

## **Prolonged-release fampridine in multiple sclerosis: clinical data and real-world experience – report of an expert meeting**

Philipp Albrecht, Ingrid Kristine Bjørnå, David Brassat, Rachel Farrell, Peter Feys, Jeremy Hobart, Raymond Hupperts, Michael Linnebank, Jožef Magdič, Celia Oreja-Guevara, Carlo Pozzilli, Antonio Vasco Salgado and Tjalf Ziemssen

Correspondence to: Philipp Albrecht, Department of Neurology, Medical Faculty, Heinrich Heine University, Moorenstr. 5, 40225 Duesseldorf, Germany. Email: [phil.albrecht@gmail.com](mailto:phil.albrecht@gmail.com).

### **Philipp Albrecht**

Department of Neurology, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany

### **Ingrid Kristine Bjørnå**

Neurological Department, Drammen sykehus, Vestre Viken, Drammen, Norway

### **David Brassat**

Centre de ressource et de competence-SEP CHU-Toulouse et UMR1043, Université de Toulouse III, Toulouse, France

### **Rachel Farrell**

Department of Neuroinflammation, UCL Institute of Neurology, London and National Hospital for Neurology and Neurosurgery, UCLH NHS Foundation Trust, London, UK

### **Peter Feys**

REVAL/BIOMED, Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium

### **Jeremy Hobart**

Department of Clinical Trials and Health Research: Translational & Stratified Medicine, Plymouth University Peninsula Schools of Medicine and Dentistry, UK

### **Raymond Hupperts**

Department of Neurology, Zuyderland Medical Center, Sittard-Geleen, Netherlands

### **Michael Linnebank**

Department of Neurology, Helios Clinic Hagen-Ambrock, Hagen, Germany

### **Jožef Magdič**

Department of Neurology, University Medical Center Maribor, Maribor, Slovenia

### **Celia Oreja-Guevara**

Neurología, Hospital Clínico San Carlos, Departamento de Medicina, Universidad Complutense de Madrid (UCM); Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, España

### **Carlo Pozzilli**

Department of Neurology, University La Sapienza, Rome, Italy

**Antonio Vasco Salgado**

Serviço de Neurologia, Hospital Fernando Fonseca, Amadora, Portugal

**Tjalf Ziemssen**

Center of Clinical Neuroscience, Department of Neurology, MS Center Dresden, University Hospital Carl Gustav Carus, Dresden University of Technology, Dresden, Germany

**Abstract**

Prolonged-release (PR) fampridine is the only approved medication to improve walking in multiple sclerosis (MS), having been shown to produce a clinically meaningful improvement in walking ability in the subset of MS patients with EDSS 4–7. Recent responder subgroup analyses in the Phase 3 ENHANCE study show a large effect size in terms of an increase of 20.58 points on the patient-reported 12-item Multiple Sclerosis Walking Scale in the 43% of patients classified as responders to PR-fampridine, corresponding to a standardised response mean of 1.68. Use of PR-fampridine in clinical practice varies across Europe, depending partly on whether it is reimbursed. A group of European MS experts met in June 2017 to discuss their experience with using PR-fampridine, including their views on the patient population for treatment, assessment of treatment response, re-testing and re-treatment, and stopping criteria. This article summarises the experts' opinions on how PR-fampridine can be used in real-world clinical practice to optimise the benefits to people with MS with impaired walking ability.

**Key words**

multiple sclerosis, prolonged-release fampridine, real-world experience, treatment response, walking ability

## Introduction

Multiple sclerosis (MS) causes a wide variety of neurological deficits, but ambulatory impairment is the most common form of disability. Within 15 years of disease onset, 50% of people with MS will require assistance with walking and 80% will experience gait problems due to muscle weakness, spasticity, fatigue and balance impairment [Souza 2010]. In a large US cohort, 15% of MS patients reported needing ambulatory aid in the first year of disease, increasing to 40% after 10 years; after 45 years of disease, 76% of patients required ambulatory aid and 52% needed at least bilateral assistance [Kist *et al.* 2013]. Impaired mobility is associated with reductions in quality of life, activities of daily living and productivity, and patients with MS rank maintaining mobility as one of their highest priorities [Sutliff 2010; Heesen 2008].

