23 March 2017
EMA/305262/2017 - Corr*
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fampyra

International non-proprietary name: fampridine

Procedure No. EMEA/H/C/002097/II/0036/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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*Sections 4.3.1 and 4.3.2 have been updated – sentences removed on pages 22-23 and 29.

Assessment Timetable / Steps taken for the assessment

Timetable	Planned dates	Actual dates
Start of procedure:	28 November 2016	28 November 2016
CHMP Rapporteur Assessment Report	23 December 2016	3 January 2017
PRAC Rapporteur Assessment Report	3 January 2017	3 January 2017
PRAC members comments	4 January 2017	4 January 2017
Updated PRAC Rapporteur Assessment Report	5 January 2017	n/a
PRAC Outcome	12 January 2017	12 January 2017
CHMP members comments	16 January 2017	16 January 2017
Updated CHMP Rapporteur Assessment Report	19 January 2017	20 January 2017
Request for supplementary information	26 January 2017	26 January 2017
PRAC Rapporteur Assessment Report	27 February 2017	8 March 2017
PRAC members comments	1 March 2017	8 March 2017
Updated PRAC Rapporteur Assessment Report	2 March 2017	n/a
CHMP Rapporteur Assessment Report	8 March 2017	14 March 2017
PRAC Outcome	9 March 2017	9 March 2017
CHMP members comments	13 March 2017	n/a
Updated CHMP Rapporteur Assessment Report	16 March 2017	n/a
Opinion	23 March 2017	23 March 2017

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1. Background information on the procedure

1.1. Requested group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Biogen Idec Ltd submitted to the European Medicines Agency on 25 November 2016 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II, IIIA and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II, IIIA and IIIB

This is a grouped variation proposing updates to the SmPC sections 4.2, 5.1, Annex II and Package Leaflet based on the clinical study ENHANCE; to the SmPC section 4.6 based on the data from the FOLLOW pregnancy registry. Further changes to the PI, section 4.2 and 5.2 of the SmPC have been introduced based on the Core Data Sheet (CDS) and PRAC review of the Fampyra PSUR 03. The RMP (version 11) has been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.0. Finally, with this application the MAH requests to switch the conditional marketing authorisation to a marketing authorisation not subject to specific obligations.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

1.2. Rationale for the proposed changes

Fampyra is a prolonged release (PR) tablet formulation containing fampridine or 4-aminopyridine (4-AP). Fampridine is indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability (Expanded Disability Status Scale 4-7).

Fampyra received a conditional marketing authorisation in 2011 subject to the provision of results of a long-term efficacy and safety study to investigate a broader primary endpoint that is clinically meaningful in terms of walking ability and to further evaluate the early identification of responders.

In this group of variations the MAH submitted final data from the outstanding specific obligation study ENHANCE (218MS305), a multicenter, randomised, double blind, placebo controlled parallel group study to assess the long-term efficacy and safety of prolonged release Fampridine 10 mg, administered twice daily in subjects with multiple sclerosis.

Changes to the Product Information and the RMP are proposed consequently. As submission of the ENHANCE data fulfils the specific obligation, the MAH requested to convert the marketing authorisation from conditional to one no longer subject to specific obligations.

Additionally, the MAH submitted results of the pregnancy registry FOLLOW (218MS402) and proposed PI

updates accordingly. Minor PI updates based on the recent PSUR assessment have also been proposed.

2. Overall conclusion and impact on the benefit/risk balance

As part of CMA the Applicant conducted the ENHANCE study which now has been completed. The aim of the study was to evaluate the clinical meaningfulness of the effect of fampridine in terms of walking ability as well as the long-term efficacy and safety.

The ENHANCE study is a randomised placebo-controlled parallel group study in 636 subjects with multiple sclerosis and walking disability. Subjects were randomised to placebo or fampridine PR 10 mg BID. The duration of the double-blind part was 24 weeks with a 2 week post–treatment follow-up. Primary endpoint was the proportion of responders defined as subjects with a mean improvement on the Multiple Sclerosis Walking Scale of ≥ 8 points as compared to baseline. An improvement of 8 points on the MSWS-12 has been accepted as a clinical meaningful change in earlier assessment of the study protocol of the ENHANCE study.

The ENHANCE study met its primary endpoint. The responder rate was 33.6% for placebo and 43.2% for fampridine PR 10 mg BID (Risk difference 10.4%, $CI_{95\%}$ 3%; 17.8%, p=0.006). The LS mean change in MSWS score was –6.73 point and–2.59 points in subjects treated with fampridine PR and placebo respectively (Difference –4.14, $CI_{95\%}$ –6.22, –2.06; $p < 0.001$). The effect of fampridine treatment was evident as early as week 2 and was sustained throughout the 24-week treatment period. Discontinuation of treatment resulted in worsening of the MSWS-12 score in the fampridine-PR group but not in the placebo group.

Efficacy on the MSWS-12 was consistent with the findings with respect to the Time Up and GO responders score and the MSIS29-physical score. There were no statistical significant differences with respect to the Berg Balance Scale (BBS; a measure of static balance) and ABILHAND (measure of subject's perceived difficulty in performing everyday manual activities). The proportion of subjects reporting an improvement on the Patient Global Impression of Change (PGIC) at Week 2 was 31% vs 38% for placebo and fampridine PR respectively. This was 22% and 28% at week 24. Findings for the EQ-5D-3L, SDMT, SF-36, and HRU showed relatively little change from baseline and minimal differences between the groups.

The results of the ENHANCE study confirm that treatment with fampridine results in a clinically meaningful improvement in walking in a proportion of patients with multiple sclerosis with walking disability despite the fact that the effect size may be considered as modest. The safety profile of fampridine observed in the ENHANCE is not different from what is already known for fampridine, and no new signals were raised.

Summarising the aim of the ENHANCE study, i.e. to establish the clinical meaningfulness of fampridine in improving walking so as to establish the long term efficacy and safety, this is considered met. Overall the benefit/risk of fampridine remains positive and the granting of a MA not subject to specific obligations is considered justified.

Furthermore, the CHMP agreed to the Product Information changes reflecting data from the pregnancy registry. Conversely, the CHMP refused changes to the statement that fampridine should be taken without food as the Committee considered that more data substantiating this change were needed.

Scientific Summary for the EPAR

In this group of variations the MAH submitted data from the Enhance study (218MS305) conducted in 636 subjects with multiple sclerosis and walking disability. Duration of double-blind treatment was 24 weeks with a 2 week post–treatment follow-up. The primary endpoint was improvement in walking ability,

measured as the proportion of patients achieving a mean improvement of ≥ 8 points from baseline MSWS-12 score over 24 weeks. In this study there was a statistically significant treatment difference, with a greater proportion of Fampyra treated patients demonstrating an improvement in walking ability, compared to placebo-controlled patients (relative risk of 1.38 (95% CI: [1.06, 1.70]). Improvements generally appeared within 2 to 4 weeks of initiation of treatment, and disappeared within 2 weeks of treatment cessation. Based on the results of the study it was agreed that specific obligation has been fulfilled, and therefore it is deleted from the Annex II.

Furthermore, the MAH submitted results of the pregnancy registry FOLLOW which was terminated early due to lack of subject exposure to prolonged-release fampridine during pregnancy. The limited data available indicated no adverse effect of fampridine on the pregnancy outcomes.

3. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II, IIIA and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

This is a grouped variation proposing updates to the SmPC sections 4.2, 4.8, 5.1, Annex II and Package Leaflet based on the clinical study ENHANCE and to the SmPC section 4.6 based on the data from the FOLLOW pregnancy registry. The RMP (version 11) has been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.0. Finally, the CHMP recommends the granting of a marketing authorisation no longer subject to specific obligations.

☒ is recommended for approval.

The group of variations leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

In addition, the following changes in the group are not acceptable:

Variations refused		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	none

Updates to sections 4.2 and 5.2 of the SmPC based on the Core Data Sheet (CDS) and PRAC review of the Fampyra PSUR 03.

Grounds for refusal:

Whereas:

- insufficient data were submitted to support the proposed Product Information changes following the conclusion of the PSUR 3 assessment that the MAH should comment and reconsider the need of a Product

Information update in line with the current CCDS regarding information of 'no clinically meaningful consequences when fampridine is administered with food',

the CHMP has recommended the refusal of the variation to the terms of the marketing authorisation.

The following obligation has been fulfilled, and therefore it is recommended that it be deleted from the Annex II to the Opinion:

Description	Due date
To provide results of a double-blinded, placebo-controlled, long-term efficacy and safety study to investigate a broader primary endpoint clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide further treatment based on a CHMP agreed protocol. An update of the progress in completing the obligation should be provided every 6 months.	31 December 2016

Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Fampyra (fampridine) is removed from the additional monitoring list as the specific obligation has been fulfilled and the medicinal product was authorised more than 5 years ago.

Therefore the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the summary of product characteristics and the package leaflet.

4. Scientific discussion

4.1. Introduction

Fampyra is a prolonged release (PR) tablet formulation containing fampridine or 4-aminopyridine (4-AP). Fampyra is also known as Ampyra (dalfampridine).

Fampridine is indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability.

Fampridine is a potassium channel blocker effective at selective types of voltage-gated potassium channels. Fampridine facilitates signal transmission in demyelinated axons, improving impaired neurological function induced by demyelination.

Fampridine has been granted a conditional approval as the product demonstrated benefits in terms of improving walking speed together with an improvement on the multiple-sclerosis walking scale score. The conditional marketing authorization application for fampridine was supported by 1 Phase 2 study (MS-F202), 2 pivotal Phase 3 studies (MS-F203 and MS-F204), and 3 extension studies (MS-F202EXT, MS-F203EXT, and MS-F204EXT).

However, approximately only one third of the patients may benefit from treatment, and the extent of benefit provided by fampridine was not completely explained by the data generated. In particular the clinical meaningfulness of walking endpoints, long term safety, and efficacy needed further evaluation. Therefore, at the time of approval the CHMP was of the opinion that additional efficacy data was required, i.e. from a double-blinded, placebo-controlled, long-term efficacy and safety study in order to investigate a broader primary endpoint, which is clinically meaningful in terms of walking ability and to further

evaluate the early identification of responders in order to guide further treatment. Hence, the marketing authorisation was granted subject to a following condition:

"To conduct a double-blinded, placebo-controlled, long-term efficacy and safety study to investigate a broader primary endpoint clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide further treatment based on a CHMP protocol. An update of the process in completing the obligation should be provided every 6 months. (SOB10.1)."

To fulfil this obligation the Applicant has submitted a clinical development plan containing a two step plan with a phase 2 exploratory study (MOBILE) and a phase 3 confirmatory study (ENHANCE).

Study 218MS205 (MOBILE) in 132 subjects was performed to explore the impact of prolonged release fampridine on overall walking disability and to further elucidate the clinical relevance of changes over the 24 week treatment duration. Using the Patient Global Impression of Change (PGIC) and other anchor and distribution-based analyses, the minimum clinically important difference (MCID) on the 12-item Multiple Sclerosis Walking Scale (MSWS-12) was estimated at 8 points and the MCID for improvement of Timed Up and Go (TUG) speed was estimated to be a ≥15% mean increase in speed over a 24-week treatment period.

The ENHANCE study (study 218MS305) now has been completed and is submitted. Based on the results from the ENHANCE study the Applicant concludes that the specific obligations of the conditional marketing authorization have been fulfilled and requests for a full marketing authorization.

4.2. Clinical Efficacy aspects

Enhance study (study 218MS305)

4.2.1. Methods – analysis of data submitted

The Enhance study concerned a randomised, multicentre (n=92) double blind, placebo controlled parallel group study to evaluate the long tem efficacy and safety of fampridine PR 10 mg BID in 646 subjects with multiple sclerosis.

The study was performed in in Bulgaria (13 sites), Czech Republic (9 sites), Finland (4 sites), Great Britain (13 sites), Italy (5 sites), Lithuania (3 sites), Netherlands (3 sites), Poland (16 sites), Russia (6 sites), Serbia (3 sites), and US (17 sites).

The primary objective was to determine whether prolonged-release fampridine 10 mg twice daily has a clinically meaningful effect on patient-reported walking ability over a 24-week treatment period.
Main inclusion criteria were a documented diagnosis of MS (RRMS, PRMS SPMS, PPMS) of at least 3 months duration, an EDSS score of 4 and ≤7 and the presence of a walking impairment as deemed by the investigator. Main exclusion criteria were the presence of history of seizures, MS exacerbation < 60 days prior screening, concurrent medications and/or conditions that interferes with walking capacity, initiation of disease modifying treatments, renal dysfunction and hepatitis.

After a 2 week screening period, subjects were randomised to fampridine PR 10 mg BID or matching placebo. Randomisation ratio was 1:1 and randomisation was stratified by baseline EDSS score (≤6 or >6) and after an protocol amendment by prior amino-pyridine use. Duration of double-blind was 24 weeks. This was followed by a 14 day post-dosing follow-up.

The following efficacy assessments were performed:

MSWS-12: The Multiple Sclerosis Walking Scale is a 12-item questionnaire that asks subjects to rate

limitations of their mobility due to MS during the preceding 2 weeks on a 5-point Likert scale from not at all (1) to extremely (5). Subjects were asked if they cannot walk at all at the beginning of the questionnaire, and if the subject indicated this was the case, then they did not respond to the 12 questions. The transformed scale ranges from 0 to 100, with higher scores showing a greater degree of limitation in walking due to MS.

***TUG*:** The Timed up en Go test is a mobility assessment in which subjects must stand from a seated position in a chair, walk 3 meters, and turn and return to seated. The time to complete the task is recorded.

MSIS-29 physical score: The Multiple Sclerosis Impact Scale is a subject completed questionnaire that comprises 29 questions to measure the physical (questions 1 to 20) and psychological (questions 21 to 29) impact of MS. The physical score is calculated by summing across the 20 relevant items and transformed to a scale from 1 (no impact of MS) to 100 (extreme impact of MS).

BBS: The Berg Balance Scale is a clinical test of a subject's static and dynamic balance ability, and includes 14 balance-related tasks, each scored from unable to perform (0) to able to perform independently (4). The total score ranges from 0 (poor balance) to 56 (good balance).

ABILHAND: The ABILHAND is a subject-completed questionnaire that measures a subject's perceived difficulty in performing everyday manual activities during the preceding 3 months. Subjects rate a list of 56 activities as impossible (0), difficult (1), or easy (2). The transformed scale ranges from 0 to 100, where higher scores indicate greater manual ability.

***PGIC**:* The Patient Global Impression of Change elicits a subject's rating of change in overall walking compared with the prior study visit using a 7-point Likert scale including very much worse (1), unchanged (4), and very much improved (7).

***EQ-5D-3L*:** The EuroQol health-related quality of life questionnaire is an assessment of 5 aspects of health-related quality of life (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each on a 3-point scale ranging from no problems (1) to extreme problems (3). The assessment also includes a visual analog scale (VAS) ranging from worst imagined health state (0) to best imagined health state (100); positive change indicates improvement.

***SDMT*:** The Symbol Digit Modalities Test is a substitution test that assesses changes in cognitive function over time. Subjects have 90 seconds to pair numbers with geometric figures, and the score is the number of correct responses during that time. Positive change indicates improvement.

***SF-36*:** The Short Form Health Survey is a health survey with 36 questions split across several categories (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, Mental Health, and Reported Health Transition) that are used to construct a physical component summary (PCS) and a mental component summary (MCS).

