (%)	41/315 (13%)	45/318 (14%)
Progressive-relapsing n/total analysed (%)	10/315 (3%)	19/318 (6%)
Median time since diagnosis (years) Sample size	n = 315	n = 318
Median time since diagnosis (years) Median	10.0	10.0
Median time since most recent relapse (years) Sample size	n = 315	n = 318
Median time since most recent relapse (years) Median	1.6	1.7
Prior 4-aminopyridine use n/total analysed (%)	31/315 (10%)	24/318 (8%)
0 m n/total analysed (%)	77/304 (25%)	85/302 (28%)

Characteristic	Prolonged-release fampridine (N = 317)	Placebo (N = 319)
>0 to <100 m n/total analysed (%)	56/304 (18%)	44/302 (15%)
≥100 to <300 m n/total analysed (%)	81/304 (27%)	82/302 (27%)
≥300 m n/total analysed (%)	90/304 (30%)	91/302 (30%)
Coordination/balance problems n/total analysed (%)	294/311 (95%)	300/316 (95%)
Fatigue n/total analysed (%)	195/312 (63%)	211/315 (67%)
Spasticity n/total analysed (%)	276/312 (88%)	265/315 (84%)
Weakness n/total analysed (%)	274/312 (88%)	281/315 (89%)
EDSS score Sample size	n = 315	n = 318
EDSS score Median (range)	6.0 (4.0-7.0)	5.5 (4.0-7.0)

Characteristic	Prolonged-release fampridine (N = 317)	Placebo (N = 319)
EDSS score Score ≤6.0 - n/total analysed (%)	246/315 (78%)	246/318 (77%)
EDSS score EDSS score 6.5 and 7.0 - n/total analysed (%)	69/315 (22%)	72/318 (23%)
TUG speed (feet/second) Timed Up and Go test Range	0 to 1	0 to 1.2
TUG speed (feet/second) Timed Up and Go test Sample size	n = 315	n = 318
TUG speed (feet/second) Timed Up and Go test Mean (SD)	0.38 (0.19)	0.38 (0.2)
TUG time (seconds) Timed Up and Go test Range	6.3 to 239.8	0 to 436.8
TUG time (seconds) Timed Up and Go test Sample size	n = 315	n = 318
TUG time (seconds) Timed Up and Go test	24.9 (26.6)	27.1 (42)

Characteristic	Prolonged-release fampridine (N = 317)	Placebo (N = 319)
Mean (SD)		
BBS score Berg Balance Scale Range	6 to 56	4 to 56
BBS score Berg Balance Scale Sample size	n = 315	n = 318
BBS score Berg Balance Scale Mean (SD)	40.6 (11.6)	40.2 (11.8)
MSWS-12 score 12-item MS Walking Scale Range	0 to 100	0 to 100
MSWS-12 score 12-item MS Walking Scale Sample size	n = 315	n = 318
MSWS-12 score 12-item MS Walking Scale Mean (SD)	63.6 (21.7)	65.4 (21.9)
MSIS-29 PHYS score MS Impact Scale physical impact subscale Range	0 to 98.3	3.3 to 95.8

Characteristic	Prolonged-release fampridine (N = 317)	Placebo (N = 319)
MSIS-29 PHYS score MS Impact Scale physical impact subscale Sample size	n = 315	n = 318
MSIS-29 PHYS score MS Impact Scale physical impact subscale Mean (SD)	52.4 (21.1)	55.3 (21)
ABILHAND score Range	0.9 to 100	26 to 100
ABILHAND score Sample size	n = 315	n = 318
ABILHAND score Mean (SD)	86.9 (15.8)	84.3 (16.5)

Patient characteristics are reported according to modified intention to treat groups rather than as randomised, with n=315 in the prolonged-release fampridine group and n=318 in the placebo group for each characteristic unless otherwise indicated

Outcomes

Study timepoints

- Baseline
- 24 week (Study reports results following 24 weeks of treatment. Matches 6-month time-point in protocol.)

Results – raw data

Outcome	Prolonged-release fampridine, Baseline, N = 315	Prolonged-release fampridine, 24-week, N = 315	Placebo, Baseline, N = 318	Placebo, 24-week, N = 318
Clinically meaningful mean improvement in TUG speed from baseline to 24 weeks ≥15% improvement from baseline on Timed Up and Go test No of events	n = NA ; % = NA	n = 137 ; % = 43.4	n = NA ; % = NA	n = 110 ; % = 34.7
Clinically meaningful improvement in mean MSWS-12 score from baseline to 24 weeks ≥8 point improvement from baseline on 12-item Multiple Sclerosis Walking Scale No of events	n = NA ; % = NA	n = 136 ; % = 43.2	n = NA ; % = NA	n = 107 ; % = 33.6
Mortality Custom value	NA	1/267 (0.37%)	NA	1/255 (0.39%)
Adverse events leading to study withdrawal Custom value	NA	22/288 (7.6%)	NA	24/278 (8.6%)
Urinary tract infection Custom value	NA	41/316 (13%)	NA	30/319 (9%)
Seizures Custom value	NA	0/266 (0%)	NA	0/254 (0%)

Outcome	Prolonged-release fampridine, Baseline, N = 315	Prolonged-release fampridine, 24-week, N = 315	Placebo, Baseline, N = 318	Placebo, 24-week, N = 318
Fall Custom value	NA	24/316 (8%)	NA	19/319 (6%)
Headache Custom value	NA	15/316 (5%)	NA	15/319 (5%)

Note that the number of participants in the analysis differed for different outcomes, depending on whether the modified intention-to-treat or safety sample were used. The numbers given at the top of the table represent the denominators when the modified intention-to-treat sample was used as this was the primary analysis used in the study. Where different dominators have been used this has been indicated in the table for each outcome. Where possible, outcomes have been extracted as available-case analyses due to missing data.

Results - difference in change score from baseline between groups

Outcome	Prolonged-release fampridine vs Placebo, 24-week vs Baseline , N2 = 318, N1 = 315
Change in TUG speed (feet/second) Timed Up and Go test. Mean (SD) baseline values were: 0.38 (0.19, n=315) vs. 0.38 (0.20, n=318) feet/second. Mean (95% CI)	0.02 (0.01 to 0.03)
Change in TUG time (seconds) Timed Up and Go test. Mean (SD) baseline values were: 24.9 (26.6, n=315) vs. 27.1 (42.0, n=318) seconds. Mean (95% CI)	-1.36 (-2.85 to 0.12)

Outcome	Prolonged-release fampridine vs Placebo, 24-week vs Baseline , N2 = 318, N1 = 315
Change in MSWS-12 score 12-item Multiple Sclerosis Walking Scale (scale of 0-100). Mean (SD) baseline values were: 63.6 (21.7, n=315) vs. 65.4 (21.9, n=318). Mean (95% CI)	-4.14 (-6.22 to -2.06)
Change in ABILHAND score Scale of 0-100. Mean (SD) baseline values were: 86.9 (15.8, n=315) vs. 84.3 (16.5, n=318). Sample size	n1 = 312, n2 = 315
Change in ABILHAND score Scale of 0-100. Mean (SD) baseline values were: 86.9 (15.8, n=315) vs. 84.3 (16.5, n=318). Mean (95% CI)	0.74 (-0.38 to 1.86)
EDSS score ≤6.0 Baseline values for this outcome not reported for this subgroup. Sample size	n1 = 244, n2 = 244
EDSS score ≤6.0 Baseline values for this outcome not reported for this subgroup. Mean (95% CI)	0.1 (-1.04 to 1.24)
EDSS score 6.5 and 7.0 Baseline values for this outcome not reported for this subgroup. Sample size	n1 = 68, n2 = 71

Outcome	Prolonged-release fampridine vs Placebo, 24-week vs Baseline , N2 = 318, N1 = 315
EDSS score 6.5 and 7.0 Baseline values for this outcome not reported for this subgroup. Mean (95% CI)	3.05 (-0.09 to 6.19)
Change in MSIS-29 PHYS score Physical Impact subscale of Multiple Sclerosis Impact Scale (scale of 0-100). Mean (SD) baseline values were: 52.4 (21.1, n=315) vs. 55.4 (21.0, n=318). Mean (95% CI)	-3.31 (-5.13 to -1.5)

Change in TUG speed - Polarity - Higher values are better

Change in TUG time - Polarity - Lower values are better

Change in MSWS-12 score - Polarity - Lower values are better

Change in ABILHAND score - Polarity - Higher values are better

Change in MSIS-29 PHYS score - Polarity - Lower values are better

Changes from baseline over 24 weeks were analysed 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). Analyses were performed in the modified intention-to-treat population, with n=315 and n=318 in the intervention and control groups, respectively (unless otherwise indicated).

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (Pharma)

Clinically meaningful improvement in TUG speed from baseline_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information on allocation concealment and protocol was altered in to allow stratification by aminopyridine use after some had already been treated)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(More limited information provided for other time-points despite them being reported and provides dichotomous version for this outcome but not other similar outcomes)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Clinically meaningful improvement in MSWS-12 score from baseline_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information on allocation concealment and protocol was altered in to allow stratification by aminopyridine use after some had already been treated)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(More limited information provided for other time-points despite them being reported and provides dichotomous version of this outcome but not other similar outcomes)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Mortality_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information on allocation concealment and protocol*

Section	Question	Answer
		was altered in to allow stratification by aminopyridine use after some had already been treated)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(proportion missing for this outcome is higher than event rate and adverse events was the reason some withdrew, but proportion without data at this time-point similar between groups)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Adverse events leading to study withdrawal_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information on allocation concealment and*

Section	Question	Answer
		protocol was altered in to allow stratification by aminopyridine use after some had already been treated)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Rate of missing data for this outcome at this time-point similar to event rate but proportion missing similar between groups)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Urinary tract infection_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information on allocation concealment and protocol was altered in to allow stratification by aminopyridine use after some had already been treated)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(rate of missing data for this outcome unclear but reasons patients withdrew unlikely to have affected this outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Seizures_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information on allocation concealment and protocol was altered in to allow stratification by aminopyridine use after some had already been treated)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Rate of missing data for this outcome at this time-point is much higher than the event rate but reasons patients withdrew unlikely to have affected this outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Fall_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information on allocation concealment and protocol was altered in to allow stratification by aminopyridine use after some had already been treated)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(rate of missing data for this outcome unclear but reasons patients withdrew unlikely to have affected this outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Headache_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information on allocation concealment and protocol was altered in to allow stratification by aminopyridine use after some had already been treated)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(rate of missing data for this outcome unclear but reasons patients withdrew unlikely to have affected this outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Change in TUG speed from baseline relative to placebo_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information on allocation concealment and protocol was altered in to allow stratification by aminopyridine use after some had already been treated)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Proportion with missing data is 18% with some having been imputed for this time-point and is possible that missing data may be related to the true value of the outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No results for earlier time-points despite measurements being performed and provides dichotomous version of this outcome but for other similar ones)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Change in TUG time from baseline relative to placebo_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information on allocation concealment and protocol was altered in to allow stratification by aminopyridine use after some had already been treated)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Proportion with missing data is 18% with some having been imputed for this time-point and is possible that missing data may be related to the true value of the outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No results for earlier time-points despite measurements being performed and does not report dichotomous version of this outcome despite this being provided for similar outcomes)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Change in MSWS-12 score from baseline relative to placebo_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information on allocation concealment and protocol was altered in to allow stratification by aminopyridine use after some had already been treated)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Proportion with missing data is 18% with some having been imputed for this time-point and is possible that missing data may be related to the true value of the outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No results for earlier time-points despite measurements being performed and provides dichotomous version of this outcome but for other similar ones)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Change in ABILHAND score from baseline relative to placebo_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information on allocation concealment and protocol was altered in to allow stratification by aminopyridine use after some had already been treated)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Proportion with missing data is 18% with some having been imputed for this time-point and is possible that missing data may be related to the true value of the outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No results for earlier time-points despite measurements being performed and does not report dichotomous version of this outcome despite this being provided for similar outcomes)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(Unclear whether ABILHAND is a validated outcome measure in the MS population but is a measure of upper limb mobility/dexterity)*

Change in ABILHAND score from baseline relative to placebo_24 weeks_EDSS score 6 or below

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information on allocation concealment and protocol was*

Section	Question	Answer
		altered in to allow stratification by aminopyridine use after some had already been treated)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Proportion with missing data was unclear within this subgroup but was 18% for the whole study population, with some having been imputed for this time-point and is possible that missing data may be related to the true value of the outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High *(No results for earlier time-points despite measurements being performed and does not report dichotomous version of this outcome despite this being provided for similar outcomes. Also only reports results for this subgroup for this outcome and not others.)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Unclear whether ABILHAND is a validated outcome measure in the MS population but is a measure of upper limb mobility/dexterity)*

Change in ABILHAND score from baseline relative to placebo_24 weeks_EDSS score 6.5 or 7.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information on allocation concealment and protocol was altered in to allow stratification by aminopyridine use after some had already been treated)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Proportion with missing data was unclear within this subgroup but was 18% for the whole study population, with some having been imputed for this time-point and is possible that missing data may be related to the true value of the outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High *(No results for earlier time-points despite measurements being performed and does not report dichotomous version of this outcome despite this being provided for similar outcomes. Also only reports results for this subgroup for this outcome and not others.)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Unclear whether ABILHAND is a validated outcome measure in the MS population but is a measure of upper limb mobility/dexterity)*

Change in MSIS-29 PHYS score from baseline relative to placebo_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information on allocation concealment and protocol was altered in to allow stratification by aminopyridine use after some had already been treated)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Proportion with missing data is 18% with some having been imputed for this time-point and is possible that missing data may be related to the true value of the outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No results for earlier time-points despite measurements being performed and does not report dichotomous version of this outcome despite this being provided for similar outcomes)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Hupperts, 2016

Bibliographic Reference	Hupperts, R.; Lycke, J.; Short, C.; Gasperini, C.; McNeill, M.; Medori, R.; Tofil-Kaluza, A.; Hovenden, M.; Mehta, L. R.; Elkins, J.; Prolonged-release fampridine and walking and balance in MS: randomised controlled MOBILE trial; Multiple Sclerosis; 2016; vol. 22 (no. 2); 212-21

Study details

Other publications associated with this study included in review	• Gasperini, C.; Hupperts, R.; Lycke, J.; Short, C.; McNeill, M.; Zhong, J.; Mehta, L. R.; Prolonged-release fampridine treatment improved subject-reported impact of multiple sclerosis: Item-level analysis of the MSIS-29; Journal of the Neurological Sciences; 2016; vol. 370; 123-131
Trial name / registration number	MOBILE trial. ClinicalTrials.gov, identifier NCT01597297. European Union Clinical Trials Register, EudraCT number 2012-000368-90.
Study location	24 sites across Belgium, Canada, Italy, The Netherlands, Sweden and UK
Study setting	Outpatient?
Study dates	First patient treated on 30th August 2012 and trial ended on 8th August 2013.
Sources of funding	Study funded by Biogen. Most authors have received compensation from industry (including Biogen, Genzyme, Merck, Novartis, Teva and Bayer HealthCare), for one or more of the following: consulting, advisory boards, research grants and speaking in lectures. Four listed authors were full-time employees of Biogen and one was an employee for Biogen at the time of study and manuscript development. One author was a full-time employee of Excel Scientific Solutions.
Inclusion criteria	Aged 18-70 years; EDSS score of 4.0-7.0; and diagnosis of primary-progressive MS, secondary-progressive MS or relapsing-remitting MS according to revised McDonald criteria for ≥3 months. Most stable concomitant therapies for the treatment of MS were permitted.
Exclusion criteria	Treatment with 4-aminopyridine or 3,4-diaminopyridine in any formulation ≤30 days before screening; known allergy to pyridine-containing substances; any history of seizure, epilepsy or other convulsive disorder; renal impairment (creatinine clearance <80 ml/min); onset of MS exacerbation ⩽60 days before screening; and body mass index ≥40 kg/m2.

Recruitment / selection of participants	Patients were screened for eligibility during a 14-day screening period. Eligible patients were randomised.
Intervention(s)	Prolonged-release fampridine. N=68. Received prolonged-release fampridine 10 mg tablets or twice daily every 12 hours for 24 weeks. Scheduled visits took place at screening, day 1 and weeks 2, 4, 8, 12, 16, 20 and 24. A post-dosing follow-up visit was conducted two weeks after the end of treatment. Blinding was achieved by using matched fampridine and placebo tablets. Results were analysed as intention to treat but only 55/68 randomised to this group completed treatment (others discontinued due to adverse event in n=7, lack of efficacy in n=1, consent withdrawal in n=2, creatinine clearance out of range in n=1 and unacceptable concomitant medication required in n=2).
Comparator	Placebo. N=64. Received placebo tablets twice daily every 12 hours for 24 weeks. Scheduled visits took place at screening, day 1 and weeks 2, 4, 8, 12, 16, 20 and 24. A post-dosing follow-up visit was conducted two weeks after the end of treatment. Blinding was achieved by using matched fampridine and placebo tablets. Results were analysed as intention to treat but only 52/64 randomised to this group completed treatment (others discontinued due to adverse event in n=5, lack of efficacy in n=1, creatinine clearance out of range in n=4 and unacceptable concomitant medication required in n=2).
Number of participants	132 randomised. Intention to treat analyses (all those randomised, receiving at least one dose of treatment and at least one post-baseline assessment for a given parameter) were used with imputation for missing data for efficacy outcomes. Last observation carried forward method when at least one post-baseline value was available. Other imputation methods specific to each questionnaire are also reported (for example for partially completed questionnaires). No imputation was done for EQ-5D-5L for those with data missing.
Duration of follow-up	Up to 24 weeks on treatment and a 2-week post-treatment follow-up visit.
Additional comments	Noted to be an exploratory study with no formal statistical hypothesis testing being planned ahead. Poor reporting of results as for most outcomes results only given in a figure with and results had to be estimated from graphs.

Study arms

Prolonged-release fampridine (N = 68)

Randomised to receive prolonged-release fampridine (10 mg twice daily) for 24 weeks. Tablets were taken every 12 hours.

Placebo (N = 64)

Randomised to receive placebo (twice daily) for 24 weeks. Tablets were taken every 12 hours.

Characteristics

Arm-level characteristics

Characteristic	Prolonged-release fampridine (N = 68)	Placebo (N = 64)
% Female Sample size	n = 38 ; % = 56	n = 33 ; % = 52
Mean age (SD) Mean	49.8	49.8
White Sample size	n = 66 ; % = 97	n = 63 ; % = 98
Comorbidities Text	Not reported	Not reported
Body mass index (kg/m²) Mean (SD)	26.8 (4.9)	26.5 (6.2)
Time since first MS diagnosis (years) Mean (SD)	10.9 (6.8)	12.4 (8.4)

Characteristic	Prolonged-release fampridine (N = 68)	Placebo (N = 64)
Relapsing-remitting MS Sample size	n = 24 ; % = 35	n = 20 ; % = 31
Secondary-progressive MS Sample size	n = 31 ; % = 46	n = 37 ; % = 58
Primary-progressive MS Sample size	n = 12 ; % = 18	n = 6 ; % = 9
Progressive-relapsing MS Sample size	n = 1 ; % = 1	n = 1 ; % = 2
Time since most recent relapse (years) Mean (median)	4.2 (3.5), n=56	3.3 (2.4), n=56
EDSS score Expanded Disability Status Scale Mean (median) [min, max]	5.6 (6.0) [4.0, 7.0]	5.9 (6.0) [4.0, 7.0]
MSWS-12 score 12-item Multiple Sclerosis Walking Scale Mean (median) [min, max]	71.7 (75.0) [25.0, 100.0]	75.9 (81.3) [8.3, 100.0]
TUG speed (m/s) Timed Up and Go Test. Mean (median) [min, max]	0.38 (0.38) [0.1, 0.7]	0.34 (0.32) [0.0, 0.8], n=63

Characteristic	Prolonged-release fampridine (N = 68)	Placebo (N = 64)
PHYS subscale Mean (median) [min, max]	50.9 (50.0) [8.1, 100.0]	53.0 (57.5) [13.1, 91.9]
PSYCH subscale Mean (median) [min, max]	36.0 (32.6) [NR]	36.3 (34.0) [NR]
EQ-5D-5L utility index score Mean (median) [min, max]	0.540 (0.584) [0.04, 0.85]	0.509 (0.547) [–0.19, 1.00]
EQ-5D-5L visual analogue scale Mean (median) [min, max]	59.1 (60.0) [4.0, 90.0], n=63	61.6 (60.0) [25.0, 90.0]
Number of relapses within past year Mean (SD)	0.2 (0.4)	0.3 (0.7)

Outcomes

Study timepoints

- Baseline
- 2 week (Outcome date for Patient Global Impression of Change scale only reported at the 2-week visit. Indirect to protocol as 2 weeks rather than 6 months.)
- 24 week (End of 24-week treatment period. Matches 6-month time-point in protocol.)

Results - raw data

Outcome	Prolonged-release fampridine, Baseline, N = 68	Prolonged-release fampridine, 2-week, N = 68	Prolonged-release fampridine, 24-week, N = 68	Placebo, Baseline, N = 64	Placebo, 2-week, N = 64	Placebo, 24-week, N = 64
Improvement on PGIC Patient Global Impression of Change scale. Scale 1-7. Patient assessment of how the study drug affected their overall walking during the previous 7 days, ranging from worsened at the lower end to improved at the higher end. No definition of the level of improvement (just state any improvement). Post-hoc analysis. No of events	n = NA ; % = NA	n = 31 ; % = 46	n = NR ; % = NR	n = NA ; % = NA	n = 16 ; % = 25	n = NR ; % = NR
Withdrawal due to adverse events events/number analysed (%)	NA	NA	7/62 (11.29%)	NA	NA	5/57(8.77%)
Urinary tract infection No of events	n = NA ; % = NA	n = NA ; % = NA	n = 6 ; % = 9	n = NA ; % = NA	n = NA ; % = NA	n = 12 ; % = 19
Seizures No of events	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0
Fall No of events	n = NA ; % = NA	n = NA ; % = NA	n = 4 ; % = 6	n = NA ; % = NA	n = NA ; % = NA	n = 8 ; % = 13
Headache No of events	n = NA ; % = NA	n = NA ; % = NA	n = 5 ; % = 7	n = NA ; % = NA	n = NA ; % = NA	n = 5 ; % = 8

Outcome	Prolonged-release fampridine, Baseline, N = 68	Prolonged-release fampridine, 2-week, N = 68	Prolonged-release fampridine, 24-week, N = 68	Placebo, Baseline, N = 64	Placebo, 2-week, N = 64	Placebo, 24-week, N = 64
Improvement in MSWS-12 score (≥8 point mean reduction in MSWS-12 score compared to baseline) No of events	n = NA ; % = NA	n = NA ; % = NA	n = 33 ; % = 48.5	n = NA ; % = NA	n = NA ; % = NA	n = 18 ; % = 28.1
Improvement in MSIS-29 PHYS score (≥7 point improvement compared to baseline) No of events	n = NA ; % = NA	n = NA ; % = NA	n = 31 ; % = 45.6	n = NA ; % = NA	n = NA ; % = NA	n = 19 ; % = 29.7
≥15% change from baseline in TUG speed Multiple thresholds reported in the paper but reported the threshold that is also reported by the ENHANCE trial. No of events	n = NA ; % = NA	n = NA ; % = NA	n = 32 ; % = 47.1	n = NA ; % = NA	n = NA ; % = NA	n = 19 ; % = 30.2
≥15% change from baseline in TUG speed Multiple thresholds reported in the paper but reported the threshold that is also reported by the ENHANCE trial. Sample size	n = NA	n = NA	n = 68	n = NA	n = NA	n = 63

Improvement on PGIC - Polarity - Higher values are better

There was missing data at the 24-week time-point but results were analysed as intention to treat. Where possible, available case analyses have been extracted and denominators indicated in the table below.

Results - effect sizes

Outcome	Prolonged-release fampridine vs Placebo, Baseline, N2 = 64, N1 = 68	Prolonged-release fampridine vs Placebo, 2 week, N2 = NA, N1 = NA	Prolonged-release fampridine vs Placebo, 24 week, N2 = 64, N1 = 68
EQ-5D-5L visual analogue scale Scale 0-100. Values reported in text. Median treatment difference (95% CI)	NR	NA	0.00 (-4.17 to 4.67)
EQ-5D-5L utility index score Scale -0.594 to 1.000. Median treatment difference (95% CI)	NR	NA	0.00 (-0.04 to 0.04)

EQ-5D-5L visual analogue scale - Polarity - Higher values are better

EQ-5D-5L utility index score - Polarity - Higher values are better

There was missing data at 24 weeks but intention to treat analyses were used. Missing data were not imputed for EQ-5D-5L outcomes.

Results - change from baseline

Outcome	Prolonged-release fampridine, Baseline vs 24-week, N = 68	Placebo, Baseline vs 24-week, N = 64
TUG speed (m/s) Timed Up and Go test. Values not reported in text and could not be analysed. Sample size	n = 68	n = 63

Outcome	Prolonged-release fampridine, Baseline vs 24-week, N = 68	Placebo, Baseline vs 24-week, N = 64
TUG speed (m/s) Timed Up and Go test. Values not reported in text and could not be analysed. Median % change from baseline (95% CI)	NR	NR
MSWS-12 score 12-item Multiple Sclerosis Walking Scale. Values reported in text of secondary paper. Scale 0-100. Sample size	n = 68	n = 64
MSWS-12 score 12-item Multiple Sclerosis Walking Scale. Values reported in text of secondary paper. Scale 0-100. Median (95% CI) change from baseline	-6.9 (-11.6 to -1.6)	-2.9 (-5.4 to 1.0)
MSIS-29 PHYS score 29-item Multiple Sclerosis Impact Scale - physical subscale. Values not reported in text and could not be analysed. Sample size	n = 68	n = 64
MSIS-29 PHYS score 29-item Multiple Sclerosis Impact Scale - physical subscale. Values not reported in text and could not be analysed. Median % change from baseline (95% CI)	NR	NR
MSIS-29 PSYCH score 29-item Multiple Sclerosis Impact Scale - psychological subscale. Values not reported in text and could not be analysed.	NR	NR

Outcome	Prolonged-release fampridine, Baseline vs 24-week, N = 68	Placebo, Baseline vs 24-week, N = 64
Mean (median) change from baseline		

TUG speed - Polarity - Higher values are better

MSWS-12 score - Polarity - Lower values are better

MSIS-29 PHYS score - Polarity - Lower values are better

MSIS-29 PSYCH score - Polarity - Lower values are better

Study reports % change from baseline for most outcomes and also reports mean (median) change from baseline in a separate paper for MSIS-29 physical and psychological subscales.

There was missing data at the 24-week time-point but results were analysed as intention to treat, with data imputed for missing data.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (Pharma)

Improvement on PGIC_2 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of detail about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Withdrawal due to adverse events_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of detail about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(missing data rate for this outcome at this time-point is similar to the event rate)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Urinary tract infection_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of detail about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(unclear missing data rate for this outcome but overall dropout from study was similar to event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Seizures_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of detail about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(unclear missing data rate for this outcome but overall dropout from study was higher than event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Fall_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of detail about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(unclear missing data rate for this outcome but overall dropout from study was higher than event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Headache_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of detail about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(unclear missing data rate for this outcome but overall dropout from study was higher than event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

MSWS-12 8-point improvement_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of detail about allocation concealment)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(dropout across study is 19% and could be linked to outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

MSIS-29 PHYS 7-point improvement_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of detail about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(dropout across study is 19% and could be linked to outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

EQ-5D-5L visual analogue scale change from baseline compared to placebo_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of detail about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(dropout across study is 19% and most reasons were health-related and may have affected EQ-5D)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

EQ-5D-5L utility index score change from baseline compared to placebo_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of detail about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(dropout across study is 19% and most reasons were health-related and may have affected EQ-5D)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

TUG speed % change from baseline_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of detail about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(dropout across study is 19% and could be linked to outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

MSWS-12 score change from baseline_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of detail about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(dropout across study is 19% and could be linked to outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

MSIS-29 PSYCH score change from baseline (mean change)_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of detail about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(dropout across study is 19% and could be linked to outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

MSIS-29 PHYS score change from baseline (median change)_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of detail about allocation concealment)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(dropout across study is 19% and could be linked to outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

TUG speed 15% improvement_24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(lack of detail about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(dropout across study is 19% and could be linked to outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Jacques, 2018

Bibliographic Reference	Jacques, F.; Schembri, A.; Nativ, A.; Paquette, C.; Kalinowski, P.; Prolonged-Release Fampridine as Adjunct Therapy to Active Motor Training in MS Patients: A Pilot, Double-Blind, Randomized, Placebo-Controlled Study; Multiple Sclerosis Journal Experimental Translational & Clinical; 2018; vol. 4 (no. 1); 2055217318761168

Study details

Secondary publication of another included study- see primary study for details	No additional studies

Other publications associated with this study included in review	No additional studies
Trial name / registration number	Clinical trial registration number with Clinicaltrial.gov: NCT02146534
Study location	Canada
Study setting	Outpatient follow up
Study dates	No additional information
Sources of funding	The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported financially by Biogen Canada Inc, which also provided the experimental drug and the placebo.
Inclusion criteria	People diagnosed with MacDonald criteria for multiple sclerosis; age 18 and older; subjects who meet the prescribing criteria for fampridine as per product monograph; therapeutic stability (ms and symptomatic treatment) for 3 months prior to screening and for the duration of the study; pyramidal system functional assessment score of 2 or greater and the ability to complete all the assessments with or without aids; female subjects of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 30 days after their last dose of study treatment
Exclusion criteria	Any contraindication to receiving fampridine as per product monograph including but not limited to prior history of epilepsy, renal dysfunction (abnormal serum creatinine), concomitant treatment with cimetidine or quinidine; ongoing treatment with fampridine or prior history of fampridine intolerance or ineffectiveness; any other condition that would preclude them from undergoing the NeuroGym training
Recruitment / selection of participants	No additional information
Intervention(s)	Prolonged-release fampridine 10mg twice a day (n=21). All people were clinically stable at entry and had an Expanded Disability Status Scale score between 3.5 and 7.0 with a pyramidal system functional assessment score of 2 or greater and the ability to complete all the assessments at baseline with or without aids. All people underwent rehabilitation as per the NeuroGym EAMT approach, consisting of three sessions of one hour per week for a period of six weeks. This protocol combined biofeedback with a significant element of strengthening and biomechanics optimisation. Movements

	necessary for walking are enabled despite significant disability with the help of specialised equipment such as the Bunger Mobility Trainer or the sit-to-stand apparatus. Biofeedback is attained using electromyography triggered video games. Walking balance is regained through controlled repetition of relearning exercises. This was followed by an eight-week observational period where people kept taking their medication and were encouraged to continue a training program at home.
Comparator	Placebo twice a day (n=20). All people were clinically stable at entry and had an Expanded Disability Status Scale score between 3.5 and 7.0 with a pyramidal system functional assessment score of 2 or greater and the ability to complete all the assessments at baseline with or without aids. All people underwent rehabilitation as per the NeuroGym EAMT approach, consisting of three sessions of one hour per week for a period of six weeks. This protocol combined biofeedback with a significant element of strengthening and biomechanics optimisation. Movements necessary for walking are enabled despite significant disability with the help of specialised equipment such as the Bunger Mobility Trainer or the sit-to-stand apparatus. Biofeedback is attained using electromyography triggered video games. Walking balance is regained through controlled repetition of relearning exercises. This was followed by an eight-week observational period where people kept taking their medication and were encouraged to continue a training program at home.
Number of participants	41
Duration of follow-up	14 weeks (6 weeks with rehabilitation programme and medication, 8 weeks with just medication)
Additional comments	Subgroup information: Type of multiple sclerosis - see characteristics table EDSS score - see characteristics table Disease modifying treatment status - Not stated/unclear Drug doses - Famipridine 10mg twice a day Routes of administration - Oral People receiving palliative care - Not stated/unclear

Study arms

Fampridine (N = 21)

Prolonged-release fampridine 10mg twice a day. All people were clinically stable at entry and had an Expanded Disability Status Scale score between 3.5 and 7.0 with a pyramidal system functional assessment score of 2 or greater and the ability to complete all the assessments at baseline with or without aids. All people underwent rehabilitation as per the NeuroGym EAMT approach, consisting of three sessions of one hour per week for a period of six weeks. This protocol combined biofeedback with a significant element of strengthening and biomechanics optimisation. Movements necessary for walking are enabled despite significant disability with the help of specialised equipment such as the Bunger Mobility Trainer or the sit-to-stand apparatus. Biofeedback is attained using electromyography triggered video games. Walking balance is regained through controlled repetition of relearning exercises. This was followed by an eight-week observational period where people kept taking their medication and were encouraged to continue a training program at home.