Prolonged-release (PR) fampridine (known as sustained/modified-release fampridine in some countries and extended-release dalfampridine in the US) is the only approved medication for MS that improves walking. It received full approval from the European Medicines Agency (EMA) in May 2017, following approval in 2011 conditional on further studies being conducted. PR-fampridine is indicated for the improvement of walking in adult MS patients with walking disability (Expanded Disability Status Scale [EDSS] score 4–7) [Fampyra SmPC 2017]. Fampridine is thought to block voltage-gated potassium channels, restoring signal conduction in demyelinated nerve fibres [Dunn 2011].

This article describes new responder subgroup analyses of the ENHANCE study, which clarify treatment effects in patients who respond to PR-fampridine. It also reports on the clinical experience of 14 MS experts from 10 European countries (Belgium, France, Germany, Italy, Netherlands, Norway, Portugal, Slovenia, Spain and the UK), which was discussed at a meeting held in June 2017. Topics discussed include real-world experience with PR-fampridine, expert views on the patient population for PR-fampridine, assessment of treatment response, re-testing and re-treatment, and stopping criteria, based on early EU clinical experience.

## New analyses of the fampridine study program – understanding the real patient impact

Two Phase 3 multicentre, randomised, double-blind, placebo-controlled trials showed that PR-fampridine produced clinically meaningful improvement in walking ability in a subset of MS patients [Goodman 2009, 2010]. In the first trial, the proportion of patients with any type of MS who responded (consistent improvement on Timed 25-Foot Walk [T25FW] over 14 weeks) was significantly higher in the PR-fampridine group than in the placebo group (35% vs. 8%;  $p < 0.0001$ ). T25FW responders showed greater improvement on the 12-item Multiple Sclerosis Walking Scale (MSWS-12) than did non-responders ( $p = 0.0002$ ) [Goodman 2009]. The T25FW is considered the most well-characterised objective, specific assessment of walking disability, and is moderately to strongly correlated with self-reported walking disability on the MSWS-12 [Kieseier 2012]. The second trial confirmed these findings, with 43% of the PR-fampridine group being T25FW responders compared with 9% of the placebo group ( $p < 0.0001$ ) [Goodman 2010]. Long-term extensions of the two trials showed that improvements in walking speed were lost after PR-fampridine was discontinued in the parent trial, but returned by the 2-week assessment after re-initiation. Although

walking speed decreased over time, PR-fampridine responders sustained an improved walking speed compared with non-responders for up to 5 years [Goodman 2015].

The MOBILE trial explored the effect of PR-fampridine on patients' self-assessed walking ability and dynamic/static balance, assessed using the MSWS-12, the Timed Up and Go (TUG) test and the Berg Balance Scale (BBS) [Hupperts 2016]. PR-fampridine therapy resulted in greater median improvements from baseline in MSWS-12 score, TUG speed and BBS total score versus placebo over 24 weeks, as well as greater improvements in the 29-item MS Impact Scale (MSIS-29) physical impact subscale (PHYS) [Hupperts 2016]. A post-hoc analysis showed a mean reduction from baseline of 97% versus placebo in MSIS-29 PHYS among patients who achieved a clinically significant  $\geq 8$ -point mean reduction in MSWS-12 score over 24 weeks with PR-fampridine, and a reduction of 111% in the psychological subscale of MSIS-29 [Gasperini 2016].

ENHANCE, the largest and longest randomised trial of PR-fampridine to date, was a Phase 3 multicentre, randomised, double-blind, placebo controlled study to evaluate whether PR-fampridine provided sustained, clinically meaningful benefits compared with placebo on patient-reported walking ability and other functional outcome measures [Hobart 2016]. Patients aged 18–70 years with relapsing or progressive MS and impaired walking (EDSS 4–7) were randomised to PR-fampridine 10 mg (n=317) or placebo (n=319) twice daily for 24 weeks. Significantly more patients in the PR-fampridine group than in the placebo group achieved a clinically meaningful  $\geq 8$ -point mean improvement from baseline on the MSWS-12 over 24 weeks. Significant differences in favour of PR-fampridine were also reported for TUG speed and improvement from baseline MSIS-29 PHYS [Hobart *et al.* 2016]. Overall tolerability of prolonged-release fampridine in the ENHANCE trial was consistent with previous clinical trials.