***HRU*:** The Health Resources Utilization questionnaire collects information on how MS affects subjects' lives and how they use health care services. The questions are grouped into sections for Work Status (whether a subject is employed and whether lack of employment is due to walking problems) and Absenteeism (days missed due to walking problems), Health Care Services (types of health care providers visited due to MS), and Caregiver Services (use and frequency of visits to the subject by caregivers).

The primary endpoint was the proportion of subjects who achieved a mean improvement on the MSWS-12 of ≥8 points from baseline over the 24-week treatment period. If a subject's mean MSWS-12 was <8 points at baseline, the subject was counted as having a ≥8-point mean improvement from baseline if their mean MSWS-12 score during the treatment period was <0.5.

Secondary efficacy endpoints were the Timed Up and Go (TUG), 29-Item Multiple Sclerosis Impact Scale (MSIS-29), the Berg Balance Scale (BBS) and the ABILHAND.

Exploratory endpoints concerned the Patient Global Impression of Change (PGIC), the EuroQol-5 Dimensions-3 Levels (EQ-5D-3L) visual analog scale (VAS) and utility score, the Symbol Digit Modalities Test (SDMT) and the 36-Item Short Form Health Survey (SF-36), with physical component subscale (PCS) and mental component subscale (MCS) and Health resource utilization (HRU).

Safety variables concerned the occurrence of adverse events, physical examination, vital signs, electrocardiogram, and clinical laboratory assessments (including urine culture for suspected urinary tract infection).

Sample Size Calculations: a sample size of approximately 590 subjects (295 subjects in each treatment group) was expected to provide at least 90% power at a 2-sided 5% significance level to detect a minimum of 14.5% absolute improvement in the on-treatment response rate (i.e. ≥ 8-point mean improvement on MSWS-12 over 24 weeks) for the prolonged-release fampridine group relative to the placebo group, assuming a response rates of 50% under the null hypothesis and a 15% dropout rate.

Analysis population: The main population for efficacy analyses was the ITT population defined as all subjects who were randomized and received at least 1 dose of study treatment and had at least 1 post-baseline efficacy assessment, excluding subjects from one site due to GCP noncompliance. The safety population consisted of all subjects who were randomized and received at least 1 dose of study treatment, excluding subjects from one site.

Methods of analyses

Primary efficacy analysis

The primary efficacy analysis was performed in the ITT population with missing data handled using the multiple imputation method. Comparisons between the prolonged-release fampridine and placebo treatment groups were made using a logistic regression model adjusted for treatment group, baseline MSWS-12 score, baseline TUG speed, age, prior AP use, and screening EDSS score.

Sensitivity analysis of the primary endpoint concerned analysis of the PP population, analysis of observed data, analysis including the one site analysis exclusion subjects with prior use of amino-pyridine, among others.

Secondary efficacy analysis

TUG: The proportion of subjects who achieved a mean improvement in TUG speed of ≥15% from baseline over a 24-week period was compared between treatment groups using a logistic regression model adjusted for treatment group, baseline TUG speed, prior aminopyridine use, and screening EDSS score. Baseline was defined as the mean speed over the Screening and Day 1 Visits.

MSIS-29 physical score, BBS, and ABILHAND: The mean changes from baseline over 24 weeks in the MSIS-29 physical score, BBS, and ABILHAND scores were compared using a mixed effects model adjusted for treatment group, corresponding baseline score, screening EDSS score, prior AP use, and visit-by-treatment interaction.

Multiplicity

Hypothesis testing was performed at the 2-sided 5% significance level overall, with adjustment for testing multiple secondary endpoints using a combination of the sequential stepdown procedure and the Hochberg procedure to control the overall Type I error rate. 1. The 4 secondary endpoints were divided into the following 2 groups i.e. Group 1: TUG responders, change from baseline in the MSIS-29, physical

score, Group 2: change in BBS, change in ABILHAND. If the each endpoint in group 1 was were statistically significant at the 5% significance level, then each of the endpoints in Group 2 were tested at the 5% significance level. If one of the endpoints in Group 1 had a p-value greater than 0.05, then the other endpoint in Group 1 was tested at the 2.5% significance level, and then the Group 2 endpoints were each tested at the 2.5% significance level. If neither of the endpoints in Group 1 were statistically significant based on either of the 2 criteria above, the endpoints in Group 2 were not considered statistically significant.

Secondary en exploratory efficacy analysis

Least squares (LS) means, LS mean differences, and 95% confidence intervals (CIs) were presented for the EQ-5D-3L VAS and utility score and SDMT using a mixed model for repeated measures with randomized treatment group, visit, baseline score, EDSS score at screening, treatment group-by-visit interaction, and prior AP use included in the model. Analyses of SF-36 were performed using an analysis of covariance with adjustment for treatment group, baseline score (PCS or MCS), screening EDSS score, and prior AP use, and LS means, LS mean differences, and 95% CIs were presented. The proportions of subjects with an improvement on the PGIC and changes in HRU over time were also summarized.

Evaluation of Early Assessment of Response

Analyses were also performed to assess the predictive values of different measures of early response.

Study data were also used for evaluating the early identification of responders. The following analyses were performed using MSWS-12 and TUG speed data to assess whether subjects who showed benefit after 2 or 4 weeks of treatment were the same subjects who were responders on the MSWS-12 over 24 weeks: Positive predictive value (PPV), Negative predictive value (NPV): Sensitivity and Specificity. Different definitions of early response at each of 2 and 4 weeks were used to predict the overall response on MSWS-12.

Subgroup analysis

Analyses of MSWS-12 response, TUG speed, MSIS-29 physical component scores, BBS scores, and ABILHAND were performed for the following subgroups: EDSS score (≤6, >6), MS disease phenotype (RRMS, SPMS, PPMS, PRMS), MSWS-12 baseline score (≤ median, > median). Analyses of MSWS-12 and TUG speed were also performed for Age group (≤45 years, >45 years), Sex (male, female), BMI (<18.5 kg/m^2, 18.5 to 24.9 kg/m^2, 25 to 29.9 kg/m^2, ≥30 kg/m^2) and concomitant immunomodulator use (yes, no).

4.2.2. Results

Patient disposition, baseline feature

In table 4.2.2.1a and table 4.2.2.1b the number of subjects, demographics and baseline features are presented. A total of 636 subjects were randomised at 92 sites worldwide. Data from one site were excluded due to serious Good Clinical Practice (GCP) noncompliance. The decision to close this site was based primarily on the lack of appropriate source documents to support the accuracy completeness, and reliability of the data entered in the case report form. Ten subjects were randomized at the site. Sensitivity analyses that include data from this site showed no appreciable difference in the overall outcomes of efficacy evaluations relative to analyses that exclude these data.

Treatment was discontinued in 15% of the subjects treated with fampridine-and in 19% of in the placebo group. The most common reason for discontinuation in both groups was adverse events (7% in both treatment groups). Subject's perception of lack of efficacy was reason to discontinue in 2 subjects (<1%) treated with fampridine-PR and in 10 subjects (3%) treated with placebo.

TABLE 4.2.2.1a: Subjects disposition			
	Placebo	**Fampridine 10 mg BID**	Comments
Subject disposition			
$n_{randomised}$	319	317	Excluding one site due to serious GCP non-compliance issues observed during the conduct of the study. The site closed primarily because of the lack of appropriate source documents to support the accuracy, completeness, and reliability of the data entered in the CRF. There were 10 subjects randomized at the site, and 6 were active at the time the decision was made to close the site. These 6 subjects were discontinued from the study at the request of the Sponsor.
n_{ITT}	318	315	
$n_{completed\ treatment}$	258	271	
$n_{completed\ study}$	254	266	
Discontinuation of treatment due to :			
Adverse events	23	21	
Non-compliance	10	6	
Lack of efficacy	10	2	
Consent withdrawn	10	5	
Other	6	11	
Lost in FU	2	1	

Demographics, baseline disease characteristics, are presented in table 4.2.2.1b. Demographics features, baseline disease characteristics, and medical history of were comparable for both study arms.

The proportions of subjects with each MS type, duration of disease were similar in the fampridine-PR and placebo groups.

The treatment groups were balanced with respect to EDSS score, MSWS-12 score, TUG speed, MSIS-29 physical score, BBS score and ABILHAND score. Concomitant medication use was similar in treatment groups and prior aminopyridine use was also balanced. Most frequent immunomodulators used were glatiramer, (8%/9% for placebo and fampridine respectively), fingolimod (7%/7%), interferon beta-1a (7%/6%) and natalizumab (6%/7%). Anti-epileptic agents affecting sodium-potassium was were used in: 43 subjects (14%) treated with prolonged-release fampridine and 44 subjects (14%) treated with placebo. The most common agents used were gabapentin, clonazepam, and pregabalin.

TABLE 4.2.2.1b Demographics, baseline features

		Placebo	Fampridine 10 mg BID
Demographics			
Age		48.8 (10.5)	49.0 (9.83)
≥ 65 years of age		5%	4%
Female		57%	59%
Disease features			
MS Phenotype	RRMS	49%	54%
	SPMS	31%	30%
	PPMS	14%	13%
	PRMS	6%	3%
Time since first MS symptoms		15.8	16.0
Time since MS diagnosis (Y)		11.4	11.5
Relapse past 12 months		33%	32%
Time since most recent relapse (yrs, median)		1.7	1.6
EDSS score (median)		5.5	6.0
Distribution EDSS score			
EDSS 4.0-4.5		29%	28%
EDSS 5.0-5.5		22%	17%
EDSS 6.0		27%	33%
EDSS> 6.0		23%	22%
Baseline performance (mean , SD)			
MSWS-12 score		65.4 (21.9)	63.6 (21.7)
TUG (ft/sec)		0.38 (0.20)	0.38 (0.19)
MSIS-29		55.3 (21.0)	52.4 (21.1)
BBS score		40.2 (11.8)	40.6 (11.6)
ABILHAND score		84.3 (16.5)	86.9 (15.8)
Cardiovascular History[A]		28%	31%
Medication			
Prior Amino-pyridine use		8%	10%
Concomitant medication :			
Immunomodulators		39%	40%
AED		14%	14%
Baclofen		20%	21%

[A]Not further specified

Study treatment exposures in the fampridine-PR and placebo groups in the ITT population were similar. The mean (SD) duration of exposure was 22.64 weeks (4.567) in the fampridine-PR group and 21.52 weeks (6.012) in the placebo group, and the mean (SD) time on study was 25.18 (4.89) and 24.34 (6.14) reflecting the 2-week follow-up period. Mean (SD) compliance with study drug dosing based on accountability was 98.7% (3.90) in the fampridine-PR group and 98.4% (4.59) in the placebo group.

Efficacy

Primary endpoints, primary efficacy analysis

The primary efficacy endpoint was the proportion of subjects who achieved a mean improvement on the MSWS-12 of ≥8 points from baseline over a 24-week treatment period. A higher proportion of subjects treated with prolonged-release fampridine demonstrated a ≥8-point mean improvement on the MSWS-12 over 24 weeks compared with subjects treated with placebo. The primary efficacy analysis using a logistic regression model showed that the treatment difference was statistically significant; the odds ratio was 1.61 (95%CI: [1.15, 2.26]; p = 0.006 in favour of prolonged-release fampridine. These findings are supported by the relative risk of 1.38 (95% CI: [1.06, 1.70]) and the risk difference of 0.104 (95% CI: [0.030, 0.178]. See table 2a.

TABLE 4.2.2.2a Primary endpoint

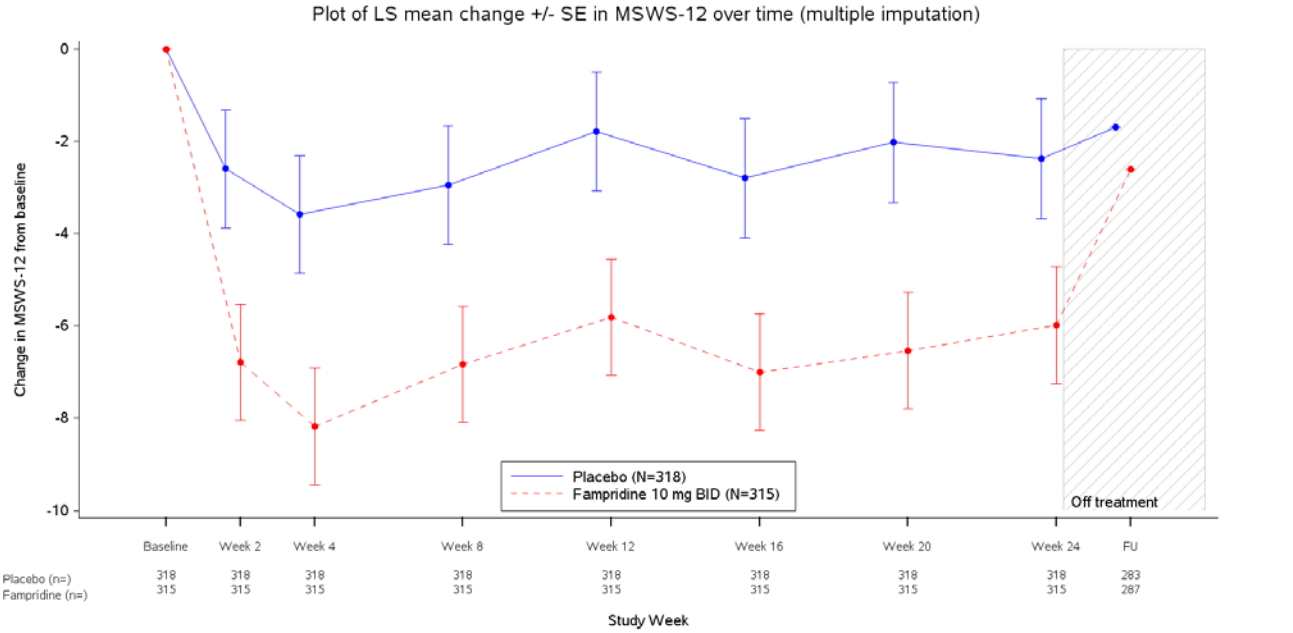
	Placebo	**Fampridine 10 mg BID**	
n	318	315	
Responders[A]	33.6%	43.2%	
Odd ratio, $CI_{95\%}$[B]	1.61 (1.15 ; 2.26)		
Risk ratio, $CI_{95\%}$	1.38 (1.06 ; 1.70)		
Risk difference, $CI_{95\%}$	10.4% (3% ; 17.8%)		
p-value[B]	0.006		

[A]A responder is defined as a subject with a mean improvement of at least 8 points over 24 weeks compared to baseline. If a subjects has a mean MSWS-12 score of <0.5 over the double-blind period, and a baseline MSWS-12 score of <8 points, the subject is counted as a responder.

[B]Based on logistic regression, adjusting for baseline MSWS-12 score, baseline TUG speed, age, screening EDSS score and prior aminopyridine use.

The LS mean change in MSWS score was –6.73 point and–2.59 points in subjects treated with fampridine PR and placebo respectively. The LS mean difference between the groups was –4.14 (95% CI: –6.22, –2.06; p < 0.001). The effect of prolonged-release fampridine treatment was evident as early as Week 2, and was sustained throughout the 24-week treatment period (figure 1). Upon discontinuation of double-blind treatment after 24 weeks, scores worsened among subjects treated with prolonged-release fampridine but not among those treated with placebo.