Placebo (N = 20)

Placebo twice a day. All people were clinically stable at entry and had an Expanded Disability Status Scale score between 3.5 and 7.0 with a pyramidal system functional assessment score of 2 or greater and the ability to complete all the assessments at baseline with or without aids. All people underwent rehabilitation as per the NeuroGym EAMT approach, consisting of three sessions of one hour per week for a period of six weeks. This protocol combined biofeedback with a significant element of strengthening and biomechanics optimisation. Movements necessary for walking are enabled despite significant disability with the help of specialised equipment such as the Bunger Mobility Trainer or the sit-to-stand apparatus. Biofeedback is attained using electromyography triggered video games. Walking balance is regained through controlled repetition of relearning exercises. This was followed by an eight-week observational period where people kept taking their medication and were encouraged to continue a training program at home.

Characteristics

Study-level characteristics

Characteristic	Study (N = 41)
% Female Sample size	n = 26 ; % = 63
Mean age (SD) Mean (SD)	52.22 (8.91)
Ethnicity Custom value	NS
Comorbidities Custom value	NS

Arm-level characteristics

Characteristic	Fampridine (N = 21)	Placebo (N = 20)
EDSS ≥6 No of events	n = 6 ; % = 29	n = 7 ; % = 35
Type of multiple sclerosis Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Fampridine (N = 21)	Placebo (N = 20)
Relapsing remitting MS Sample size	n = 10 ; % = 48	n = 10 ; % = 50
Secondary progressive MS Sample size	n = 5 ; % = 24	n = 7 ; % = 35
Primary progressive MS Sample size	n = 6 ; % = 28	n = 3 ; % = 15
Years since first symptoms (years) Mean (SD)	18.71 (10.04)	17.4 (10.93)
Years since first diagnosis (years) Mean (SD)	14.19 (8.04)	13.2 (10.94)
EDSS score Mean (SD)	4.62 (1.05)	4.82 (1.15)

Outcomes

Study timepoints

- 14 week (Values reported at 6 weeks and 14 weeks, only 14 weeks is included as this is closest to 6 months.)

Results - Raw data

Outcome	Fampridine, 14-week, N = 21	Placebo, 14-week, N = 20
Timed 8-meter walk % change from baseline (seconds) Change score. A shorter time indicates a faster walking speed. Baseline values were not reported for this outcome. Paper reports as a % improvement, with higher numbers indicating a bigger improvement. Plus/minus signs for the percentages reported in the paper have been swapped so that it matches the polarity of the outcome (fewer seconds taken is a better result). Mean (SD)	-6.69 (14.64)	2.25 (22.94)
Six-minute walk % change from baseline (metres) Change score. The higher the value, the longer the person could walk Baseline values were 330.54 (130.16) and 300.25 (141.14) metres. Mean (SD)	24.67 (11.79)	18.8 (18.03)
Withdrawal due to adverse events All said to have completed the trial, with no drop-outs. No of events	n = 0 ; % = 0	n = 0 ; % = 0

Timed 8-meter walk % change from baseline - Polarity - Lower values are better

Six-minute walk % change from baseline - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (Pharma)

Timed 8-Metre Walk % change from baseline_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

6-Minute Walk Test % change from baseline_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Withdrawal due to adverse events_14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Jensen, 2016

Bibliographic Reference	Jensen, H. B.; Nielsen, J. L.; Ravnborg, M.; Dalgas, U.; Aagaard, P.; Stenager, E.; Effect of slow release-Fampridine on muscle strength, rate of force development, functional capacity and cognitive function in an enriched population of MS patients. A randomized, double blind, placebo-controlled study; Multiple Sclerosis and Related Disorders; 2016; vol. 10; 137-144

Study details

Trial name / registration number	NCT01656148
Study location	Four MS centres across Denmark
Study setting	MS centres - outpatient?
Study dates	Not reported
Sources of funding	Funded by an unrestricted research grant from Biogen Idec., a research grant from Region of Southern Denmark and from The Research Fund of the MS clinic of Southern Jutland. Biogen Idec. supplied fampridine and placebo tablets. Various authors have received research support and other support from industry, including Biogen Idec.
Inclusion criteria	Diagnosis of MS based on McDonald criteria; aged 18-60 years; EDSS score between 4.0 and 7.0 with a pyramidal functional sub score ≥2.0; and fulfil responder criterion from the previous open-label enrichment phase on fampridine treatment (those with top 40% improvements on fampridine compared to baseline measures in the 5-Times Sit-To-Stand test).
Exclusion criteria	History of epileptic seizures; MS relapse or change in immunomodulatory treatment within 60 days; cancer within 5 years; clinically important systemic disease; and concomitant treatment with carvedilol, propranolol or metformin.
Recruitment / selection of participants	Eligible patients for the open-label enrichment trial were identified through the four MS clinics in the southern region of Denmark by going through patient files or by personal consultation. The corresponding author of the paper recruited all patients. Those entering the randomised trial were those with the top 40% improvements from baseline in the 5-Times

	Sit-To-Stand test in the open-label enrichment phase. Therefore, may be an issue with generalisability of the population included as more likely to see a benefit of fampridine in this population. Also doesn't include any that withdrew from open-label phase due to adverse events so may represent a population less likely to experience adverse events associated with fampridine.
Intervention(s)	Slow-release fampridine (10 mg twice daily for 4 weeks). N=17. Fampridine and placebo tablets were similar in appearance. Patients were selected from a previous open-label enrichment trial where all patients received slow-release fampridine (10 mg twice daily) for 26-28 days. Responders to fampridine treatment (the top 40% with the most marked improvement compared to baseline in the 5-Times Sit-To-Stand test) were selected to be included in the randomised study. Randomised treatment began after a 1-week washout period from the enrichment study. N=1 patient was lost to follow-up - N=16 completed the treatment in this group and were analysed.
Comparator	Placebo twice daily for 4 weeks. N=20. Fampridine and placebo tablets were similar in appearance. Patients were selected from a previous open-label enrichment trial where all patients received slow-release fampridine (10 mg twice daily) for 26-28 days. Responders to fampridine treatment (the top 40% with the most marked improvement compared to baseline in the 5-Times Sit-To-Stand test) were selected to be included in the randomised study. Randomised treatment began after a 1-week washout period from the enrichment study. N=1 patient was lost to follow-up - N=19 completed the treatment in this group and were analysed.
Number of participants	N=37 were randomised (n=17 in fampridine group and n=20 in placebo group). A total of n=16 and n=19 were analysed in the fampridine and placebo groups, respectively, due to n=1 lost to follow-up in each group before the end of treatment.
Duration of follow-up	Up to the end of the 4-week treatment period.
Additional comments	Population may be less applicable to general population as those with highest response to fampridine in a previous treatment period were selectively included and randomised. Population may also be less likely to experience adverse events of fampridine as some with adverse events withdrew during the open-label phase.

Study arms

Slow-release fampridine (N = 17)

Randomised to slow-release fampridine (10 mg twice daily) for 4 weeks.

Placebo (N = 20)

Randomised to placebo twice daily for 4 weeks.

Characteristics

Arm-level characteristics

Characteristic	Slow-release fampridine (N = 17)	Placebo (N = 20)
% Female Sample size	n = 8 ; % = 47	n = 13 ; % = 65
Mean age (SD) (years) Mean (SD)	50.8 (6.5)	48.4 (6.4)
Ethnicity Text	Not reported	Not reported
Comorbidities Text	Not reported	Not reported
EDSS score Expanded Disability Status Scale Mean (SD)	5.8 (0.8)	5.5 (0.7)
MS disease duration (years) Mean (SD)	9.5 (5.4)	9.8 (5.9)

Characteristic	Slow-release fampridine (N = 17)	Placebo (N = 20)
T25FW test (seconds) Timed 25-Foot Walk Test Mean (SD)	14.1 (17)	8.3 (3.8)
SSST score (seconds) Six Spot Step Test. Mean (SD)	20.2 (14.8)	13.9 (6.5)
5-STS test (seconds) 5-times Sit to Stand test Mean (SD)	16.4 (6.2)	13.6 (4.9)
9-HPT (seconds) 9-Hole Peg Test Mean (SD)	29.2 (10.7)	27.9 (11.4)

Outcomes

Study timepoints

- Baseline
- 4 week (Measured at end of 4-week treatment period. Matches 6-month time-point in protocol but indirect as 4 weeks rather than 6 months.)

Results - change from baseline

Outcome	Slow-release fampridine, 4-week vs Baseline, N = 16	Placebo, 4-week vs Baseline, N = 19
T25FW test change from baseline (Unclear - possibly seconds rather than speed as describes a reduction in value as an improvement) Timed 25-Foot Walk Test. Baseline values were 14.1 (7.0) and 8.3 (3.8) for fampridine and placebo groups, respectively. Final values for each group reported to be: 11.3 (9.2, n=16) and 8.6 (4.2, n=19) for fampridine and placebo groups, respectively. % change from baseline reported to be -13.6 (18.3)% vs. 4.7 (24.1)% Mean (SD)	-3.3 (9.5)	0.3 (1.8)
SSST score change from baseline (seconds? - based on how test is usually reported) Six Spot Step Test. Baseline values were 20.2 (14.8) and 13.9 (6.5) for fampridine and placebo groups, respectively. Final values for each group reported to be: 17.5 (9.6, n=16) and 14.5 (7.4, n=19) for fampridine and placebo groups, respectively. % change from baseline reported to be -11.4 (17.7)% vs. 3.8 (19.6)% Mean (SD)	-3.25 (8)	0.6 (3.2)
9-HPT change from baseline (seconds? - based on how test is usually reported) 9-Hole Peg Test. Baseline values were 29.2 (10.7) and 27.9 (11.4) for fampridine and placebo groups, respectively. Final values for each group reported to be: 29.1 (11.2, n=16) and 28.5 (9.3, n=19) for fampridine and placebo groups, respectively. % change from baseline reported to be -1.0 (8.4)% vs. 4.1 (12.0)% Mean (SD)	-0.3 (2.6)	0.6 (4.4)

T25FW test change from baseline - Polarity - Lower values are better

SSST score change from baseline - Polarity - Lower values are better

9-HPT change from baseline - Polarity - Lower values are better

Total analysed was n=16 in the fampridine group and n=19 in the placebo group, as n=1 was lost to follow-up in each group.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (Pharma)

T25FW test change from baseline_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months and population randomised selected from a previous trial, enriching for those with the highest response to fampridine in an open-label trial)*

SSST score change from baseline_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months and population randomised selected from a previous trial, enriching for those with the highest response to fampridine in an open-label trial)*

9-HPT change from baseline_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months and population randomised selected from a previous trial, enriching for those with the highest response to fampridine in an open-label trial)*

Kantor, 2015

Bibliographic Reference	Kantor, D.; Chancellor, M. B.; Snell, C. W.; Henney, H. R., 3rd; Rabinowicz, A. L.; Assessment of confirmed urinary tract infection in patients treated with dalfampridine for multiple sclerosis; Postgraduate Medicine; 2015; vol. 127 (no. 2); 218-22

Study details

Secondary publication of another included study- see primary study for details	Primary study: Yapundich, R.; Applebee, A.; Bethoux, F.; Goldman, M. D.; Hutton, G. J.; Mass, M.; Pardo, G.; Klingler, M.; Henney, H. R., 3rd; Blight, A. R.; Carrazana, E. J.; Evaluation of Dalfampridine Extended Release 5 and 10 mg in Multiple Sclerosis: A Randomized Controlled Trial; International Journal of Ms Care; 2015; vol. 17 (no. 3); 138-45 This secondary paper provides further detail on one of the outcomes reported in the primary study (urinary tract infection) - data from this secondary paper has been extracted where appropriate into the evidence table for the primary study.
Other publications associated with this study included in review	• Applebee, A.; Goodman, A. D.; Mayadev, A. S.; Bethoux, F.; Goldman, M. D.; Klingler, M.; Blight, A. R.; Carrazana, E. J.; Effects of Dalfampridine Extended-release Tablets on 6-minute Walk Distance in Patients With Multiple Sclerosis: A Post Hoc Analysis of a Double-blind, Placebo-controlled Trial; Clinical Therapeutics; 2015; vol. 37 (no. 12); 2780-7

Marion, 2020

Bibliographic Reference	Marion, S.; Leonid, C.; Belinda, B.; Joanne, D.; Elise, H.; Leeanne, C.; Richard, M.; Effects of modified-release fampridine on upper limb impairment in patients with Multiple Sclerosis; Multiple Sclerosis and Related Disorders; 2020; vol. 40; 101971

Study details

Secondary publication of another included	No additional studies

study- see primary study for details	
Other publications associated with this study included in review	No additional studies
Trial name / registration number	No additional information
Study location	Australia
Study setting	Outpatient follow up
Study dates	No additional information
Sources of funding	Funding for the study was provided by a scholarship from the National Health and Medical Research Council (ID 1056294) and by Biogen (Australia). Biogen also provided supplies of drug and placebo treatments.
Inclusion criteria	Adults with clinically definite multiple sclerosis (as per Macdonald criteria) of any duration and any disease subtype with subjective and objective dysfunction of one or both upper limbs due to multiple sclerosis.
Exclusion criteria	Unable to provide informed consent, if they had contraindications to fampridine therapy, if they had suffered an MS relapse within 60 days of randomisation, if they had commenced new disease-modifying or symptomatic therapies for multiple sclerosis within 60 days.
Recruitment / selection of participants	No additional information
Intervention(s)	Fampridine-modified release (MR) 10mg twice a day for 8 weeks (n=20)
Comparator	Placebo twice a day for 8 weeks (n=20)
Number of participants	40
Duration of follow-up	8 weeks

Additional comments	Subgroup information: Type of multiple sclerosis: See characteristics table EDSS: See characteristics table Disease modifying treatment status: Not stated

Study arms

Fampridine (N = 20)

Fampridine-MR 10mg twice a day for 8 weeks

Placebo (N = 20)

Placebo twice a day for 8 weeks

Characteristics

Study-level characteristics

Characteristic	Study (N = 40)
% Female Sample size	n = 24 ; % = 60

Characteristic	Study (N = 40)
Mean age (SD) Custom value	Drug treated (median [IQR): 53.5 (47-64) years. Placebo (median [IQR]): 51.5 (43.5-63) years
Ethnicity Custom value	Not stated
Comorbidities Custom value	Not stated
Disease duration (years) Custom value	median: 13.5

Arm-level characteristics

Characteristic	Fampridine (N = 20)	Placebo (N = 20)
Relapsing remitting MS No of events	% = 20	% = 25
Secondary progressive MS No of events	% = 40	% = 50
Primary progressive MS No of events	% = 40	% = 25
Mild (0-3)	% = 15	% = 5

Characteristic	Fampridine (N = 20)	Placebo (N = 20)
No of events		
Moderate (3.5-5.5) No of events	% = 20	% = 55
Severe (at least 6) **No of events**	**% = 65**	**% = 40**

Outcomes

Study timepoints

8 week (Less than or equal to 6 months)

Results - raw data

Outcome	Fampridine, 8-week, N = 20	Placebo, 8-week, N = 20
Withdrawal due to adverse events Presumed side effects (after 28 days' treatment) No of events	n = 0 ; % = 0	n = 1 ; % = 5.56

Outcome	Fampridine, 8-week, N = 20	Placebo, 8-week, N = 20
Withdrawal due to adverse events Presumed side effects (after 28 days' treatment) Sample size	n = 20	n = 18
Urinary tract infection Reports that n=1 was hospitalised with a urinary tract infection. Unclear if other less serious urinary tract infection events may have occurred but not reported. No of events	n = 1 ; % = 5	n = 0 ; % = 0
Urinary tract infection Reports that n=1 was hospitalised with a urinary tract infection. Unclear if other less serious urinary tract infection events may have occurred but not reported. Sample size	n = 20	n = 17

Numbers randomised are given in the table heading. Available case analyses have been extracted where possible and numbers analysed indicated in the table below. Although the study also reported results on the 9-Hole Peg Test and Modified Fatigue Impact Scale, these were only reported as median z-scores and were therefore not extracted.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (Pharma)

Withdrawal due to adverse events_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Urinary tract infection_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Pickering, 2017

Bibliographic Reference	Pickering, H.; Murray, J.; Lin, C. S.; Cormack, C.; Martin, A.; Kiernan, M. C.; Krishnan, A. V.; Fampridine treatment and walking distance in multiple sclerosis: A randomised controlled trial; Clinical Neurophysiology; 2017; vol. 128 (no. 1); 93-99

Study details

Trial name / registration number	Australian and New Zealand Trials Registry: ACTRN12611000799954.
Study location	Australia
Study setting	MS clinic - outpatient?
Study dates	Patients were recruited consecutively from August 2011 and the last assessment took place in October 2013.
Sources of funding	Study supported by a grant from Biogen. One author has served on the fampridine international advisory board for Biogen, received consulting fees from Biogen and speaker fees from Biogen and other companies.

Inclusion criteria	Aged 18-80 years; and diagnosis of MS according to 2010 McDonald criteria.
Exclusion criteria	History of seizures; current pregnancy; moderate-severe renal impairment; history of relapses in 60 days prior to enrolment; and EDSS >6.0 due to potential difficulties in completing the outcome measures.
Recruitment / selection of participants	Patients were recruited consecutively from August 2011 at a single MS clinic at the Prince of Wales Hospital in Sydney.
Intervention(s)	Fampridine. N=25. Randomised to receive 10 mg fampridine twice daily during first or second treatment period as part of a crossover trial. Each treatment period was 3 months long and the two periods were separated by a 30 days washout phase. Fampridine and placebo tablets were matched and packaged in identical bottles. Bottles were identifiable only to pharmacy staff authorised to work on the study, and they were unblinded to treatment assignment. 13 patients were randomised to fampridine in period 1 followed by placebo in period 2 and 12 patients were randomised to the opposite sequence. Outcome data on 3 patients was incomplete in those randomised to placebo followed by fampridine, with 3 assessments missing during the placebo phase (1 at week 4 and 2 at week 12) and 7 assessments missing during the fampridine phase (2 at weeks 4 and 8, and 3 at week 12).
Comparator	Placebo. N=25. Randomised to receive placebo twice daily during first or second treatment period as part of a crossover trial. Each treatment period was 3 months long and the two periods were separated by a 30 days washout phase. Fampridine and placebo tablets were matched and packaged in identical bottles. Bottles were identifiable only to pharmacy staff authorised to work on the study, and they were unblinded to treatment assignment. 12 patients were randomised to placebo in period 1 followed by fampridine in period 2 and 13 patients were randomised to the opposite sequence. Outcome data on 3 patients was incomplete in those randomised to placebo followed by fampridine, with 3 assessments missing during the placebo phase (1 at week 4 and 2 at week 12) and 7 assessments missing during the fampridine phase (2 at weeks 4 and 8, and 3 at week 12).
Number of participants	N=25 participants included, randomised to fampridine followed by placebo or placebo followed by fampridine.
Duration of follow-up	Follow-up to end of each 3-month treatment period, separated by 30 days washout period.

Study arms

Fampridine (N = 25)

Randomised to receive 10 mg fampridine twice daily during first or second treatment period as part of a crossover trial. Each treatment period was 3 months long and the two periods were separated by a 30 days washout phase.

Placebo (N = 25)

Randomised to receive placebo twice daily during first or second treatment period as part of a crossover trial. Each treatment period was 3 months long and the two periods were separated by a 30 days washout phase.

Characteristics

Study-level characteristics

Characteristic	Study (N = 25)
% Female Sample size	n = 19 ; % = 76
Mean age (SD) (years) Range	23 to 68
Mean age (SD) (years) Mean (SD)	54.4 (11)

Characteristic	Study (N = 25)
Ethnicity Text	Not reported
Comorbidities Text	Not reported
EDSS 0-2 Sample size	n = 8 ; % = 32
EDSS 2.5-4.0 Sample size	n = 11 ; % = 44
EDSS 4.5-6.0 Sample size	n = 6 ; % = 24
Right-hand Range	18 to 254
Right-hand Mean (SD)	35 (46.12)
Left-hand Range	20 to 55
Left-hand Mean (SD)	29 (8.01)

Characteristic	Study (N = 25)
Fatigue Severity Scale Range	26 to 63
Fatigue Severity Scale Mean (SD)	48.3 (11.63)
Overall disability sum score Range	1 to 6
Overall disability sum score Mean (SD)	3 (1.51)
Manual ability Unclear how this was measured - ABILHAND questionnaire? Range	12 to 46
Manual ability Unclear how this was measured - ABILHAND questionnaire? Mean (SD)	33.3 (8.61)
Locomotion ability Unclear how this was measured - ABILOCO questionnaire? Range	5 to 13
Locomotion ability Unclear how this was measured - ABILOCO questionnaire? Mean (SD)	10.1 (2.36)

Characteristic	Study (N = 25)
6MWT (metres) 6-Minute Walk Test. Range	91 to 444
6MWT (metres) 6-Minute Walk Test. Mean (SD)	313.9 (103.34)
25-FWT (seconds) Timed 25-Foot Walk Test. Range	4 to 20
25-FWT (seconds) Timed 25-Foot Walk Test. Mean (SD)	7.3 (3.6)
TUG test (unclear) Timed Up and Go test. Unclear if time or speed. Range	8 to 41
TUG test (unclear) Timed Up and Go test. Unclear if time or speed. Mean (SD)	14.1 (7.3)
Relapsing-remitting MS Sample size	n = 13 ; % = 52
Primary progressive MS	n = 4 ; % = 16

Characteristic	Study (N = 25)
Sample size	
Secondary progressive MS Sample size	n = 7 ; % = 28

Outcomes

Study timepoints

- Baseline
- 12 week (Measured at the end of each 12-week treatment period. Matches 6-month time-point in protocol but indirect as measured at 3 months rather than 6 months.)

Results - raw data

Outcome	Fampridine, Baseline, N = 25	Fampridine, 12-week, N = 25	Placebo, Baseline, N = 25	Placebo, 12-week, N = 25
9-HPT right hand improvement compared to baseline 9-Hole Peg Test. Baseline values were 29.0 (8.01). Appears to be any improvement rather than a specific threshold. No paired data reported so analysed as a parallel trial according to the number and percentages reported. No of events	n = NA ; % = NA	n = 15 ; % = 65	n = NA ; % = NA	n = 17 ; % = 74

Outcome	Fampridine, Baseline, N = 25	Fampridine, 12-week, N = 25	Placebo, Baseline, N = 25	Placebo, 12-week, N = 25
9-HPT right hand improvement compared to baseline 9-Hole Peg Test. Baseline values were 29.0 (8.01). Appears to be any improvement rather than a specific threshold. No paired data reported so analysed as a parallel trial according to the number and percentages reported. Sample size	n = 25	n = 22	n = 25	n = 22
Discontinuation due to adverse events No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Headache No of events	n = NA ; % = NA	n = 3 ; % = 12	n = NA ; % = NA	n = 2 ; % = 8

This table includes outcomes where paired data was not available, and data have been extracted as if it was a parallel trial.

Results - difference relative to placebo (final values)

Outcome	Fampridine vs Placebo, Baseline, N2 = 25, N1 = 25	Fampridine vs Placebo, 12 week, N2 = 25, N1 = 25
6-MWT difference relative to placebo (metres) 6-Minute Walk Test. Baseline values were 313.9 (103.34). Appears to report paired data as repeated-measures analysis said to be performed. Adjusted for baseline. 90% CI	NA	1.1 to 32.1

Outcome	Fampridine vs Placebo, Baseline, N2 = 25, N1 = 25	Fampridine vs Placebo, 12 week, N2 = 25, N1 = 25
6-MWT difference relative to placebo (metres) 6-Minute Walk Test. Baseline values were 313.9 (103.34). Appears to report paired data as repeated-measures analysis said to be performed. Adjusted for baseline. P-value	NA	0.08
6-MWT difference relative to placebo (metres) 6-Minute Walk Test. Baseline values were 313.9 (103.34). Appears to report paired data as repeated-measures analysis said to be performed. Adjusted for baseline. Mean (SE)	NA (NA)	16.6 (9.3)
T25FW improvement compared to baseline Timed 25-Foot Walk test. Baseline values were 7.3 (3.6). Appears to be any improvement rather than a specific threshold. Appears to have reported paired data as a repeated measures analysis used. Adjusted for baseline. n=14 under fampridine and n=12 under placebo. Odds ratio (90% CI)	NA	1.2 (0.31 to 4.71)
T25FW improvement compared to baseline Timed 25-Foot Walk test. Baseline values were 7.3 (3.6). Appears to be any improvement rather than a specific threshold. Appears to have reported paired data as a repeated measures analysis used. Adjusted for baseline. n=14 under fampridine and n=12 under placebo. P-value	NA	0.60
TUG improvement compared to baseline Timed Up and Go test. Baseline values were 14.1 (7.3). Appears to be any improvement rather than a specific threshold. Appears to have reported paired data as a repeated	NA	0.8 (0.21 to 3.18)

Outcome	Fampridine vs Placebo, Baseline, N2 = 25, N1 = 25	Fampridine vs Placebo, 12 week, N2 = 25, N1 = 25
measures analysis used. Adjusted for baseline. n=17 under fampridine and n=18 under placebo. Odds ratio (90% CI)		
TUG improvement compared to baseline Timed Up and Go test. Baseline values were 14.1 (7.3). Appears to be any improvement rather than a specific threshold. Appears to have reported paired data as a repeated measures analysis used. Adjusted for baseline. n=17 under fampridine and n=18 under placebo. P-value	NA	0.80
9-HPT left improvement compared to baseline 9-Hole Peg Test. Baseline values were 29.0 (8.01). Appears to be any improvement rather than a specific threshold. Appears to have reported paired data as a repeated measures analysis used. Adjusted for baseline. n=15 under fampridine and n=15 under placebo. Odds ratio (90% CI)	NA	1.2 (0.3 to 4.61)
9-HPT left improvement compared to baseline 9-Hole Peg Test. Baseline values were 29.0 (8.01). Appears to be any improvement rather than a specific threshold. Appears to have reported paired data as a repeated measures analysis used. Adjusted for baseline. n=15 under fampridine and n=15 under placebo. P-value	NA	0.80
Manual ability (ABILHAND?) difference relative to placebo Appears to be ABILHAND but unclear reporting throughout the paper. Scale unclear but usually 0-100 for ABILHAND? Baseline values were 33.3 (8.61). Appears to report paired data as repeated-measures analysis said to be performed. Adjusted for baseline.	NA	-3.4

Outcome	Fampridine vs Placebo, Baseline, N2 = 25, N1 = 25	Fampridine vs Placebo, 12 week, N2 = 25, N1 = 25
90% CI		
Manual ability (ABILHAND?) difference relative to placebo Appears to be ABILHAND but unclear reporting throughout the paper. Scale unclear but usually 0-100 for ABILHAND? Baseline values were 33.3 (8.61). Appears to report paired data as repeated-measures analysis said to be performed. Adjusted for baseline. P-value	NA	0.6
Manual ability (ABILHAND?) difference relative to placebo Appears to be ABILHAND but unclear reporting throughout the paper. Scale unclear but usually 0-100 for ABILHAND? Baseline values were 33.3 (8.61). Appears to report paired data as repeated-measures analysis said to be performed. Adjusted for baseline. Mean (SE)	NA (NA)	-1.4 (1.2)
Locomotion ability (ABILOCO?) difference relative to placebo Appears to be ABILOCO but unclear reporting throughout the paper. Scale unclear. Baseline values were 10.1 (2.36). Appears to report paired data as repeated-measures analysis said to be performed. Adjusted for baseline. 90% CI	NA	-0.9 to 0.2
Locomotion ability (ABILOCO?) difference relative to placebo Appears to be ABILOCO but unclear reporting throughout the paper. Scale unclear. Baseline values were 10.1 (2.36). Appears to report paired data as repeated-measures analysis said to be performed. Adjusted for baseline. P-value	NA	0.33
Locomotion ability (ABILOCO?) difference relative to placebo Appears to be ABILOCO but unclear reporting throughout the paper. Scale unclear.	NA (NA)	-0.3 (0.3)

Outcome	Fampridine vs Placebo, Baseline, N2 = 25, N1 = 25	Fampridine vs Placebo, 12 week, N2 = 25, N1 = 25
Baseline values were 10.1 (2.36). Appears to report paired data as repeated-measures analysis said to be performed. Adjusted for baseline. Mean (SE)		
Overall Disability Sum Score improvement compared to baseline Baseline values were 3.0 (1.51). Appears to be any improvement rather than a specific threshold. Appears to have reported paired data as a repeated measures analysis used. Adjusted for baseline. n=17 under fampridine and n=18 under placebo. Odds ratio (90% CI)	NA	0.7 (0.14 to 3.39)
Overall Disability Sum Score improvement compared to baseline Baseline values were 3.0 (1.51). Appears to be any improvement rather than a specific threshold. Appears to have reported paired data as a repeated measures analysis used. Adjusted for baseline. n=17 under fampridine and n=18 under placebo. P-value	NA	0.70
Fatigue (Fatigue Severity Scale) improvement compared to baseline Baseline values were 48.3 (11.63). Appears to be any improvement rather than a specific threshold. Appears to have reported paired data as a repeated measures analysis used. Adjusted for baseline. n=8 under fampridine and n=9 under placebo. Odds ratio (90% CI)	NA	0.80 (0.21 to 3.11)
Fatigue (Fatigue Severity Scale) improvement compared to baseline Baseline values were 48.3 (11.63). Appears to be any improvement rather than a specific threshold. Appears to have reported paired data as a repeated measures analysis used. Adjusted for baseline. n=8 under fampridine and n=9 under placebo. P-value	NA	0.80

6-MWT difference relative to placebo - Polarity - Higher values are better

Manual ability (ABILHAND?) difference relative to placebo - Polarity - Higher values are better

Locomotion ability (ABILOCO?) difference relative to placebo - Polarity - Higher values are better

Despite outcome data being missing at week 12 for n=2 under placebo treatment and n=3 under fampridine treatment, all n=25 were reported to have been included in analyses. No details about how missing data was accounted for in the analysis. This table includes outcomes where paired data appears to be available.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial (Pharma)

9-HPT right hand improvement compared to baseline_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and whether allocation was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	High

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Discontinuation due to adverse events_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and whether allocation was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns *(proportion with missing data across study is higher than event rate)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Headache_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and whether allocation was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns *(proportion with missing data across study is similar to event rate)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

6-MWT difference relative to placebo_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and whether allocation was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns *(12% with missing data at this time-point)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

T25FW improvement compared to baseline_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and whether allocation was concealed)*

Section	Question	Answer
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

TUG test improvement compared to baseline_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and whether allocation was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

9-HPT left improvement compared to baseline_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and whether allocation was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Manual ability (ABILHAND?) difference relative to placebo_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and whether allocation was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns *(12% with missing data at this time-point)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Locomotion ability (ABILOCO?) difference relative to placebo_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and whether allocation was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns *(12% with missing data at this time-point)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Overall Disability Sum Score improvement compared to baseline_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and whether allocation was concealed)*

Section	Question	Answer
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Fatigue (Fatigue Severity Scale) improvement compared to baseline_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(unclear method of randomisation and whether allocation was concealed)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Prosperini, 2020

Bibliographic Reference	Prosperini, L.; Castelli, L.; De Giglio, L.; Bonanno, V.; Gasperini, C.; Pozzilli, C.; Dalfampridine to Improve Balance in Multiple Sclerosis: Substudy from a Randomized Placebo-Controlled Trial; Neurotherapeutics; 2020; vol. 17 (no. 2); 704-709

Study details

Secondary publication of another included study- see primary study for details	Primary study: De Giglio, L.; De Luca, F.; Gurreri, F.; Ferrante, I.; Prosperini, L.; Borriello, G.; Quartuccio, E.; Gasperini, C.; Pozzilli, C.; Effect of dalfampridine on information processing speed impairment in multiple sclerosis; Neurology; 2019; vol. 93 (no. 8); e733-e746 Reports subset of original trial with EDSS <6.0, which is one of the subgroups in our protocol to be used if heterogeneity is observed in the results of meta-analyses. However, the study does not report data for any outcomes matching our protocol in a form that could be used for this purpose. Though falls are reported, this is as a rate ratio whereas the data from the main paper is events per group.