Recent responder subgroup analyses in ENHANCE showed an improvement in MSWS-12 score of 20.58 points among PR-fampridine MSWS-12 responders, compared with a deterioration of 2.17 points (least square mean [LSM] difference -22.76 [95% CI -25.25, -20.26]) in non-responders and an improvement of 3.64 (LSM difference -16.94 [95% CI -19.21, -14.68]) in placebo-treated patients [Hobart *et al.* 2017]. The proportion of patients with clinically significant improvements ( $\geq 15\%$ ) in TUG speed was significantly higher in PR-fampridine responders (52.4% [95% CI, 1.47 to 3.53]) than in non-responders (36.6%) or the placebo group (34.7%). Improvements in MSWS-12 scores and TUG speeds in responders were observed as early as Week 2 and were sustained over 24 weeks. Benefits were also seen in responders versus non-responders/placebo for changes in MSIS-29 PHYS, BBS and ABILHAND scores over 24 weeks [Hobart 2017]. LSM changes from baseline were -17.4 in responders, -1.9 in non-responders and -5.3 with placebo for MSIS-29 PHYS; 2.6, 1.2 and 1.4, respectively for BBS; and 3.3, 0.3 and 0.9, respectively, for ABILHAND. The experts who met in June 2017 considered that this responder subgroup analysis approach was justified because, in clinical practice, only patients who respond to PR-fampridine remain on treatment.

New effect size analyses have been conducted with the aim of contextualising the effect sizes seen in the PR-fampridine responder and non-responder subgroups in ENHANCE. These examined the mean change in points on the MSWS-12 scale relative to the standard deviation of change and have specific criteria for interpretation. Standardised response mean (SRM) values were calculated for PR-fampridine MSWS-12 responder and non-responder groups as 1.68 and 0.36, respectively, for MSWS-12. As many studies are powered to detect an effect size of 0.3, an effect size of 1.68 in

responders was thought to represent an impressive result. Similar calculations were conducted for other outcome measures from ENHANCE, such as effect versus baseline disability and Berg Balance Scale at baseline, with PR-fampridine MSWS-12 responders showing strong results relative to non-responders.

### **Real-world experience with PR-fampridine**

PR-fampridine received full EMA approval in May 2017, following conditional approval in 2011. However, worldwide experience is much more extensive and, as of 30 April 2017, more than 318,565 patients had been treated with PR-fampridine, representing more than 341,163 patient-years of exposure (including ~8321 patients and ~3367 patient-years from clinical trials) (Data on file, Biogen 2017).

Use of PR-fampridine in clinical practice varies across Europe, depending partly on whether it is reimbursed. Healthcare systems in many European countries now reimburse PR-fampridine subject to certain response criteria. However, reimbursement is not currently available in the UK and several other countries, meaning that access to PR-fampridine treatment for people with MS remains variable. PR-fampridine is less well documented in real-world multicentre activities or national MS registries than other products, although the first publications describing multicentre observational studies, rather than single-centre cohorts, are beginning to appear [Fragoso 2016; Costa-Arpin 2016; Rodriguez-Leal 2017].