Figure 1 Plot of Least Squares Mean Change (± Standard Error) in MSWS-12 Over Time (Multiple imputation).



Subjects from Site 513 are excluded from the analysis. Multiple imputation is used for missing data for post-baseline visits except FU where observed data is used.
Note 1. Baseline is defined as mean of Screening and Day 1 visits.
2. Solid lines denote standard error for the LS mean change at each visit. For FU mean value has been plotted.
3. LS mean and SE are based on MMRM model using a common variance AR(1) variance-covariance matrix structure. Treatment, time and treatment by time interaction were included in the model as explanatory variables, adjusting for screening EDSS, baseline MSWS-12, baseline TUG speed, age and prior aminopyridine as covariates.
4. A negative change indicates an improvement in walking.
Abbreviations: MSWS-12 = Multiple Sclerosis Walking Scale-12; MMRM = Mixed model for repeated measures; SE = Standard error; FU = 2 week follow-up; LS = Least Squares.
SOURCE: 218MS/218MS305/CSR/F-EFF-MSWS-LSM-CHG-MI.SAS
DATE: 14JUL2016

Subgroup analysis primary endpoint

Subgroup analysis largely supported the main findings. See figure 2. The proportions of responders were higher among subjects with RRMS, and lower among subjects with SPMS and PPMS, relative to the overall population. The results among subjects with PRMS were inconsistent with those of the main analysis. For subjects with less disability (i.e., a lower baseline MSWS-12 score), the difference in proportions and odds ratio are larger than those for the overall population. For subjects with greater disability, the difference in proportions and odds ratio are smaller than for the overall population.

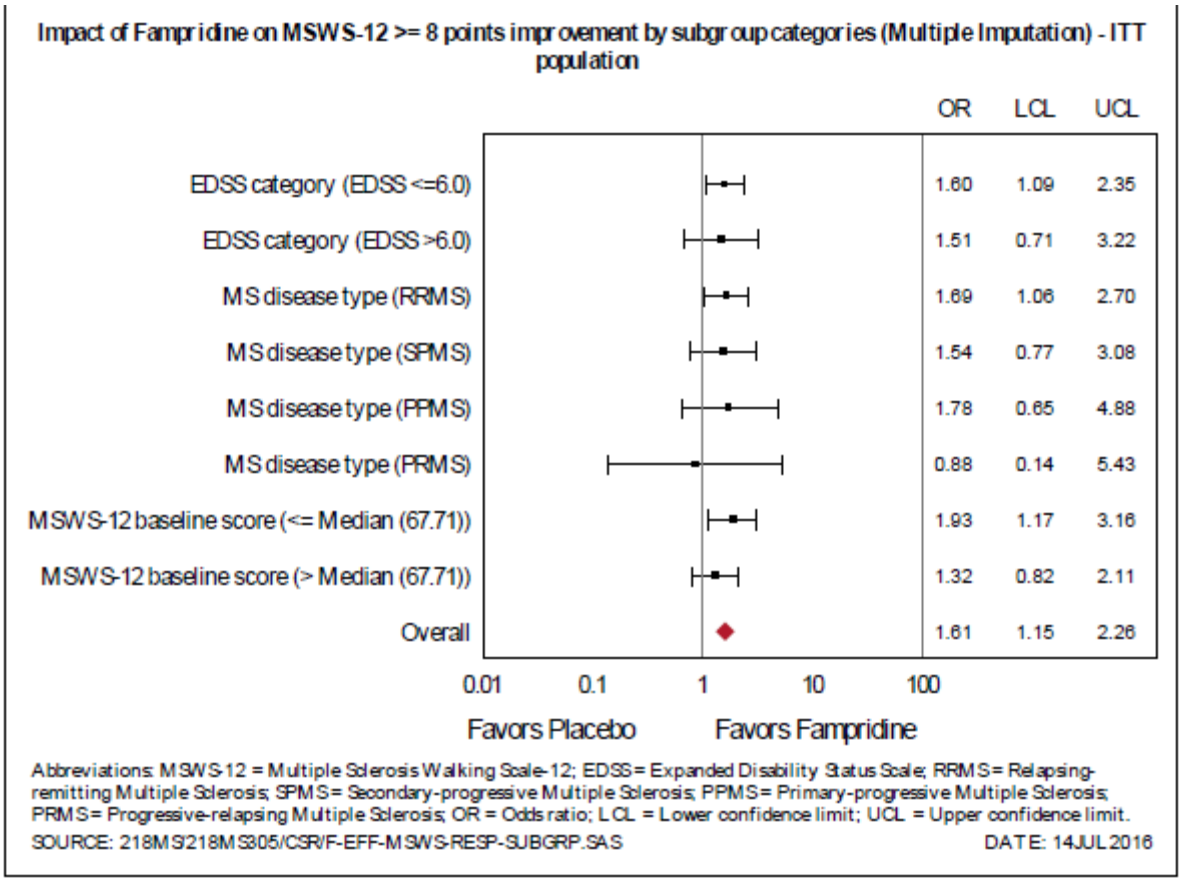
Among subjects with a baseline EDSS score >6, the proportion of MSWS-12 responders was lower and the difference between the groups was smaller for both measures.

Among subjects with RRMS, results were generally more favourable in both groups than for the population overall, and among subjects with SPMS, results were generally slightly less favorable in both groups than for the population overall, which may be expected given the natural course of the disease, but treatment differences in favour of fampridine-PR remained.

Among subjects with PPMS and PRMS, differences between the groups were generally smaller than for the population overall or, in some instances favored placebo treatment, particularly for PRMS. These findings were likely affected by the small sample sizes in these subgroups and also by the greater disability and likelihood of progression among subjects with these disease types.

The difference between the groups in proportions of responders on the MSWS-12 was greater among those with baseline MSWS-12 lower than the median (67.71) and smaller among those with higher baseline scores.

Figure 2



Within the subgroups of only males and only females, the proportions of responders were similar to that of the overall population for subjects treated with prolonged-release fampridine. For subjects treated with placebo, the proportions of responders were lower among males and higher among females relative to the overall population. Male: 0.431 for prolonged-release fampridine and 0.301 for placebo; odds ratio 1.91 (95% CI: [1.11, 3.28]). Female: 0.434 for prolonged-release fampridine and 0.362 for placebo; odds ratio 1.52 (95% CI: [0.96, 2.39]).

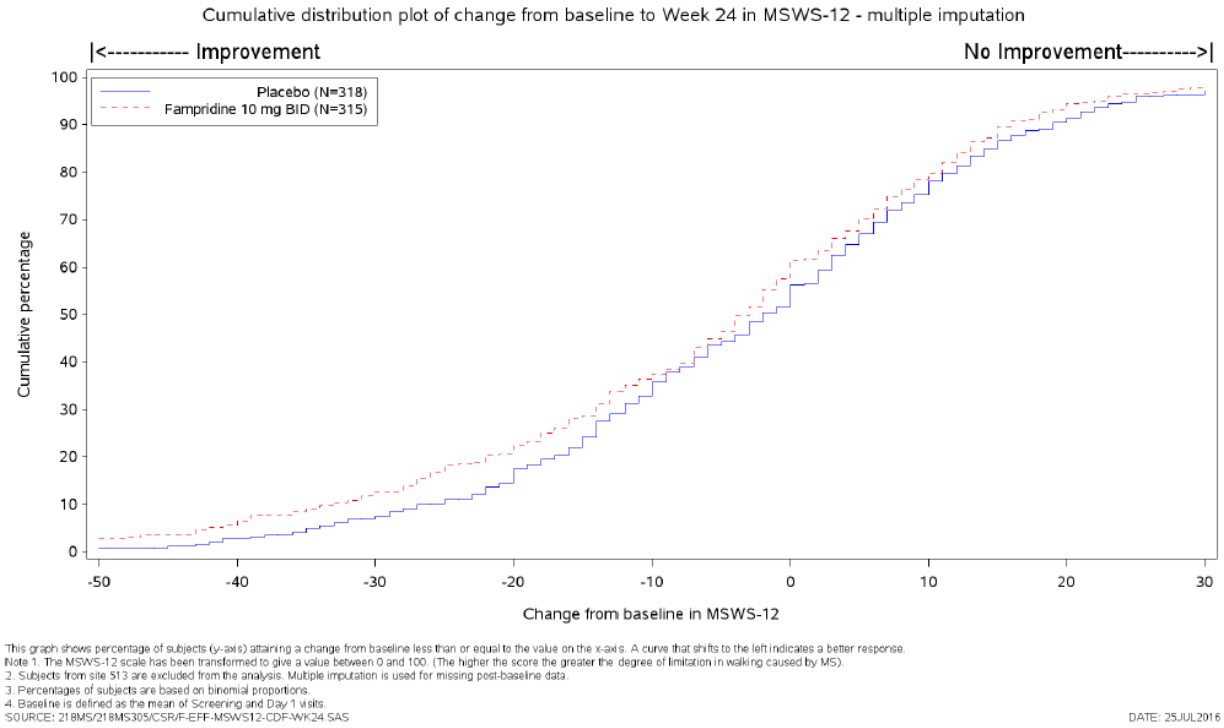
Because the number of subjects over 64 years of age was small, these subjects were combined with those >45 years of age. The proportions of responders in both treatment groups were slightly larger among younger subjects and slightly smaller among older subjects than those of the overall population. ≤45 years: 0.452 for prolonged-release fampridine and 0.373 for placebo; odds ratio 1.48 (95% CI: [0.84, 2.61]). >45 years: 0.422 for prolonged-release fampridine and 0.315 for placebo; odds ratio 1.73 (95% CI: [1.13, 2.65]).

Relative to the overall population, proportions of responders were higher among subjects with concomitant use of immunomodulators and lower among subjects without, but the treatment differences were similar to that of the overall population in favour of prolonged-release fampridine. Using immunomodulators: 0.483 for prolonged-release fampridine and 0.386 for placebo; odds ratio 1.58 (95% CI: [0.91, 2.73]). Not using immunomodulators: 0.399 for prolonged-release fampridine and 0.304 for placebo; odds ratio 1.60 (95% CI: [1.02, 2.50]).

Exploratory analysis primary endpoint

Exploratory analysis showed that the benefit from treatment with fampridine-PR was robust at each threshold of improvement from 0 to 10 points (figure 3).

Figure 3: Cumulative Distribution Plot of Change From Baseline to Week 24 in MSWS-12 (Multiple Imputation)



Sensitivity analysis primary endpoint

ITT population using a placebo imputation method: The proportion of responders in the fampridine-PR group (0.419) was smaller than the proportion in the main analysis (0.432), but it was still greater than the proportion of responders in the placebo group (0.336), and the treatment difference was statistically significant (p =0.013; odds ratio: 1.53; 95% CI: [1.09, 2.15]).

ITT population with adjustment for any major protocol deviation related to IP compliance: The proportions of responders in each group were the same as those observed in the main analysis. The treatment difference was statistically significant (p = 0.007; odds ratio: 1.60 in favor of fampridine-PR; 95% CI: [1.14, 2.25]), and the interaction was not statistically significant (p=0.720 for the IP compliance-by-treatment interaction).

Secondary endpoints

Results with respect to the secondary endpoints are summarised in table 4.2.2.2.b.

A greater proportion of subjects treated with fampridine-PR demonstrated a mean improvement of at least 15% in TUG speed over 24 weeks compared with subjects treated with placebo. The results from the logistic regression analysis showed a statistically significant treatment difference with an odds ratio of 1.46 (95% CI: [1.04, 2.07]; p = 0.030). The relative risk was 1.25 (95% CI: [0.99, 1.51]) and the risk difference was 0.092 (95% CI: [0.009, 0.175]).

TABLE 4.2.2.2.b : Results main secondary outcomes

	Placebo	**Fampridine 10 mg BID**	Analyses			
n	318	315	Estimate		CI95%	p-value
TUG						
			OR	1.46	1.04 ; 2.07	
TUG-responders[A]	43.%	35%	RR	1.25	0.99 ; 1.51	0.03
			RD	9%	0.9% ; 17.5%	
Baseline (sec)	27.1	24.9				
Change from BL (sec)	-1.94	-3.3	LSM_{diff}	-1.36	-2.85 ; 0.12	0.07
MSIS29 physical						
Baseline score	55.29	52.44				
Change from BL	-4.68	-8.00	LSM_{diff}	-3.31	-5.13 ; -1.50	< .001
≥7.5 point improvement	34%	44%	Post-hoc Observed data , no analysis			
BBS						
BL-score	40.2	40.6				
Change from baseline	1.34	1.75	LSM_{diff}	0.41	-0.13 ; 0.95	0.14
ABILHAND						
BL-score	84.3	86.9				
Change from baseline	0.75	1.49	LSM_{diff}	0.74	-0.38 ;1.86	0.20
$PGIC_{week\ 2}$ (median)	4.0	4.0				
Very much improved	<1%	<1%				
Much improved	2% | 31%	5% | 38%	Exploratory, no analysis			
Slightly improved	28%	33%				
Unchanged	53%	52%				
Worse	17%	10%				
$PGIC_{week\ 24}$ (median)	4.0	4.0				
Very much improved	1%	2%				
Much improved	3% | 25%	7% | 28%	Exploratory, no analysis			
Slightly improved	18%	19%				
Unchanged	42%	44%				
Worse	36%	29%				

[A] TUG-responders: proportion of subjects who achieved a mean improvement in TUG speed of ≥15% from baseline over a 24-week period.
[B]MSIS-29 score ranges from 0 (no impact of MS) to 100(extreme impact of MS).A negative change indicates an improvement in function.
[C]BBS: (c) BBS scores range from 0 (poor balance) to 56 (good balance). A positive change indicates an improvement in balance.
[D]ABILHAND scores range from 0 (poor manual ability) to 100 (good manual ability). A positive change indicates an improvement in manual ability.

[E] PGIC patients global impression of change

A greater LS mean improvement in MSIS-29 physical score was observed among subjects treated with fampridine-PR over 24 weeks than among subjects treated with placebo. The LS mean difference between the groups showed a statistically significant treatment difference.

A greater LS mean improvement in BBS was observed in subjects treated with fampridine-PR than in subjects treated with placebo. The treatment difference was not statistically significant.

A greater LS mean improvement in ABILHAND score was observed for subjects treated with fampridine-PR than for subjects treated with placebo. The treatment difference was not statistically significant.

The proportion of subjects reporting any improvement on the PGIC, which, like the MSWS-12, is a patient-reported assessment of walking ability, was greater in the fampridine-PR group than in the placebo group at each time point. At Week 2, which showed change since the onset of treatment (because the PGIC assessed changes since the previous visit), improvement was reported by 116 subjects (38%) treated with fampridine-PR and 95 subjects (31%) treated with placebo.

Findings for the EQ-5D-3L, SDMT, SF-36, and HRU showed relatively little change from baseline and minimal differences between the groups.

Identification of Responders

Among subjects treated with fampridine-PR, **any** improvement on the MSWS-12 at Week 2 or 4 showed strong PPV and NPV for the response (≥8-point mean improvement) over the 24-week treatment period.

Among subjects who had any improvement on the MSWS-12 at Week 2 (197 subjects), the probability that a subject was a responder based on ≥8-point mean improvement in the MSWS-12 over 24 weeks (120 subjects), or the PPV, was 61.1%. Of subjects who were responders based on ≥8-point mean improvement in the MSWS-12 over 24 weeks (136 subjects), the probability that a subject had any improvement on the MSWS-12 at Week 2, or sensitivity, was 88.3%.