Satchidanand, 2020

Bibliographic Reference	Satchidanand, N.; Drake, A.; Smerbeck, A.; Hojnacki, D.; Kolb, C.; Patrick, K.; Weinstock-Guttman, B.; Motl, R.; Benedict, R. H.; Dalfampridine benefits ambulation but not cognition in multiple sclerosis; Multiple Sclerosis; 2020; vol. 26 (no. 1); 91-98

Study details

Secondary publication of another included study- see primary study for details	No additional studies
Other publications associated with this study included in review	No additional studies
Trial name / registration number	No additional information
Study location	United States of American
Study setting	Tertiary multiple sclerosis care centre in the Western New York region
Study dates	No additional information
Sources of funding	The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors disclose that this research was funded by an Acorda IIS
Inclusion criteria	Age 18-65; ≥9th grade education and no evidence of learning disability; MS diagnosis; no steroid treatment in the last 30 days or a relapse in the last 90 days, and MS considered stable; cognitive impairment as indicated by an age-corrected z-score <1.5 in at least one cognitive domain or an informant report MS Neuropsychological Screening Questionnaire >28; Expanded Disability Scale Score of at least 6.5; capable of performing requirements of an NP test

	battery including at least 20/70 near visual acuity by near vision chart, with correction allowed; if female, neither pregnant or breast feeding and must either be >12 months post-menopausal or surgically sterilized, or agree to use acceptable method of birth control through study duration. Abstinence was not considered an acceptable method.
Exclusion criteria	Having cognitive deficits caused by concomitant medication usage or other significant neurological/psychological disease (e.g., Alzheimer's disease, Parkinson's disease, stroke, transient ischaemic attack, vascular dementia, Huntington' disease, traumatic brain injury, or cerebrovascular disease; history of seizure disorder; optic neuritis within 6 months of enrollment; trigeminal neuralgia; prior exposure to aminopyradines within the previous 6 months
Recruitment / selection of participants	No additional information
Intervention(s)	Dalfampridine 10mg twice daily orally (n=45)
Comparator	Placebo twice daily orally (n=15)
Number of participants	60
Duration of follow-up	12 weeks
Additional comments	Information about subgroups: Type of multiple sclerosis - see characteristics table EDSS - unclear - states inclusion had to be at least 6.5 but reports median of 3.5 in each group (ranging from 1.0/1.5-6.5 in the two groups). Disease modifying treatment status - Not stated/unclear

Study arms

Dalfampridine (N = 45)

Dalfampridine 10mg twice daily orally

Placebo (N = 16)

Placebo twice daily orally

Characteristics

Study-level characteristics

Characteristic	Study (N = 61)
% Female Sample size	n = 48 ; % = 78.7
Mean age (SD) Mean (SD)	49.3 (9.8)
Ethnicity Custom value	NS
Comorbidities Custom value	NS

Arm-level characteristics

Characteristic	Dalfampridine (N = 45)	Placebo (N = 16)
Relapsing-remitting Sample size	n = 37 ; % = 82.3	n = 12 ; % = 75
Secondary progressive Sample size	n = 7 ; % = 15.5	n = 4 ; % = 25
Primary progressive Sample size	n = 1 ; % = 2.2	n = 0 ; % = 0
EDSS score Median (range) Custom value	3.5 (1.0-6.5)	3.5 (1.5-6.5)
Disease duration (years) Mean (SD)	13.5 (7.4)	13.8 (11.9)

Outcomes

Study timepoints

- 12 week (Study end-point, for the 6 months category)

Results - mean differences table

Outcome	Dalfampridine vs Placebo, 12 week, N2 = 16, N1 = 41
Timed 25-Foot Walk (seconds) Values from ANCOVA model adjusted for baseline values and age. Baseline values unclear for this outcome. SD	7.12
Timed 25-Foot Walk (seconds) Values from ANCOVA model adjusted for baseline values and age. Baseline values unclear for this outcome. Mean (SE)	-17.53 (11.54)
6-minute walk test (metres) Values from ANCOVA model adjusted for baseline values and age. Baseline values not reported for this outcome. SD	49.70
6-minute walk test (metres) Values from ANCOVA model adjusted for baseline values and age. Baseline values not reported for this outcome. Mean (SE)	98.75 (52.14)
Fatigue Severity Scale Scale not reported in paper but based on information from elsewhere appears to be 9-63. Mean (SE)	0.05 (0.05)
Walk speed on T25FW test (ft/sec) Values from ANCOVA model adjusted for baseline values and age. Baseline values unclear for this	0.77 (0.48)

Outcome	Dalfampridine vs Placebo, 12 week, N2 = 16, N1 = 41
outcome. Final values for the two groups were reported to be 4.14 (1.15) ft/sec vs. 3.80 (1.80) ft/sec in mean (SD). Mean (SE)	

Timed 25-Foot Walk - Polarity - Lower values are better

6-minute walk test - Polarity - Higher values are better

Fatigue Severity Scale - Polarity - Lower values are better

Walk speed on T25FW test - Polarity - Higher values are better

This study only reports mean differences and standard error/95% confidence intervals for outcomes

Note that the numbers given in the heading of the table are those analysed. A total of n=45 and n=16 were randomised, respectively, to dalfampridine and placebo groups but n=4 withdrew from the study in the dalfampridine group

Results - raw data

Outcome	Dalfampridine, 12-week, N = 43	Placebo, 12-week, N = 16
Withdrawal due to adverse events Headache, dizziness, tremors No of events	n = 2	n = 0

For withdrawal due to adverse events

Note that the numbers given in the heading of the table are those analysed as an available case analysis. A total of n=45 and n=16 were randomised, respectively, to dalfampridine and placebo groups but n=2 withdrew from the study in the dalfampridine group for reasons other than adverse events

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (Pharma)

Timed 25-Foot Walk Test time mean difference_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

6-Minute Walk Test mean difference_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Fatigue Severity Scale mean difference_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Timed 25-Foot Walk Test speed mean difference_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Withdrawal due to adverse events_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Valet, 2021

Bibliographic Reference	Valet, M.; El Sankari, S.; Van Pesch, V.; Detrembleur, C.; Lejeune, T.; Stoquart, G.; Effects of prolonged-release fampridine on multiple sclerosis-related gait impairments. A crossover, double-blinded, placebo-controlled study; Clinical Biomechanics; 2021; vol. 86; 105382

Study details

Other publications associated with	

this study included in review	
Trial name / registration number	EudraCT number: 2012-005076-34
Study location	Belgium
Study setting	Outpatient
Study dates	Recruitment period lasted two years
Sources of funding	Funded by investigator-initiated trial grant from Biogen. Biogen did not participate in any aspect of design or performance (data collection, data management, data analysis and data interpretation).
Inclusion criteria	Definite MS based on McDonald criteria; between 18 and 65 years; presented with a subjective complaint of walking disability and EDSS ≤6.0; and fampridine responder following 4-week run-in period (defined as 10% improvement on Timed 25-Foot Walk Test and any improvement in the MS Walking Scale-12 at end of 4-week run-in period).
Exclusion criteria	Experiencing a relapse within the last 4 weeks; pregnant or breastfeeding women; unable to sustain a 3-min walk on a treadmill; presenting gait impairment not attributable to MS; concurrent treatment with 4-aminopyridine; contraindication to fampridine (e.g., renal impairment); concomitant use of OCT2 inhibitors; history of seizure; participants that underwent the 4-week run in period on fampridine and were found to be non-responders.
Recruitment / selection of participants	Consecutive patients recruited from MS consultation at the Department of Neurology within the institution. Recruitment lasted two years and was prematurely stopped due to restrictions on the potential number of participants. Patients meeting inclusion criterion first underwent 4-week run-in period where they were treated with 10 mg prolonged-release fampridine twice daily to test for responder status (defined as 10% improvement on Timed 25-Foot Walk Test and any improvement in the MS Walking Scale-12 at end of 4-week run-in period). Non responders then excluded from the study.
Intervention(s)	Prolonged-release fampridine: 2-week washout between run-in period and main phase of study. Randomised groups either received this intervention first or second, separated by a further 2-week washout period. Intervention involved 6-week treatment with prolonged-release fampridine (Fampyra®; Biogen) at a dose of 10 mg twice daily.
Comparator	Placebo: 2-week washout between run-in period and main phase of study. Randomised groups either received this placebo treatment first or second, separated by a further 2-week washout period. Intervention involved 6-week treatment with placebo (identical to Fampyra® in appearance) twice daily.

Number of participants	24 randomised, 23 analysed (22 eventually received both treatments, with n=1 dropping out without receiving fampridine n=1 that did not receive either treatment)
Duration of follow-up	6-weeks - total trial duration was 14 weeks, including 6-week treatment within each group and a 2-week washout period in between
Additional comments	Indirectness - fampridine responders (any improvement) selected during 2-week run-in period to be included in the trial and may not represent general MS population

Study arms

Prolonged-release fampridine (N = 24)

Placebo (N = 24)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 23)**
% Female Sample size	n = 11 ; % = 48
Mean age (SD) Mean (SD)	46 (10)
Ethnicity	NR

Characteristic	Study (N = 23)
Custom value	
Comorbidities Custom value	NR
Relapsing-remitting Sample size	n = 8 ; % = 35
Primary progressive Sample size	n = 3 ; % = 13
Secondary progressive Sample size	n = 12 ; % = 52
EDSS score Median (IQR)	4 (4 to 5)
Disease duration (years) Median (IQR)	10 (6 to 16)
Time since last relapse (Months) Range	5.0-166.0
Interferon Sample size	n = 11 ; % = 48
Natalizumab Sample size	n = 4 ; % = 17

Characteristic	Study (N = 23)
Fingolimod Sample size	n = 1 ; % = 4
Azathioprine Sample size	n = 1 ; % = 4

Outcomes

Study timepoints

- Baseline
- 6 week (6-week treatment periods with fampridine and placebo as part of the crossover trial)

Results - fampridine relative to placebo

Outcome	Prolonged-release fampridine vs Placebo, Baseline, N2 = 24, N1 = 24	Prolonged-release fampridine vs Placebo, 6 week, N2 = 23, N1 = 23
6-minute walk test (metres) Mean (SD) baseline value 310.0 (128). Mean (95% CI)	NA (NA to NA)	17.6 (-3.7 to 38.8)
Timed 25-Foot Walk Test (seconds) Mean (SD) baseline value 10.3 (8.4) Mean (95% CI)	NA (NA to NA)	-0.2 (-1.45 to 1.03)

Outcome	Prolonged-release fampridine vs Placebo, Baseline, N2 = 24, N1 = 24	Prolonged-release fampridine vs Placebo, 6 week, N2 = 23, N1 = 23
MSWS-12 Multiple Sclerosis Walking Scale-12. Scale 0-60. Median (IQR) baseline value: 66.7 (55.0-80.0). Results appear to be given for median values not mean as no SE reported and reported as median at baseline Mean (95% CI)	NA (NA to NA)	1.7 (-10 to 11.3)
EMIF - total score on French version of Fatigue Impact Scale Scale 0-100. Median (IQR) baseline value: 55.2 (42.2-65.35). Results appear to be given for median values not mean as no SE reported and reported as median at baseline Mean (95% CI)	NA (NA to NA)	-1.7 (-12.9 to 9.5)
EMIF Phys - physical score on French version of Fatigue Impact Scale. Results appear to be given for median values not mean as no SE reported and reported as median at baseline Scale 0-100. Median (IQR) baseline value: 71.2 (47.1-81.75) Mean (95% CI)	NA (NA to NA)	-2.1 (-17.6 to 13.3)
SEP-59 - French quality of life instrument Scale 0-100. Median (IQR) baseline value: 42.4 (36.45-55.95). Results appear to be given for median values not mean as no SE reported and reported as median at baseline Mean (95% CI)	NA (NA to NA)	-2.2 (-10.3 to 5.9)

6-minute walk test - Polarity - Higher values are better

Timed 25-Foot Walk Test - Polarity - Lower values are better

MSWS-12 - Polarity - Lower values are better

EMIF - total score on French version of Fatigue Impact Scale - Polarity - Lower values are better

EMIF Phys - physical score on French version of Fatigue Impact Scale. Results appear to be given for median values not mean as no SE reported and reported as median at baseline - Polarity - Lower values are better

SEP-59 - French quality of life instrument - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial (Pharma)

Results_6MWT_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months, selected fampridine responders during run-in period for inclusion in the trial)*

Results_T25FW_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months, selected fampridine responders during run-in period for inclusion in the trial)*

Results_MSWS-12_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months, selected fampridine responders during run-in period for inclusion in the trial)*

Results_EMIF total fatigue_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months, selected fampridine responders during run-in period for inclusion in the trial)*

Results_EMIF fatigue physical_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months, selected fampridine responders during run-in period for inclusion in the trial)*

Results_SEP-59 quality of life_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months, selected fampridine responders during run-in period for inclusion in the trial)*

Weller, 2020

Bibliographic Reference	Weller, D.; Lorincz, L.; Sutter, T.; Reuter, K.; Linnebank, M.; Weller, M.; Zorner, B.; Filli, L.; Fampridine-induced changes in walking kinetics are associated with clinical improvements in patients with multiple sclerosis; Journal of the Neurological Sciences; 2020; vol. 416; 116978

Study details

Secondary publication of another included study- see primary study for details	Primary study: Zorner, B.; Filli, L.; Reuter, K.; Kapitza, S.; Lorincz, L.; Sutter, T.; Weller, D.; Farkas, M.; Easthope, C. S.; Czaplinski, A.; Weller, M.; Linnebank, M.; Prolonged-release fampridine in multiple sclerosis: Improved ambulation effected by changes in walking pattern; Multiple Sclerosis; 2016; vol. 22 (no. 11); 1463-1475

Yapundich, 2015

Bibliographic Reference	Yapundich, R.; Applebee, A.; Bethoux, F.; Goldman, M. D.; Hutton, G. J.; Mass, M.; Pardo, G.; Klingler, M.; Henney, H. R., 3rd; Blight, A. R.; Carrazana, E. J.; Evaluation of Dalfampridine Extended Release 5 and 10 mg in Multiple Sclerosis: A Randomized Controlled Trial; International Journal of Ms Care; 2015; vol. 17 (no. 3); 138-45

Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	• Applebee, A.; Goodman, A. D.; Mayadev, A. S.; Bethoux, F.; Goldman, M. D.; Klingler, M.; Blight, A. R.; Carrazana, E. J.; Effects of Dalfampridine Extended-release Tablets on 6-minute Walk Distance in Patients With Multiple Sclerosis: A Post Hoc Analysis of a Double-blind, Placebo-controlled Trial; Clinical Therapeutics; 2015; vol. 37 (no. 12); 2780-7

	• Kantor, D.; Chancellor, M. B.; Snell, C. W.; Henney, H. R., 3rd; Rabinowicz, A. L.; Assessment of confirmed urinary tract infection in patients treated with dalfampridine for multiple sclerosis; Postgraduate Medicine; 2015; vol. 127 (no. 2); 218-22
Trial name / registration number	NCT01328379
Study location	65 sites across the USA.
Study setting	Outpatient?
Study dates	Performed between 7th April 2011 and 30th April 2012.
Sources of funding	Study was funded by Acorda Therapeutics. Various authors received research support or have other connections with industry, including Acorda Therapeutics, Biogen, Roche, Pfizer, among others. Three authors were employees and stockholders of Acorda Therapeutics, Inc.
Inclusion criteria	Aged 18-70 years; clinical diagnosis of MS defined by the 2005 revision to the McDonald criteria; and presence of MS-related walking impairment as determined by the clinician, but with sufficient ambulatory ability to complete all evaluations of the T25FW test.
Exclusion criteria	Had not taken any formulation of dalfampridine extended-release within 1 month prior to screening; pregnant or lactating women (women of childbearing potential required to use adequate contraception); history of seizures; presence or history of moderate or severe renal impairment (creatinine clearance ≤50 ml/min); presence of active urinary tract infection at screening within 4 weeks prior to screening; initiation of an MS-modifying therapy within 90 days prior to screening or a change in regimen of these drugs within 30 days prior to screening; and onset of an MS exacerbation within 60 days prior to screening.
Recruitment / selection of participants	Not reported.
Intervention(s)	10 mg dalfampridine extended-release. N=143 randomised (some also randomised to 5 mg dose but not relevant to our protocol). After a 1-week screening period, patients randomised to 10 mg oral dalfampridine taken twice daily at 12-hour intervals for 4 weeks. Active treatment and placebo tablets were identical in appearance and placebo tablets contained the same inactive ingredients as dalfampridine extended-release. Of those randomised, 143/143 received treatment (128 completed treatment) and 15 (10.5%) withdrew before the end of the study. These were due to non-compliance (n=1) and adverse events (n=14). A total of n=136 were included in the analysed population, which was a modified

	intention to treat population consisting of all of those randomised that took at least one dose of double-blind treatment and had at least one post-baseline assessment of the T25FW test.
Comparator	Placebo. N=143 randomised. After a 1-week screening period, patients randomised to placebo taken twice daily at 12-hour intervals for 4 weeks. Active treatment and placebo tablets were identical in appearance and placebo tablets contained the same inactive ingredients as dalfampridine extended-release. Of those randomised, 142/143 received treatment (132 completed treatment) and 10 (7.0%) withdrew before the end of the study. These were due to non-compliance (n=1), adverse events (n=5), request by subject (n=1), lost to follow-up (n=2) and other (n=1). A total of n=136 were included in the analysed population, which was a modified intention to treat population consisting of all of those randomised that took at least one dose of double-blind treatment and had at least one post-baseline assessment of the T25FW test.
Number of participants	429 (286 relevant to our protocol) randomised (n=143 to dalfampridine 10 mg and n=143 to placebo - n=144 also randomised to dalfampridine 5 mg but this dose was not relevant to our protocol). A total of 136 participants in each arm were included in the analysis population, which was a modified intention to treat population (all of those randomised that took at least one dose of double-blind treatment and had at least one post-baseline assessment of the T25FW test).
Duration of follow-up	Follow-up up to the end of the 4-week treatment period.

Study arms

Extended-release dalfampridine (10 mg) (N = 143)

10 mg dalfampridine extended-release. N=143 randomised. After a 1-week screening period, patients randomised to 10 mg oral dalfampridine taken twice daily at 12-hour intervals for 4 weeks. Active treatment and placebo tablets were identical in appearance and placebo tablets contained the same inactive ingredients as dalfampridine extended-release.

Placebo (N = 143)

Placebo. N=143 randomised. After a 1-week screening period, patients randomised to placebo taken twice daily at 12-hour intervals for 4 weeks. Active treatment and placebo tablets were identical in appearance and placebo tablets contained the same inactive ingredients as dalfampridine extended-release.

Characteristics

Arm-level characteristics

Characteristic	Extended-release dalfampridine (10 mg) (N = 143)	Placebo (N = 143)
% Female number/analysed (%)	98/143 (68.5%)	100/142 (70.4%)
Mean age (SD) (years) Sample size	n = 143	n = 142
Mean age (SD) (years) Mean (SD)	53.4 (9.5)	52.2 (9.9)
Asian number/analysed (%)	1/143 (0.7%)	1/142 (0.7%)
White number/analysed (%)	114/143 (79.7%)	117/142 (82.4%)
African-American	24/143 (16.8%)	22/142 (15.5%)

Characteristic	Extended-release dalfampridine (10 mg) (N = 143)	Placebo (N = 143)
number/analysed (%)		
Other number/analysed (%)	4/143 (2.8%)	2/142 (1.4%)
Comorbidities Text	Not reported	Not reported
Body mass index (kg/m2) Sample size	n = 143	n = 142
Body mass index (kg/m2) Mean (SD)	29.1 (5.8)	28.3 (7.1)
Relapsing-remitting number/analysed (%)	107/143 (74.8%)	103/142 (72.5%)
Secondary progressive number/analysed (%)	21/143 (14.7%)	23/142 (16.2%)
Primary progressive number/analysed (%)	11/143 (7.7%)	12/142 (8.5%)
Progressive relapsing number/analysed (%)	4/143 (2.8%)	4/142 (2.8%)
Disease duration (years)	n = 143	n = 142

Characteristic	Extended-release dalfampridine (10 mg) (N = 143)	Placebo (N = 143)
Sample size		
Disease duration (years) Mean (SD)	12.1 (9)	13 (9.5)
EDSS score Expanded Disability Status Scale. Sample size	n = 143	n = 142
EDSS score Expanded Disability Status Scale. Mean (SD)	4.7 (1.5)	4.8 (1.6)
Walking speed (T25FW test) (feet/sec) Measured on the Timed-25 foot Walk Test. Sample size	n = 143	n = 142
Walking speed (T25FW test) (feet/sec) Measured on the Timed-25 foot Walk Test. Mean (SD)	2.84 (1.21)	2.78 (1.16)
MSWS-12 score 12-item Multiple Sclerosis Walking Scale. Sample size	n = 143	n = 142
MSWS-12 score 12-item Multiple Sclerosis Walking Scale. Mean (SD)	61.29 (25.7)	60.7 (25.1)

Characteristic	Extended-release dalfampridine (10 mg) (N = 143)	Placebo (N = 143)
Walking distance (6-MWT) (feet) Assessed on 6-Minute Walk Test. This was only measured in 26/65 sites as they had the ability to perform this test. Sample size	n = 51	n = 49
Walking distance (6-MWT) (feet) Assessed on 6-Minute Walk Test. This was only measured in 26/65 sites as they had the ability to perform this test. Mean (SD)	842.6 (322.9)	860.9 (428.6)

Numbers at the top of the table are the numbers randomised to each group. However, the study reports baseline data within the population that were randomised and received at least one dose of study drug, which was n=143 in the dalfampridine group and n=142 in the placebo group, as indicated in the table.

Outcomes

Study timepoints

- Baseline
- 2 week (Follow-up at 2 weeks into the 4-week treatment period. Indirect to protocol as measured at 2 weeks rather than 6 months. This was the longest follow-up time-point for some outcomes.)
- 4 week (Follow-up at the end of the 4-week treatment period. Indirect to protocol as measured at 4 weeks rather than 6 months.)

Results - raw data

Outcome	Extended-release dalfampridine (10 mg), Baseline, N = 143	Extended-release dalfampridine (10 mg), 2-week, N = NR	Extended-release dalfampridine (10 mg), 4-week, N = 136	Placebo, Baseline, N = 142	Placebo, 2-week, N = NR	Placebo, 4-week, N = 136
6-MWT - change from baseline ≥55.06 metres 6-Minute Walk Test. An improvement of 55.06 metres previously calculated to be a minimally important change from baseline. Post-hoc analysis. number/analysed (%)	NA	19/51 (37.3%)	NR	NA	6/49 (12.2%)	NR
6-MWT - change from baseline ≥20% 6-Minute Walk Test. 20% threshold set based on clinically meaningful improvement for T25FW test. Post-hoc analysis. number/analysed (%)	NA	23/51 (45.1%)	NR	NA	7/49 (14.3%)	NR
T25FW test - change from baseline ≥20% Timed 25-Foot Walk test. 20% threshold previously reported to be clinically relevant for this outcome. Post-hoc analysis. number/analysed (%)	NA	NA	60/136 (44.1%)	NA	NA	37/136 (27.2%)
Mortality No of events	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0
Mortality Number analysed	143	NA	142	142	NA	143

Outcome	Extended-release dalfampridine (10 mg), Baseline, N = 143	Extended-release dalfampridine (10 mg), 2-week, N = NR	Extended-release dalfampridine (10 mg), 4-week, N = 136	Placebo, Baseline, N = 142	Placebo, 2-week, N = NR	Placebo, 4-week, N = 136
Withdrawal due to adverse events No of events	n = NA ; % = NA	n = NA ; % = NA	n = 14 ; % = 9.86	n = NA ; % = NA	n = NA ; % = NA	n = 5 ; % = 3.5
Withdrawal due to adverse events Number analysed	143	NA	142	142	NA	137
Urinary tract infection Number of events reported for this outcome differed between papers, as different definitions were used. The definition that led to the most UTIs being reported has been extracted (defined as criterion B regardless of symptomatology in Kantor 2015 paper - leukocytes >5 high-power field and ≥10 to the power of 4 colony-forming units/ml) No of events	n = NA ; % = NA	n = NA ; % = NA	n = 16 ; % = 11.3	n = NA ; % = NA	n = NA ; % = NA	n = 15 ; % = 10.5
Urinary tract infection Number of events reported for this outcome differed between papers, as different definitions were used. The definition that led to the most UTIs being reported has been extracted (defined as criterion B regardless of symptomatology in Kantor 2015 paper - leukocytes >5 high-power field and ≥10 to the power of 4 colony-forming units/ml) Number analysed	143	NA	142	142	NA	143

Outcome	Extended-release dalfampridine (10 mg), Baseline, N = 143	Extended-release dalfampridine (10 mg), 2-week, N = NR	Extended-release dalfampridine (10 mg), 4-week, N = 136	Placebo, Baseline, N = 142	Placebo, 2-week, N = NR	Placebo, 4-week, N = 136
Seizures No of events	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0
Seizures Number analysed	143	NA	142	142	NA	143
Headache No of events	n = NA	n = NA ; % = NA	n = 9 ; % = 6.34	n = NA ; % = NA	n = NA ; % = NA	n = 7 ; % = 4.9
Headache Number analysed	143	NA	142	142	NA	143

The numbers given at the top of the table for 4-weeks represent the total number included in the modified intention to treat population and analysed for the efficacy analyses. The number analysed differed for adverse events and for the 6-MWT outcome and have been indicated in the table below. One patient assigned to dalfampridine received placebo instead and was analysed in the placebo group for safety analyses. Available case analyses have been extracted where possible.