The experts who met in June 2017 have a broad experience of using PR-fampridine in their MS patients, which was assessed by questionnaires at the meeting: The group of experts oversees a total of over 11000 patients, over 1400 of these under treatment with PR-fampridine. Due to different local situations regarding health-care systems as well as license and reimbursement of the drug in the different countries the rate of fampridine treated patients differs between the experts' centres, ranging from below 10% in Belgium and Italy to around 25% in Germany and Spain to about 40% in Denmark. The majority of the PR-fampridine treated patients at the centres were classified as secondary progressive MS (48%), followed by relapsing remitting (35%) and primary progressive (17%) MS with a rather homogenous distribution over the EDSS steps 4(21%), 5(23%), 6(35%) and 7(21%). The experts often use PR-fampridine in combination with disease-modifying therapies, as well as with non-pharmacological approaches such as physiotherapy and occupational therapy. Half of their currently treated patients have been taking PR-fampridine for 3–4 years, with another 30% taking it for 5 or more years.

### **Patient population – which patients are most likely to benefit from PR-fampridine?**

PR-fampridine is currently indicated for the improvement of walking in adults with MS who have walking disability (EDSS 4–7). However, the experts believe that some people with MS even with EDSS scores below 4 may already have impaired walking [Langeskov-Christensen 2017] and other deficits such as visual impairment, nystagmus or ataxia, and may receive considerable benefit from PR-fampridine treatment. This is supported by reports on an improvement of visual acuity and visual

evoked potential latencies in patients with optic neuropathy [Horton 2013], an amelioration of downbeat nystagmus [Kalla 2007, Claassen 2013] and ataxia [Schiepp 2012] under therapy with 4-aminopyridine also in non-MS patients. How patients walk can be as important as how far or how fast they can walk. Similarly, at higher EDSS levels, meaningful and impactful improvements in hand function may be achievable; these are less apparent as study populations do not include patients with major hand dysfunction. As PR-fampridine works by improving neuronal function, the experts suggested that it may lead to greater improvement in patients with more deficits. Even very disabled patients may be able to use their wheelchairs more easily and effectively. Overall, more data on the use of PR-fampridine in patients with EDSS scores below 4 and above 7 would be welcome, including information on walking impairment, fatigue, upper limb function and cognition.

Newer tools that have a potential role in identifying patients with mobility impairment who may benefit from PR-fampridine treatment were discussed. For example, the Early Mobility Impairment Questionnaire (EMIQ) is a nine-item questionnaire designed to capture MS patients' experience with mobility impairment [Ziemssen 2016]. It includes more high level motor activities than the MSWS-12, such as items on walking in crowds and stability while walking on flat or uneven ground. Early experience suggests that it has the potential to be used as a screening tool to identify mobility impairment at an earlier stage.

With regards to a concordant relationship and shared decision making, clear communication is needed when prescribing PR-fampridine, so that patients have realistic expectations. It is important to explain to patients that not everyone experiences an improvement; however, they will know very quickly whether the drug works for them or not. The experience of the experts suggests that most patients are very positive about trying the drug.

### **Assessing treatment response**

The EU label for PR-fampridine has recently been updated to recommend that clinical benefit is evaluated on the basis of walking ability rather than walking speed as specified previously, and the timescale for initial evaluation is now 'within 2–4 weeks', rather than 'after 2 weeks', which had been recommended previously. Both MSWS-12 and T25FW are included in the label as suitable tools for evaluating response to allow both clinical and patient-reported assessments.

Variations exist across Europe in terms of the documented evidence of response required by the various authorities for reimbursement purposes, and in some cases this drives the methods used to evaluate response. At the meeting, the experts agreed that the patient-reported MSWS-12 is currently the most commonly used measure for formal assessment of treatment response, along with T25FW. Some would use extra measures, such as assessment of hand function using the 9-Hole Peg Test or ABILHAND, if a patient has additional deficits. A recent single-centre study found that a combination of the T25FW and MSWS-12 offered the best sensitivity and specificity for determining response to both neurologists' and patients' classification [Rodriguez-Leal 2017]. Thresholds for reimbursement need to be pragmatic; each authority sets its own threshold, with an improvement of 30% on MSWS-12 or 20% on T25FW being commonly used. The experts noted that in many cases, it is obvious after 2 weeks whether a patient is responding to PR-fampridine; however, some patients may need to continue treatment for a further 2 weeks to be certain.