Among subjects who had no improvement on the MSWS-12 at Week 2 (118 subjects), the probability that a subject was also not a responder based on ≥8-point mean improvement in the MSWS-12 over 24 weeks (102 subjects), or the NPV, was 86.5%. Of subjects who were not responders over 24 weeks, the probability that a subject had no improvement on the MSWS-12 at Week 2, or specificity, was 57.2%.

Among subjects treated with fampridine-PR, any improvement in TUG speed at Week 2 or 4 showed reasonable PPV and strong NPV for the response (≥15% improvement) over the 24- week treatment period. Early improvement in TUG speed did not have strong predictive values for MSWS-12 response over 24 weeks and early improvement in MSWS-12 did not have strong predictive values for TUG speed response over 24 weeks. A composite definition of early response, including any improvement in either measure, did not have any stronger predictive power than the definition including the given endpoint alone.

TABLE 4.2.2.3

Early Responder Analysis to Predict Response Over 24 Weeks Among Subjects Treated With Prolonged-Release Fampridine – ITT Population

	Subjects meeting early criteria (%)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
Any improvement in MSWS-12 (early criterion) to predict ≥8 point mean improvement on MSWS-12 over 24 weeks					
At Week 2	197/315 (62.5)	120/197 (61.1)	102/118 (86.5)	120/136 (88.3)	102/179 (57.2)
At Week 4	206/315 (65.3)	121/206 (58.7)	94/109 (85.8)	120/136 (88.6)	94/179 (52.5)
Any improvement in TUG speed (early criterion) to predict ≥15% mean improvement in TUG speed over 24 weeks					
At Week 2	245/315 (77.7)	123/245 (50.3)	56/70 (80.3)	123/137 (89.8)	56/178 (31.7)
At Week 4	245/315 (77.9)	127/245 (51.8)	60/70 (85.9)	127/137 (92.8)	60/178 (33.6)

Source: Table 172, Table 173, Table 176, and Table 177.
Notes:
1: Subjects from Site 513 are excluded from the analysis. Multiple imputation is used for MSWS-12 and TUG missing data for postbaseline visits.
2: PPV was defined as [the number of subjects who achieved the overall threshold and early criterion] divided by the number of subjects who achieved the early criterion.
3: NPV was defined as [the number of subjects who did not achieve both the overall threshold and early criterion] divided by the number of subjects who did not achieve the early criterion.
4: Sensitivity was defined as [the number of subjects who achieved the overall threshold and early criterion] divided by the number of subjects who achieved the overall threshold.
5: Specificity was defined as [the number of subjects who did not achieve both the overall threshold and early criterion] divided by the number of subjects who did not achieve the overall threshold.
Abbreviations: MSWS-12 = 12-item Multiple Sclerosis Walking Scale; NPV = negative predictive value; PPV = positive predictive value; TUG = Timed Up and Go

Different cut-off values for improvement on the MSWS-12 or combination of MSWS–TUG did not lead to better values.

CONCLUSION

The Enhance study met its primary and first 2 secondary endpoints, showing statistically significant differences between the treatment groups in improvements on MSWS-12, TUG speed, and MSIS-29 physical component score results, and trends in favour of treatment with prolonged release fampridine in the BBS and ABILHAND assessments and several exploratory assessments.

In general, treatment response was evident across patient-reported and clinician assessed measures of walking ability as early as Week 2 and was sustained throughout the treatment period and then returned to baseline after treatment was stopped in the post-treatment follow-up period. Results of analyses in subgroups defined by demographic or baseline disease characteristics were consistent with those for the overall study population.

Other analyses support the use of assessments performed at approximately 2 or 4 weeks after the initiation of treatment to predict the likelihood of longer-term response.

These findings were supported in a variety of sensitivity analyses, including one performed excluding subjects with prior AP use, which indicated that the improvement shown among subjects treated with prolonged-release fampridine was not dependent upon any greater propensity to benefit among subjects with prior AP treatment.

The findings in the ENHANCE trial were consistent with previous study results of fampridine-PR as well as with experience in clinical use, and confirm that fampridine-PR treatment results in clinically meaningful improvements in walking for MS patients with pre-existing walking disability.

4.2.3. Discussion

As part of CMA the Applicant conducted the ENHANCE study which now has been completed. The aim of the study was to evaluate the clinical meaningfulness of the effect of fampridine in terms of walking ability as well as the long term efficacy and safety.

The ENHANCE study concerned a randomised placebo controlled parallel group study in 636 subjects with multiple sclerosis and walking disability. Subjects were randomised to placebo or fampridine PR 10 mg BID. Duration of double-blind was 24 weeks with a 2 week post–treatment follow-up. Primary endpoint was the proportion responders defined as a subject with a mean improvement on the Multiple Sclerosis Walking Scale of ≥ 8 points as compared to baseline. If a subject's mean MSWS-12 was <8 points at baseline, the subject was counted as having a ≥8-point mean improvement from baseline if their mean MSWS-12 score during the treatment period was <0.5.

A main inclusion criterion was the presence of a walking impairment as deemed by the investigator. This appears rather subjective. However, considering the baseline EDSS score and baseline MSWS-12 scores (table 4.2.2.1b) this is not an issue.

An improvement of 8 points on the MSWS-12 has been accepted as a clinical meaningful change in earlier assessment of the study protocol of the ENHANCE study. This was based on the results of the MOBILE study. In this pilot study the impact of fampridine PR on overall walking disability was evaluated over a 24 weeks in a 132 patients. Using the Patient Global Impression of Change (PGIC) and other anchor and distribution-based analyses, the minimum clinically important difference (MCID) on the 12-item Multiple Sclerosis Walking Scale (MSWS-12) was estimated at 8 points. However, the relevance of the MCID for improvement of Timed Up and Go i.e. ≥15% mean increase in speed over a 24-week treatment period has been questioned in the same assessment. This appears to be confirmed by current data . See TABLE 4.2.2.2.b Results main secondary outcomes.

The ENHANCE study met its primary endpoint. The responder rate was 33.6% for placebo and 43.2% for fampridine PR 10 mg BID (Risk difference 10.4%, $CI_{95\%}$ 3%; 17.8%, p=0.006). The LS mean change in MSWS score was–6.73 point and–2.59 points in subjects treated with fampridine PR and placebo respectively (Difference –4.14, $CI_{95\%}$ –6.22, –2.06; p < 0.001). The effect of prolonged-release fampridine treatment was evident as early as week 2, and was sustained throughout the 24-week treatment period (see figure 1). Upon discontinuation of double-blind treatment after 24 weeks, scores worsened among subjects treated with prolonged-release fampridine but not among those treated with placebo. Of note in the earlier 12 weeks studies the MSWS-12 was measured as secondary endpoint. In study MS-F203 the mean change from baseline (BL_{score}71.1) under fampridine was -2.84 points. In study MS-F204 the change from baseline (BL_{score} 73.8) was -2.77 points.

Efficacy on the primary endpoint was consistent with the findings with respect to the TUG responders and MSIS29-physical score. There were no statistical significant differences with respect to the BBS and ABILHAND. The proportion of subjects reporting an improvement on the PGIC was at Week 2 was 31% vs 38% for placebo and fampridine PR respectively. This was 22% and 28% at week 24. Findings for the EQ-5D-3L, SDMT, SF-36, and HRU showed relatively little change from baseline and minimal differences between the groups. The results with respect to PGIC are unexpected as this assessment instrument as part of the validation of the relevance of the MSWS-responders i.e. the relevance of a 8 point shift from baseline MSWS-12. The results with respect to the Berg Balance Scale are also unexpected considering the results of the pilot study and the results of the TUG assessment. The BBS and TUG both assesses balance.

Results with respect to the subgroups were consistent although for subjects with greater disability, the effects size are smaller (see figure 2).

Nevertheless the effect size observed is modest. The absolute 14.5% difference in responders assuming a 50% response rate under the null hypothesis was not met, the cumulative distribution curves of points change from baseline only slightly separated (see figure 3) and there was little change the several secondary endpoints.

In the earlier fampridine studies (studies MS-F203 & MS-F204) a responder was defined as a patient who consistently had a faster walking speed for at least three visits out of a possible four during the double blind period as compared to the maximum value among five non-double blind off-treatment visits. Walking speed was measured by the Timed 25-foot Walk. In study MS-F203 responder rates was 8.3% versus 35% for placebo and fampridine respectively. For study MS-F204 responder rates were 9.3%. versus 43% respectively. It is noted that in the ENHANCE study responders rate in the placebo group is much higher. This may reflects the difference between a more objective (T25FT) and subjective (MSWS-12) assessment of response.

Whereas the clinical meaningfulness of the walking speed as primary endpoint was questioned (reason for the CMA) it points at the fact that not all patient respond on fampridine. This is confirmed in the ENHANCE study. This is not unexpected. Walking disability in multiple sclerosis is the result of combination of axonal loss and dysfunction of demyelinated axons. Fampridine only affects the latter.

Unfortunately the positive predictive value of any improvement on the MSWS-12 at week 2 or 4 is not large i.e. 61% and 59% respectively. However, the negative predictive of lack of any improvement is reasonable i.e. 87% and 86% for lack of any response at week 2 and 4 respectively. Different cut-off values for improvement on the MSWS-12 or combination of MSWS–TUG did not lead to better values. For subjects with greater disability, the effects size are smaller than for the overall population. This emphasises the need stopping rules. In the current SPC it is stated that the initial prescription of fampridine should be limited to 2 weeks of therapy as clinical benefits should generally be identified within 2-weeks after starting treatment. The timed walking test (T25FW) is recommended as assessment instrument. If no improvement is observed fampridine should be discontinued. In addition it is stated that the benefits of fampridine should be reassessed if a decline in walking ability is observed. This re-evaluation should include withdrawal of fampridine should be discontinued if patients no longer receive walking benefit. There seems no reason to change the concept. i.e. when no improvement is seen within 2-4 weeks continuing fampridine is not useful and users should be re-evaluated if a decline in walking ability is observed.
In conclusion the results of the ENHANCE study confirm that treatment with fampridine results in a clinically meaningful improvement in a proportion of patients with multiple sclerosis with walking abilities. The aim of the ENHANCE study i.e. to evaluate the clinical meaningfulness of the effect of fampridine in terms of walking ability and to evaluate long term efficacy is considered met. Efficacy was maintained over 24 weeks and disappeared after stopping treatment. Early detection of non-responders facilitates the decision to discontinue treatment. However, it is also confirmed that the effect remains modest.

4.3. Clinical Safety aspects

4.3.1. ENHANCE (study 218MS305)

This Summary of Clinical Safety summarizes the findings from the Phase 3 Study 218MS305 (Study 305) and the pregnancy registry Study 218MS402 (FOLLOW).

The latter study was initiated in 2011 and the first subject was enrolled on 18 August 2015. The study was stopped by agreement with the PRAC due to lack of subject exposure to fampridine-PR during pregnancy. At the time of study closure on 23 March 2016, 1 patient was enrolled in the registry.

The safety data base included 635 subjects, 316 receiving fampridine and 319 receiving placebo. The mean duration of exposure to fampridine-PR was 22.6 (SD 4.72) weeks. Most fampridine-PR-treated subjects (98.7%) complied with dosing of study treatment. The majority of fampridine-PR-treated subjects (85%) took between ⩾90% to ⩽100% of study treatment. Exposure and compliance were similar for the placebo-treated subjects.

Fampridine-PR and placebo-treated groups were balanced with respect to demographics. The mean age of fampridine-PR-treated subjects 49.0 (SD 9.82) with the majority of subjects ⩽64 years old; 59% were female; and the mean body mass index was 25.6 kg/m^2. Most subjects did not report race and ethnicity due to confidentiality regulations. Similarly, the baseline disease characteristics of the fampridine-PR-treated safety population and the placebo groups were comparable. See table 1b.

Concomitant medication used was comparable between the safety population and the placebo group. The most common medications used by ⩾10% of fampridine-PR-treated subjects included baclofen (21%), colecalciferol (15%), tizanidine, methylprednisolone (11% each), ibuprofen, and paracetamol (10% each).

In table 4.3.1.1 a general overview of the adverse events is presented.

The incidence of AEs reported in Study 305 was similar between the 2 treatment groups (66% fampridine-PR, 60% placebo). Most subjects had AEs that were considered mild or moderate in severity, and the incidence of AEs that were considered severe was the same (3%) in each treatment group. The incidence of AEs related to study treatment was higher in fampridine-PR-treated subjects than in placebo-treated subjects (18% vs. 13%).

One subject in each group had an AE that led to death during the study (i.e., during the 2-week follow-up period after the end of treatment); 2 additional deaths (1 subject in each group) occurred after the end of the study.

Serious events also occurred at a similar incidence (8% vs. 7%). The incidence of AEs leading to study treatment discontinuation (7% each group) or withdrawal from the study (8% vs. 7%) was also balanced. The incidence of AEs leading to dose interruption was slightly higher for fampridine-PR-treated subjects than for those treated with placebo (6% vs. 3%).

Table 4.3.1.1 General overview of the adverse event

	Placebo	**Fampridine** 10 mg BID
n dosed	319	316
% with adverse event	60%	66%
% treatment related event	13%	18%
% with serious event	7%	8%
% with dose interruption	3%	6%
% discontinuing due to AE	7%	7%
% withdrawing due to AE	8%	7%
% moderate or severe AE	30%	35%
% severe AE	3%	3%
Deaths during study (n)	1	1

Common adverse events and some adverse events interest (by assessor) are presented with table 4.3.1.2.

Most the most common system organ class for reported AEs were infections and infestations (31% vs. 28%), nervous system disorders (27% vs. 21%), and musculoskeletal and connective tissue disorders (18% vs. 13%). In addition there were more AEs reported for gastrointestinal disorders for fampridine-PR-treated subjects (14% vs. 8%).

The most common AEs among nervous system disorders were MS relapse, headache, and dizziness, and the most common AEs among musculoskeletal and connective tissue disorders were back pain, arthralgia, and pain in extremity. Otherwise, the incidence of AEs in particular system organ class was similar between the 2 treatment groups.

The most frequently reported AEs in both treatment groups were MS relapse and urinary tract infection, consistent with the MS study population. The AEs that occurred at an incidence ≥3% among fampridine-PR-treated subjects compared with the placebo group were UTI and insomnia. No other AEs were more common among subjects treated with placebo than among those treated with fampridine-PR.

Table 4.3.1.2. Most common Adverse events / other events of interest

	Placebo	**Fampridine** 10 mg BID
n	319	316
Infections and infestations	**28%**	**31%**
Urinary tract infection	12%	18%
Nasopharyngitis	6%	5%
Upper respiratory tract infection	3%	5%
Nervous system disorders	**21%**	**27%**
Multiple sclerosis relapse	10%	11%
Headache	5%	5%
Dizziness	2%	3%
Insomnia	<1%	4%
Musculoskeletal & connective tissue disorders	**13%**	**18%**
Back pain	3%	5%
Arthralgia	2%	4%
Pain in extremity	3%	3%
Injury, poisoning and procedural complications	9%	11%
Fall	6%	8%
Other AEs of interests[1]		
Asthenia	2%	3%
Fatigue	3%	3%
Muscle spasticity	<1%	3%
Muscular weakness	<1%	3%
Muscular spasm	<1%	1%

Gait disturbances	2%	2%

[1]By assessor. A difference in occurrence of these events may indicate overstimulation.