Results - change from baseline

Outcome	Extended-release dalfampridine (10 mg), 2-week vs Baseline, N = 51	Placebo, 2-week vs Baseline, N = 49
6-MWT change from baseline (feet) 6-Minute Walk Test. Baseline values were 842.6 (322.9) and 860.9 (428.6) in dalfampridine and placebo groups, respectively. Mean (SD)	128.6 (154.7)	41.7 (163.5)

6-MWT change from baseline - Polarity - Higher values are better

Note that the 6-MWT could only be completed by some of the centres included in the trial, explaining the large reduction in number analysed for this outcome compared to those randomised. Additionally, results were only reported at 2 weeks rather than 4 weeks as for other outcomes.

Results - change from baseline relative to placebo

Outcome	Extended-release dalfampridine (10 mg) vs Placebo, 4-week vs Baseline, N2 = 136, N1 = 136
T25FW test change from baseline relative to placebo (feet/second) Timed 25-Foot Walk Test. Baseline values were 2.84 (1.21, n=143) and 2.78 (1.16, n=142) in the dalfampridine and placebo arms, respectively. P-value	0.107
T25FW test change from baseline relative to placebo (feet/second) Timed 25-Foot Walk Test. Baseline values were 2.84 (1.21, n=143) and 2.78 (1.16, n=142) in the dalfampridine and placebo arms, respectively. Mean (SE)	0.12 (0.071109993)
MSWS-12 change from baseline relative to placebo 12-Item Multiple Sclerosis Walking Scale. Scale 0-100. Baseline values were 61.29 (125.7, n=143) and 60.7 (25.1, n=142) in the dalfampridine and placebo arms, respectively. P-value	0.286
MSWS-12 change from baseline relative to placebo 12-Item Multiple Sclerosis Walking Scale. Scale 0-100. Baseline values were 61.29 (125.7, n=143) and 60.7 (25.1, n=142) in the dalfampridine and placebo arms, respectively. Mean (SE)	-2.7 (2.53)

T25FW test change from baseline relative to placebo - Polarity - Higher values are better

MSWS-12 change from baseline relative to placebo - Polarity - Lower values are better

Standard errors not reported in the paper but calculated from other information given in the paper (mean values and P-values). A total of n=136 were analysed in each group for efficacy analyses, according to the modified intention to treat population.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT (Pharma)

6-MWT change from baseline of 55.06 metres_2 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(large amount of missing data as outcome only measured at some centres. Also unclear how many of those analysed completed treatment)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(post-hoc analysis)*

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

6-MWT change from baseline of 20%_2 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(large amount of missing data as outcome only measured at some centres. Also unclear how many of those analysed completed treatment)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(post-hoc analysis)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

T25FW test change from baseline of 20%_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(post-hoc analysis)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Mortality_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Withdrawal due to adverse events_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(dropout higher than event rate)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Urinary tract infection_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(dropout higher than event rate and could be related to outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(post-hoc analysis)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Seizures_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable

Section	Question	Answer
		(time-point <3 months)

Headache_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

6-MWT change from baseline continuous_2 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(large amount of missing data as outcome only measured at some centres. Also unclear how many of those analysed completed treatment)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

T25FW test change from baseline relative to placebo_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(limited reporting meant some data had to be calculated using other available information)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

MSWS-12 change from baseline relative to placebo_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(limited reporting meant some data had to be calculated using other available information and dichotomous version mentioned but not reported)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Zorner, 2016

Bibliographic Reference	Zorner, B.; Filli, L.; Reuter, K.; Kapitza, S.; Lorincz, L.; Sutter, T.; Weller, D.; Farkas, M.; Easthope, C. S.; Czaplinski, A.; Weller, M.; Linnebank, M.; Prolonged-release fampridine in multiple sclerosis: Improved ambulation effected by changes in walking pattern; Multiple Sclerosis; 2016; vol. 22 (no. 11); 1463-1475

Study details

Other publications associated with this study included in review	• Weller, D.; Lorincz, L.; Sutter, T.; Reuter, K.; Linnebank, M.; Weller, M.; Zorner, B.; Filli, L.; Fampridine-induced changes in walking kinetics are associated with clinical improvements in patients with multiple sclerosis; Journal of the Neurological Sciences; 2020; vol. 416; 116978 - study is a secondary analysis of the primary trial and does not report any further outcomes relevant to the protocol.

Trial name / registration number	FAMPKIN trial. NCT01576354.
Study location	Recruited from a single university hospital in Switzerland.
Study setting	University hospital - outpatients
Study dates	Patients recruited in 2012 and 2013.
Sources of funding	Study said to be supported by various foundations/programmes but also by Biogen. Various authors had received honoraria, grants and funding from Biogen. Two authors were consultants for Biogen, and another was an employee of Biogen. Fampridine and matching placebo tablets provided by Biogen.
Inclusion criteria	Aged 18-65 years; diagnosis of relapsing-remitting, primary progressive or secondary progressive MS; and a clinically apparent walking impairment (e.g., ataxia, paresis of leg muscles or restricted walking duration) but able to cover at least 50 metres in 6 minutes with or without walking aids.
Exclusion criteria	History of seizure; prior exposure to 4-aminopyridine; and other conditions impeding gait, such as cardiac, pulmonary or orthopaedic diseases. Subjects who experienced MS relapses or whose MS therapy changed during the study were excluded from final analyses.
Recruitment / selection of participants	Recruited from a single university hospital in 2012 and 2013.
Intervention(s)	Prolonged-release fampridine. N=61 randomised. Initial single-blind placebo run-in period of 2 weeks. Oral prolonged-release fampridine (10 mg twice daily) for 6 weeks (tablets taken every 12 hours). Randomised to receive this treatment first or second as part of a placebo-controlled crossover trial. 61 randomised (n=31 to receive fampridine first and n=30 to receive placebo first). The two treatment periods were separated by a 2-week washout period. A 2-week observation period occurred following the second treatment period. Fampridine and placebo tablets were matched.
Comparator	Placebo. N=61 randomised. Initial single-blind placebo run-in period of 2 weeks. Oral placebo tablets twice daily for 6 weeks (tablets taken every 12 hours). Randomised to receive this treatment first or second as part of a placebo-controlled crossover trial. 61 randomised (n=30 to receive placebo first and n=31 to receive fampridine first). The two treatment periods were separated by a 2-week washout period. A 2-week observation period occurred following the second treatment period. Fampridine and placebo tablets were matched.
Number of participants	N=61 randomised (n=31 to receive fampridine followed by placebo and n=30 to receive placebo followed by fampridine). N=1 did not complete the second period of the trial as they said it was time-consuming (appears to be in

	the group that received placebo second), meaning n=60 completed the trial. A further 5 were excluded from analyses (n=1 MS relapse, n=1 leg fracture and n=3 non-compliance - appear to have been excluded rather than dropping out), meaning n=55 were included in the final analyses.
Duration of follow-up	Up to the end of each 6-week treatment period and a subsequent 2-week post-treatment follow-up at the end of the two periods.

Study arms

Prolonged-release fampridine (N = 61)

Oral prolonged-release fampridine (10 mg twice daily) for 6 weeks. Randomised to receive this treatment first or second as part of a placebo-controlled crossover trial. 61 randomised (n=31 to receive fampridine first and n=30 to receive placebo first). The two treatment periods were separated by a 2-week washout period.

Placebo (N = 61)

Oral placebo tablets twice daily for 6 weeks. Randomised to receive this treatment first or second as part of a placebo-controlled crossover trial. 61 randomised (n=30 to receive placebo first and n=31 to receive fampridine first). The two treatment periods were separated by a 2-week washout period.

Characteristics

Study-level characteristics

Characteristic	Study (N = 55)
% Female	n = 34 ; % = 62

Characteristic	**Study (N = 55)**
Sample size	
Mean age (SD) (years) Range	27 to 64
Mean age (SD) (years) Mean (SD)	48.6 (9.8)
Ethnicity Text	Not reported
Comorbidities Text	Not reported
Relapsing-remitting Sample size	n = 29 ; % = 53
Primary progressive Sample size	n = 5 ; % = 9
Secondary progressive Sample size	n = 21 ; % = 38
Disease duration (years) Range	1 to 37
Disease duration (years) Mean (SD)	11.9 (7.4)

Characteristic	Study (N = 55)
EDSS score Expanded Disability Status Scale Range	2.5 to 6.5
EDSS score Expanded Disability Status Scale Mean (SD)	4.9 (1.3)
Concomitant MS treatment Sample size	n = 34 ; % = 62
With an interferon Sample size	n = 9 ; % = 16
With glatiramer acetate Sample size	n = 2 ; % = 4
With natalizumab Sample size	n = 21 ; % = 38
With fingolimod Sample size	n = 2 ; % = 4

Outcomes

Study timepoints

- Baseline
- 6 week (Followed up at the end of each 6-week treatment period (fampridine and placebo in a crossover design). Matches 6-month time-point in protocol but indirect as measured at 6 weeks rather than 6 months.)

Results - raw data

Outcome	Prolonged-release fampridine, Baseline, N = 61	Prolonged-release fampridine, 6-week, N = 55	Placebo, Baseline, N = 61	Placebo, 6-week, N = 55
TUG test (seconds) Timed Get Up and Go test. Reported as final values at end of each treatment and does not report baseline values. Results not reported in text and could not be analysed. Unpaired data. Mean (SE)	NA (NA)	NR (NR)	NA (NA)	NR (NR)
Dynamic Gait Index Reported as final values at end of each treatment and does not report baseline values. Results not reported in text and could not be analysed. Scale not reported in study but elsewhere suggests 0-24. Unpaired data. Mean (SE)	NA (NA)	NR (NR)	NA (NA)	NR (NR)
Urinary tract infection No paired data reported so reported as a parallel trial. No of events	n = NA ; % = NA	n = 9 ; % = 16.36	n = NA ; % = NA	n = 9 ; % = 16.36

Outcome	Prolonged-release fampridine, Baseline, N = 61	Prolonged-release fampridine, 6-week, N = 55	Placebo, Baseline, N = 61	Placebo, 6-week, N = 55
Headache No paired data reported so reported as a parallel trial. No of events	n = NA ; % = NA	n = 7 ; % = 12.7	n = NA ; % = NA	n = 5 ; % = 9.09
Ankle fracture Reported that one patient had a serious adverse event of ankle fracture. Unclear whether other fractures may have occurred but not reported as not considered to be a serious adverse event. No of events	n = NA ; % = NA	n = 1 ; % = 1.82	n = NA ; % = NA	n = 0

TUG test - Polarity - Lower values are better

Dynamic Gait Index - Polarity - Higher values are better

Note that although n=61 were randomised to treatment, only n=55 were included in the final analysis as indicated in the table.

Results - change or % change from baseline

Outcome	Prolonged-release fampridine, 6-week vs Baseline, N = 55	Placebo, 6-week vs Baseline, N = 55
6MWT % change from baseline (metres) 6-Minute Walk Test. Does not report baseline values. Results not reported in text and could not be analysed. Unpaired data. Mean (SE)	4 (NR)	NR (NR)

Outcome	Prolonged-release fampridine, 6-week vs Baseline, N = 55	Placebo, 6-week vs Baseline, N = 55
T25FW % change from baseline (feet/second) Timed 25-Foot Walk test. Does not report baseline values. Results incompletely reported in text and could not be analysed. Unpaired data. Mean (SE)	9 (NR)	2 (NR)
12-Item Walking Scale change from baseline Referring to MSWS-12? If so, scale not reported but is usually 0-100. Does not report baseline values. Results not reported in text and could not be analysed. Absolute change rather than % change. Unpaired data. Mean (SE)	NR (NR)	NR (NR)
Motor fatigue (WEIMuS scale) change from baseline Wurzburg Fatigue Inventory for Multiple Sclerosis. Scale not reported but elsewhere suggested to be 0-32 for motor (physical) fatigue. Does not report baseline values. Results not reported in text and could not be analysed. Absolute change rather than % change. Unpaired data. Mean (SE)	NR (NR)	NR (NR)
Cognitive fatigue (WEIMuS scale) change from baseline Wurzburg Fatigue Inventory for Multiple Sclerosis. Scale not reported but elsewhere suggested to be 0-36 for cognitive fatigue. Does not report baseline values. Results not reported in text and could not be analysed. Absolute change rather than % change. Unpaired data. Mean (SE)	NR (NR)	NR (NR)

6MWT % change from baseline - Polarity - Higher values are better

T25FW % change from baseline - Polarity - Higher values are better

12-Item Walking Scale change from baseline - Polarity - Lower values are better

Motor fatigue (WEIMuS scale) change from baseline - Polarity - Lower values are better

Cognitive fatigue (WEIMuS scale) change from baseline - Polarity - Lower values are better

Note that although n=61 were randomised to treatment, only n=55 were included in the final analysis as indicated in the table.

Results - effect estimates

Outcome	Prolonged-release fampridine vs Placebo, Baseline, N2 = 61, N1 = 61	Prolonged-release fampridine vs Placebo, 6 week, N2 = 55, N1 = 55
T25FW responder Timed 25-Foot Walk. Responder defined as patients with a faster walking speed in T25FW test for at least three of the four visits during double blind treatment periods compared with the maximum speed achieved in the five baseline visits. Paired results and estimate of standard error for ln(RR) calculated using information available in the paper (n=17 only under fampridine, n=3 only under placebo, n=5 under both and n=30 under none of the treatments). Relative risk, SE (lnRR)	NA	2.7586, 0.3371

Note that although n=61 were randomised to treatment, only n=55 were included in the final analysis as indicated in the table.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial (Pharma)

TUG test_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Dynamic Gait Index_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Urinary tract infection_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Headache_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Ankle fracture_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

6MWT % change from baseline_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

T25FW % change from baseline_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable

Section	Question	Answer
		(time-point <3 months)

12-Item Walking Scale_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Motor fatigue change from baseline_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Cognitive fatigue change from baseline_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

T25FW responder_6 weeks

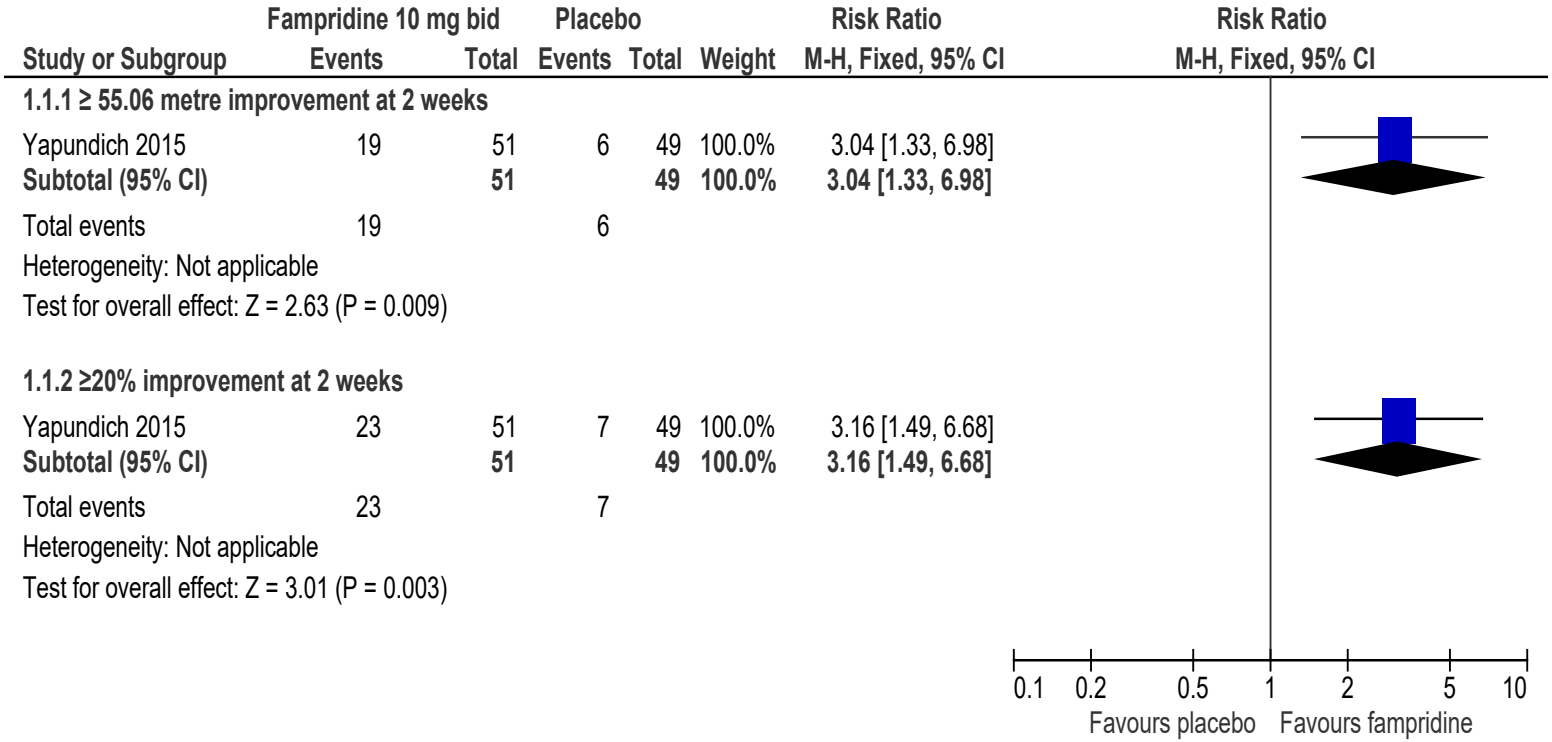
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months)*

Appendix E – Forest plots

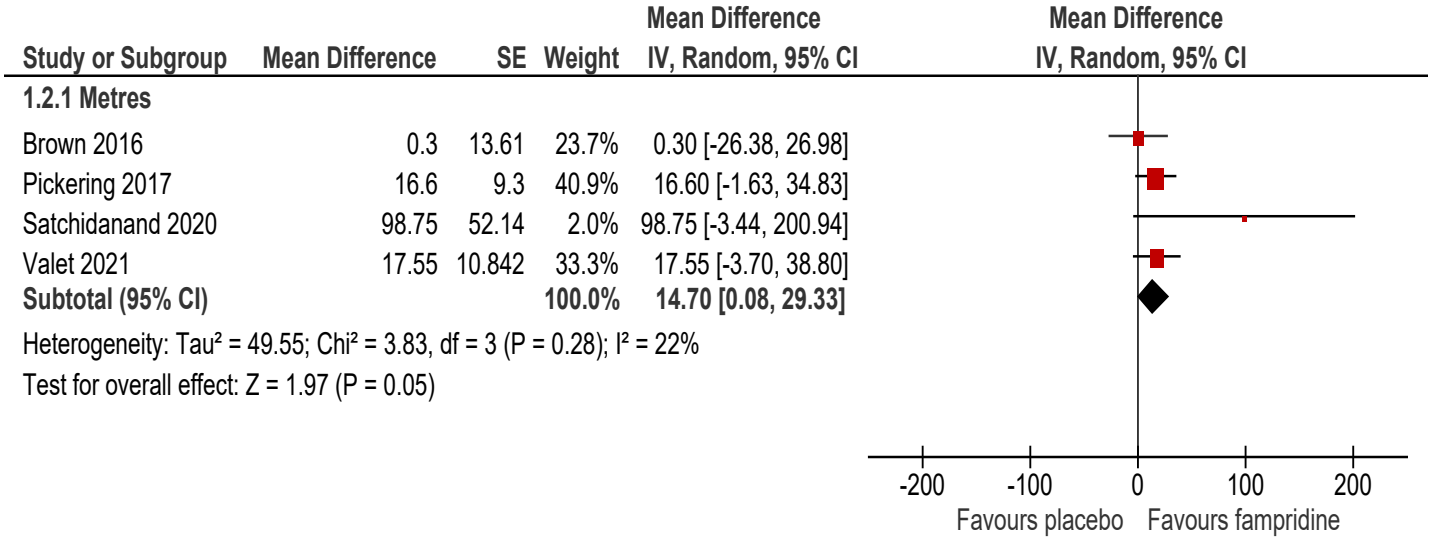
E.1 Fampridine compared to placebo

Figure 3: 6-Minute Walk Test improvement at 2 weeks compared to baseline



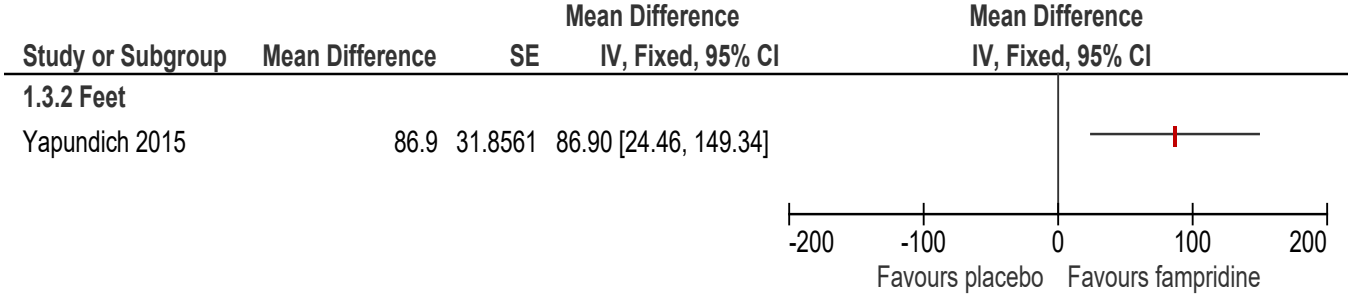
Parallel trial.

Figure 4: 6-Minute Walk Test at 4-12 weeks – mixture of change and final scores (metres, higher is better)



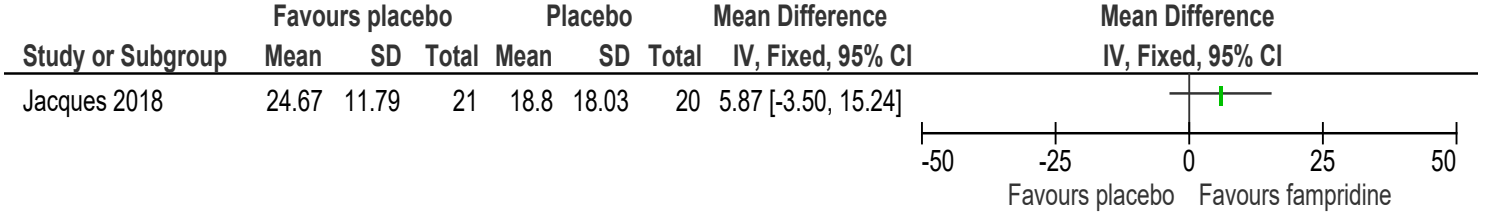
Random effects analysis used and downgraded for unexplained heterogeneity. Mixture of parallel and crossover trials.

Figure 5: 6-Minute Walk Test change from baseline at 2 weeks (feet, higher is better)



Parallel trial.

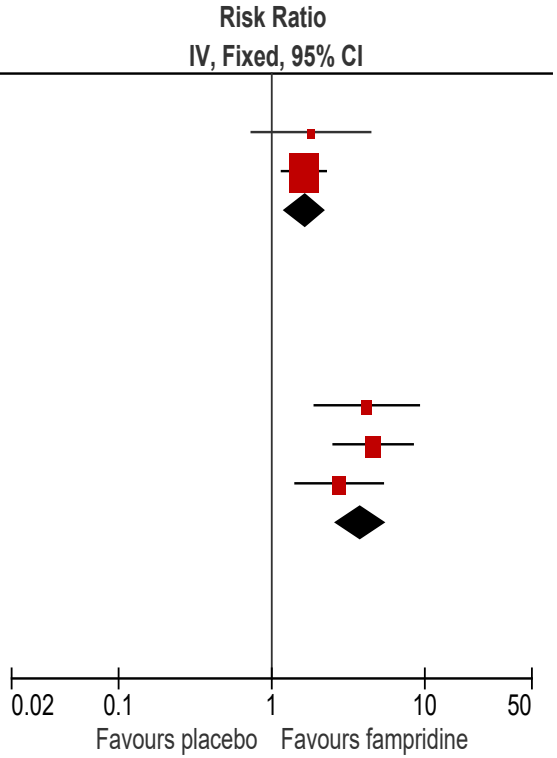
Figure 6: 6-Minute Walk Test % change from baseline at 14 weeks (higher is better)



Parallel trial.

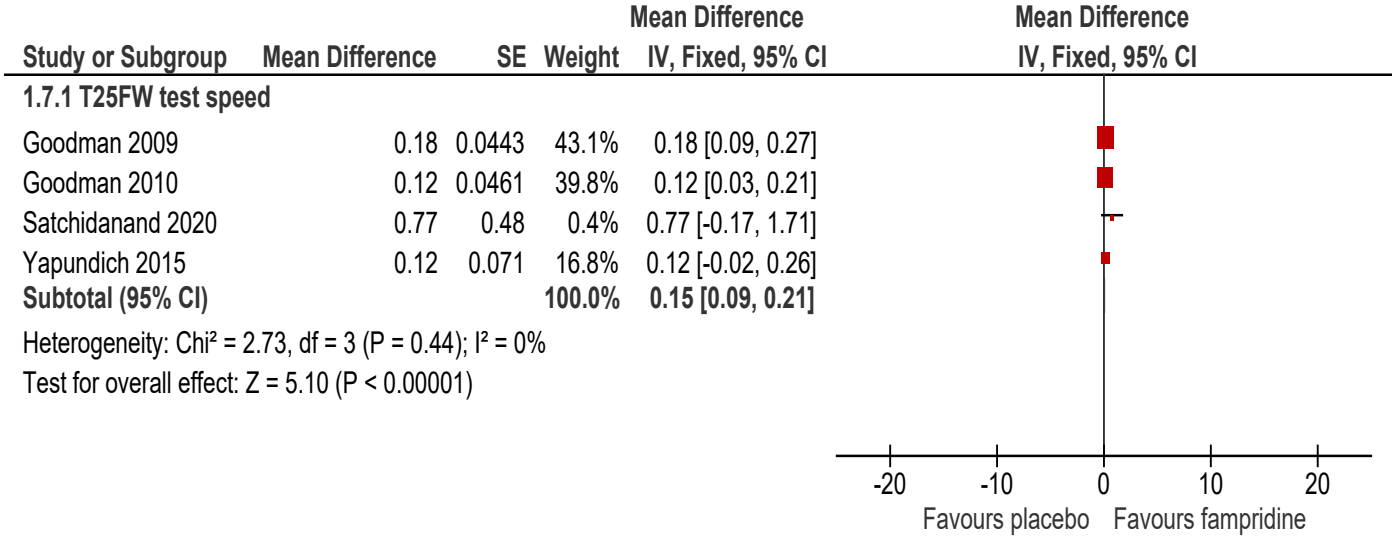
Figure 7: Timed 25-Foot Walk test improvement compared to baseline over 4-14 weeks

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
1.5.1 Improvement of >20% or ≥20% from baseline at 4-14 weeks				
Goodman 2008	0.59	0.4568	12.2%	1.80 [0.74, 4.42]
Yapundich 2015	0.4834	0.1703	87.8%	1.62 [1.16, 2.26]
Subtotal (95% CI)			**100.0%**	**1.64 [1.20, 2.25]**
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%				
Test for overall effect: Z = 3.11 (P = 0.002)				
1.5.2 Faster walking speed for 3/4 on-treatment visits (across 6-14 weeks) compared to max speed during off-treatment visits				
Goodman 2009	1.43	0.4014	24.2%	4.18 [1.90, 9.18]
Goodman 2010	1.5255	0.306	41.6%	4.60 [2.52, 8.37]
Zorner 2016	1.0147	0.3371	34.3%	2.76 [1.42, 5.34]
Subtotal (95% CI)			**100.0%**	**3.77 [2.56, 5.55]**
Heterogeneity: Chi² = 1.34, df = 2 (P = 0.51); I² = 0%				
Test for overall effect: Z = 6.73 (P < 0.00001)				



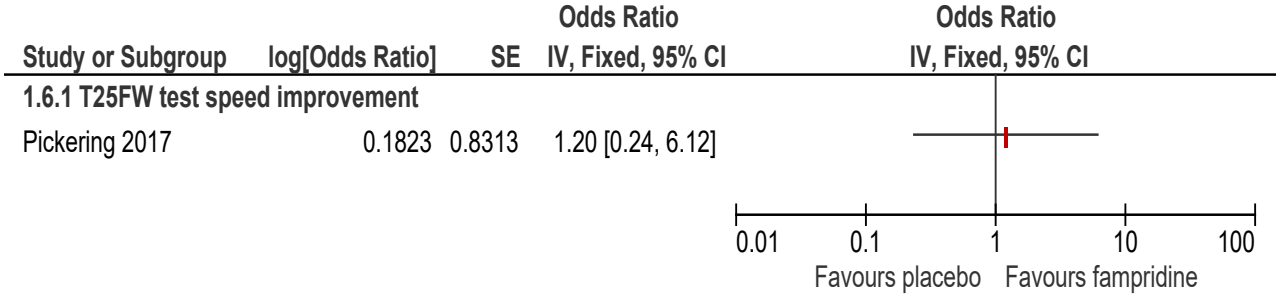
Mixture of parallel and crossover trials.

Figure 8: Timed 25-Foot Walk test speed at 4-14 weeks – mixture of change and final scores (feet/second, higher is better)



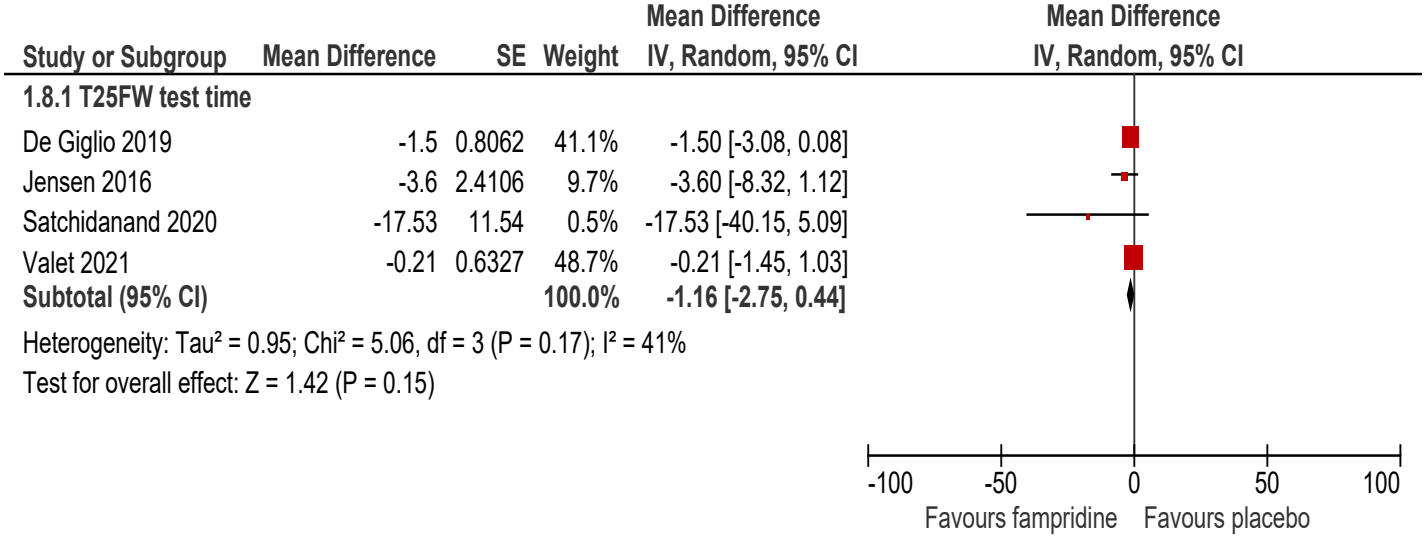
Parallel trials.