Based on the experts' real-world experience with PR-fampridine, there was agreement that the benefits of PR-fampridine to patients may be broader than just on walking speed. Several experts stated that patients could see improvements in terms of gait pattern, walking endurance, balance and fatigability. The experts noted that patients have better balance when taking PR-fampridine; they may not walk faster but they feel safer [Gonzalez 2016; Gonzalez-Suarez 2015, 2016; Prosperini 2014]. The Timed 100-Meter Walk Test may be useful for assessing walking speed over a longer distance [Phan-Ba 2011], while a cut-off of 15% change from the first to the last minute of the 6-Minute Walk Test (6MWT) has been suggested to identify walking-related motor fatigue [Leone 2016], which may be affected by PR-fampridine. Some experts also reported improvements in vision and ataxia, although these are not included in the label indication. As the mode of action of PR-fampridine is to improve nerve conduction, it was thought that treatment benefits were unlikely to be confined to walking ability alone. Indeed, PR-fampridine has been shown to improve arm function, fatigue and quality of life in T25FW/MSWS-12/2-minute walk test responders [Allart 2015]. The 9-Hole Peg Test is likely to be useful for monitoring hand function, as it is a simple, validated measure of upper limb function in MS and is highly correlated with a wide range of other upper limb tests [Feys 2017]. Improvement has also been demonstrated with PR-fampridine treatment [Savin 2016]. In addition, PR-fampridine has been shown to significantly improve cognitive impairment in a single-centre study, as measured by processing speed according to the Symbol Digit Modalities Test [De Giglio 2017].

This expert group agreed that patient-reported outcomes were particularly important for a treatment that improves symptoms, and that predefined questionnaires and rating scales inevitably have their limitations in assessing overall clinical improvements. Specific goal-related outcomes such as the ability to walk upstairs or reach the bathroom may be of real practical significance to people with MS and can be measured using goal attainment scaling [Turner-Stokes 2009]. The ability to walk confidently with one walking aid rather than two could also be a meaningful outcome in some cases.

Overall, as PR-fampridine is a symptomatic treatment, the experts agreed that it would seem reasonable to be able to continue treatment if both the physician and the patient believe that the drug is working, and that patients would generally be unwilling to take a drug that was not effective for them. This is evident in countries such as the UK, where PR-fampridine is not reimbursed and patients must decide whether to pay for the drug themselves.

Based on the label recommendation, treatment should be stopped if the patient reports no benefit from PR-fampridine after 2–4 weeks. However, the experts noted that some patients may deteriorate when the drug is stopped, suggesting that they were receiving some benefit from treatment. The effect of stopping PR-fampridine appears to distinguish quite well between responders and non-responders. Furthermore, disease activity and clinical symptoms may progress, and the experts noted that in some cases response to fampridine may change later in the course of disease despite an earlier negative response (see below).

### **Re-testing, stopping treatment and re-treating**

On the basis of their practical experience, the experts considered that asking PR-fampridine-treated patients every 6 months whether the drug is still working for them was good practice, as well as

assessing them for side effects, walking ability and other outcomes. Drug holidays could be used to determine whether the drug still has a therapeutic benefit. If it no longer appears to be effective, the drug should be stopped. However, there is the possibility of re-starting treatment if the clinical situation changes. EDSS >7 is generally used as a stopping criterion for PR-fampridine treatment in current clinical practice, based on the label, but different criteria may be needed for other domains such as hand function.

A recent long-term extension of a randomised controlled trial of PR-fampridine found that 80% of patients who showed greater than 10% improvement in T25FW and 6MWT in the original study maintained their response over 2 years in the extension. However, 40% of patients who did not achieve this level of response during short-term treatment (6 weeks) showed greater than 10% improvements after 2 years [Filli 2017]. The authors speculate that responsiveness to PR-fampridine may change over time, as MS is a dynamic disease and appearance of new demyelinated lesions may result in clinical deterioration amenable to improvement; enhanced drug efficacy over time may also be the result of training effects made possible by the improved neurological state induced by PR-fampridine [Filli 2017].