Adverse Events by Severity

The majority of AEs in the fampridine-PR and placebo groups were considered to be mild (30% vs. 29% placebo) or moderate (33% vs. 28%) in severity. The incidence of AEs considered severe was the same for the 2 treatment groups (3% each). The following severe events occurred in <1% (1 subject) of fampridine-PR treated subjects: UTI, diverticulitis, gallbladder empyema, breast cancer, MS relapse, balance disorder, MS, coronary artery stenosis, constipation, pain in extremity, chest pain, white blood cell count (WBC) increased, blood alkaline phosphatase increased, hemoglobin decreased, and neutrophil count increased.

Treatment related Adverse Events

Most AEs in both treatment groups were considered not related to study treatment (48% vs. 46%). The incidence of AEs considered related to study treatment in the fampridine-PR group was 18% as compared with 13% in the placebo group.

Deaths

Four events with a fatal outcome (2 per treatment group) were reported during or shortly after completion of the study. All deaths occurred after the subject discontinued study treatment. The events leading to death were considered not related to study treatment. Events of coronary artery stenosis (n=1, fampridine-PR group) and acute myocardial infarction (n=1, placebo group) led to fatal outcomes that occurred prior to the end of the 2-week post-treatment follow-up period. Events of lung cancer with liver and brain metastasis (n=1, fampridine-PR) and ovarian endometrioid carcinoma (n=1, placebo) led to death that occurred after the 2-week follow-up period after the last dose of study treatment.

Other Serious Adverse Events

In Study 305, the incidence of SAEs was comparable between the 2 treatment groups (8% vs.7%). MS relapse was the most frequently reported SAE in both groups (4% [14 subjects] vs. 3% [10 subjects]). All other SAEs in both groups occurred at a low frequency of <1%.

Excluding MS relapse, SAEs reported in the fampridine-PR group were UTI, fall (2 subjects each), diverticulitis, gallbladder empyema, bladder cancer, breast cancer, uterine leiomyoma, vertigo positional, coronary artery stenosis, peripheral ischemia, chest pain, humerus fracture, and joint dislocation (1 subject each).

Excluding MS relapse, serious events reported in the placebo group were fall (2 subjects), UTI, injection site infection, ovarian endometrioid carcinoma, dizziness, anxiety, mental disorder, acute myocardial infarction, atrioventricular block second degree, intervertebral disc disorder, abortion spontaneous, endometrial atrophy, metrorrhagia, ankle fracture, and femur fracture (1 subject each).

Other than the SAEs of anxiety and mental disorder experienced by one subject in the placebo group, none of the other SAEs were considered related to study treatment.

Adverse Events leading to discontinuation or dose interruption

The incidence of AEs leading to discontinuation of study treatment or study withdrawal was comparable between the 2 treatment groups (7% vs. 8%). MS relapse and MS led to discontinuation or withdrawal (MS relapse, 3 subjects vs. 1 subject; MS, 2 fampridine-PR-treated subjects).

Excluding the events of MS relapse and MS, AEs leading to discontinuation or withdrawal in the fampridine-PR group were creatinine renal clearance decreased (5 subjects), pain in extremity (2 subjects

each), UTI, breast cancer, anxiety, insomnia, balance disorder, vertigo, coronary artery stenosis, constipation, renal impairment, asthenia, fatigue, gastric pH increased, and fall (1 subject each).

Excluding the events of MS relapse and MS, AEs leading to discontinuation or withdrawal in the placebo group were creatinine renal clearance decreased (6 subjects), trigeminal neuralgia (2 subjects), UTI, injection site infection, ovarian endometrioid carcinoma, tension, acute myocardial infarction, arrhythmia, palpitations, drug eruption, limb discomfort, muscle spasms, renal impairment, chest pain, creatinine renal clearance abnormal, and femur fracture (1 subject each).

The incidence of AEs leading to dose interruption was 6% and 3% in the fampridine-PR and placebo groups, respectively. The incidence of SAEs leading to dose interruption was low (<1%).

AEs leading to dose interruption in the fampridine-PR group were nausea (3 subjects), UTI, fall (2 subjects each), diverticulitis, gallbladder empyema, gastroenteritis, influenza, lower respiratory tract infection, nasopharyngitis, balance disorder, migraine, MS relapse, constipation, dyspepsia, pruritus generalized, rash, back pain, pain in extremity, micturition urgency, chest pain, creatinine clearance abnormal, creatinine clearance decreased, contusion, and laceration (1 subject each)

AEs leading to dose interruption that occurred in the placebo group were MS relapse (2 subjects), gastroenteritis, pneumonia, tooth abscess, viral infection, anxiety, insomnia, panic attack, hemianaesthesia, motion sickness, cough, nausea, food poisoning, rash, and myalgia (1 subject each)

Adverse Events of Special Interest

Adverse events of special interest include seizures, hypersensitivity, urinary tract infection, cardiac events and AEs related to creatinine clearance (CrCl). In table 4.3.1.3. the occurrence of the events of special interests is summarised.

Table 4.3.1.3. Occurrence of Adverse events of interest (n)

	Placebo (n=319)	**Fampridine** 10 mg BID (n=316)
Urinary tract infection	**37**	**56**
URT	30	41
Serious	1	2
SAE related to study treatment	-	-
Cardiac disorders	**5**	**8**
Palpitations	1	4
Tachycardia	0	2
Bundle branch block right	0	1
Serious event	2	1
SAE related to study treatment	-	-
Serious hypersensitivity Rash	4	8
Convulsions	0	0
Falls (serious)	19 (2)	24 (2)
Serious	2	2
Decreased or abnormal CrCL	9	8

Adverse Events in Subgroups of Interest

To identify potential drug-drug interactions, AEs of subjects who received any concomitant Organic cation transport 2 (OCT2) inhibitors, OCT2 substrates, concomitant medications with a potential to lower seizure threshold, or anti-epileptic agents affecting the sodium-potassium current were evaluated. AEs were also evaluated as a function of subjects' CrCl at screening. In addition, AEs in subjects who had a Post-baseline CrCl value <80 mL/min were assessed.

The incidence of AEs in the specified concomitant medications subgroups was similar for each treatment group. No patterns were observed in AEs reported for fampridine-treated subjects receiving the specified concomitant medications. No events of seizure or convulsion activity were reported for fampridine-PR- and placebo-treated subjects in any of these subgroups.

Concomitant OCT2 inhibitors
In this subgroup, AEs were reported for 27 of 30 subjects (90%) in the fampridine-PR group and 26 of 27 subjects (96%) in the placebo group. UTI was reported for 3 and 5 fampridine-PR- and placebo-treated subjects, respectively, rash was reported for 2 and 1 subjects, MS relapse was reported for 16 and 9 subjects, hypoesthesia was reported for 3 and 1 subjects, and balance disorder was reported for 1 subject in each group. Cardiac disorders were reported in 2 fampridine-PR-treated subjects who also received concomitant OCT2 inhibitors (extrasystoles and tachycardia, 1 subject; atrioventricular block first degree, 1 subject) and in 1 placebo-treated subject.

Concomitant OCT2 substrates
AEs were reported for 22 of 29 (76%) fampridine-PR-treated subjects and 10 of 15 (67%) placebo-treated subjects who received concomitant OCT2 substrates, i.e., any medication coded to carvedilol, propranolol, metformin, amantadine, or varenicline (use of cimetidine was not reported for any subject). UTI was reported for 5 and 0 fampridine-PR- and placebo-treated subjects, respectively, headache was reported for 2 and 0 subjects, balance disorder was reported for 1 and 0 subjects, tachycardia was reported for 1 and 0 subjects, constipation was reported for 3 and 0 subjects, micturition urgency was reported for 2 and 0 subjects, increased creatinine renal clearance was reported for 1 and 0 subjects asthenia was reported for 4 and 0 patients, fall was reported for 3 and 1 subjects, and vertigo was reported for 1 subject in each group.

Concomitant medications with a potential to lower seizure threshold
Among subjects who received potential seizure threshold-lowering medications, AEs were reported for 135 of 165 subjects (82%) in the fampridine-PR group and 113 of 157 subjects (72%) in the placebo group. No seizure or convulsion activity was reported among these subjects. Nervous system disorders reported for 38% and 33% of subjects in the fampridine-PR and placebo groups, respectively, included MS relapse (19% [32 subjects] fampridine-PR, 18% [29 subjects] placebo), dizziness (4% [7 subjects] fampridine-PR, 4% [6 subjects] placebo), and headache (6% [7 subjects] fampridine-PR), 4% [10 subjects] placebo).

Concomitant anti-epileptic agents affecting the sodium-potassium
In this subgroup, AEs were reported for 32 of 43 subjects (74%) in the fampridine-PR group and 32 of 44 subjects (73%) in the placebo group. No seizure or convulsion activity was reported among these subjects. Nervous system disorders reported for 33% and 32% of fampridine-PR and placebo-treated subjects, respectively, included MS relapse (12% [5 subjects] fampridine-PR, 14% [6 subjects] placebo).

Creatinine clearance at screening (<80 mL/min, ≥80 mL/min)

Four subjects in each group had screening CrCl <80 mL/min of whom 2 subjects in the fampridine-PR group and 3 subjects in the placebo group had at least 1 AE of any type during the study. Notable non-serious AEs in this subgroup were abnormal creatinine renal clearance and micturition urgency (both events reported in 1 fampridine-treated and decreased creatinine renal clearance (reported for 2 placebo-treated subjects).

Any post-baseline creatinine clearance <80 mL/min
In this subgroup, AEs were reported for 31 of 39 subjects (79%) in the fampridine-PR group and 30 of 41 subjects (73%) in the placebo group (73%). No seizure or convulsion activity was reported among these subjects. Arrhythmia was reported for 1 subject treated with placebo, and atrioventricular block first degree was reported for 1 subject treated with fampridine-PR.

Clinical laboratory evaluations
There were no clinically meaningful changes in group mean laboratory hematology, blood chemistry and there was no clear pattern in the occurrence of abnormal values, including numbers of shifts from baseline.

Vital signs, physical findings and other observations related to safety
There were notable changes in vital signs were observed during the study.

ECG: Two subjects treated with fampridine-PR had a normal ECG at baseline and a shift to an abnormal ECG that was considered an AE. Neither event was serious, and both were considered mild in severity and not related to study treatment. Shifts from normal to abnormal (but not an AE) were reported for 16 fampridine-PR-treated subjects and 20 placebo-treated subjects.

MS-relapse: Suspected MS relapse was reported for 31 subjects (10%) treated with fampridine-PR (27 of whom were treated with methylprednisolone) and for 28 subjects (9%) treated with placebo (15 of whom were treated with methylprednisolone).

Overdose: Three subjects (2 treated with fampridine-PR and 1 treated with placebo) mistakenly took a double dose during the study. Four subjects (2 in each group) did not have confirmed overdose but returned fewer tablets than expected at a compliance check, and it was not clear whether the tablets were lost or the subject took extra tablets. No AEs as a result of overdose were reported.

CONCLUSION
The Applicant concludes that the safety findings for fampridine-PR in Study 305 are consistent with the known safety profile of fampridine-PR as observed in previous clinical trials and post-marketing experience. Review of the Study 305 safety data with respect to the important risks of seizures, serious hypersensitivity, UTIs, and interactions with OCT2 inhibitors did not reveal any new safety findings. No unexpected AEs were observed in Study 305, and there are no new safety signals with potential impact to the benefit-risk assessment of fampridine.

Discussion

It was concluded that the observed safety profile in study 305 was not different from what was already known and that no new signals were raised.

4.3.2. Follow registry

The primary objective of the FOLLOW registry (Study 218MS402) was to evaluate the outcomes of pregnancy in women with multiple sclerosis (MS) who were exposed to prolonged-release fampridine since the first day of their last menstrual period (LMP) prior to conception or at any time during pregnancy.

In agreement with the PRAC 10 September 2015 (EMEA/H/C/PSUSA/00001352/201501), the study was terminated early due to lack of subject exposure to prolonged-release fampridine during pregnancy. The PRAC agreed with the Applicant proposal of using a targeted follow-up pregnancy questionnaire in all cases (maternal/paternal exposure during pregnancy) reported to the Applicant.

At the time of study closure (23 March 2016), only 1 patient was enrolled in the registry.

Discussion

The MAH provided the final study report of the FOLLOW registry which was terminated early following the PRAC recommendation in PSUSA procedure EMEA/H/C/PSUSA/00001352/201501. One patient was enrolled As agreed in PSUSA procedure EMEA/H/C/PSUSA/00001352/201501 all future pregnancy cases will be followed using a targeted follow-up pregnancy questionnaire.

4.4. Risk management plan

As submission of the ENHANCE data fulfils the specific obligation, the MAH requests to convert the marketing authorisation from conditional to a full licence.

The MAH submitted an updated RMP version with this application. The main proposed RMP changes were the following:

- Updated information (results) on the completed study ENHANCE (218MS305)
- Removed the safety concern Lack of efficacy from the missing information section based on ENHANCE data

The MAH has also taken the opportunity to remove redundant information to improve readability.

Safety concerns

Removed text indicated by strikethrough. New text is underlined.

Table 21: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	~~Seizures~~ Seizure Serious hypersensitivity Urinary tract infections Interaction with OCT2 inhibitors
Important potential risks	Cardiovascular disorders Interaction with OCT2 substrates Interaction with drugs with potential to lower seizure ~~lower~~ threshold
Missing information	Special populations: ~~Children and adolescents~~ ~~Patients >65 years of age~~ Pregnancy exposure ~~Renal~~Elderly population >65 years of age Paediatric and adolescent patients Patients with impaired renal function ~~impairment~~ Interaction with anti-epileptic agents affecting sodium-potassium current Long-term safety ~~Lack of efficacy~~

OCT2 = organic cation transporter 2.

Long-term efficacy (which had been included as missing information) has been removed by the MAH. As part of the conditional approval long-term efficacy data should be obtained from the ENHANCE study: a double-blinded, placebo-controlled, long-term efficacy and safety study to investigate a broader primary endpoint clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide further treatment. As the obligatory ENHANCE study has been finalised, the MAH removed long-term efficacy as missing information. This is accepted, depending of the outcome of the CHMP discussion on the results of this study.

Pharmacovigilance plan

Table: On-going and planned studies in the post-authorisation pharmacovigilance development plan

III.5.1 Table of on-going and planned additional pharmacovigilance~~PhV~~ studies/activities in the ~~P~~pharmacovigilance ~~P~~plan

Study/activity Type, Title and Category (1-3)	Objectives	Safety ~~concerns addressed~~Concerns Addressed	Status (planned, started)	Date for ~~submission~~Submission of ~~interim~~Interim or ~~final reports~~Final Reports (planned or actual)
Post authorisation safety study 218MS401 (LIBERATE) Fampridine ~~PR~~ Observational Study (Category 3)	To collect additional safety data and to characterise the utilisation patterns of fampridine ~~PR~~ in clinical practice	Incidence rate of seizures and other AEs of interest; and utilisation patterns of fampridine ~~PR.~~	Study ongoing.	Annual progress report with the PSUR (with the 21 ~~July~~ January data cut-off date) and target final study report submission for ~~Q1 2018~~Q3 2021
~~Clinical trial~~ ~~Phase 3 long-term confirmatory Study 218MS305 (ENHANCE) (Category 2)~~	~~To investigate a broader primary endpoint clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide further treatment.~~	~~Data from this study will also be used to assess safety of fampridine in an unselected population, including those with cardiovascular diseases.~~	~~Study ongoing~~	~~Annual progress report with the PSUR (with the 21 Jul data cut-off date) and target final study report for submission for Q4 2016~~

The PRAC Rapporteur is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product, depending on the outcome of the CHMP discussion on long-term efficacy (ENHANCE study).