Figure 9: Timed 25-Foot Walk test improvement compared to baseline at 12 weeks – reported odds ratio



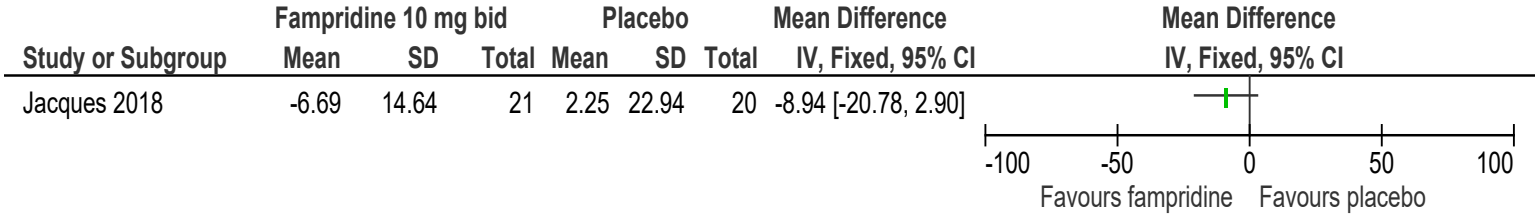
Crossover trial.

Figure 10: Timed 25-Foot Walk test time at 4-12 weeks – mixture of change and final scores (seconds, lower is better)



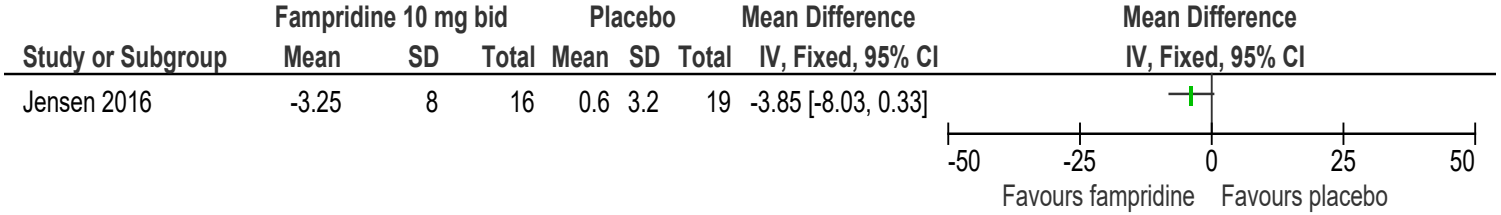
Mix of parallel and crossover trials.

Figure 11: Timed 8-Metre Walk test time % change from baseline at 14 weeks (lower is better)



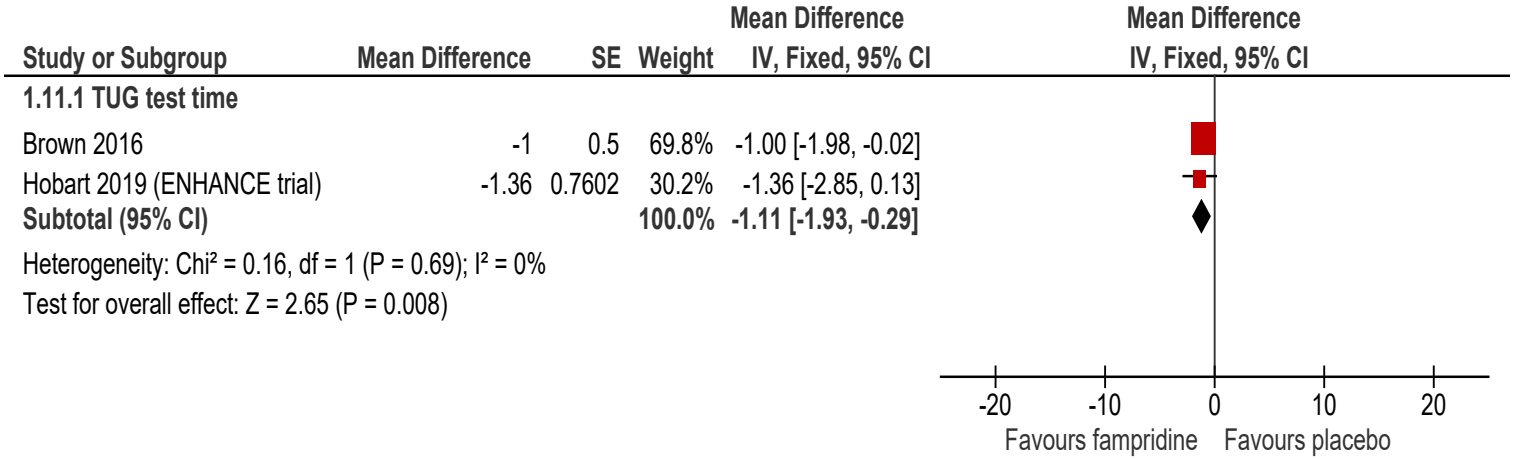
Parallel trial.

Figure 12: Six Spot Step test change from baseline at 4 weeks (seconds, lower is better)



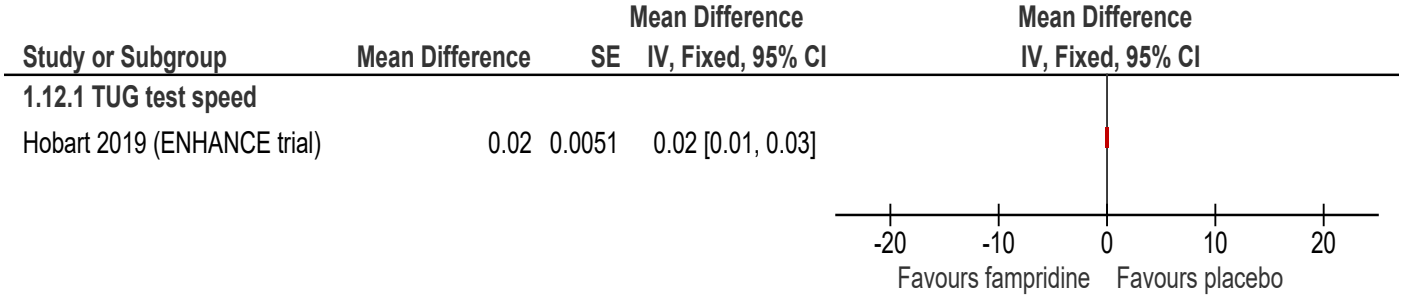
Parallel trial.

Figure 13: Timed Up and Go test time change from baseline at 4-24 weeks (seconds, lower is better)



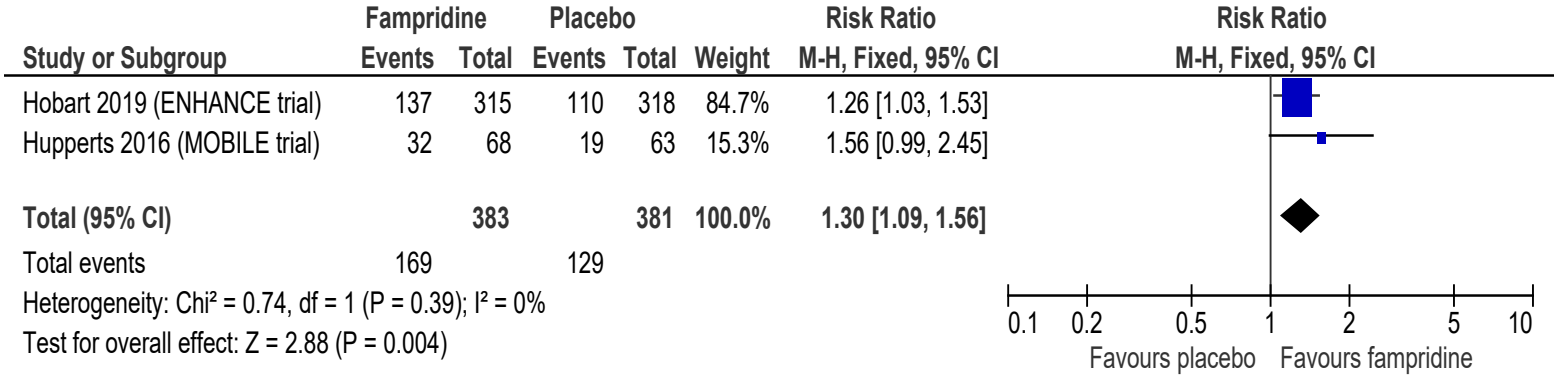
Mixture of parallel and crossover trials.

Figure 14: Timed Up and Go test speed change from baseline at 24 weeks (feet/second, higher is better)



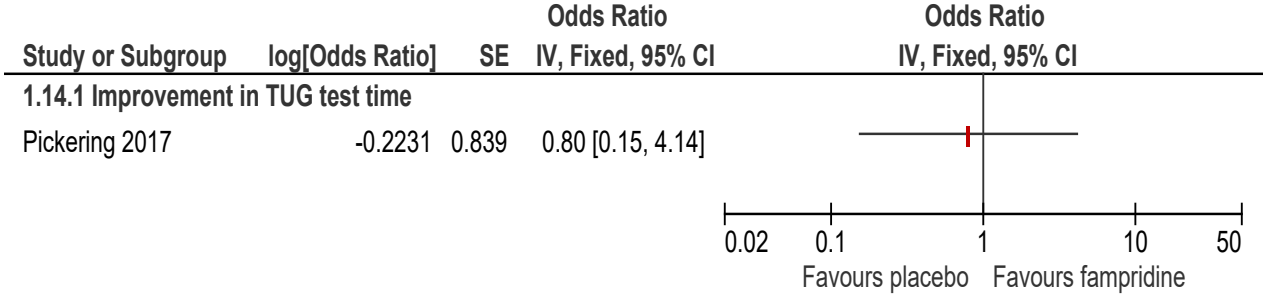
Parallel trial.

Figure 15: Timed Up and Go test speed improvement from baseline at 24 weeks



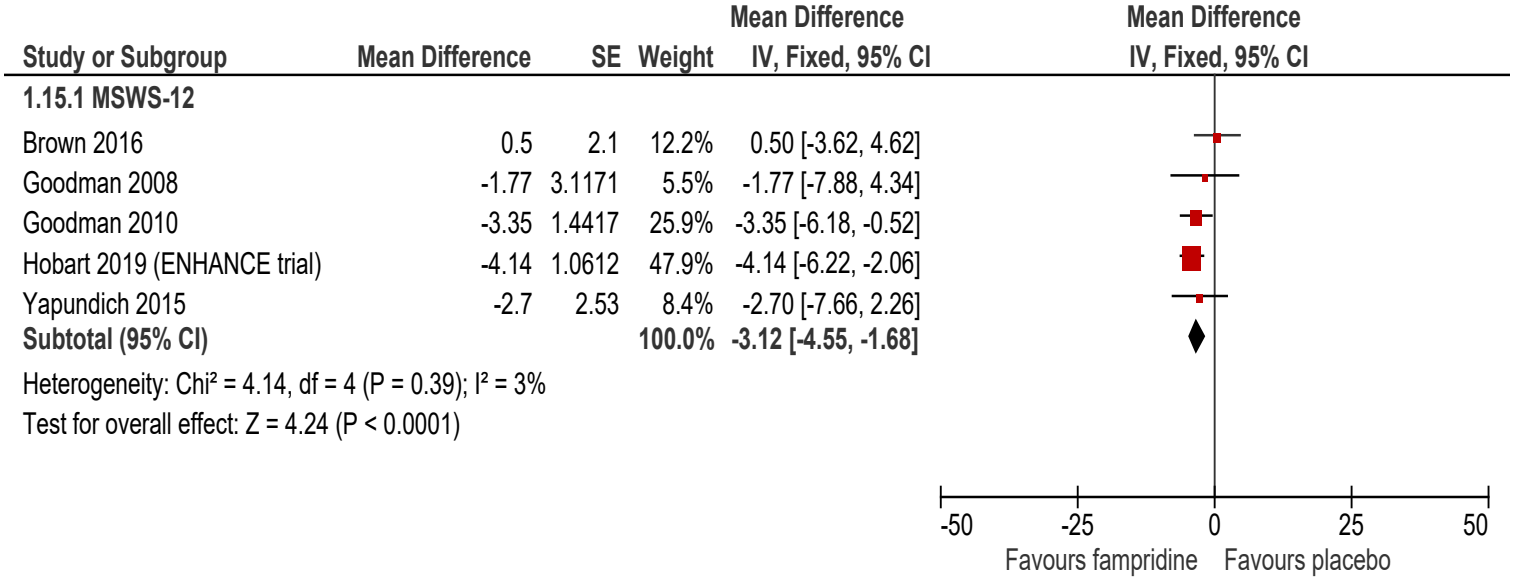
Parallel trials.

Figure 16: Timed Up and Go test improvement from baseline at 12 weeks (appears to be time based on baseline values given)



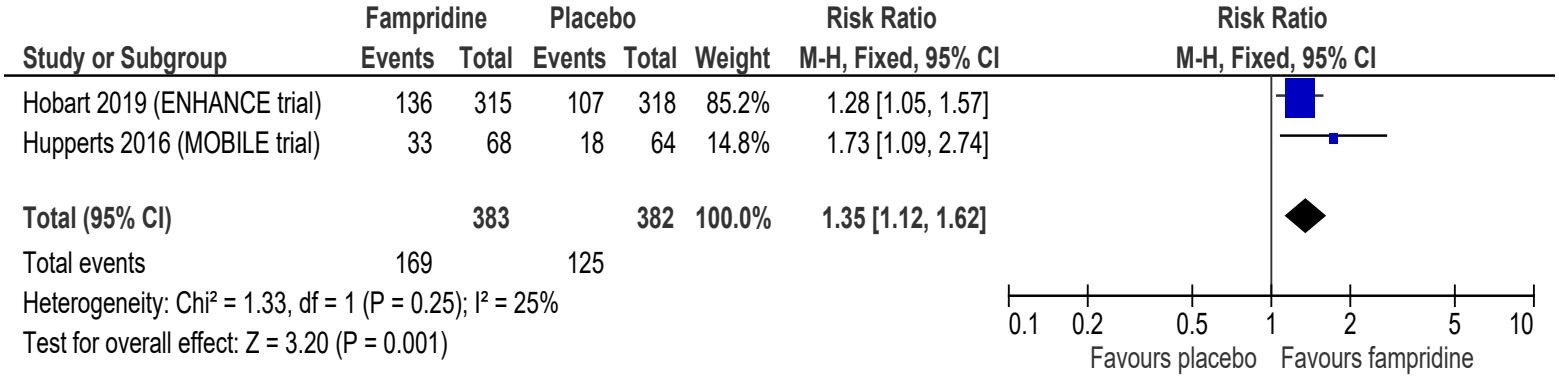
Crossover trial.

Figure 17: 12-Item MS Walking Scale change from baseline at 4-24 weeks (scale 0-100, lower is better)



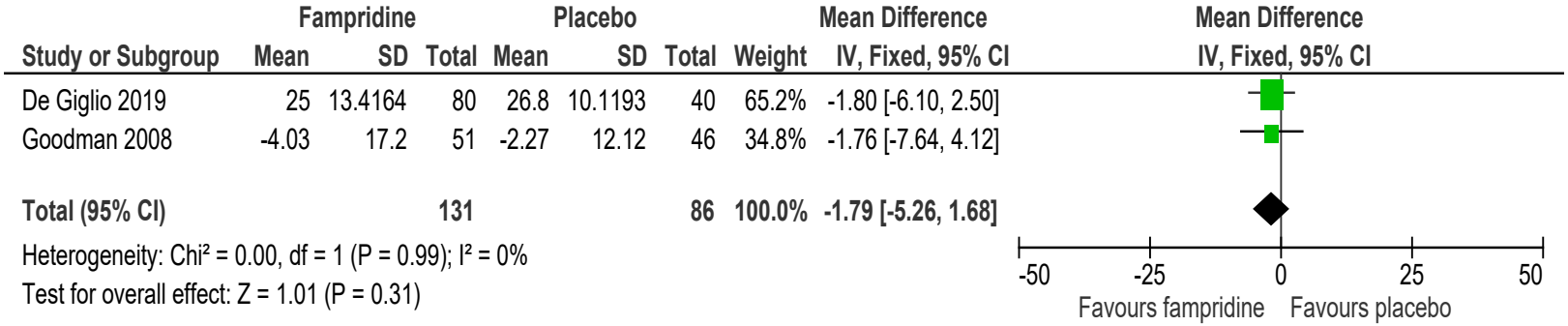
Mixture of parallel and crossover trials.

Figure 18: 12-Item MS Walking Scale improvement compared to baseline at 24 weeks



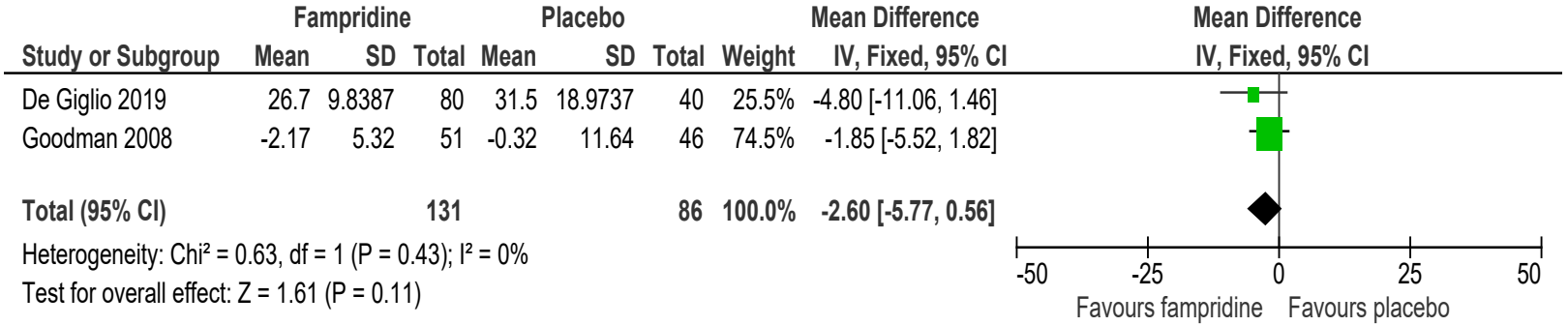
Parallel trials.

Figure 19: 9-Hole Peg Test time, dominant hand at 12-14 weeks – mixture of change and finals scores (seconds, lower is better)



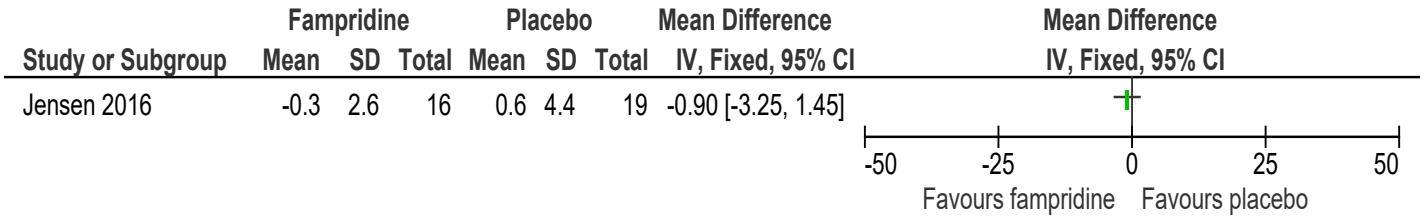
Parallel trials.

Figure 20: 9-Hole Peg Test time, non-dominant hand at 12-14 weeks – mixture of change and finals scores (seconds, lower is better)



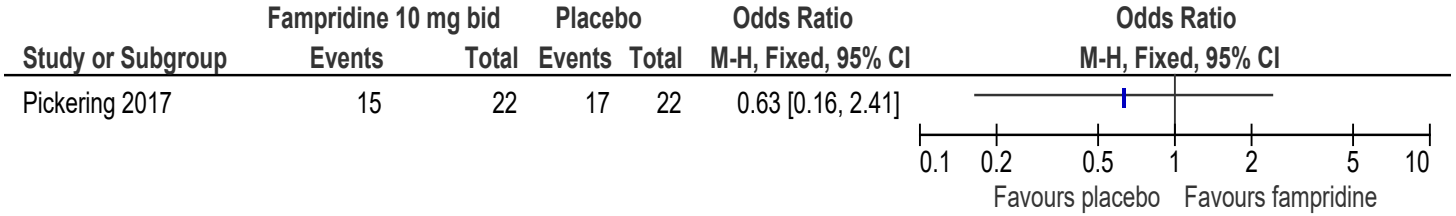
Parallel trials.

Figure 21: 9-Hole Peg Test time change from baseline at 4 weeks, unclear if dominant or non-dominant hand (seconds, lower is better)



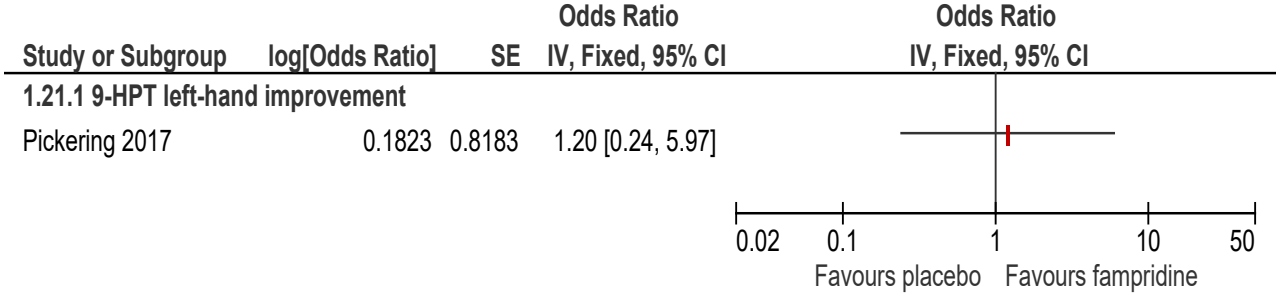
Parallel trial.

Figure 22: 9-Hole Peg Test right-hand improvement compared to baseline at 12 weeks



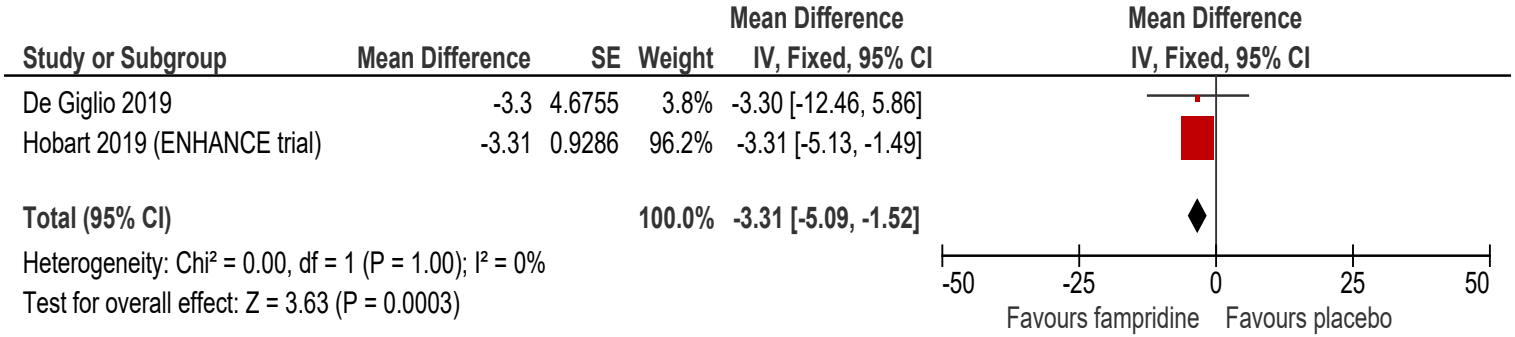
Crossover trial.

Figure 23: 9-Hole Peg Test left-hand improvement compared to baseline at 12 weeks



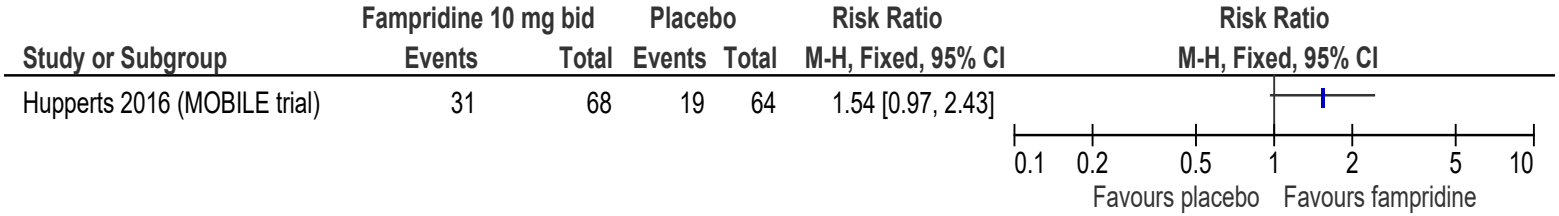
Crossover trial.

Figure 24: 29-Item MS Impact Scale at 12-24 weeks – mixture of change and final scores (scale 0-100, lower is better)



Parallel trials. One clearly refers to the physical subscale and unclear whether the other is the same or an overall score.

Figure 25: 29-Item MS Impact Scale Physical subscale improvement compared to baseline at 24 weeks

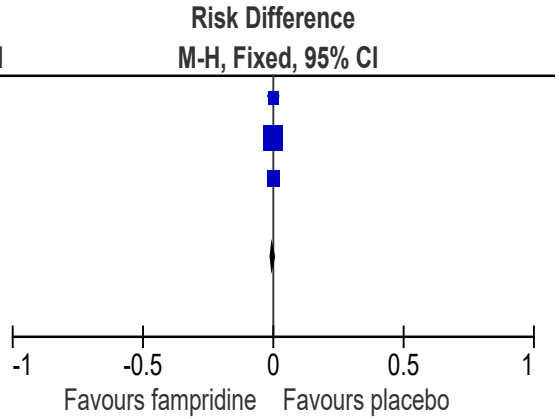


Parallel trial.

Figure 26: Mortality during treatment period (4-24 weeks)

Study or Subgroup	Fampridine 10 mg bid Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Goodman 2009	0	211	0	71	20.8%	0.00 [-0.02, 0.02]
Hobart 2019 (ENHANCE trial)	1	267	1	255	51.2%	-0.00 [-0.01, 0.01]
Yapundich 2015	0	142	0	143	28.0%	0.00 [-0.01, 0.01]
Total (95% CI)		**620**		**469**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	1		1			

Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.98)



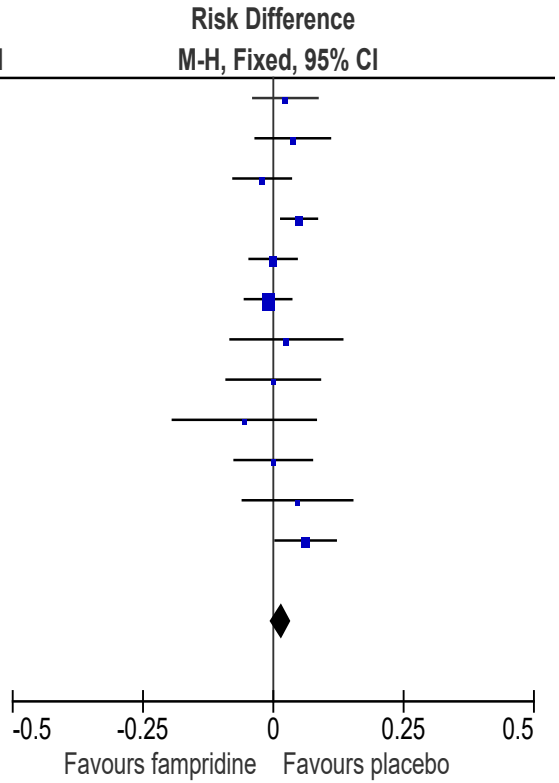
Parallel trials.