In the experts' experience, some people with MS (possibly as many as a third) who initially do not respond to fampridine may respond to a second attempt at treatment. A re-trial of PR-fampridine between 6 and 12 months after an initial failure is a reasonable approach, especially if the disease course has changed and if the person with MS is willing to try the treatment again. Some patients may not wish to try a drug again if it did not work for them on the first attempt, but an increase in symptoms or disability may prompt a second attempt.

## **Conclusions**

PR-fampridine has been shown to improve walking ability in a subset of MS patients with impaired mobility, and recent responder subgroup analyses of the ENHANCE study have shown very large effect sizes in terms of an average increase in MSWS-12 score of 20.58 points among PR-fampridine MSWS-12 responders. Similarly, more than 52% of PR-fampridine MSWS-12 responders showed meaningful improvements in TUG speed.

Early real-world experience suggests that the benefits of PR-fampridine may extend beyond those on walking ability, based on its mode of action which involves restoring neuronal function.

This article has provided expert opinions on how PR-fampridine can be used in real-world clinical practice to optimise the benefits to people with MS with impaired walking ability.

## **Acknowledgements**

Editorial support was provided by Synergy Medical Communications Ltd.

## **Conflict of interest statement**



Philipp Albrecht has received research grants from Biogen, Ipsen, Merz Pharmaceuticals, Novartis and Teva, and travel/accommodation/meeting expenses/speaker honoraria from Allergan, Bayer Healthcare, Biogen, Ipsen, Merck, Merz Pharmaceuticals, Novartis and Teva.

Ingrid Kristine Bjørnå has received compensation for travel and advisory boards, speaker honoraria and consultant fees from Merck, Biogen, Sanofi Genzyme, Bayer, Novartis, Roche and Teva, as well as support for participation in clinical trials in multiples sclerosis sponsored by Schering, Serono, Biogen, Novartis, Genzyme and Roche.

David Brassat has received travel and lecture fees from Bayer, Biogen, Merck, Novartis Pharma, Roche and Sanofi Genzyme.

Rachel Farrell has received speaker honoraria, compensation for advisory roles, hospitality and educational grants from Merck, Canbex Pharmaceuticals Ltd, Allergan, Merz, TEVA, Novartis, Genzyme and Biogen. Dr Farrell's current research activity is supported by the NIHR Biomedical Research Centre UCLH.

Peter Feys has received consulting/advisory board fees for Biogen and Novartis; speaker fees from Excemed; he is an editorial board member for Multiple Sclerosis Journal.

Jeremy Hobart has received consulting/advisor fees/honoraria/support for clinical service or research from Acorda, Biogen, Global Blood Therapeutics, F. Hoffmann-La Roche, LORA group, Merck Serono, Novartis, Sanofi-Genzyme, Tigercat Pharma, and Vantia.

Raymond Hupperts has received institutional research grants from Merck and Biogen, patient care support from Biogen, Merck and Sanofi-Genzyme, and honoraria for SC memberships and speaking fees from Merck, Biogen and Sanofi-Genzyme.

Michael Linnebank has received compensation for advisory boards and speaker honoraria from Almirall, Bayer, Biogen, Merck, Novartis, Sanofi Genzyme, and Teva.

Jožef Magdič has received compensation for advisory boards and speaker honoraria from Bayer, Biogen, Merck, Novartis, Roche, Sanofi Genzyme, Teva, AstraZeneca, Boehringer Ingelheim, Medis and Krka.

Celia Oreja-Guevara has received compensation for advisory boards and speaker honoraria from Almirall, Biogen, Sanofi Genzyme, Roche, Merck, Novartis and Teva.

Carlo Pozzilli has received consultant fees from Actelion, Biogen, Genzyme, Merck Serono, Novartis, and Teva Neuroscience, and grant or research support from Biogen, Merck Serono, Novartis, and Teva Neuroscience.

Antonio Vasco Salgado has received financial fees from Biogen, Novartis, Merck Serono, Sanofi and Roche.