The PRAC Rapporteur also considers that the studies in the post-authorisation development plan remain sufficient to monitor the effectiveness of the risk minimisation measures (RMMs).

Risk minimisation measures (RMMs)

The following changes were made to the summary table of the RMMs:

Part V.3 Summary table of risk minimisation measures

Safety ~~concern~~Concern	Routine ~~risk minimisation measures~~Risk Minimisation Measures	Additional ~~risk minimisation measures~~Risk Minimisation Measures
Seizure	**Text in SmPC~~:~~** **Section 4.2 Posology and method of administration** Treatment with Fampyra is restricted to prescription and supervision by physicians experienced in the management of MS. The recommended dose is one 10 mg tablet, twice daily, taken 12 hours apart (~~one~~1 tablet in the morning and ~~one~~1 tablet in the evening). Fampyra should not be administered more frequently or at higher doses than recommended (see section 4.4). The tablets ~~should~~can be taken with or without food (see section 5.2) Initial prescription should be limited to 2 to 4 weeks of therapy as clinical benefits should generally be identified within 2~~-~~ to 4 weeks after starting Fampyra ~~A timed~~An assessment of walking ~~test~~ability, e.g~~-~~., the ~~Timed 25 Foot Walk (~~T25FW~~)~~, or MSWS-12, is recommended to evaluate improvement ~~after two~~ within 2 to 4 weeks. If no improvement is observed, Fampyra should be discontinued Fampyra should be discontinued if benefit is not reported by patients. If decline in walking ability is observed, physicians should consider an interruption to treatment in order to reassess the benefits of Fampyra (see above). The re-evaluation should include withdrawal of Fampyra and performing ~~the~~an assessment of walking ~~test~~ ability. Fampyra should be discontinued if patients no longer receive walking benefit. The usual dosing ~~regime~~regimen should always be followed. A double dose should not be taken if a dose is missed. **Section 4.3 Contraindications** Patients with prior history or current presentation of seizure.	None

Safety ~~concern~~Concern	Routine ~~risk minimisation measures~~Risk Minimisation Measures	Additional ~~risk minimisation measures~~Risk Minimisation Measures
	Section 4.4 Special warnings and precautions for use Seizure risk Treatment with fampridine increases seizure risk (see section 4.8). Fampyra should be administered with caution in the presence of any factors which may lower seizure threshold. Fampyra should be discontinued in patients who experience a seizure while on treatment. **Section 4.8 Undesirable effects** Description of selected adverse reactions Seizure In post-marketing experience, there have been reports of seizure, the frequency is not known (cannot be estimated from the available data). For further information on seizure risk, please refer to sections 4.3 and 4.4. **Section 4.9 Overdose** Symptoms Acute symptoms of overdose with Fampyra were consistent with central nervous system excitation and included confusion, tremulousness, diaphoresis, seizure, and amnesia. Central nervous system side effects at high doses of 4-~~aminopyridine~~-AP include confusion, seizures, status epilepticus, involuntary and choreoathetoid movements. Management Patients who overdose should be provided supportive care. Repeated seizure activity should be treated with benzodiazepine, phenytoin, or other appropriate acute anti-seizure therapy. Other routine risk minimisation measures	

Safety ~~concern~~Concern	Routine ~~risk minimisation measures~~Risk Minimisation Measures	Additional ~~risk minimisation measures~~Risk Minimisation Measures
	Packaging: Blister packaging with calendar and design elements to reinforce the required posology of twice daily dosing spaced by 12 hours. This helps to minimize the risk associated with high plasma levels if the twice daily dosing are not spaced adequately, which may increase the risk of seizure. A 'starter pack' for the initial prescriptions will ~~limit~~be provided to ~~2 weeks of medication to reinforce~~ the ~~section 4.2 posology of the SmPC that benefit of treatment should be evaluated after 2 weeks and only to be continued in~~ patients ~~responding to fampridine and thereby improving benefit/risk in those continuing therapy.~~	
Serious hypersensitivity	~~Text in SmPC:~~ Section 4.3 of the SmPC includes hypersensitivity to as a contraindication. Section 4.4 of the SmPC includes a warning for serious hypersensitivity reactions the majority of which have occurred in the first week of treatment. Section 4.8 of the SmPC includes reference to hypersensitivity and anaphylaxis as recognised ~~Adverse Events.~~AEs.	None
~~Urinary tract infections~~UTIs	**Text in SmPC~~:~~** **4.8 Undesirable effects** UTI is included as a very common ADR.	None
Interaction with OCT2 inhibitors	**Text in SmPC~~:~~** **Section 4.3 Contraindications** Concomitant use of Fampyra with medicinal products that are inhibitors of ~~Organic Cation Transporter 2 (~~OCT2~~)~~ for example, cimetidine.	None
Cardiovascular disorders	**Text in SmPC~~:~~** **4.4. Special warnings and precautions for use**	None

Safety ~~concern~~Concern	Routine ~~risk minimisation measures~~Risk Minimisation Measures	Additional ~~risk minimisation measures~~Risk Minimisation Measures
	Fampyra should be administered with caution to patients with cardiovascular symptoms of rhythm and sinoatrial or atrioventricular conduction cardiac disorders (these effects are seen in overdose). There is limited safety information in these patients. **Section 4.9 Overdose** Symptoms Other side effects at high doses include cases of cardiac arrhythmias (for example, supraventricular tachycardia and bradycardia) and ventricular tachycardia as a consequence of potential QT prolongation. Reports of hypertension have also been received.	
Interaction with OCT2 substrates	**Text in SmPC~~:~~** **4.4. Special warnings and precautions for use** Caution is required when Fampyra is prescribed concurrently with medicinal products that are substrates of OCT2 for example, carvedilol, ~~propanolol~~propranolol, and metformin.	None
Interaction with drugs with potential to lower seizure threshold	**Text in SmPC~~:~~** **4.4 Special warnings and precautions for use** Fampyra should be administered with caution in the presence of any factors which may lower seizure threshold.	None
Population not studied: paediatric and adolescent patients	**Text in SmPC~~:~~** **Section 4.2 Posology and method of administration** Paediatric population The safety and efficacy of Fampyra in children aged 0 to 18 years have not been established. No data are available. **Section 5.1 Pharmacodynamic properties** The European Medicines Agency has waived the obligation to submit the results of studies with Fampyra in all subsets of the	None

Safety ~~concern~~Concern	Routine ~~risk minimisation measures~~Risk Minimisation Measures	Additional ~~risk minimisation measures~~Risk Minimisation Measures
	paediatric population in treatment of multiple sclerosis with walking disability (see section 4.2 for information on paediatric use). **Section 5.2 Pharmacokinetic properties** Paediatric Population: No data are available.	
Population not studied: aged > 65 years	**Text in SmPC:** **Section 4.2. Posology and method of administration** ~~Elderly~~ Older people Renal function should be checked in ~~elderly patients~~older people before starting treatment with Fampyra. Monitoring renal function to detect any renal impairment is recommended in ~~elderly patients~~older people (see section 4.4). **Section 5.2. Pharmacokinetic properties** Special Populations ~~Elderly patients~~Older people: Clinical studies of Fampyra did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger patients. Fampyra is primarily excreted unchanged by the kidneys, and with creatinine clearance known to decrease with age, monitoring of renal function in ~~elderly~~older patients should be considered (see section 4.2).	None
Pregnancy	**Text in SmPC:** **4.6. Fertility, pregnancy and lactation** Pregnancy There are no or limited amount of data from the use of fampridine in pregnant women.	None

Safety ~~concern~~Concern	Routine ~~risk minimisation measures~~Risk Minimisation Measures	Additional ~~risk minimisation measures~~Risk Minimisation Measures
	Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure it is preferable to avoid the use of Fampyra in pregnancy.	
Population with renal impairment	**Text in SmPC~~:~~** **Section 4.2 Posology and methods of administration** Patients with renal impairment Fampyra is contraindicated in patients with mild, moderate and severe renal impairment (creatinine clearances <80 ~~ml~~mL/min) (see section 4.3). **Section 4.3 Contraindications** Patients with mild, moderate or severe renal impairment (creatinine clearances <80 ~~ml~~mL/min). **Section 4.4 Special warnings and precautions for use** Renal impairment Fampyra is primarily excreted unchanged by the kidneys. Patients with renal impairment have higher plasma concentrations which are associated with increased adverse reactions, in particular neurological effects. Determining renal function before treatment and its regular monitoring during treatment is recommended in all patients (particularly ~~the elderly~~in older people in whom renal function might be reduced). Creatinine clearance can be estimated using the Cockroft-Gault formula. Fampyra should not be administered to patients with renal impairment (creatinine clearance <80 ~~ml~~mL/min) (see section 4.3). Caution is required when Fampyra is prescribed concurrently with medicinal products that are substrates of OCT2 for example, carvedilol, propanolol, and metformin. **4.5 Interaction with other medicinal products and other forms of interaction** Fampridine is eliminated mainly via the kidneys with active renal	None

Safety ~~concern~~Concern	Routine ~~risk minimisation measures~~Risk Minimisation Measures	Additional ~~risk minimisation measures~~Risk Minimisation Measures
	secretion accounting for about 60% (see section 5.2). OCT2 is the transporter responsible for the active secretion of fampridine. Thus, the concomitant use of fampridine with medicinal products that are inhibitors of OCT2 for example, cimetidine are contraindicated (see section 4.3) and concomitant use of fampridine with medicinal products that are substrates of OCT2 for example, carvedilol, propanolol, and metformin is cautioned (see section 4.4.) **Section 5.2 Pharmacokinetic properties** Elimination: The major route of elimination for fampridine is renal excretion, with approximately 90% of the dose recovered in urine as parent medicinal product within 24 hours. Renal clearance (CLR 370 ~~ml~~mL/min) is substantially greater than glomerular filtration rate due to combined glomerular filtration and active excretion by the renal OCT2 transporter. Faecal excretion accounts for less than 1% of the administered dose. Fampyra is characterized by linear (dose-proportional) ~~pharmacokinetics~~PKs with a terminal elimination half-life of approximately 6 hours. ~~The maximum plasma concentration (~~The C_{max}~~)~~ and, to a smaller extent, ~~area under the plasma concentration time curve (~~AUC~~)~~ increase proportionately with dose. There is no evidence of clinically relevant accumulation of fampridine taken at the recommended dose in patients with full renal function. In patients with renal impairment, accumulation occurs relative to the degree of impairment. Patients with renal impairment: Fampridine is eliminated primarily by the kidneys as unchanged medicinal product and therefore renal function should be checked in patients where renal function might be compromised. Patients with mild renal impairment can be expected to have approximately 1.7 to 1.9 times the fampridine concentrations achieved by patients with normal renal function. Fampyra must not be administered to patients with mild, moderate and severe renal impairment (see section 4.3).	

Safety ~~concern~~Concern	Routine ~~risk minimisation measures~~Risk Minimisation Measures	Additional ~~risk minimisation measures~~Risk Minimisation Measures
Interaction with anti-epileptic agents affecting sodium-potassium current	None	None
Long-term safety	None	None
~~Lack of efficacy~~	~~None~~	~~None~~

The PRAC Rapporteur is of the opinion that the proposed RMMs remain sufficient to minimise the risks of the product in the proposed indication(s).

Please include only a brief summary of the SmPC text in the summary table of risk minimisation measures, instead of the exact wording, in order to avoid unnecessary updates of the RMP.

Elements for a public summary of the RMP

The elements for a public summary of the RMP have been updated accordingly.

Annexes

The annexes have been updated appropriately.

Overall conclusion on the RMP

The changes to the RMP are considered acceptable, depending on the outcome of the CHMP discussion on the results of the ENHANCE study on long-term efficacy.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

4.5. Changes to the Product Information

Red indicates additions and strike through indicates deletions as proposed by the MAH initially.

Blue indicates additions and strike through indicates deletions as proposed by the Rapporteur with the Request for Supplementary Information.

▼~~This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.~~

CHMP comment

The MAH proposed to remove the product from the list of products with additional monitoring (see removal additional monitoring and black triangle from the SmPC). This was agreed as there are no outstanding conditions to the MA and the active substance has been authorised for more than 5 years.

1. NAME OF THE MEDICINAL PRODUCT

Fampyra 10 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 10 mg of fampridine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

An off-white, film coated, oval biconvex 13 x 8 mm tablet with flat edge debossed with A10 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fampyra is indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability (EDSS 4-7).

4.2 Posology and method of administration

Treatment with Fampyra is restricted to prescription and supervision by physicians experienced in the management of MS.

Posology

The recommended dose is one 10 mg tablet, twice daily, taken 12 hours apart (one tablet in the morning and one tablet in the evening). Fampyra should not be administered more frequently or at higher doses than recommended (see section 4.4). ~~The tablets should can be taken with or without food (see section 5.2).~~ The tablets should be taken without food (see section 5.2).

CHMP comment 1st round

Insufficient justification is provided in support of this change i.e.

The guidance regarding administration with food has been clarified in line with the Core Data Sheet (CDS) that was amended to "can be taken with or without food" in version 04 (14 September 2012). The CDS update was included with submission of PSUR 03. On review of PSUR 03 (EMEA/H/C/2097/PSU 004, PRAC maintenance recommendation 05 September 2013), PRAC recommended the SmPC be updated to align with the CDS"

However this was apparently was general recommendation. With respect to the claim of 'no clinically meaningful consequences when administered with food' it was stated that should comment on the differences in this respect between the US and EU labelling and reconsider the need of a type II variation to update the EU SmPC.

Hence the Applicant should provided a further justification for this change or the current text should remain.

Applicant's response

The applicant dropped the initial proposal: *The tablets ~~should~~ can be taken with or without food (see section 5.2)* and reintroduced the original text: *The tablets should be taken without food (see section 5.2).*

Assessment of the response

Resolved

Starting and Evaluating Fampyra Treatment

- Initial prescription should be limited to two to four ~~2~~ weeks of therapy as clinical benefits should generally be identified within two to four ~~2~~ weeks after starting Fampyra
- ~~A timed walking test~~ An assessment of walking ability, e.g. the Timed 25 Foot Walk (T25FW) or Twelve Item Multiple Sclerosis Walking Scale (MSWS-12), is recommended to evaluate improvement ~~after two weeks~~ within two to four weeks. If no improvement is observed, Fampyra should be discontinued Fampyra should be discontinued if benefit is not reported by patients.

Re-Evaluating Fampyra Treatment

If decline in walking ability is observed, physicians should consider an interruption to treatment in order to reassess the benefits of Fampyra (see above). The re-evaluation should include withdrawal of Fampyra and performing ~~the walking test~~ an assessment of walking ability. Fampyra should be discontinued if patients no longer receive walking benefit.

CHMP comment 1st round

Agreed changes are consistent with results of the ENHANCE studies.

4.3 Contraindications

Hypersensitivity to fampridine or to any of the excipients listed in section 6.1.

Concurrent treatment with other medicinal products containing fampridine (4-aminopyridine).

Patients with prior history or current presentation of seizure.

Patients with mild, moderate or severe renal impairment (creatinine clearances <80 ml/min).