Figure 27: Withdrawal due to adverse events at 4-24 weeks

Study or Subgroup	Fampridine 10 mg bid Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Brown 2016	1	43	0	43	4.6%	0.02 [-0.04, 0.09]
De Giglio 2019	5	80	1	40	5.7%	0.04 [-0.03, 0.11]
Goodman 2008	0	52	1	47	5.2%	-0.02 [-0.08, 0.03]
Goodman 2009	11	222	0	71	11.4%	0.05 [0.01, 0.08]
Goodman 2010	4	120	4	119	12.7%	-0.00 [-0.05, 0.05]
Hobart 2019 (ENHANCE trial)	22	288	24	278	30.0%	-0.01 [-0.06, 0.04]
Hupperts 2016 (MOBILE trial)	7	62	5	57	6.3%	0.03 [-0.08, 0.13]
Jacques 2018	0	21	0	20	2.2%	0.00 [-0.09, 0.09]
Marion 2020	0	20	1	18	2.0%	-0.06 [-0.19, 0.08]
Pickering 2017	0	25	0	25	2.7%	0.00 [-0.07, 0.07]
Satchidanand 2020	2	43	0	16	2.5%	0.05 [-0.06, 0.15]
Yapundich 2015	14	142	5	137	14.8%	0.06 [0.00, 0.12]
Total (95% CI)		**1118**		**871**	**100.0%**	**0.02 [-0.00, 0.04]**
Total events	66		41			

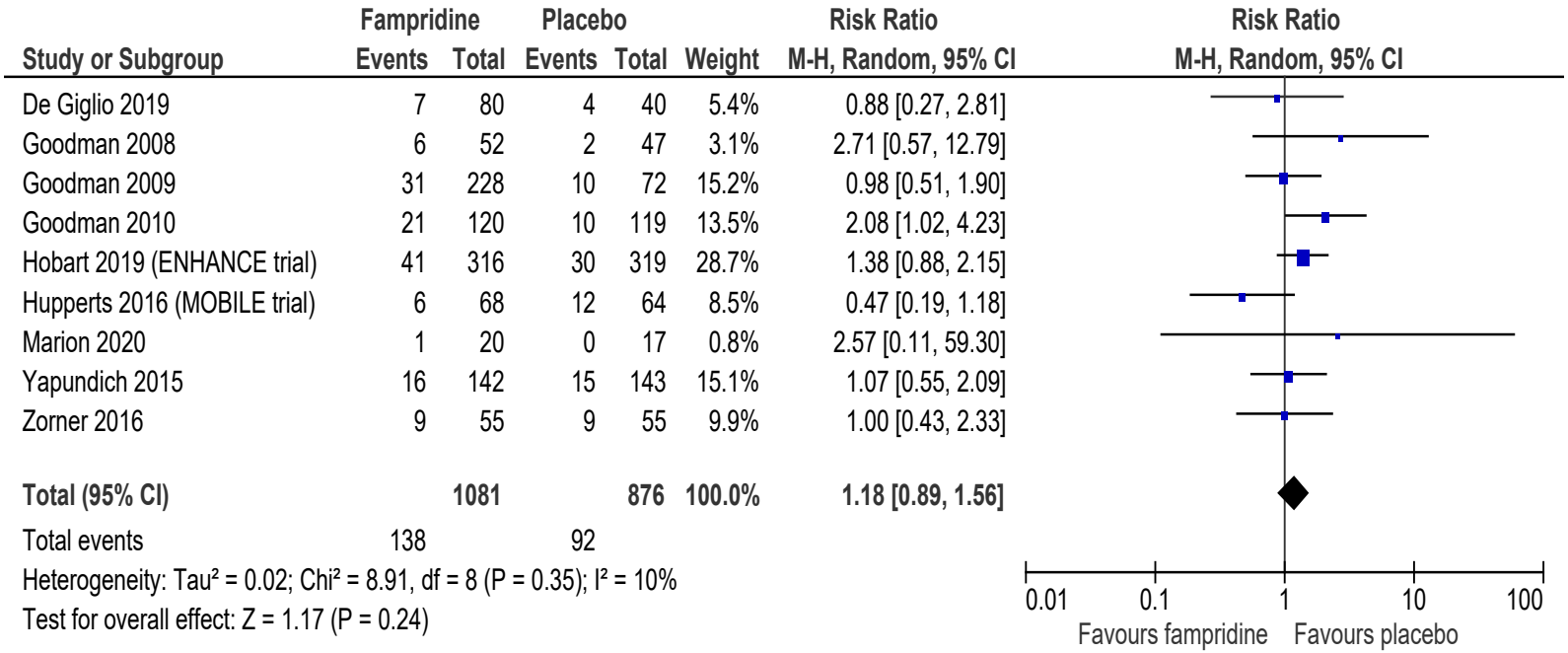
Heterogeneity: Chi² = 11.58, df = 11 (P = 0.40); I² = 5%

Test for overall effect: Z = 1.50 (P = 0.13)



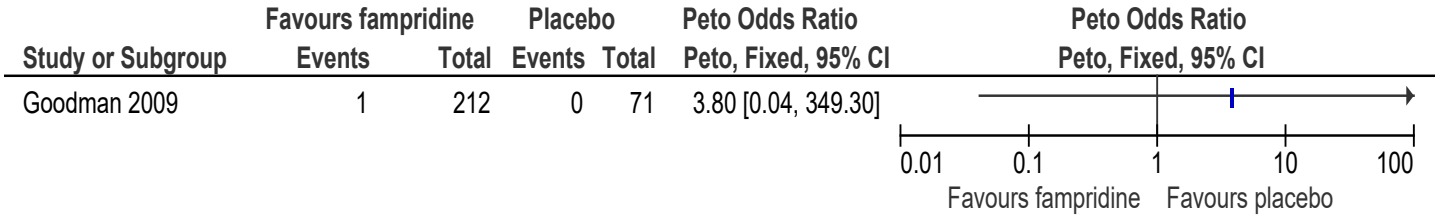
Mixture of parallel and crossover trials.

Figure 28: Urinary tract infection at 4-24 weeks



Mixture of parallel and crossover trials.

Figure 29: Confusional state at 14 weeks

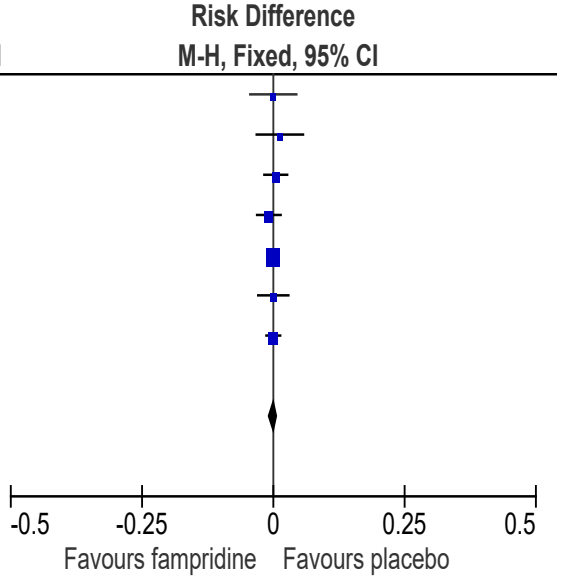


Reports 1 patient withdrew from the study for this reason, unclear whether any more minor confusion events may have occurred. Parallel trial.

Figure 30: Seizures at 4-24 weeks

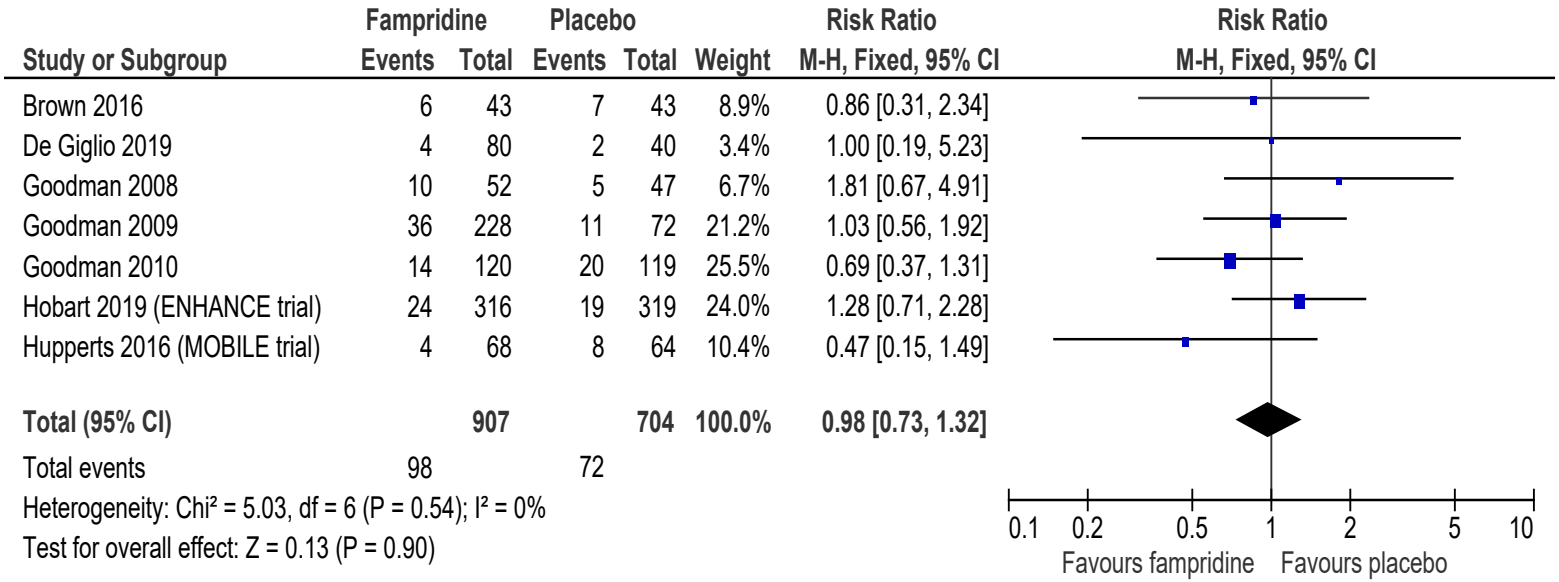
Study or Subgroup	Fampridine Events	Fampridine Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Brown 2016	0	43	0	43	5.4%	0.00 [-0.04, 0.04]
De Giglio 2019	1	80	0	40	6.7%	0.01 [-0.03, 0.06]
Goodman 2009	1	212	0	71	13.5%	0.00 [-0.02, 0.03]
Goodman 2010	0	120	1	119	15.1%	-0.01 [-0.03, 0.01]
Hobart 2019 (ENHANCE trial)	0	266	0	254	32.9%	0.00 [-0.01, 0.01]
Hupperts 2016 (MOBILE trial)	0	68	0	64	8.3%	0.00 [-0.03, 0.03]
Yapundich 2015	0	142	0	143	18.0%	0.00 [-0.01, 0.01]
Total (95% CI)		**931**		**734**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	2		1			

Heterogeneity: Chi² = 1.00, df = 6 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)



Definition varies across studies, with some only reporting those that led to withdrawal and it being unclear whether other minor events may have occurred. Mixture of parallel and crossover trials.

Figure 31: Falls at 4-24 weeks



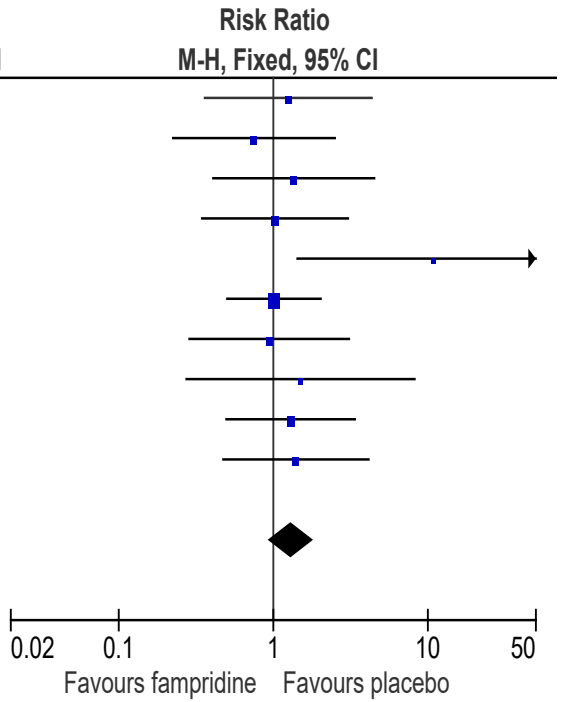
Mixture of parallel and crossover trials.

Figure 32: Headache at 4-24 weeks

Study or Subgroup	Fampridine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brown 2016	5	43	4	43	7.3%	1.25 [0.36, 4.34]
De Giglio 2019	6	80	4	40	9.8%	0.75 [0.22, 2.51]
Goodman 2008	6	52	4	47	7.7%	1.36 [0.41, 4.51]
Goodman 2009	13	228	4	72	11.1%	1.03 [0.35, 3.05]
Goodman 2010	11	120	1	119	1.8%	10.91 [1.43, 83.17]
Hobart 2019 (ENHANCE trial)	15	316	15	319	27.3%	1.01 [0.50, 2.03]
Hupperts 2016 (MOBILE trial)	5	68	5	64	9.4%	0.94 [0.29, 3.10]
Pickering 2017	3	25	2	25	3.7%	1.50 [0.27, 8.22]
Yapundich 2015	9	142	7	143	12.8%	1.29 [0.50, 3.38]
Zorner 2016	7	55	5	55	9.1%	1.40 [0.47, 4.14]
Total (95% CI)		**1129**		**927**	**100.0%**	**1.30 [0.92, 1.82]**
Total events	80		51			

Heterogeneity: Chi² = 6.01, df = 9 (P = 0.74); I² = 0%

Test for overall effect: Z = 1.49 (P = 0.14)

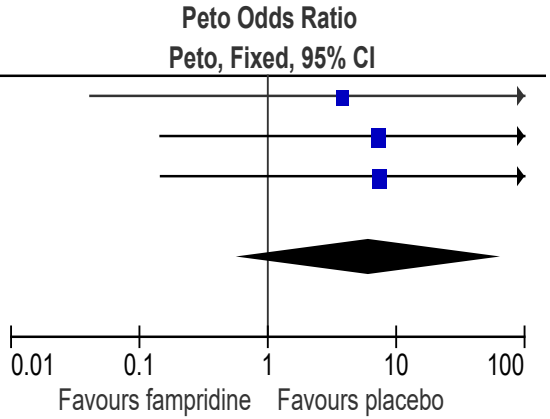


Mixture of parallel and crossover trials.

Figure 33: Fracture at 6-14 weeks

Study or Subgroup	Favours fampridine Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Goodman 2009	1	212	0	71	27.3%	3.80 [0.04, 349.30]
Goodman 2010	1	120	0	119	36.3%	7.33 [0.15, 369.31]
Zorner 2016	1	55	0	55	36.3%	7.39 [0.15, 372.38]
Total (95% CI)		**387**		**245**	**100.0%**	**6.14 [0.58, 65.26]**
Total events	3		0			

Heterogeneity: Chi² = 0.06, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.51 (P = 0.13)

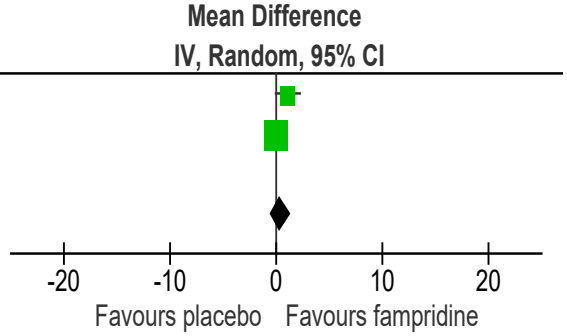


Definition varies across studies, with all studies only reporting those that led to withdrawal and it being unclear whether other minor events may have occurred. Mixture of parallel and crossover trials.

Figure 34: MS Functional Composite score at 12-14 weeks – mixture of change and final scores (scale unclear, higher is better)

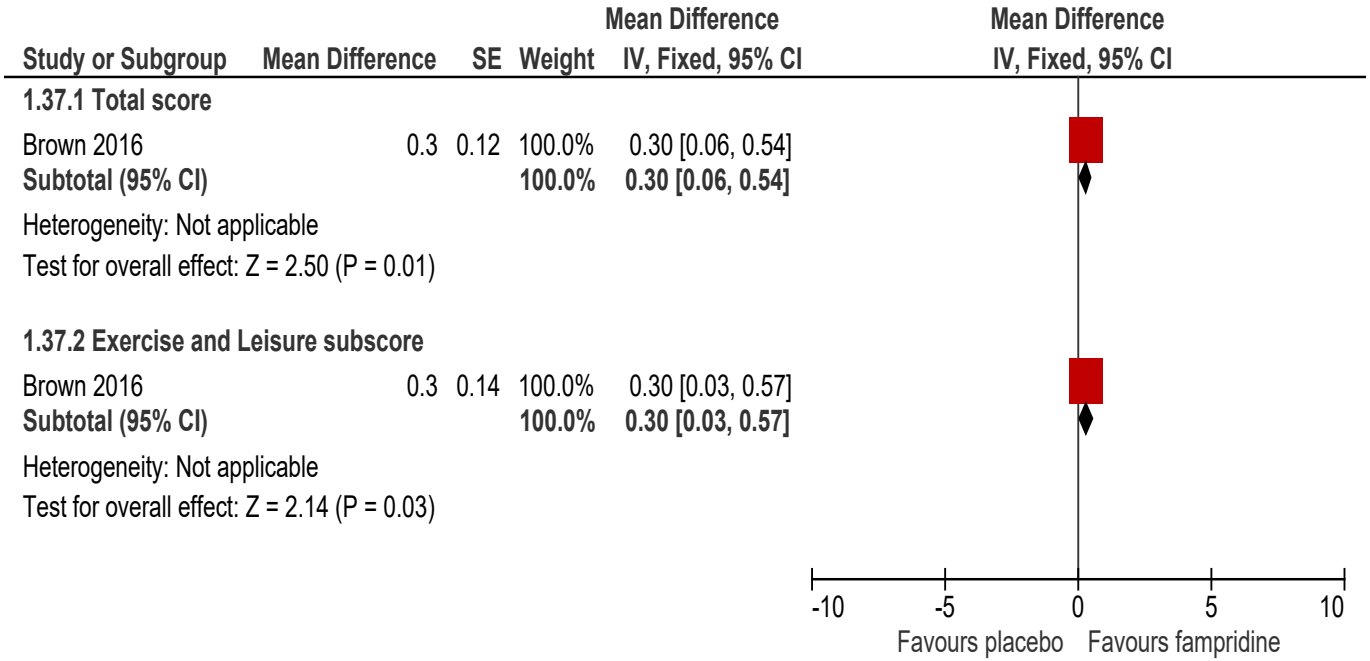
Study or Subgroup	Fampridine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
De Giglio 2019	0.6	2.6833	80	-0.5	3.1623	40	35.5%	1.10 [-0.04, 2.24]
Goodman 2008	0.1	0.31	51	0.08	0.2	46	64.5%	0.02 [-0.08, 0.12]
Total (95% CI)			**131**			**86**	**100.0%**	**0.40 [-0.61, 1.42]**

Heterogeneity: Tau² = 0.41; Chi² = 3.40, df = 1 (P = 0.07); I² = 71%
Test for overall effect: Z = 0.78 (P = 0.43)



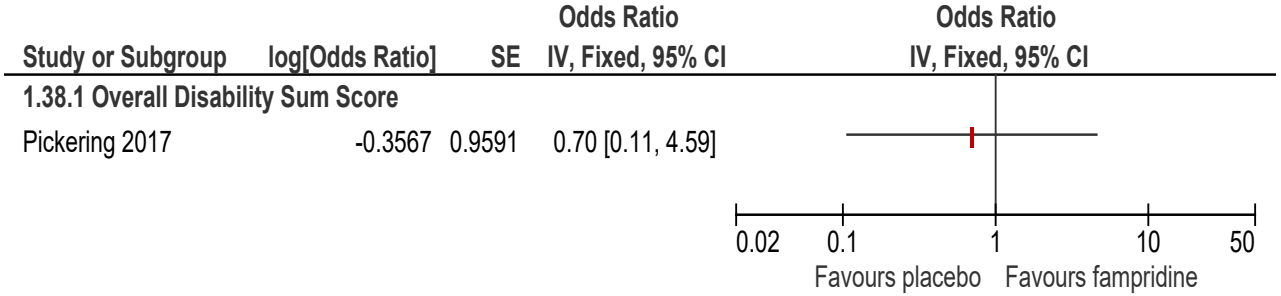
Random effects analysis used and downgraded for unexplained heterogeneity. Parallel trials.

Figure 35: Physical Activity and Disability Survey-Revised (Total score, and Exercise and Leisure sub score) change from baseline at 4 weeks (scale unclear, higher is better)



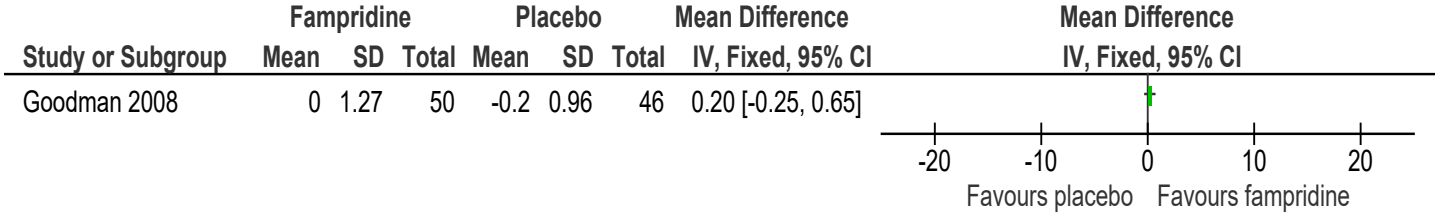
Crossover trial.

Figure 36: Overall Disability Sum Score improvement compared to baseline at 12 weeks



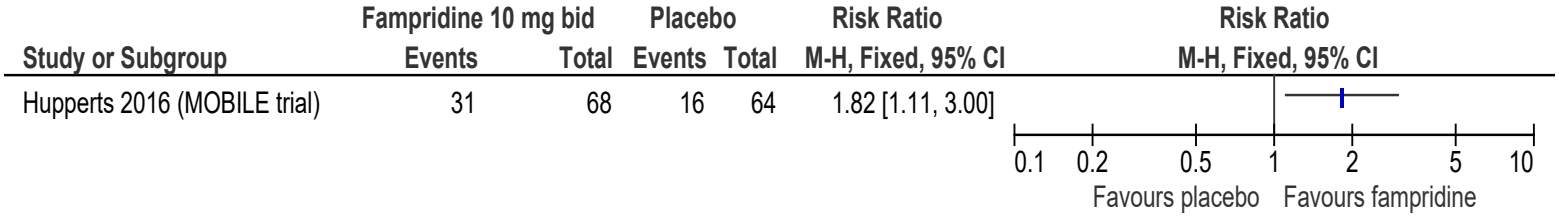
Crossover trial.

Figure 37: Subject Global Impression of Change – change from baseline at 14 weeks (scale 1-7, higher is better)



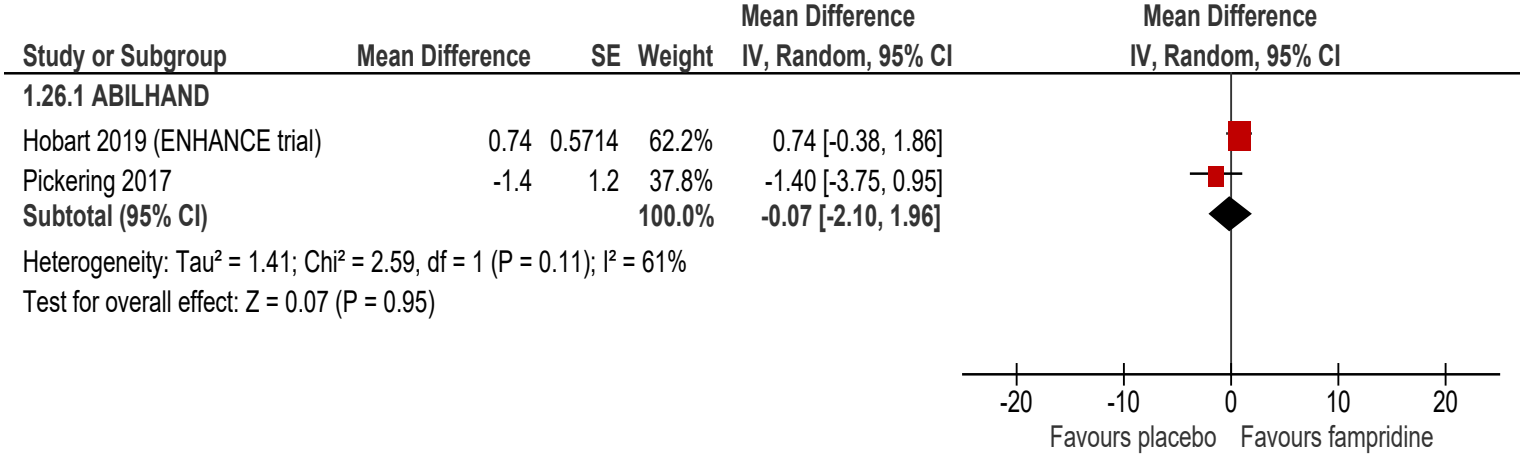
Parallel trial.

Figure 38: Patient Global Impression of Change improvement compared to baseline at 2 weeks



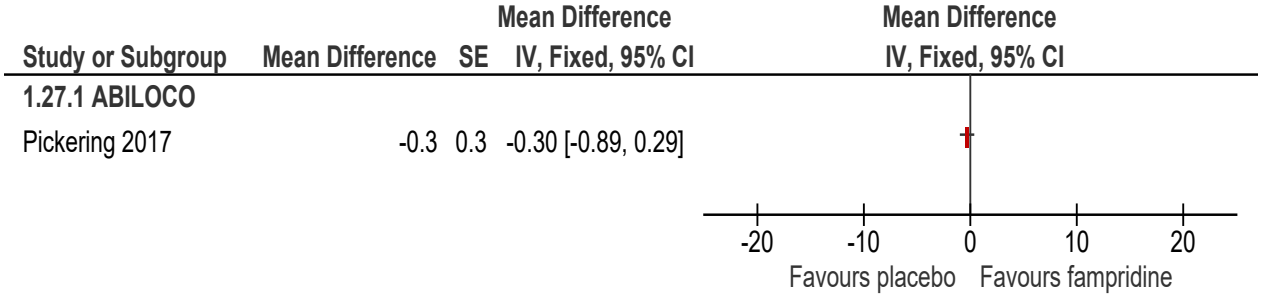
Parallel trial.

Figure 39: ABILHAND score at 12-24 weeks – mixture of change and final scores (scale 0-100, higher is better)



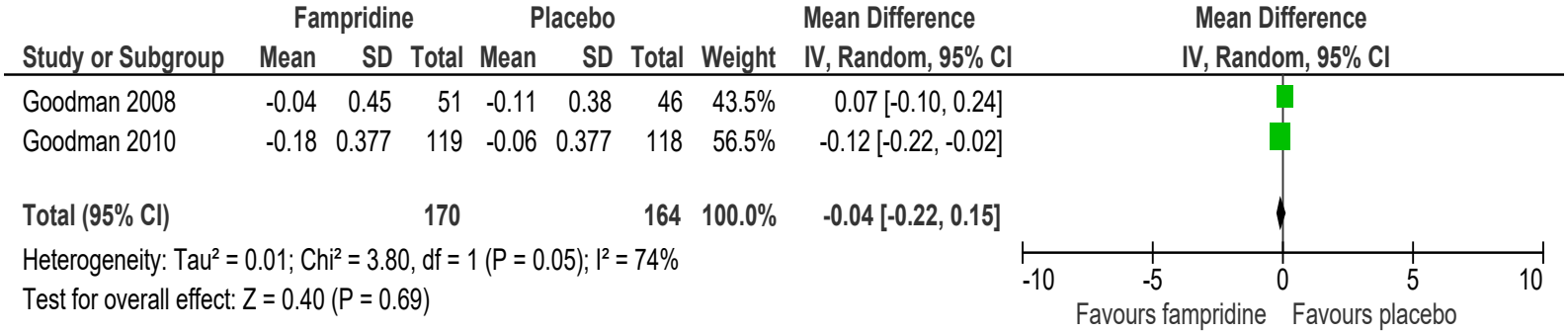
Random effects analysis used and downgraded for unexplained heterogeneity. Mixture of parallel and crossover trials.

Figure 40: ABILOCO score at 12 weeks (scale unclear, higher is better)



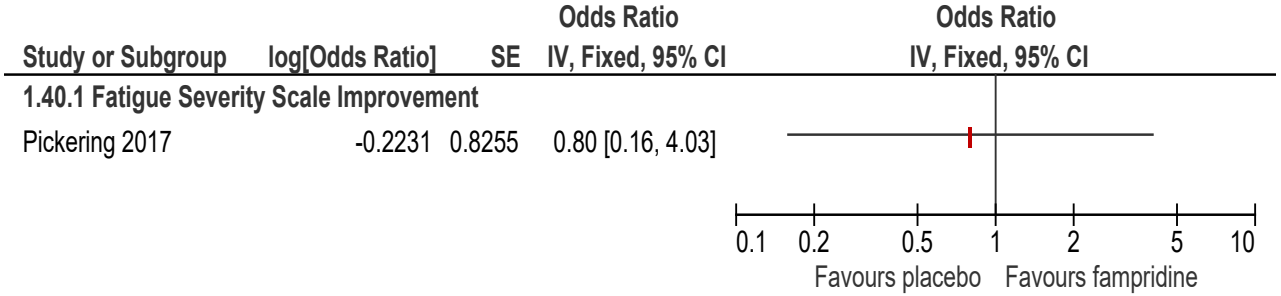
Crossover trial.

Figure 41: Ashworth score (spasticity) change from baseline at 9-14 weeks (scale 0-4, lower is better)



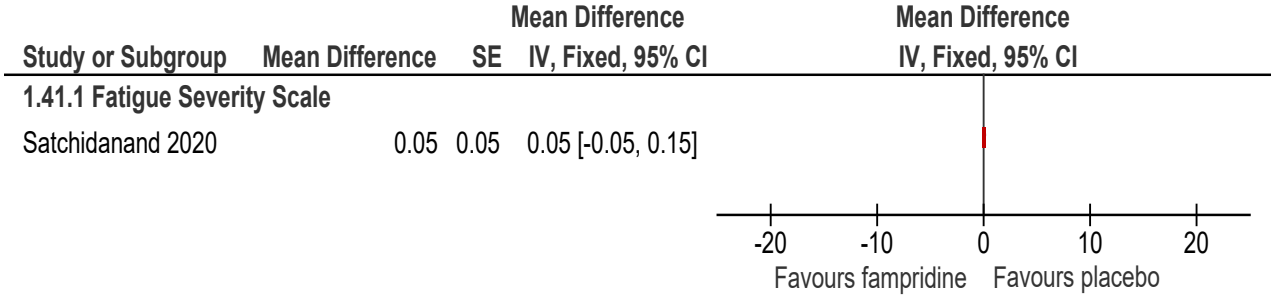
Parallel trials.