Tjalf Ziemssen has received compensation for consulting services from Almirall, Biogen, Bayer, Merck, Novartis, Roche, Sanofi and Teva, and has received research support from Bayer, Biogen Idec, the Hertie Foundation, the Roland Ernst Foundation, the German Diabetes Foundation, Biogen, Merck, Novartis, Teva and Sanofi.

## Funding

The expert meeting was supported financially by Biogen.

## References

Allart E, Benoit A, Blanchard-Dauphin A, et al. Sustained-released fampridine in multiple sclerosis: effects on gait parameters, arm function, fatigue, and quality of life. *J Neurol* 2015; 262: 1936–1945.

Claassen J, Spiegel R, Kalla R, Faldon M, Kennard C, Danchaivijitr C, Bardins S, Rettinger N, Schneider E, Brandt T, Jahn K, Teufel J, Strupp M, Bronstein A. A randomised double-blind, cross-over trial of 4-aminopyridine for downbeat nystagmus--effects on slowphase eye velocity, postural stability, locomotion and symptoms. *J Neurol Neurosurg Psychiatry*. 2013; 84(12):1392-9.

Costa-Arpín E, Pato A, Rodríguez-Regal A, et al. Clinical response and tolerability of fampridine in clinical practice. *Neurodegener Dis Manag* 2016; 6: 99–105.

De Giglio L, De Luca F, Gurreri F, et al. Dalfampridine improves cognition impairment in multiple sclerosis (MS): results from a randomised, double-blind, placebo-controlled trial. American Academy of Neurology 69<sup>th</sup> Annual Meeting, Boston, USA, 2017.

Dunn J and Blight A. Dalfampridine: a brief review of its mechanism of action and efficacy as a treatment to improve walking in patients with multiple sclerosis. *Curr Med Res Opin* 2011; 27: 1415–1423.

Fampyra Summary of Product Characteristics. Available at: <https://www.medicines.org.uk/emc/medicine/25003> (2017, accessed 11 August 2017).

Feys P, Lamers I, Francis G, et al. The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. *Mult Scler* 2017; 23: 711–720.

Filli L, Zörner B, Kapitza S, et al. Monitoring long-term efficacy of fampridine in gait-impaired patients with multiple sclerosis. *Neurology* 2017; 88: 832–841.

Fragoso YD, Adoni T, Alves-Leon SV, et al. Real-life experience with fampridine (Fampyra®) for patients with multiple sclerosis and gait disorders. *NeuroRehabilitation* 2016; 39: 301–304.

Gasparini C, Hupperts R, Lycke J, et al. Prolonged-release fampridine treatment improved subject-reported impact of multiple sclerosis: Item-level analysis of the MSIS-29. *J Neurol Sci* 2016 ;370: 123–131.

Gonzalez I, Pulido-Valdeolivas I, Gomez-Andres D, et al. Improvement of the spatiotemporal parameters in walking in primary progressive patients treated with fampridine. American Academy of Neurology 68<sup>th</sup> Annual Meeting, Vancouver, Canada, 2016.

Gonzalez-Suarez I, Gomez-Andres D, Montero-Atalaya A, et al. Could fampridine change gait kinematics to improve walking speed in primary progressive multiple sclerosis? [Abstract P468]. *Mult Scler* 2016; 22: 199–200.

Gonzalez-Suarez I, Pulido-Valdeolivas I, Gomez-Andres D, et al. Primary progressive multiple sclerosis patients use walking pattern adaptation revealing by instrumented gait analysis: a hierarchical clustering approach [abstract EP1425]. *Mult Scler* 2015; 21(Suppl 11): 744–745.

Goodman AD, Bethoux F, Brown TR, et al. Long-term safety and efficacy of dalfampridine for walking impairment in patients with multiple sclerosis: results of open-label extensions of two Phase 3 clinical studies. *Mult Scler* 2015; 21: 1322–1331.

Goodman AD, Brown TR, Edwards KR, et al. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann Neurol* 2010; 68: 494–502.

Goodman AD, Brown TR, Krupp LB, et al. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet* 2009; 373: 732–738.