Concomitant use of Fampyra with medicinal products that are inhibitors of Organic Cation Transporter 2 (OCT2) for example, cimetidine.

4.4 Special warnings and precautions for use

Seizure risk

Treatment with fampridine increases seizure risk (see section 4.8).

Fampyra should be administered with caution in the presence of any factors which may lower seizure threshold.

Fampyra should be discontinued in patients who experience a seizure while on treatment.

Renal impairment

Fampyra is primarily excreted unchanged by the kidneys. Patients with renal impairment have higher plasma concentrations which are associated with increased adverse reactions, in particular neurological effects. Determining renal function before treatment and its regular monitoring during treatment is recommended in all patients (particularly in older people in whom renal function might be reduced). Creatinine clearance can be estimated using the Cockroft-Gault formula.
Fampyra should not be administered to patients with renal impairment (creatinine clearance <80 ml/min) (see section 4.3).

Caution is required when Fampyra is prescribed concurrently with medicinal products that are substrates of OCT2 for example, carvedilol, propanolol and metformin.

Hypersensitivity Reactions

In post-marketing experience, serious hypersensitivity reactions (including anaphylactic reaction) have been reported, the majority of these cases occurred within the first week of treatment. Particular attention should be given to patients with a previous history of allergic reactions. If an anaphylactic or other serious allergic reaction occurs, Fampyra should be discontinued and not restarted.

Other warnings and precautions

Fampyra should be administered with caution to patients with cardiovascular symptoms of rhythm and sinoatrial or atrioventricular conduction cardiac disorders (these effects are seen in overdose). There is limited safety information in these patients.

The increased incidence of dizziness and balance disorder seen with Fampyra may result in an increased risk of falls. Therefore, patients should use walking aids as needed.

~~In clinical studies low white blood cell counts were seen in 2.1% of Fampyra patients versus 1.9% of patients on placebo. Infections were seen in the clinical studies as stated below. An increased infection rate and impairment of the immune response cannot be excluded.~~

	~~Placebo-Controlled Studies 202/203/204~~		
~~System Organ Class – Preferred Term~~	~~Placebo (N=238)~~	~~Fampyra 10 mg BID (N=400)~~	~~TEAEs* with Incidence ≥1% in Fampyra vs Placebo~~
~~Infections and Infestations (202/203/204)~~	~~59 (24.8%)~~	~~124 (31.0%)~~	~~6.2%~~
~~– Gastroenteritis viral~~	~~4 (1.7%)~~	~~6 (1.5%)~~	~~–~~
~~– Influenza~~	~~0 (0%)~~	~~6 (1.5%)~~	~~1.5%~~
~~– Nasopharyngitis~~	~~4 (1.7%)~~	~~14 (3.5%)~~	~~1.8%~~
~~– Pneumonia~~	~~1 (0.4%)~~	~~4 (1.0%)~~	~~–~~
~~– Sinusitis~~	~~8 (3.4%)~~	~~6 (1.5%)~~	~~–~~
~~– Upper respiratory tract infection~~	~~15 (6.3%)~~	~~20 (5.0%)~~	~~–~~
~~– Urinary tract infection~~	~~20 (8.4%)~~	~~48 (12.0%)~~	~~3.6%~~
~~– Viral infection~~	~~1 (0.4%)~~	~~6 (1.5%)~~	~~1.1%~~

~~* TEAEs – Treatment Emergent Adverse Events~~

Member state comment 1st round

The table above seems to be doubling that of section 4.8 and might be considered confusing as it doesn't reflect adverse reactions but adverse events. This is endorsed by the Rapporteur and the table should be deleted.

Applicant's response

The applicant deleted the text and table as indicated.

Assessment of the response

Resolved

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Concurrent treatment with other medicinal products containing fampridine (4-aminopyridine) is contraindicated (see section 4.3).

Fampridine is eliminated mainly via the kidneys with active renal secretion accounting for about 60% (see section 5.2). OCT2 is the transporter responsible for the active secretion of fampridine. Thus, the concomitant use of fampridine with medicinal products that are inhibitors of OCT2 for example, cimetidine are contraindicated (see section 4.3) and concomitant use of fampridine with medicinal products that are substrates of OCT2 for example, carvedilol, propanolol and metformin is cautioned (see section 4.4.)

Interferon: fampridine has been administered concomitantly with interferon-beta and no pharmacokinetic medicinal product interactions were observed.

Baclofen: fampridine has been administered concomitantly with baclofen and no pharmacokinetic medicinal product interactions were observed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of fampridine in pregnant women.

Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure it is preferable to avoid the use of Fampyra in pregnancy.

Breast-feeding

It is unknown whether fampridine is excreted in human or animal milk. Fampyra is not recommended during breast-feeding.

Fertility

In animal studies no effects on fertility were seen.

CHMP comment 1st round

Preferred is: There are limited data from the use of fampridine in pregnant women.

Applicant's response

The applicant maintained the initial proposal.

Assessment of the response

Issue not further pursued

4.7 Effects on ability to drive and use machines

Fampyra has a moderate influence on the ability to drive and use machines because Fampyra can cause dizziness.

4.8 Undesirable effects

The safety of Fampyra has been evaluated in randomised controlled clinical studies, in open label long term studies and in the post marketing setting.

Adverse reactions identified are mostly neurological and include seizure, insomnia, anxiety, balance disorder, dizziness, paraesthesia, tremor, headache and asthenia. This is consistent with fampridine's pharmacological activity. The highest incidence of adverse reactions identified from placebo-controlled trials in multiple sclerosis patients with Fampyra given at the recommended dose, are reported as urinary tract infection (in approximately 12% of patients).

Adverse reactions are presented below by system organ class and absolute frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

MedDRA SOC	Adverse Reaction	Frequency category
Infections and infestations	Urinary tract infection	Very Common
Immune system disorders	Anaphylaxis Angioedema Hypersensitivity	Uncommon Uncommon Uncommon
Psychiatric disorders	Insomnia Anxiety	Common Common
Nervous system disorders	Dizziness Headache Balance disorder Paraesthesia Tremor Seizure Exacerbation of trigeminal neuralgia	Common Common Common Common Common Uncommon Uncommon
Cardiac disorders	Palpitations	Common
	Tachycardia	Uncommon
Vascular disorders	Hypotension*	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea Pharyngolaryngeal pain	Common Common
Gastrointestinal disorders	Nausea Vomiting Constipation Dyspepsia	Common Common Common Common
Skin and subcutaneous tissue disorders	Rash Urticaria	Uncommon Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Common
General disorders and administration site conditions	Asthenia Chest discomfort*	Common Uncommon

* These symptoms were observed in the context of hypersensitivity

Description of selected adverse reactions

Seizure

In post-marketing experience, there have been reports of seizure, the frequency is not known (cannot be estimated from the available data). For further information on seizure risk, please refer to sections 4.3 and 4.4.

Hypersensitivity

In post-marketing experience, there have been reports of hypersensitivity reactions (including anaphylaxis) which have occurred with one or more of the following: dyspnoea, chest discomfort, hypotension, angioedema, rash and urticaria. For further information on hypersensitivity reactions, please refer to sections 4.3 and 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

Member state comment 1st round:

Palpitations and tachycardia have been noted in ENHANCE and should be reflected in the SmPC which is endorsed by the Rapporteur. The Applicant should also define the frequency of these adverse reactions.

Applicant's response

Cardiovascular disorders are an important potential risk of fampridine based on the pharmacologic properties of Fampridine as a potassium channel blocker. It is an important potential risk described in the current EU RMP and caution is advised in the EU SmPC when administering to patients with cardiovascular symptoms (Section 4.4 Special Warnings and Precautions for Use).

Since the MAHs last review of Cardiac Dysrhythmic events in PSUR 8 (DLP 21 January 2016) new clinical trial data from Study 305 has become available showing: Cardiac Dysrhythmic event: Fampridine 6 (1.9%) vs Placebo 2 (0.6%), Palpitations: Fampridine 4 (1.3%) vs Placebo 1 (0.3%).

Table 1: Incidence of treatment-emergent adverse events of special interest by preferred term

AE of interest: Cardiovascular disorders	Placebo N= 319	Fampridine 10mg BID N = 316
Number of subjects with an event	2 (<1)	6 (2)
Palpitations	1 (<1)	4 (1)
Tachycardia	0	2 (<1)
Arrhythmia	1 (<1)	0
Bundle branch block right	0	1 (<1)

SOURCE: 218MS/218MS305/CSR/T-AE-PT-SLINTERST-EXD513.SAS

However, the numbers of events is small and the incidence of palpitations in this study is lower than might be expected in the general population, based on epidemiological data. The data for these events from Study 305 are not supported by that from previous or ongoing studies involving fampridine.

Disproportionality analyses using EB05 scores are not suggestive of a causal relationship and review of post-marketing data remains inconclusive and unchanged.

It is concluded by the MAH that on balance that the most recent review of cardiac dysrhythmic events does not reveal any significant new safety information and is consistent with current known risks and labelling. Therefore the MAH concludes that no changes to the prescribing information for fampridine are required.

Assessment of the response

As stated cardiovascular disorders is an important potential risk of fampridine based on the pharmacologic properties of Fampridine as a potassium channel blocker. This is an argument sufficient on its own for a causal relationship between fampridine use and cardiac dysrhythmic events. Further cardiac arrhythmias and ventricular tachycardia are reported as with an overdose of 4-AP. It is acknowledged that, the numbers of Cardiac Dysrhythmic events reported is small. However there is a consistent higher incidence as compared to placebo.

Considering al this the MAA is requested to incorporate palpitations and tachycardia in section 4.8 with corresponding frequency category.

Issue resolved upon subsequent submission of updated PI by the MAH.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC code: N07XX07.

Pharmacodynamic effects

Fampyra is a potassium channel blocker. By blocking potassium channels, Fampyra reduces the leakage of ionic current through these channels, thereby prolonging repolarization and thus enhancing action potential formation in demyelinated axons and neurological function. Presumably, by enhancing action potential formation, more impulses might be conducted in the central nervous system.

Clinical efficacy and safety

~~Two~~ Three phase III, randomised, double-blind, placebo controlled confirmatory studies, (MS-F203 and MS-F204 and 218MS305) have been performed. The proportion of responders was independent of concomitant immunomodulatory therapy (including interferons, glatiramer acetate, fingolimod and natalizumab). ~~The majority of patients in these studies were using immunomodulatory medicines~~ The Fampyra dose was 10 mg BID.

CHMP comment 1st round
Agreed

Studies MS-F203 and MS-F204

The primary endpoint in studies MS-F203 and MS-F204 was the responder rate in walking speed as measured by the Timed 25-foot Walk (T25FW). A responder was defined as a patient who consistently had a faster walking speed for at least three visits out of a possible four during the double blind period as compared to the maximum value among five ~~non-double-blind~~ off-treatment visits.

A significantly greater proportion of Fampyra treated patients ~~taking Fampyra 10 mg BID~~ were responders as compared to placebo (MS-F203: 34.8% vs. 8.3%, $p<0.001$; MS-F204: 42.9% vs. 9.3%, $p<0.001$). -

Patients who responded to Fampyra increased their walking speed on average by 26.3% vs 5.3% on placebo (p<0.001) (MS-F203) and 25.3% vs 7.8% (p< 0.001) (MS-F204). The improvement appeared rapidly (within weeks) after starting Fampyra.

Statistically and clinically meaningful improvements in walking were seen, as measured by the 12- item Multiple Sclerosis Walking Scale.

Table 1: ~~Pivotal~~ Studies MS-F203 and MS-F204

STUDY *	MS-F203		MS-F204	
	Placebo	**Fampyra 10 mg BID**	**Placebo**	**Fampyra 10 mg BID**
n of subjects	72	224	118	119
Consistent improvement	**8.3%**	**34.8%**	**9.3%**	**42.9%**
Difference		**26.5%**		**33.5%**
$CI_{95\%}$		17.6%, 35.4%		23.2%, 43.9%
P-value		< 0.001		< 0.001
≥20% improvement	11.1%	31.7%	15.3%	34.5%
Difference		20.6%		19.2%
$CI_{95\%}$		11.1%,30.1%		8.5%,29.9%
P-value		<0.001		<0.001
Walking speed Feet/sec	Ft per sec	Ft per sec	Ft per sec	Ft per sec
Baseline	2.04	2.02	2.21	2.12
Endpoint	2.15	2.32	2.39	2.43
Change	0.11	0.30	0.18	0.31
Difference		0.19		0.12
p-value		0.010		0.038
Average % Change	5.24	13.88	7.74	14.36
Difference		8.65		6.62
p-value		< 0.001		0.007
MSWS-12-score (mean, sem) ~~(Multiple Sclerosis Walking Scale)~~				
Baseline	69.27 (2.22)	71.06 (1.34)	67.03 (1.90)	73.81 (1.87)
Average change	-0.01 (1.46)	-2.84 (0.878)	0.87 (1.22)	-2.77 (1.20)
Difference		2.83		3.65
p-value		0.084		0.021
LEMMT (mean, sem) (Lower Extremity Manual Muscle Test)				
Baseline	3.92 (0.070)	4.01 (0.042)	4.01 (0.054)	3.95 (0.053)
Average change	0.05 (0.024)	0.13 (0.014)	0.05 (0.024)	0.10 (0.024)
Difference		0.08		0.05
p-value		0.003		0.106
Ashworth Score (A test for muscle spasticity)				
Baseline	0.98 (0.078)	0.95 (0.047)	0.79 (0.058)	0.87 (0.057)
Average change	-0.09 (0.037)	-0.18 (0.022)	-0.07 (0.033)	-0.17 (0.032)
Difference		0.10		0.10
p-value		0.021		0.015

CHMP comment

Agreed

Study 218MS305

The primary endpoint in study 218MS305 was improvement in walking ability, measured as the proportion of patients achieving a mean improvement of ≥ 8 points from baseline MSWS-12 score over 24 weeks. In this study there was a statistically significant treatment difference, with a greater proportion of Fampyra treated patients demonstrating an improvement in walking ability, compared to placebo-controlled patients (0.432 vs. 0.336; odds ratio: 1.61; p=0.006). A higher proportion of Fampyra treated patients displayed improvement in walking ability at all magnitudes of change in MSWS-12 score (from 1 to 10 points), compared to placebo. Improvements generally appeared within 2 to 4 weeks of initiation of treatment, and disappeared within 2 weeks of treatment cessation.

Fampyra treated patients also demonstrated a statistically significant improvement in the Timed Up and Go (TUG) test, a measure of static and dynamic balance and physical mobility. In this secondary endpoint, a greater proportion of Fampyra treated patients achieved ≥ 15% mean improvement from baseline TUG speed over a 24 week period, compared to placebo (0.434 vs. 0.347; odds ratio: 1.46; p=0.030).

The Multiple Sclerosis Impact Scale (MSIS-29), a patient reported outcome (PRO) measure to assess the change from baseline in a patient's physical well-being over 24 weeks, was an additional secondary endpoint in study 218MS305. In this measure, patients treated with Fampyra demonstrated a statistically significant mean improvement from baseline compared to placebo (Least Squares (LS) mean difference -3.31, p<0.001).