Figure 42: Fatigue Severity Scale improvement compared to baseline at 12 weeks



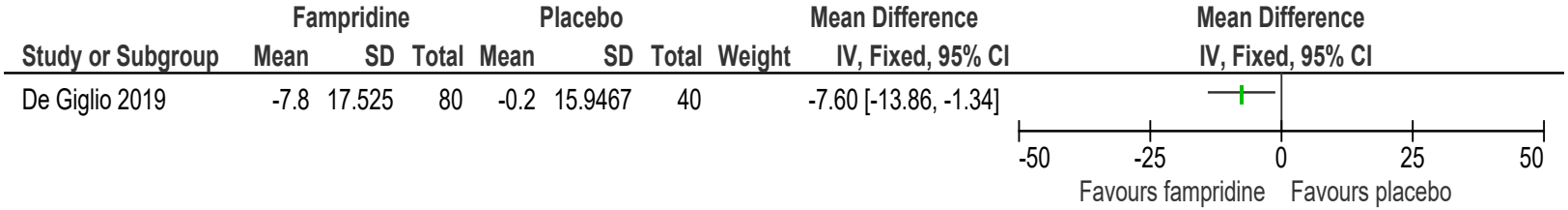
Crossover trial.

Figure 43: Fatigue Severity Scale at 12 weeks (scale 9-63, lower is better)



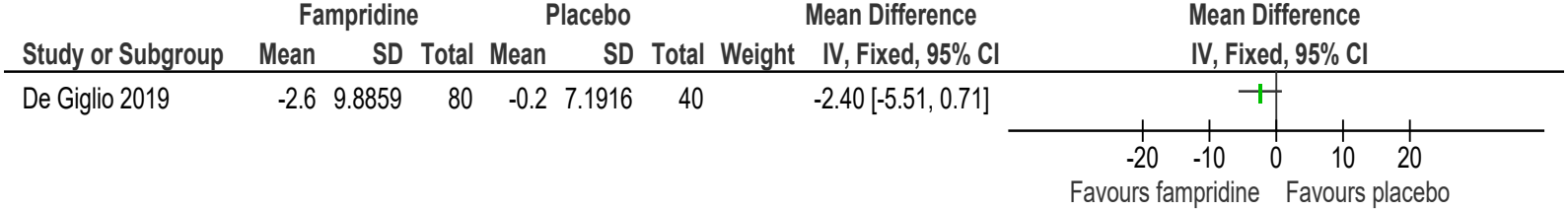
Parallel trial.

Figure 44: Modified Fatigue Impact Scale (Total score) change from baseline at 12 weeks (scale 0-84, lower is better)



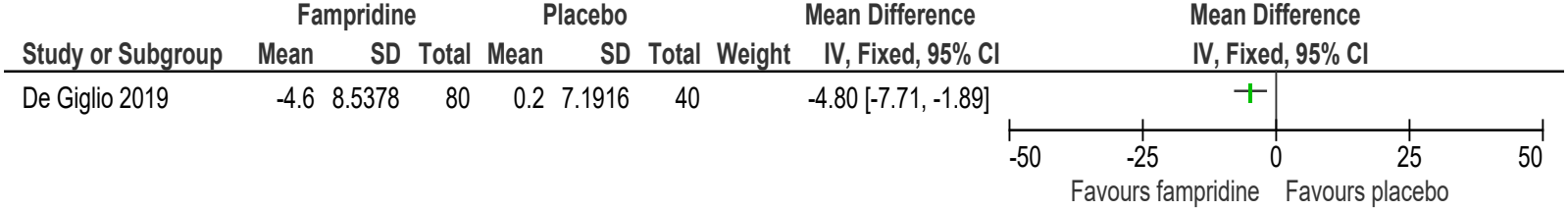
Parallel trial.

Figure 45: Modified Fatigue Impact Scale (Physical subscale) change from baseline at 12 weeks (scale 0-36, lower is better)



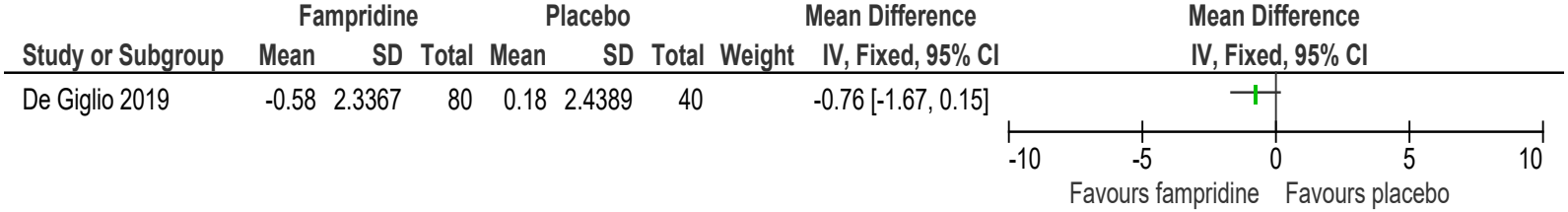
Parallel trial.

Figure 46: Modified Fatigue Impact Scale (Cognitive subscale) change from baseline at 12 weeks (scale 0-40, lower is better)



Parallel trial.

Figure 47: Modified Fatigue Impact Scale (Psychosocial subscale) change from baseline at 12 weeks (scale 0-8, lower is better)



Parallel trial.

Appendix F – GRADE tables

Table 11: Clinical evidence profile: fampridine vs. placebo for mobility in MS

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fampridine	placebo	Relative (95% CI)	Absolute (95% CI)		
6-Minute walk test improvement at 2 weeks compared to baseline - ≥ 55.06 metre improvement (follow-up: 2 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	not serious	none	19/51 (37.3%)	12.2%	**RR 3.04** (1.33 to 6.98)	**250 more per 1,000** (from 40 more to 732 more)	⨁⨁◯◯ Low	CRITICAL
6-Minute walk test improvement at 2 weeks compared to baseline - ≥20% improvement (follow-up: 2 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	not serious	none	23/51 (45.1%)	14.3%	**RR 3.16** (1.49 to 6.68)	**309 more per 1,000** (from 70 more to 812 more)	⨁⨁◯◯ Low	CRITICAL
6-Minute Walk Test - mixture of change and final scores at 4-12 weeks - metres (higher is better) (follow-up: 4-12 weeks)												
4	randomised trials	serious [a]	serious [c]	serious [b]	not serious [d]	none	131	106	-	MD **14.7 higher** (0.08 higher to 29.33 higher)	⨁◯◯◯ Very low	CRITICAL
6-Minute Walk Test at 2 weeks - change from baseline - feet (higher is better) (follow-up: 2 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	not serious [e]	none	51	49	-	MD **86.9 feet higher** (24.46 higher to 149.34 higher)	⨁⨁◯◯ Low	CRITICAL
6-Minute Walk Test at 14 weeks - % change from baseline (higher is better) (follow-up: 14 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fampridine	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [f]	none	21	20	-	MD **5.87 higher** (3.5 lower to 15.24 higher)	⨁◯◯◯ Very low	CRITICAL
Timed 25-Foot Walk test speed improvement of >20% or ≥20% from baseline at 4-14 weeks (follow-up: 4-14 weeks)												
2	randomised trials	serious [a]	not serious	serious [b]	serious [g]	none	72/187 (38.5%)	20.1%	**RR 1.64** (1.20 to 2.25)	**129 more per 1,000** (from 40 more to 252 more)	⨁◯◯◯ Very low	CRITICAL
Timed 25-Foot Walk test speed improvement - faster walking speed for 3/4 on-treatment visits (across 6-14 weeks) compared to max speed during off-treatment visits (follow-up: 6-14 weeks)												
3	randomised trials	serious [a]	not serious	serious [b]	not serious	none	unclear/398 (0.0%)	8.8%	**RR 3.77** (2.56 to 5.55)	**245 more per 1,000** (from 138 more to 402 more)	⨁⨁◯◯ Low	CRITICAL
Timed 25-Foot Walk Test (speed) at 4-14 weeks - mixture of change and final scores (higher is better) (follow-up: 4-14 weeks)												
4	randomised trials	serious [a]	not serious	serious [b]	not serious [h]	none	520	342	-	MD **0.15 higher** (0.09 higher to 0.21 higher)	⨁⨁◯◯ Low	CRITICAL
Timed 25-Foot Walk test speed improvement at 12 weeks (follow-up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [g]	none	14/25 (56.0%)	48.0%	**OR 1.20** (0.24 to 6.12)	**46 more per 1,000** (from 299 fewer to 370 more)	⨁◯◯◯ Very low	CRITICAL
Timed 25-Foot Walk Test (time) at 4-12 weeks - mixture of change and final scores (lower is better) (follow-up: 4-12 weeks)												
4	randomised trials	serious [a]	serious [c]	serious [b]	serious [i]	none	98	160	-	MD **1.16 lower** (2.75 lower to 0.44 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fampridine	placebo	Relative (95% CI)	Absolute (95% CI)		
Timed 8-Metre Walk Test (time) at 14 weeks - % change from baseline (lower is better) (follow-up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [j]	none	21	20	-	MD **8.94 lower** (20.78 lower to 2.9 higher)	⨁◯◯◯ Very low	CRITICAL
Six Spot Step Test (time) change from baseline at 4 weeks (lower is better) (follow-up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	very serious [k]	serious [l]	none	16	19	-	MD **3.85 lower** (8.03 lower to 0.33 higher)	⨁◯◯◯ Very low	CRITICAL
Timed Up and Go test (time) - change from baseline at 4-24 weeks (lower is better) (follow-up: 4-24 weeks)												
2	randomised trials	very serious [a]	not serious	serious [b]	not serious [m]	none	357	360	-	MD **1.11 lower** (1.93 lower to 0.29 lower)	⨁◯◯◯ Very low	CRITICAL
Timed Up and Go test (speed) - change from baseline at 24 weeks (higher is better) (follow-up: 24 weeks)												
1	randomised trials	serious [a]	not serious	not serious	not serious [n]	none	315	318	-	MD **0.02 higher** (0.01 higher to 0.03 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Timed Up and Go test improvement in speed at 24 weeks (follow-up: 24 weeks)												
2	randomised trials	serious [a]	not serious	not serious	serious [g]	none	169/383 (44.1%)	32.4%	**RR 1.30** (1.09 to 1.56)	**97 more per 1,000** (from 29 more to 181 more)	⨁⨁◯◯ Low	CRITICAL
Timed Up and Go test improvement at 12 weeks (unclear whether speed or time but likely time based on baseline value given) (follow-up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fampridine	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [g]	none	17/25 (68.0%)	72.0%	**OR 0.80** (0.15 to 4.14)	**47 fewer per 1,000** (from 442 fewer to 194 more)	⨁◯◯◯ Very low	CRITICAL
MSWS-12 - change from baseline at 4-24 weeks (lower is better) (follow-up: 4-24 weeks; Scale from: 0 to 100)												
5	randomised trials	serious [a]	not serious	not serious	not serious [o]	none	663	660	-	MD **3.12 lower** (4.55 lower to 1.68 lower)	⨁⨁⨁◯ Moderate	CRITICAL
MSWS-12 improvement compared to baseline at 24 weeks (follow-up: 24 weeks)												
2	randomised trials	serious [a]	not serious	not serious	serious [g]	none	169/383 (44.1%)	30.9%	**RR 1.35** (1.12 to 1.62)	**108 more per 1,000** (from 37 more to 192 more)	⨁⨁◯◯ Low	CRITICAL
9-Hole Peg Test - dominant hand (time) at 12-14 weeks - mix of final values and change scores (lower is better) (follow-up: 12-14 weeks)												
2	randomised trials	serious [a]	not serious	not serious	not serious [p]	none	131	86	-	MD **1.79 lower** (5.26 lower to 1.68 higher)	⨁⨁⨁◯ Moderate	CRITICAL
9-Hole Peg Test - non-dominant hand (time) at 12-14 weeks - mix of final values and change scores (lower is better) (follow-up: 12-14 weeks)												
2	randomised trials	serious [a]	not serious	not serious	not serious [q]	none	131	86	-	MD **2.6 lower** (5.77 lower to 0.56 higher)	⨁⨁⨁◯ Moderate	CRITICAL
9-Hole Peg Test - unclear if dominant or non-dominant (time) at 4 weeks (lower is better) (follow-up: 4 weeks)												
1	randomised trials	serious [a]	not serious	very serious [k]	not serious [r]	none	16	19	-	MD **0.9 lower** (3.25 lower to 1.45 higher)	⨁◯◯◯ Very low	CRITICAL
9-Hole Peg Test right-hand improvement compared to baseline at 12 weeks (follow-up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fampridine	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [g]	none	15/22 (68.2%)	77.3%	**OR 0.63** (0.16 to 2.41)	**91 fewer per 1,000** (from 420 fewer to 119 more)	⨁◯◯◯ Very low	CRITICAL
9-Hole Peg Test left-hand improvement compared to baseline at 12 weeks (follow-up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [g]	none	15/25 (60.0%)	60.0%	**OR 1.20** (0.24 to 5.97)	**43 more per 1,000** (from 335 fewer to 300 more)	⨁◯◯◯ Very low	CRITICAL
MSIS-29 - mix of change and final scores at 12-24 weeks (one is clearly physical subscale unclear if other is the same or overall score; lower is better) (follow-up: 12-24 weeks; Scale from: 0 to 100)												
2	randomised trials	serious [a]	not serious	not serious	not serious [s]	none	395	358	-	MD **3.31 lower** (5.09 lower to 1.52 lower)	⨁⨁⨁◯ Moderate	CRITICAL
MSIS-29 PHYS improvement compared to baseline at 24 weeks (follow-up: 24 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [g]	none	31/68 (45.6%)	29.7%	**RR 1.54** (0.97 to 2.43)	**160 more per 1,000** (from 9 fewer to 425 more)	⨁◯◯◯ Very low	CRITICAL
Mortality during treatment period 4-24 weeks (follow-up: 4-24 weeks)												
3	randomised trials	serious [a]	not serious	not serious	very serious [t]	none	1/620 (0.2%)	0.2%	**RD 0.00** (-0.01 to 0.01)	**0 fewer per 1,000** (from 10 fewer to 10 more) [u]	⨁◯◯◯ Very low	CRITICAL
Adverse events leading with withdrawal 4-24 weeks (follow-up: 4-24 weeks)												
12	randomised trials	serious [a]	not serious	not serious	very serious [t]	none [v]	66/1118 (5.9%)	2.3%	**RD 0.02** (0.00 to 0.04)	**20 more per 1,000** (from 0 fewer to 40 more) [u]	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fampridine	placebo	Relative (95% CI)	Absolute (95% CI)		
Urinary tract infection 4-24 weeks (follow-up: 4-24 weeks)												
9	randomised trials	serious [a]	not serious	not serious	serious [g]	none	138/1081 (12.8%)	10.0%	**RR 1.18** (0.89 to 1.56)	**18 more per 1,000** (from 11 fewer to 56 more)	⨁⨁◯◯ Low	CRITICAL
Confusional state (reports as reason for 1 withdrawing from study, unclear whether any more minor events occurred) 14 weeks (follow-up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [g]	none	1/212 (0.5%)	0.0%	**OR 3.80** (0.04 to 349.30)	**5 more per 1,000** (from 18 fewer to 27 more) [u]	⨁◯◯◯ Very low	CRITICAL
Seizures (definition varies across studies with some only reporting those that led to withdrawal and unclear if any less serious events occurred) 4-24 weeks (follow-up: 4-24 weeks)												
7	randomised trials	very serious [a]	not serious	not serious	very serious [t]	none	2/931 (0.2%)	0.1%	**RD 0.00** (-0.01 to 0.01)	**0 fewer per 1,000** (from 10 fewer to 10 more) [u]	⨁◯◯◯ Very low	CRITICAL
Falls 4-24 weeks (follow-up: 4-24 weeks)												
7	randomised trials	serious [a]	not serious	not serious	very serious [g]	none	98/907 (10.8%)	12.5%	**RR 0.98** (0.73 to 1.32)	**3 fewer per 1,000** (from 34 fewer to 40 more)	⨁◯◯◯ Very low	CRITICAL
Headache 4-24 weeks (follow-up: 4-24 weeks)												
10	randomised trials	very serious [a]	not serious	not serious	serious [g]	none [v]	80/1129 (7.1%)	7.9%	**RR 1.30** (0.92 to 1.82)	**24 more per 1,000** (from 6 fewer to 65 more)	⨁◯◯◯ Very low	CRITICAL
Fracture (definition varies across studies and all only report those that led to withdrawal, unclear if any more serious events occurred) 6-14 weeks (follow-up: 6-14 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fampridine	placebo	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	very serious [a]	not serious	serious [b]	very serious [g]	none	3/387 (0.8%)	0.0%	**OR 6.14** (0.58 to 65.26)	**10 more per 1,000** (from 10 fewer to 30 more) [u]	⨁◯◯◯ Very low	CRITICAL
MSFC total score at 12-14 weeks - mix of change and final values (higher is better) (follow-up: 12-14 weeks)												
2	randomised trials	serious [a]	serious [w]	not serious	serious [x]	none	131	86	-	MD **0.4 higher** (0.61 lower to 1.42 higher)	⨁◯◯◯ Very low	CRITICAL
PADS-R change from baseline at 4 weeks - Total score (higher is better) (follow-up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [y]	none	42	42	-	MD **0.3 higher** (0.06 higher to 0.54 higher)	⨁◯◯◯ Very low	CRITICAL
PADS-R change from baseline at 4 weeks - Exercise and Leisure sub score (higher is better) (follow-up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [z]	none	42	42	-	MD **0.3 higher** (0.03 higher to 0.57 higher)	⨁◯◯◯ Very low	CRITICAL
Overall Disability Sum Score improvement compared to baseline at 12 weeks (follow-up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [g]	none	17/25 (68.0%)	72.0%	**OR 0.70** (0.11 to 4.59)	**77 fewer per 1,000** (from 500 fewer to 202 more)	⨁◯◯◯ Very low	CRITICAL
Subject Global Impression of Change - change from baseline at 14 weeks (higher is better) (follow-up: 14 weeks; Scale from: 1 to 7)												
1	randomised trials	serious [a]	not serious	not serious	very serious [aa]	none	50	46	-	MD **0.2 higher** (0.25 lower to 0.65 higher)	⨁◯◯◯ Very low	CRITICAL
Patient Global Impression of Change improvement compared to baseline at 2 weeks (follow-up: 2 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fampridine	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [g]	none	31/68 (45.6%)	25.0%	**RR 1.82** (1.11 to 3.00)	**205 more per 1,000** (from 28 more to 500 more)	⨁◯◯◯ Very low	CRITICAL
ABILHAND at 12-24 weeks - mix of change and final scores (higher is better) (follow-up: 12-24 weeks; Scale from: 0 to 100)												
2	randomised trials	serious [a]	serious [w]	not serious	not serious [ab]	none	337	340	-	MD **0.07 lower** (2.1 lower to 1.96 higher)	⨁⨁◯◯ Low	CRITICAL
ABILOCO at 12 weeks (higher is better) (follow-up: 12 weeks)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	25	25	-	MD **0.3 lower** (0.89 lower to 0.29 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Ashworth score change from baseline at 9-14 weeks (lower is better) (follow-up: 9-14 weeks; Scale from: 0 to 4)												
2	randomised trials	very serious [a]	serious [w]	serious [b]	not serious	none	170	164	-	MD **0.04 lower** (0.22 lower to 0.15 higher)	⨁◯◯◯ Very low	CRITICAL
Fatigue Severity Scale improvement compared to baseline at 12 weeks (follow-up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [g]	none	8/25 (32.0%)	36.0%	**OR 0.80** (0.16 to 4.03)	**50 fewer per 1,000** (from 277 fewer to 334 more)	⨁◯◯◯ Very low	CRITICAL
Fatigue Severity Scale at 12 weeks (lower is better) (follow-up: 12 weeks; Scale from: 9 to 63)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ac]	none	16	41	-	MD **0.05 higher** (0.05 lower to 0.15 higher)	⨁◯◯◯ Very low	CRITICAL
Modified Fatigue Impact Scale change from baseline at 12 weeks - Total score (lower is better) (follow-up: 12 weeks; Scale from: 0 to 84)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fampridine	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [ad]	none	80	40	-	MD **7.6 lower** (13.86 lower to 1.34 lower)	⨁⨁◯◯ Low	CRITICAL
Modified Fatigue Impact Scale change from baseline at 12 weeks - Physical subscale (lower is better) (follow-up: 12 weeks; Scale from: 0 to 36)												
1	randomised trials	serious [a]	not serious	not serious	serious [ae]	none	80	40	-	MD **2.4 lower** (5.51 lower to 0.71 higher)	⨁⨁◯◯ Low	CRITICAL
Modified Fatigue Impact Scale change from baseline at 12 weeks - Cognitive subscale (lower is better) (follow-up: 12 weeks; Scale from: 0 to 40)												
1	randomised trials	serious [a]	not serious	not serious	serious [af]	none	80	40	-	MD **4.8 lower** (7.71 lower to 1.89 lower)	⨁⨁◯◯ Low	
Modified Fatigue Impact Scale change from baseline at 12 weeks - Cognitive subscale (lower is better) (follow-up: 12 weeks; Scale from: 0 to 8)												
1	randomised trials	serious [a]	not serious	not serious	serious [af]	none	80	40	-	MD **0.76 lower** (1.67 lower to 0.15 higher)	⨁⨁◯◯ Low	

a. Downgraded by 1 increment if there were some concerns about the majority of the evidence, and downgraded by 2 increments if the majority of the evidence was at high risk of bias

b. Downgraded by 1 increment as the majority of the evidence reports the outcome at a time-point <3 months

c. Downgraded by 1 increment due to unexplained heterogeneity based on point estimates differing between the studies. Although all four studies have the same direction of effect the size of the difference varies.

d. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±31.34.

e. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±187.88.

f. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MIDs calculated by multiplying the control group SD for % baseline change by 0.5 and were ±9.02

g. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Default values of 0.80 and 1.25 for dichotomous outcomes.

h. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±0.38.

i. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±1.90.

j. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MIDs calculated by multiplying the control group SD for % baseline change by 0.5 and were ±11.47.

k. Downgraded by 2 increments as population randomised was selected from people identified as fampridine responders in a previous open-label phase and may not represent the general population interested in and outcome reported at a time-point <3 months

l. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±5.33.

m. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±13.03.

n. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±0.098.

o. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±10.85.

p. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±9.80.

q. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±7.55.

r. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±5.53.

s. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±10.98.

t. Downgraded by 2 increments as imprecision was considered to be very serious based on an OIS of <80%. Imprecision was assessed based on calculated OIS value due to zero events in both arms of some studies.

u. Absolute effect calculated manually using risk difference due to zero events in one or both arms of at least one study.

v. Publication bias not assessed as evidence already graded very low quality

w. Downgraded by 1 increment due to unexplained heterogeneity based on point estimates differing in direction and a high I2 value.

x. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±0.69.

y. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±0.57.

z. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. As there were no baseline or final value SDs reported, MIDs were calculated by multiplying the SD of the mean difference by 0.5 and were ±0.32.

aa. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±0.22.

ab. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±7.90.

ac. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. As there were no baseline or final value SDs reported, MIDs were calculated by multiplying the SD of the mean difference by 0.5 and were ±0.08.

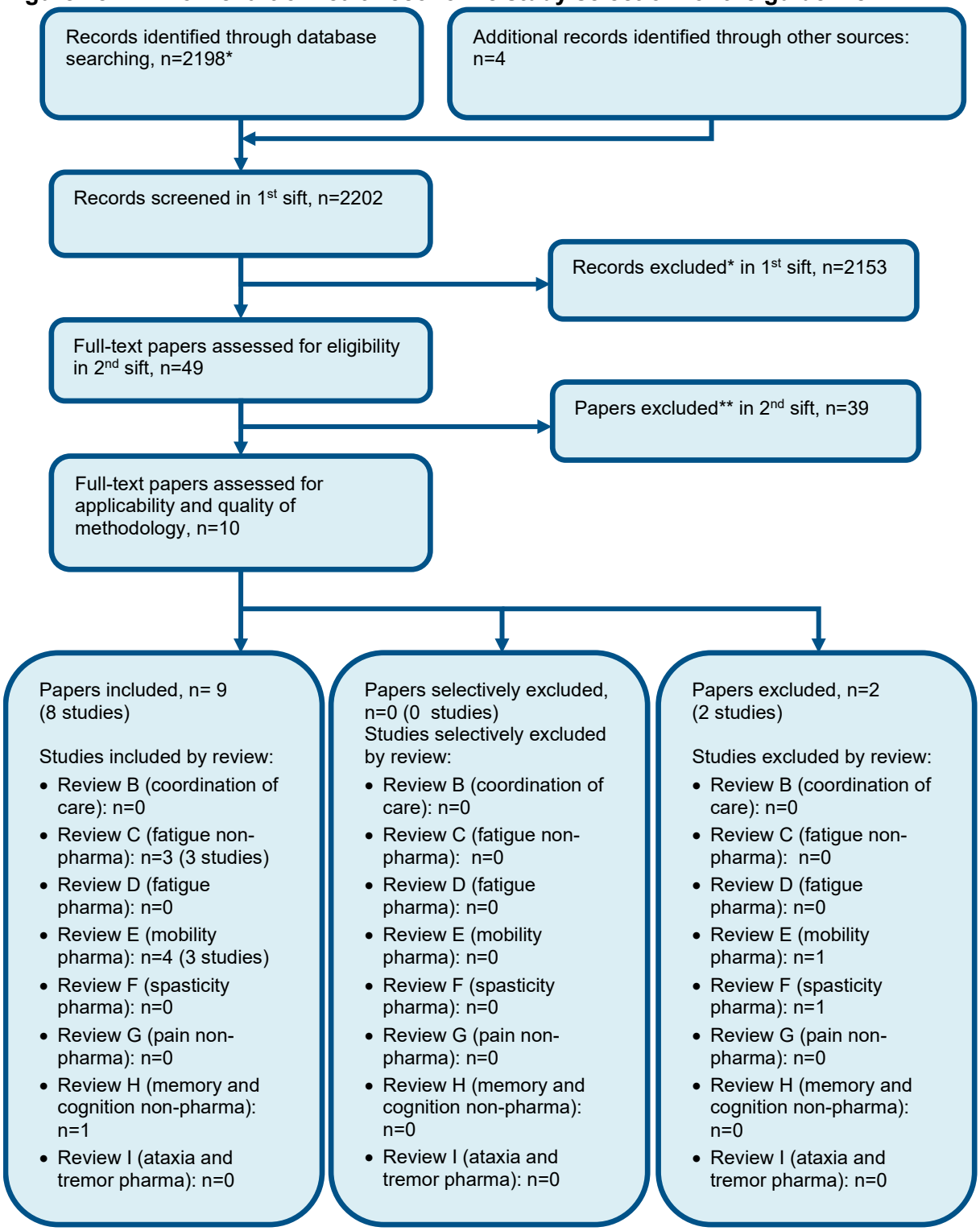
ad. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MIDs calculated by multiplying the median baseline SD across groups of those studies that reported baseline values by 0.5 and were ±4.43.

ae. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. As there were no baseline value SDs reported, MIDs were calculated by multiplying the SD final value for the control group by 0.5 and were ±3.60.

af. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. As no baseline values were reported and there is only a single study, to assess imprecision the analysis was switched to standardised mean difference and ±0.5 used.

Appendix G – Economic evidence study selection

Figure 48: Flow chart of health economic study selection for the guideline



* Excluding conference abstracts.
**Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

Study	Scottish Medicines Consortium 2020[40, 41]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (health outcome: QALYs) **Study design:** Decision tree with responder and non-responder status determined at 4 weeks, followed by a cohort Markov model to simulate outcomes with and without fampridine treatment. **Approach to analysis:** The Markov model contained three health states: response, non-response and death and a 4-week cycle length. People could withdraw from treatment following the initial 4-week assessment, and discontinued fampridine treatment if EDSS >7, which is proxied in the model by walking speed	**Population:** Adults with MS with walking disability (EDSS scores 4-7) **Cohort settings:** Median age: 48.9 years Male: NR **Intervention 1:** Best supportive care (BSC) **Intervention 2:** Fampridine treatment (10mg orally twice daily)	**Total costs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): £2,105 (95% CI: NR; p=<NR) **Currency & cost year:** 2020 UK pounds (2018 UK pounds for 2018 submission, presented in analysis of uncertainty) **Cost components incorporated:** Medicine acquisition (including a Patient Access Scheme (PAS)), monitoring and response assessment for fampridine, background resource use (GP and outpatient visits, inpatient days and emergency	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.16 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £13,156 95% CI: NR Probability that Intervention 2 was cost effective (£20k/30k threshold): NR **Analysis of uncertainty:** Results were most sensitive to the assumption that utility values persisted between week 24 to the 5-year time horizon and the withdrawal rate of BSC, when varying by 95% confidence intervals. Eight scenario analyses conducted. Scenario analyses with the greatest upward impact on the ICER were the use of utility values derived from EQ-5D-3L data from the ENHANCE study or where treatment-specific utility differences were removed from the model. Scenario | Incremental QALYs | ICER (with PAS) 1. Utilities based on EQ-5D-3L valuation set (based on ENHANCE) | 0.08 | £25,690

measured by the timed 25-foot walk (T25FW) dropping to zero. **Perspective:** NHS Scotland **Time horizon:** 5 years **Treatment effect duration:**[(a)] 24 weeks, extrapolated to 5 years **Discounting:** Costs: NR Outcomes: NR		hospital visits), and adverse events.		2. Week 16 utilities applied from week 24	0.19	£11,042
				3. Utility values applied for non-responders with no difference assumed in non-responder utility value by treatment arm (based on MOBILE) *	0.07	£28,942
				4. Utility values applied for both responders and non-responders with no difference in utility values assumed by treatment arm (based on MOBILE) *	0.04	£58,792
				5. Utility values applied for non-responders with no difference assumed in non-responder utility value by treatment arm (based on EQ-5D-3L from ENHANCE) *	0.06	£36,066
				6. Increase the time horizon to 10 years	0.28	£10,722
				7. Direct costs decrease by 25%	0.16	£16,116
				8. Societal perspective for costs	0.16	£12,587
				*Baseline utility set to the same utility for all patients, based on BSC non-responders **2018 SMC submission [40]:** A prior submission of this economic model to the SMC in 2018 reported the ICER using the list price for (instead of with a		

				PAS). The ICER was £44,739 when the MOBILE utility data was used (EQ5D-5L, not mapped to EQ5D-3L) and £149,659 when the ENHANCE utility data was used (EQ5D-3L). They included a number of other scenarios, including using the MOBILE EQ5D-5L mapped to EQ5D-3L, the ICER was £92,961.