Heeson C, Böhm J, Reich C, et al. Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable. *Mult Scler* 2008; 14: 988–991.

Hobart J, Ziemssen T, Feys P, et al. Sustained clinically meaningful improvements in walking ability with prolonged-release fampridine: results from the placebo-controlled ENHANCE study [abstract]. *Mult Scler J* 2016; 22(Suppl 3): 833–834.

Hobart J, Ziemssen T, Feys P, et al. Prolonged-release fampridine demonstrates rapid and sustained clinically meaningful improvements in walking ability over 24 weeks: MSWS-12 responders in the ENHANCE study [abstract EP3162]. *Eur J Neurol* 2017; 24(Suppl 1): 434.

Horton L, Conger A, Conger D, Remington G, Frohman T, Frohman E, Greenberg B. Effect of 4-aminopyridine on vision in multiple sclerosis patients with optic neuropathy. *Neurology*. 2013; 80(20):1862-6.

Hupperts R, Lycke J, Short C, et al. Prolonged-release fampridine and walking and balance in MS: randomised controlled MOBILE trial. *Mult Scler* 2016; 22: 212–221.

Kalla R, Glasauer S, Büttner U, Brandt T, Strupp M. 4-aminopyridine restores vertical and horizontal neural integrator function in downbeat nystagmus. *Brain*. 2007;130(Pt 9):2441-51.

Kieseier BC, Pozzilli C. Assessing walking disability in multiple sclerosis. *Mult Scler* 2012; 18: 914–924.

Kista I, Chamot E, Salter AR, et al. Disability in multiple sclerosis: a reference for patients and clinicians. *Neurology* 2013; 80: 1018–1024.

Langeskov-Christensen D, Feys P, Baert I, Riemenschneider M, Stenager E, Dalgas U. Performed and perceived walking ability in relation to the Expanded Disability Status Scale in persons with multiple sclerosis. *J Neurol Sci* 2017; 382:131-136.

Leone C, Severijns D, Doležalová V, et al Prevalence of Walking-Related Motor Fatigue in Persons With Multiple Sclerosis: Decline in Walking Distance Induced by the 6-Minute Walk Test. *Neurorehabil Neural Repair* 2016; 30: 373–383.

Phan-Ba R, Pace A, Calay P, et al. Comparison of the timed 25-foot and the 100-meter walk as performance measures in multiple sclerosis. *Neurorehabil Neural Repair* 2011; 25: 672–679.

Prosperini L, Gianni C, Fortuna D, et al. Oral dalfampridine improves standing balance detected at static posturography in multiple sclerosis. *Mult Scler Int* 2014; 2014: 802307.

Schniepp R, Wuehr M, Neuhaeusser M, Benecke AK, Adrion C, Brandt T, Strupp M, Jahn K. 4-aminopyridine and cerebellar gait: a retrospective case series. *J Neurol* 2012;259(11):2491-3.

Rodriguez-Leal FA, Haase R, Thomas K, et al. Fampridine response in MS patients with gait impairment in a real-world setting: Need for new response criteria? *Mult Scler* 2017; Jul1: 1352458517720043. [Epub ahead of print]

Savin Z, Lejbkowicz I, Glass-Marmor L, et al. Effect of fampridine-PR (prolonged released 4-aminopyridine) on the manual functions of patients with multiple sclerosis. *J Neurol Sci* 2016; 360: 102–109.

Souza A, Kelleher A, Cooper R, et al. Multiple sclerosis and mobility-related assistive technology: systematic review of literature. *J Rehabil Res Dev* 2010; 47: 213–223.

Sutliff MH. Contribution of impaired mobility to patient burden in multiple sclerosis. *Curr Med Res Opin* 2010; 26: 109–119.

Turner-Stokes L. Goal attainment scaling (GAS) in rehabilitation: a practical guide. *Clin Rehabil* 2009; 23: 362–370.

Ziemssen T, Phillips G, Shah R, et al. Development of the multiple sclerosis (MS) early mobility impairment questionnaire (EMIQ). *J Neurol* 2016; 263: 1969–1983.