Data sources

Health outcomes: The key clinical data used in the model were taken from the double-blind phase III ENHANCE study, which determined response rates for the first 24 weeks and the baseline patient demographics applied in the economic model, as well as adverse events. The ENHANCE study recruited adults (18 to 70 years) with multiple sclerosis as defined in the revised McDonald criteria for at least three months, investigator-assessed walking impairment and an expanded disability status scale (EDSS) score of 4 to 7. Randomisation was stratified by EDSS score (≤6 or >6) at screening, and after a protocol amendment, also by prior aminopyridine use (yes or no). Patients were equally assigned to fampridine 10mg orally twice daily for 24 weeks or placebo. The double-blind phase II MOBILE study, a pooled analysis of MS-F203EXT & MS-F204EXT studies, and the IMPACT study were also used to determine model parameters including discontinuation rates, health state utilities, and disease progression (T25FW). The definition of response and responder rates used in the base case analysis were taken from the ENHANCE study with response defined as a ≥8-point improvement on the MSWS-12 over 24 weeks. A pooled analysis of MS-F203EXT & MS-F204EXT studies was used to determine fampridine initial 4-week withdrawal rate (0.73%) as well as T25FW for responders in both treatment arms, while the IMPACT study was used for T25FW for non-responders. Over the base-case model time horizon it is assumed no patients would progress to EDSS score >7. **Quality-of-life weights:** Utility estimates were derived from the EQ-5D-5L data collected within the MOBILE study and mapped to the EQ-5D-3L using an algorithm by Van Hout 2012. This was analysed by treatment arm, with the EQ-5D-5L data in the placebo arm of the MOBILE study used as a proxy for the BSC alone comparator. Data were applied at baseline and weeks 2, 4, 8, 12, 16, 20 and 24, for each treatment by responders and non-responders. Beyond 24 weeks, extrapolation over the model time horizon used the last recorded EQ-5D values from week 24 carried forward. **Cost sources:** Costs included medicine acquisition (inclusive of a patient access scheme discount), monitoring and response assessment for fampridine, background resource use, and adverse events. Administration costs associated with fampridine were assumed as zero due to it being an oral treatment. Resource use estimates for responder and non-responders included GP and outpatient visits, inpatient days and emergency hospital visits. These were based on a published study by Adelphi data 2011, based on EDSS score, and assumed the same for both treatment arms. Medicine prices were those available at the time the papers were issued to SMC for consideration in February 2020. Note cost of fampridine with a patient access scheme were commercial in confidence and therefore not reported.

Comments

Source of funding: The Scottish Medicines Consortium summarized a model that was developed and submitted by Biogen **Limitations:** Utility estimates were derived from the EQ-5D-5L and mapped to the EQ-5D-3L using an algorithm. No discounting reported. Intervention effects and outcomes were obtained from several RCTs. The reason for selecting certain outcomes from certain trials was not provided and so it was difficult to assess the extent to which bias may have been introduced without referring to primary studies. The analysis was based on three out of fifteen trials included in the clinical review and has not used meta-analysed results in its analysis and so may not reflect the full body of clinical evidence available. Only the cost of the intervention differed; all other resources were assumed the same for both treatment arms. The cost of fampridine (and therefore total costs) were

withheld from the report due to commercial sensitivity. Total and incremental costs were not reported; incremental costs were back calculated given incremental QALYs and ICER. Deterministic scenario analysis was completed, and results were reported but no probabilistic sensitivity analyses were not conducted/reported. SMC authors did not include a declaration of conflicts of interest, though presumably this is publicly available through their website. **Other:** Manufacturer-submitted costing data (including a patient access scheme discount) was withheld from the SMC report due to commercial confidentiality.

Overall applicability:(b) Partially applicable **Overall quality:**(c) Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; BSC, best supportive care; CUA= cost utility analysis; da= deterministic analysis; EDSS = Expanded Disability Status Scale; *ICER= incremental cost-effectiveness ratio; NA = not applicable; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years.*

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

The SMC summarised the following as the main weaknesses with the analysis:

- The ICER results are upwardly sensitive to using the EQ-5D-3L from ENHANCE (£25,690/QALY) versus the EQ-5D (3L or 5L) data from MOBILE. The company asserted that the EQ-5D-3L is not sensitive enough to capture changes in quality of life in patients treated with fampridine due to the limited number of response categories in the questionnaire. It remains uncertain whether the EQ-5D-3L, or EQ-5D-5L mapped to the EQ-5D-3L predicts a more reliable estimate of utility outcomes or whether differences in utility data are in part due to the MOBILE study having a better response than the ENHANCE study.
- Utility values are modelled separately for responders and non-responders in each treatment arm. The submitting company justified this assumption with recourse to trial data showing not just more responders with fampridine than BSC but also that there is a greater absolute difference from baseline in the MSWS-12 between fampridine responders and BSC responders. While this is noted, it remains an area of uncertainty and leads to increased ICERs when applying the same utility values by treatment arm for responders and non-responders.
- Beyond week 24 in the model, the company estimated long-term utilities by carrying the last observed value (week 24) forward and assuming these utility values apply for the remainder of the time horizon. This approach is not aligned with the modelled time-horizon, which is longer than the observation period, therefore the degree to which this approach reflects utility in the patient population beyond 24 weeks is uncertain. The ICER is sensitive to the EQ-5D data time point applied over the model time horizon.
- The model combines a range of data sources and the compatibility of these data sources in terms of outcome measures (using MSWS-12 for efficacy and T25FW for progression) and patient characteristics is uncertain.
- There is some imbalance in the treatment and control groups at baseline in the key data source for the base case utility weights (the MOBILE study). The mean time since diagnosis was 12.4 years in the control (BSC) group and 10.9 years in the treatment (fampridine) group. This could lead to bias with patients perhaps being healthier, with less time to progression, in the fampridine arm than BSC.

Study	National Institute for Health and Care Excellence, P.188, 2014[28]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Simple cost-utility analysis (health outcome: QALYs) **Study design:** Simple cost utility analysis based on RCT by Goodman et al. (2008, 2010). **Approach to analysis:** EQ-5D improvement of patients who were given fampridine for 9 weeks was compared to a control group receiving a placebo. **Perspective:** UK NHS **Time horizon:** 1 year **Treatment effect duration:**[(a)] 9-week data extrapolated to 1 year. **Discounting:** Costs: NA	**Population:** Adults with MS who have responded to treatment with fampridine **Cohort settings:** Median age: NR Male: NR **Intervention 1:** Best Supportive care **Intervention 2:** Fampridine treatment (10mg orally twice daily for 9 weeks)	**Total costs (mean per patient):** Intervention 1: £0 Intervention 2: £4,719 Incremental (2−1): £4,716 **Currency & cost year:** 2014 UK pounds **Cost components incorporated:** Only drug costs were included in the analysis. Non-responder costs and adverse event costs have not been included.	**QALYs (mean per patient):** Intervention 1: -0.0032 Intervention 2: 0.0262 Incremental (2−1): 0.029	**ICER (Intervention 2 versus Intervention 1):** £160,884 **Analysis of uncertainty:** Sensitivity analysis conducted using EQ-5D improvement for fampridine versus control from Macdonell 2003. ICER was £133,361. Threshold analysis: change in incremental EQ-5D needed for the ICER to decrease to £20,000/QALY was 0.236. Assuming baseline MSWS-12 scores and MSWS-12 score at 9 weeks in the placebo group are unchanged, this corresponds to a decrease in the MSWS-12 score in the fampridine responders' group by 52.11 (compared to the 6.04 reported in the study). Given the magnitude of the QALY gained required for fampridine to be cost-effective relative to the QALY gained observed and the limited number of inputs in the model, it was deemed unnecessary to quantify uncertainty probabilistically.

Outcomes: NA				Fampridine would be even less cost-effective for a group of patients who had not yet been assessed as being responders to fampridine. That is the effectiveness of the drug would be diluted in a broader group which included non-responders also and the cost of identifying these (initial assessment over 4 weeks) would need to be included to overall costs.

Data sources

Health outcomes: Clinical data from Goodman et al. (2010) was used to inform the model. This was a 39-center, double-blind trial in patients with definite MS of any course type. Participants were randomized to 9 weeks of treatment with dalfampridine (10mg twice daily; n = 120) or placebo (n = 119). Response was defined as consistent improvement on the Timed 25-Foot Walk, with percentage of timed walk responders (TWRs) in each treatment group as the primary outcome. Post hoc analyses were performed to measure the change from the baseline score of the 12-item Multiple Sclerosis Walking Scale (MSWS-12) during the double-blind treatment period. **Quality-of-life weights:** A systematic search of quality of life (QoL) studies was conducted and a study (Hawton et al. (2012)) was found which provided a mapping function to estimate EQ-5D scores from MSWS-12 scores. 21 regression models were estimated using MSWS-12 and EQ-5D data collected in a longitudinal cohort study of 560 individuals with MS in the UK followed up for 6 months. The best performing model was selected by comparing the models' estimation errors which is the difference between the actual EQ-5D score for an individual and the relative EQ-5D score estimated using the model. The best performing model, based on aggregate data, was selected. The EQ-5D values were estimated at baseline and follow-up time using the algorithm developed by Hawton et al. (2012). QALY gain with fampridine was estimated assuming the effectiveness throughout the year is similar to the effectiveness observed at 9 weeks (i.e., the difference in MSWS-12 scores and therefore in EQ-5D between fampridine and placebo is constant). Since the time horizon of the analysis was one year and it is assumed no one dies in that time, the QALY gain corresponds to the improvement in EQ-5D value (0.029). **Cost sources:** Unit Drug costs were taken from Monthly Index of Medical Specialities (MIMS), 2013. *Assessment costs (4-week responder identification) were not included in the analysis but were presented separately for illustrative purposes. There were estimated to be between £274 and £544 per patient and were calculated from a 2012 analysis by North East Treatment Advisory Group (NETAG).*

Comments

Source of funding: National Institute for Health and Care Excellence (NICE). **Limitations:** The base case relies on a single RCT with a limited number of participants and all the limitations of the clinical data also apply to the economic analysis. This is one of fourteen trials included in the clinical review and therefore does not reflect the full body of clinical evidence. Utilities were estimated by mapping a condition-specific measure to a generic quality of life measure. This is associated with several limitations and uncertainty, as important domains could be lost in the mapping algorithm. As MSWS-12 only assesses mobility it may be that other treatment effects are not captured (mobility is one domain of EQ-5D, other are self-care, usual activities, pain/discomfort and anxiety and depression). Furthermore, the mapping function had not been validated. Of note, a sensitivity analysis was conducted using EQ-5D data reported directly from people receiving fampridine. This study had limitations as it was a non-randomised trial where fampridine non-responders were used as controls to fampridine responders. The incremental QALY gain using this direct data was greater than when using the mapped data, thus indicating that fampridine may have treatment effects other than improvements in mobility. Despite the greater QALY gain observed using the

direct data, it was not sufficient to make fampridine cost-effective at £20,000 per QALY. Even if there had been evidence to suggest that fampridine delayed deterioration of mobility and therefore decreased healthcare utilisation, the GC on CG186 felt that it was unlikely that these downstream cost savings would offset the cost of fampridine. Finally, fampridine was associated with a higher risk of adverse events compared to placebo; the possible impact of these on quality of life is not captured in the analysis. Incorporating this may make fampridine even less cost-effective compared to placebo.

Other: In the RCT that was the basis of this analysis (Goodman (2010), 57% of the individuals randomised to the fampridine group did not respond to treatment.

Overall applicability:[c] Partially applicable **Overall quality:**[d] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost utility analysis; da= deterministic analysis; *ICER= incremental cost-effectiveness ratio; NA = not applicable; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years.*

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Acosta 2011[1]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (health outcome: QALYs) **Study design:** Markov model was used to simulate outcomes with and without fampridine treatment. **Approach to analysis:** The Markov model contained five health states and a 4-week cycle length. The PR-	**Population:** Adults with MS with walking disability (EDSS scores 4-7) **Cohort settings:** Median age: 48.9 years Male: 42% **Intervention 1:** Best supportive care (BSC) **Intervention 2:** Fampridine treatment (10mg orally twice daily)	**Total costs (mean per patient over 20 years):** Intervention 1: £165,009 Intervention 2: £166,258 Incremental (2−1): £1,249 (95% CI: NR; p=<NR) **Currency & cost year:**	**QALYs (mean per patient):** Intervention 1: 9.15 Intervention 2: 9.27 Incremental (2−1): 0.12	**ICER (Intervention 2 versus Intervention 1):** £10,411 Probability that Intervention 2 was cost effective (£20k/30k threshold): NR Probabilistic sensitivity analysis only performed for societal perspective. **Analysis of uncertainty:** Results in the one-way sensitivity analysis (OWSA) were most sensitive to the T25FW score at baseline, the utility value

fampridine group started in a 'response evaluation' health state, where after the 4-week treatment initiation, people could move to either the 'continue with PR-fampridine and BSC' health state, the 'withdrawal from treatment' health state (where fampridine treatment was discontinued if EDSS >7, proxied in the model by walking speed measured by the timed 25-foot walk (T25FW) dropping to zero) or die. The BSC group could either 'continue treatment with BSC' or die. **Perspective:** Swedish Healthcare payer perspective **Time horizon:** 20 years **Treatment effect duration:**[(a)] 24 weeks, extrapolated to 20 years **Discounting:** Costs: 3%		2018 Swedish Krona presented here as 2018 UK pounds[(b)] **Cost components incorporated:** Treatment costs (medicine acquisition and monitoring); Direct costs (including GP and outpatient visits, inpatient days and emergency hospital visits, cost of care and modifications/aids and adverse events); Indirect costs from loss of earnings were also included in the societal perspective (presented here as a scenario analysis).		to responders at week 24 and carried forward, the cost of professional care, PR-fampridine withdrawal rate and the cost of a day off work (used in societal perspective). Scenario analysis for a societal perspective decreased the ICER to £4,445 /QALY. Probability fampridine most cost effective at ~£38K threshold: 96%. Three scenario analyses were conducted around the utility value assigned to responders at week 24 and carried forward: • Using EQ-5D-5L values from MOBILE increased the incremental QALY to 0.44 and decreased the ICER to £2,839/QALY. • Using pooled utility data from the combined ENHANCE and MOBILE trials increased the incremental QALY to 0.15 and decreased the ICER to £8,329/QALY. • Assigning the same utility values for BSC and PR-fampridine responders at baseline decreased the incremental QALY to 0.04 and increased the ICER to £31,232/QALY. The OWSA and PSA results were generally insensitive to variations in patients' baseline characteristics.

Outcomes: 3%				

Data sources

Health outcomes: The key clinical data used in the model were taken from the double-blind phase III ENHANCE study, which determined response rates for the first 24 weeks and the baseline patient demographics applied in the economic model, as well as adverse events. The ENHANCE study recruited adults (18 to 70 years) with multiple sclerosis as defined in the revised McDonald criteria for at least three months, investigator-assessed walking impairment and an expanded disability status scale (EDSS) score of 4 to 7. Randomisation was stratified by EDSS score (≤6 or >6) at screening, and after a protocol amendment, also by prior aminopyridine use (yes or no). Patients were equally assigned to fampridine 10mg orally twice daily for 24 weeks or placebo. The rate of long-term natural progression of MS with regards to walking speed in the BSC group was obtained from T25FW scores over 24 months that were reported for the placebo arm of the IMPACT trial. For PR-fampridine Responders, results from a pooled analysis of MS-F203EXT & MS-F204EXT studies were used to model the corresponding progression of T25FW over time, with a weighted linear regression fitted to the pooled data to allow extrapolation beyond the 60-months trial duration. The definition of response and responder rates used in the base case analysis were taken from the ENHANCE study with response defined as a ≥8-point improvement on the MSWS-12 over 24 weeks. A pooled analysis of MS-F203EXT & MS-F204EXT studies was used to determine fampridine 4-week withdrawal rate (0.73%). Over the base-case model time horizon it is assumed no patients would progress to EDSS score >7. Non-serious adverse events observed in the ENHANCE study (Urinary tract infection, fall, back pain, headache, nasopharyngitis, upper respiratory tract infection, Cardiovascular disorder (palpitations, tachycardia, arrhythmia) and rash), excluding MS relapse, were included in the model. Swedish general population mortality used, with MS SMR applied (Kingwell 2012). **Quality-of-life weights:** Utility estimates were derived from EQ-5D-3L data collected within the ENHANCE study. Data were applied at baseline and weeks 2, 4, 8, 12, 16, 20 and 24, for each treatment by responders and non-responders. Beyond 24 weeks, extrapolation over the model time horizon used the last recorded EQ-5D values from week 24 carried forward. As the EQ-5D-3L is not a disease-specific instrument and may not sufficiently capture utility from walking changes, three scenario analyses were conducted using utility values from the MOBILE trial, which used EQ-5D-5L and from a pooled analysis of ENHANCE and MOBILE. A conservative scenario analysis was also conducted in which the utility gains observed in the BSC group were applied to the Responder baseline utility, as utility values for BSC and Fampridine responders showed a numerical difference at baseline in the ENHANCE trial. Disutility applied for AEs. **Cost sources:** Both direct (PR-fampridine drug cost, healthcare professionals, hospitalizations, treatment of AEs, cost of care and modifications/aids) and indirect (absence from work) costs were estimated. The latter was only included as part of a societal perspective, presented here as a scenario analysis. Administration costs associated with fampridine were assumed as zero due to it being an oral treatment. Resource use was informed by the relationship between medical resource consumption and walking speed, as measured by the T25FW, collected from an Adelphi study that was conducted in five major European markets (France, Germany, Italy, Spain, and the UK). Resource use for AEs appear to be based on assumption. Univariate analyses were conducted with the T25FW as the independent variable against resource consumption, which the base-case analysis in the model used for all resource use items. All direct unit costs were from the Southern Healthcare Region prices and reimbursements list and were inflated to 2018 prices. Cost of fampridine is lower in Sweden compared to the UK list price (£109 versus £362 per 56-pack (28-day supply)).

Comments

Source of funding: This study was sponsored by Biogen (Baar, Switzerland). Writing and editorial support for the preparation of the manuscript was provided by OPEN Health; funding was provided by Biogen.

Limitations: Swedish healthcare perspective. Costs and outcomes were discounted at a rate of 3.0%, which is less than the 3.5% stated in the NICE reference case. Due to the lack of long-term clinical trial or resource use data for 12-item MS walking scale (MSWS-12) that was used to measure treatment response, disease progression was defined using a different measure (timed 25-foot walk (T25FW)). Long-term treatment effect had to be extrapolated as the T25FW Data collected in extension studies was only available up to 5 years following the end of the original Phase III trials. Long-

term utilities were estimated by carrying the last observed value (week 24) forward to 20 years; this creates uncertainty towards the degree to which these values reflect utility in the patient population in the long run, particularly in reference to the assumption that no one progressed to EDSS ≥7 (therefore discontinue treatment) over the time horizon. The values used for resource use data were not specific to the Swedish market but is related UK resource use. Probabilistic sensitivity analysis (PSA) only provided for societal not healthcare perspective. The PSA did not account for the possible pairwise correlations between relevant inputs and may therefore overestimate the variability of the probabilistic results displayed in the cost-effectiveness plane.

Other: ENHANCE and MOBILE utility values were pooled for the scenario analysis using the "crosswalk" method, developed by van Hout (2012), to map the EQ-5D-5L data to the EQ-5D-3L UK value set before calculating the utility index score.

Overall applicability:(b) Partially applicable **Overall quality:**(c) Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; BSC, best supportive care; CUA= cost utility analysis; da= deterministic analysis; EDSS = Expanded Disability Status Scale; MSWS-12 = 12-item Multiple Sclerosis Walking Scale; T25FW = timed 25-foot walk; ICER= incremental cost-effectiveness ratio; NA = not applicable; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2018 purchasing power parities[32]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I – Excluded studies

Clinical studies

Table 12: Studies excluded from the clinical review

Study	Reason
Acosta, Carlos, Gianinazzi, M, Dort, T et al. (2021) Modeling the cost-effectiveness of prolonged-release fampridine for the treatment of walking impairment in patients with multiple sclerosis in Sweden. Journal of Medical Economics 24(1): 770-780	- Study design not relevant to this review protocol
Arpin, E. C. (2020) Efficacy and safety of fampridine for walking disability in multiple sclerosis. Neurodegenerative Disease Management 10(5): 277-287	- Review article but not a systematic review
Arreola-Mora, C., Silva-Pereyra, J., Fernandez, T. et al. (2019) Effects of 4-aminopyridine on attention and executive functions of patients with multiple sclerosis: Randomized, double-blind, placebo-controlled clinical trial. Preliminary report. Multiple Sclerosis and Related Disorders 28: 117-124	- Unsuitable dosing of fampridine
Baird, J. F.; Sandroff, B. M.; Motl, R. W. (2018) Therapies for mobility disability in persons with multiple sclerosis. Expert Review of Neurotherapeutics 18(6): 493-502	- Review article but not a systematic review
Behm, K. and Morgan, P. (2018) The effect of symptom-controlling medication on gait outcomes in people with multiple sclerosis: a systematic review. Disability & Rehabilitation 40(15): 1733-1744	- Systematic review used as source of primary studies
Bever, C. T., Jr., Young, D., Anderson, P. A. et al. (1994) The effects of 4-aminopyridine in multiple sclerosis patients: results of a randomized, placebo-controlled, double-blind, concentration-controlled, crossover trial. Neurology 44(6): 1054-1059	- Unsuitable dosing of fampridine (included in previous guideline but excluded from this version based on dose)
Broicher, S. D., Filli, L., Geisseler, O. et al. (2018) Positive effects of fampridine on cognition, fatigue and depression in patients with multiple sclerosis over 2 years. Journal of Neurology 265(5): 1016-1025	- Aim was not to treat mobility and no mobility outcomes reported
Crabtree-Hartman, E. (2018) Advanced symptom management in multiple sclerosis. Neurologic Clinics 36(1): 197-218	- Review article but not a systematic review
Filli, L., Werner, J., Beyer, G. et al. (2019) Predicting responsiveness to fampridine in gait-impaired patients with multiple sclerosis. European Journal of Neurology 26(2): 281-289	- Comparator in study does not match that specified in this review protocol
Filli, L., Zorner, B., Kapitza, S. et al. (2017) Monitoring long-term efficacy of fampridine in gait-impaired patients with multiple sclerosis. Neurology 88(9): 832-841	- No washout period Appears to be no washout period for the crossover phase after 2 years of treatment

Study	Reason
Foschi, M. and Lugaresi, A. (2019) Evaluating dalfampridine for the treatment of relapsing-remitting multiple sclerosis: does it add to the treatment armamentarium? Expert Opinion on Pharmacotherapy 20(11): 1309-1320	- Review article but not a systematic review
Goodman, A. D., Brown, T. R., Schapiro, R. T. et al. (2014) A pooled analysis of two phase 3 clinical trials of dalfampridine in patients with multiple sclerosis. International Journal of MS Care 16(3): 153-60	- Review article but not a systematic review
Goodman, A. D., Cohen, J. A., Cross, A. et al. (2007) Fampridine-SR in multiple sclerosis: a randomized, double-blind, placebo-controlled, dose-ranging study. Multiple Sclerosis 13(3): 357-68	- Unsuitable dosing of fampridine (included in previous guideline but excluded from this version based on dose)
Gunn, H., Markevics, S., Haas, B. et al. (2015) Systematic Review: The effectiveness of interventions to reduce falls and improve balance in adults With multiple sclerosis. Archives of Physical Medicine & Rehabilitation 96(10): 1898-912	- Study does not contain an intervention relevant to this review protocol
Jensen, H. B., Ravnborg, M., Dalgas, U. et al. (2014) 4-Aminopyridine for symptomatic treatment of multiple sclerosis: a systematic review. Therapeutic Advances in Neurological Disorders 7(2): 97-113	- Systematic review used as source of primary studies
Kanhai, K. M. S., Nij Bijvank, J. A., Wagenaar, Y. L. et al. (2019) Treatment of internuclear ophthalmoparesis in multiple sclerosis with fampridine: A randomized double-blind, placebo-controlled cross-over trial. CNS Neuroscience & Therapeutics 25(6): 697-703	- Aim was not to treat mobility and no mobility outcomes reported - Unsuitable dosing of fampridine
Kasser, S. L. and Jacobs, J. V. (2014) Understanding and treating balance impairment in multiple sclerosis. Journal of Clinical Outcomes Management 21(9): 419-432	- Review article but not a systematic review - Study does not contain an intervention relevant to this review protocol
Kim, E. S. (2017) Fampridine prolonged release: A review in multiple sclerosis patients with walking disability. Drugs 77(14): 1593-1602	- Review article but not a systematic review
Limone, B. L.; Sidovar, M. F.; Coleman, C. I. (2013) Estimation of the effect of dalfampridine-ER on health utility by mapping the MSWS-12 to the EQ-5D in multiple sclerosis patients. Health & Quality of Life Outcomes 11: 105	- Study reports an additional outcome of an included study generated by mapping rather than an outcome that was directly measured in the trial
Liu, Y., McNeill, M., Lee, A. et al. (2014) Quality of life among patients with multiple sclerosis treated with prolonged-release fampridine 10 Mg tablets for walking impairment. Value in Health 17(7): A401-2	- Conference abstract
Lugaresi, A. (2015) Pharmacology and clinical efficacy of dalfampridine for treating multiple sclerosis. Expert Opinion On Drug Metabolism & Toxicology 11(2): 295-306	- Review article but not a systematic review
Marquer, A.; Barbieri, G.; Perennou, D. (2014) The assessment and treatment of postural disorders in cerebellar ataxia: a systematic	- Population not relevant to this review protocol

Study	Reason
review. Annals of Physical & Rehabilitation Medicine 57(2): 67-78	- Study does not contain an intervention relevant to this review protocol
Morrow, S. A.; Rosehart, H.; Johnson, A. M. (2017) The effect of Fampridine-SR on cognitive fatigue in a randomized double-blind crossover trial in patients with MS. Multiple Sclerosis and Related Disorders 11: 4-9	- Aim was not to treat mobility and no mobility outcomes reported
Plummer, P. (2016) Critical Appraisal of evidence for improving gait speed in people with multiple sclerosis: Dalfampridine versus gait training. International Journal of MS Care 18(3): 105-15	- Review article but not a systematic review
Pozzilli, C., Prosperini, L., Tommasin, S. et al. (2021) Dalfampridine improves slowed processing speed in multiple sclerosis patients with mild motor disability: post hoc analysis of a randomized controlled trial. Therapeutic Advances in Neurological Disorders 14: 17562864211011286	- Secondary publication of an included study that does not provide any additional relevant information
Rocca, M. A., Valsasina, P., Colombo, B. et al. (2021) Cortico-subcortical functional connectivity modifications in fatigued multiple sclerosis patients treated with fampridine and amantadine. European Journal of Neurology 28(7): 2249-2258	- Aim was not to treat mobility and no mobility outcomes reported
Rossini, P. M., Pasqualetti, P., Pozzilli, C. et al. (2001) Fatigue in progressive multiple sclerosis: results of a randomized, double-blind, placebo-controlled, crossover trial of oral 4-aminopyridine. Multiple Sclerosis 7(6): 354-8	- Unsuitable dosing of fampridine (included in previous guideline but excluded from this version based on dose)
Schwid, S. R., Petrie, M. D., McDermott, M. P. et al. (1997) Quantitative assessment of sustained-release 4-aminopyridine for symptomatic treatment of multiple sclerosis. Neurology 48(4): 817-21	- Unsuitable dosing of fampridine (included in previous guideline but excluded from this version based on dose)
Shi, J.; Wu, X.; Chen, Y. (2019) Study on Dalfampridine in the treatment of multiple sclerosis mobility disability: A meta-analysis. PLoS ONE 14(9): e0222288	- Systematic review used as source of primary studies
Stolyarov, I. D.; Petrov, A. M.; Boyko, A. N. (2020) Efficacy and safety of Kinezia (fampridine) in the complex therapy of multiple sclerosis. Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova 120(11): 45-52	- Study not reported in English
Valet, M., Quoilin, M., Lejeune, T. et al. (2019) Effects of fampridine in people with multiple sclerosis: A systematic review and meta-analysis. CNS Drugs 33(11): 1087-1099	- Systematic review used as source of primary studies
van Diemen, H. A., Polman, C. H., van Dongen, T. M. et al. (1992) The effect of 4-aminopyridine on clinical signs in multiple sclerosis: a randomized, placebo-controlled, double-blind, cross-over study. Annals of Neurology 32(2): 123-30	- No washout period - Unsuitable dosing of fampridine (included in previous guideline but excluded from this version based on dose)
Walker, L. A. S.; Lindsay-Brown, A. P.; Berard, J. A. (2019) Cognitive fatigability interventions in	- Systematic review used as source of primary studies

Study	Reason
neurological conditions: A systematic review. Neurology & Therapy 8(2): 251-271	
Zackowski, K. M.; Cameron, M.; Wagner, J. M. (2014) 2nd International Symposium on Gait and Balance in Multiple Sclerosis: interventions for gait and balance in MS. Disability & Rehabilitation 36(13): 1128-32	- Review article but not a systematic review
Zhang, E., Tian, X., Li, R. et al. (2021) Dalfampridine in the treatment of multiple sclerosis: a meta-analysis of randomised controlled trials. Orphanet Journal of Rare Diseases 16(1): 87	- Systematic review used as source of primary studies

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 13: Studies excluded from the health economic review

Reference	Reason for exclusion
Ziemssen 2017[47] (Germany)	Excluded due to a combination of applicability and methodological limitations. German resource use and unit costs. This cost comparison analysis (resource utilisation only, no clinical outcomes or quality of life data) is based on German claims data (rather than data from an RCT) before and after fampridine. No analyses of uncertainty.