Table 2: Study 218MS305

	Placebo N = 318	**Fampyra 10 mg BID N = 315**	**Odds ratio (95% CI)**	**P - value**
Proportion of patients with mean improvement of ≥ 8 points from baseline MSWS-12 score over 24 weeks	0.336	0.432	1.61 (1.15, 2.26)	0.006
Proportion of patients with mean improvement of ≥ 15% in TUG speed over 24 weeks	0.347	0.434	1.46 (1.04, 2.07)	0.030
LS mean change from baseline MSIS-29 physical score over 24 weeks LS mean difference (95% CI)	-4.68	-8.00 -3.31 (-5.13, -1.50)	N/A	<0.001

The European Medicines Agency has waived the obligation to submit the results of studies with Fampyra in all subsets of the paediatric population in treatment of multiple sclerosis with walking disability (see section 4.2 for information on paediatric use).
The medicinal product has been authorised under a so-called "conditional approval" scheme. This means that further evidence on this medicinal product is awaited, in particular about Fampyra's benefits beyond its effects on walking speed and with respect to early identification of responders. A study will be conducted to investigate this. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

Study 218MS305

Study 218MS305 was conducted in 636 subjects with multiple sclerosis and walking disability. Duration of double-blind treatment was 24 weeks with a 2 week post–treatment follow-up. The primary endpoint was

improvement in walking ability, measured as the proportion of patients achieving a mean improvement of ≥ 8 points from baseline MSWS-12 score over 24 weeks. In this study there was a statistically significant treatment difference, with a greater proportion of Fampyra treated patients demonstrating an improvement in walking ability, compared to placebo-controlled patients (relative risk of 1.38 (95% CI: [1.06, 1.70]). Improvements generally appeared within 2 to 4 weeks of initiation of treatment, and disappeared within 2 weeks of treatment cessation.

Fampyra treated patients also demonstrated a statistically significant improvement in the Timed Up and Go (TUG) test, a measure of static and dynamic balance and physical mobility. In this secondary endpoint, a greater proportion of Fampyra treated patients achieved ≥ 15% mean improvement from baseline TUG speed over a 24 week period, compared to placebo (~~relative risk of 1.25 (95% CI: [0.99, 1.51])~~. ~~The mean (SD) TUG time taken at baseline was 27.1 (42.03) seconds for placebo and 24.9 (26.61) seconds for Fampyra. The Least Squares Mean (LSM) change (standard error) over 24 weeks was -1.9 (0.78) seconds for placebo and -3.3 (0.75) seconds for Fampyra. In addition, a positive and sustained treatment effect was observed~~ The difference in the Berg Balance Scale (BBS; a measure of static balance~~), although the difference~~ was not statistically significant.

In addition, patients treated with Fampyra demonstrated a statistically significant mean improvement from baseline compared to placebo in the Multiple Sclerosis Impact Scale (MSIS-29) physical score (LSM difference -3.31, p<0.001).

Table 2: Study 218MS305

Over 24 weeks	**Placebo N = 318***	**Fampyra 10 mg BID N = 315***	**Difference (95% CI) *p* - value**
Proportion of patients with mean improvement of ≥ 8 points from baseline MSWS-12 score	34%	43%	Risk difference: 10.4% (3% ; 17.8%) 0.006
MSWS-12 score Baseline Improvement from baseline	65.4 -2.59	63.6 -6.73	LSM: -4.14 (-6.22 ; -2.06) <0.001
TUG Proportion of patients with mean improvement of ≥ 15% in TUG speed	35%	43%	Risk difference: 9.2% (0.9% ; 17.5%) 0.03
TUG Baseline Improvement from baseline (sec)	27.1 -1.94.	24.9 -3.3	LSM: -1.36 (-2.85 ; 0.12) 0.07
MSIS-29 physical score Baseline Improvement from baseline	55.3 -4.68	52.4 -8.00	LSM: -3.31 (-5.13 ; -1.50) <0.001
BBS score Baseline Improvement from baseline	40.2 1.34	40.6 1.75	LSM: 0.41 (-0.13 ; 0.95) 0.141

*Intent to treat population = 633 **LSM: Least square mean**

The European Medicines Agency has waived the obligation to submit the results of studies with Fampyra in all subsets of the paediatric population in treatment of multiple sclerosis with walking disability (see section 4.2 for information on paediatric use).

CHMP comment 1st round

The initial information on the study design of the ENHANCE study was considered incomplete. See above. Results should not be expressed in terms of odd-ratio's these exaggerate the treatment. The relevance of the Timed Up and GO responder definition is questioned See discussion. The TUG is claimed as a measure of static and dynamic balance and physical mobility. However no effect was seen on the Berg Balance Scale the preferred scale to measures balance. Endpoints in the table do not have to be recapitulated extensively in the text. Further the format of the table for the Enhance should be consistent with that of the study MS-F203/204. Considering al this the following text and table is proposed:

Study 218MS305

Study 218MS30 concerned a randomised double-blind placebo controlled parallel group study in 636 subjects with multiple sclerosis and walking disability. Subjects were randomised to placebo or fampridine PR 10 mg BID. Duration of double-blind was 24 weeks with a 2 week post–treatment follow-up.

The primary endpoint in study 218MS305 was improvement in walking ability, measured as the proportion of patients achieving a mean improvement of ≥ 8 points from baseline MSWS-12 score over 24 weeks.

In this study there was a statistically significant treatment difference, with a greater proportion of Fampyra treated patients demonstrating an improvement in walking ability, compared to placebo-controlled patients (43% vs. 34%. Improvements generally appeared within 2 to 4 weeks of initiation of treatment, and disappeared within 2 weeks of treatment cessation. In addition patients treated with Fampyra demonstrated a statistically significant mean improvement from baseline compared to placebo in the MS-Impact score.

Table 2: Study 218MS305

Over 24 weeks	***Placebo N = 318***	***Fampyra 10 mg BID N = 315***	***Difference (95% CI) p-value***
Proportion of patients with mean improvement of ≥ 8 points from baseline MSWS-12-score	*33%*	*43%*	*10.4% 3% ; 17.8% 0.006*
MSWS-score *Baseline* *Improvement from baseline*	 *65.4* *-2.59*	 *63.6* *-6.73*	*LSM: -4.14* *-6.22 ; -2.06* *<0.001*
MISIS-29 physical score *Baseline* *Improvement from baseline*	 *55.3* *-4.68*	 *52.4* *-8.00*	*LSM: -3.31* *-5.13 ; -1.50* *<0.001*

If the Applicant insist on maintaining the TUG responders in the labelling the baseline values and absolute change from baseline should be presented as well. It allows the reader to assess the relevance of a 1.4 second difference in TUG this between placebo and active treatment considering baseline performance is around 26 seconds. Moreover the result on the BBS should be presented for a balanced assessment. See table 4.2.2.2b results on secondary outcomes**.**

Further whether the CMA can be converted to a full MAA will depend on the response to the request for supplementary information

Applicant's response

The applicant largely adapted the text in accordance to the proposal of the CHMP. See above.

Assessment of the response

The text as proposed is largely agreed but not completely.

The following text is hardly readable hampering interpretation:
The mean (SD) TUG time taken at baseline was 27.1 (42.03) seconds for placebo and 24.9 (26.61) seconds for Fampyra. The Least Squares Mean (LSM) change (standard error) over 24 weeks was -1.9 (0.78) seconds for placebo and -3.3 (0.75) seconds for Fampyra. Moreover an effect is suggested whereas the difference was not statistically significant. Instead the information should be added to the table. See proposal above in blue. This is more readable and allows a better assessment of data by the reader.

Further that a positive and sustained treatment effect was observed in the Berg Balance Scale is misleading. It refers to an improvement from baseline and does not carry information on the magnitude of this change. More important an effect is suggested whereas the change form baseline was equal in both groups. Hence a treatment effect can not be claimed. Therefore this text should be adapted as indicated in blue.

Additional adaptations are considered needed
Issue subsequently resolved upon submission of updated PI by the MAH.

5.2 Pharmacokinetic properties

Absorption:

~~When Fampyra tablets are taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of fampridine is approximately 2-7% (10 mg dose) and The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. However C_{max} increases by 15-23%. The consequences of these changes are not considered to be clinically meaningful; Since there is a clear relationship between C_{max} and dose related adverse reactions, it is recommended to take therefore, Fampyra can be taken with or without food (see section 4.2).~~

When Fampyra tablets are taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of fampridine is approximately 2-7% (10 mg dose). The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. However, C_{max} increases by 15-23%. Since there is a clear relationship between C_{max} and dose related adverse reactions, it is recommended to take Fampyra without food (see section 4.2).

CHMP comment 1st round

Insufficient justification is provided in support of this change. The Applicant should provide further justification for this change or the current text should remain. Referred is to the comment in section 4.2.

Applicant's response

The original text was reintroduced

Assessment of the response
Issue resolved.

5. Request for supplementary information

5.1. Other concerns

Clinical aspects

1. Responders to fampridine may be more sensitive for adverse events related the pharmacodynamics of fampridine (e.g. overstimulation). These signals may be masked in the overall safety analysis including both responder and non-responders. A separate safety analysis for non-responders and responders is requested.

2. The MAH should discuss and propose a strategy to follow-up and investigate the effects in patients that need to terminate treatment with Fampyra. Currently available data seem to suggest that a rebound phenomenon may occur in such cases, and it would be interesting to know whether the patients return to a level of functioning similar to the one before treatment, or if they experience effects of worsening.

RMP aspects

3. Please include only a brief summary of the SmPC text in the summary table of risk minimisation measures, instead of the exact wording, in order to avoid unnecessary updates of the RMP.

Product Information

4. Please see section 4.5 of this AR for comments relating to the SmPC. In addition the Applicant is requested to consider these comments, where relevant, also in relation to the PL.

6. Assessment of the responses to the request for supplementary information

Other concerns

Clinical aspects

1. Responders to fampridine may be more sensitive for adverse events related the pharmacodynamics of fampridine (e.g. overstimulation). These signals may be masked in the overall safety analysis including both responder and non-responders. A separate safety analysis for non-responders and responders is requested.

Summary of the MAH's response

The safety results in this response are presented for the intent-to-treat population in the ENHANCE study excluding patients at the one site that closed due to GCP issues. Two patients (1 in each treatment group) from the original safety population have been excluded as it was not possible to determine their responder status. These two patients did not report any adverse events.

Overview of Adverse Events

The incidence of AEs reported in Study 305 was similar between the 3 groups (63% fampridine responder, 68% fampridine non-responder and 60% placebo. Most subjects had AEs that were considered mild or moderate in severity, and the incidence of AEs that were considered severe was 1% in the responder group compared to 4% in the non-responder group and 3% in placebo

The incidence of AEs considered by the Investigator to be related to study treatment was higher in fampridine responders than the non-responders or placebo-treated subjects (21% vs. 15% vs. 14%). Apart from one patient in the placebo group none of these related AEs were considered serious.

SAEs also occurred at a similar incidence (7% vs. 8% vs. 7%). The incidence of AEs leading to dose interruption was slightly higher for fampridine-treated subjects than for those treated with placebo (7% vs. 6% vs. 3%). The incidence of AEs leading to study treatment discontinuation (7% each group) or withdrawal from the study (7% vs. 7% vs 8%) was also balanced.

Table R1.1 General overview of the adverse event by responder status

	Fampridine responders 10 mg BID	**Fampridine non-responders** 10 mg BID	**Placebo**
n dosed	136	179	318
% with adverse event	63%	68%	60%
% treatment related event	21%	15%	14%
% with serious event	7%	8%	7%
% with dose interruption	7%	6%	3%
% discontinuing due to AE	7%	7%	7%
% withdrawing due to AE	7%	7%	8%
% moderate or severe AE	31%	38%	32%
% severe AE	1%	4%	3%

Common Adverse Events

The most common System Order Classes (SOCs) for reported AEs were infections and infestations (27% vs. 34% vs. 28%), nervous system disorders (25% vs. 29% vs. 21%), and musculoskeletal and connective tissue disorders (18% vs. 17% vs. 14%)

The most common AEs (incidence ≥3%) among nervous system disorders were Multiple Sclerosis (MS) relapse, headache, and dizziness, with all of these occurring more commonly in the non-responder group than responder. Balance disorder occurred more commonly in the responder group.

The most common AEs among musculoskeletal and connective tissue disorders were back pain, arthralgia, and pain in extremity, with all of these occurring slightly more frequently in the responder group compared to non-responder.

There were more AEs reported in the Psychiatric Disorders SOC by responders (11% vs. 4% vs. 3%) and this was mostly due to Insomnia (7% vs. 2% vs. <1%).

There were also more AEs reported by responders in the Renal and Urinary Disorders SOC (9% vs. 3% vs. 2%). No single Preferred Term (PT) or medical condition accounted for this difference.

The most frequently reported AEs by PT in both treatment groups were MS relapse (9% vs. 12% vs. 10%) and urinary tract infection (11% vs. 15% vs. 9%), consistent with the MS study population.

Table R1.2 Most common Adverse events / other events of interest by responder status

	Fampridine responders 10 mg BID	**Fampridine non-responders** 10 mg BID	**Placebo**
n	136	179	318
Infections and infestations	**27%**	**34%**	**28%**
Urinary tract infection	11%	15%	9%
Nasopharyngitis	5%	1%	6%
Upper respiratory tract infection	6%	4%	3%
Nervous system disorders	**25%**	**29%**	**21%**
Multiple sclerosis relapse	9%	12%	10%
Headache	4%	5%	5%
Dizziness	3%	4%	2%
Balance disorder	3%	<1%	<1%
Insomnia	7%	2%	<1%
Musculoskeletal & connective tissue disorders	**18%**	**17%**	**14%**
Back pain	7%	4%	3%
Arthralgia	4%	4%	2%
Pain in extremity	4%	2%	3%

Adverse Events by Severity

The majority of subjects in all groups experienced AEs which were considered to be mild (30% responders vs. 30% non-responders vs. 29% placebo) or moderate (31% vs. 34% vs. 28%) in severity. Only 1% of responders, 4% of non-responders and 3% of placebo treated patients experiencing severe AEs.

Adverse Events by Relationship to Study Treatment

All AEs that occurred during Study 305 were assessed by Investigators as related or not related to study treatment. Of the patients reporting AEs in all groups most experienced AEs which were considered not related to study treatment (41% vs. 53% vs. 46%)

The proportion of patients who experienced AEs considered related to study treatment was 21% in the responder group as compared with 15 % in the non-responders and 14% in the placebo.

Serious Adverse Events
In Study 305, the incidence of SAEs was comparable between all 3 groups (7% vs. 8% vs. 7%). MS relapse was the most frequently reported SAE in all groups with fewest in the responder group (2% vs. 6% vs. 3% in placebo).

Adverse Events That Led to Discontinuation of Study Treatment or Study Withdrawal
The incidence of AEs leading to discontinuation of study treatment or study withdrawal was comparable between the 3 groups (7% vs. 7% vs. 8%) MS relapse and MS led to discontinuation or withdrawal in 5 subjects in the non-responder group and 1 in the placebo and 0 in the responder.

Adverse Events That Led to Dose Interruption
The incidence of AEs leading to dose interruption was 7% (9 subjects), 6% (10 subjects) and 3% (11 subjects) in the responder, non-responder and placebo groups, respectively

Adverse events of possible overstimulation
The following list of PTs was provided by the Assessor as examples of AEs suggesting overstimulation which may be observed as a pharmacological effect in the fampridine responder group: Asthenia, Gait disturbance, Muscular weakness, Fatigue, Muscle spasticity, Muscle spasms and Trigeminal neuralgia. The MAH has included additional terms which have been included in the Progress Reports for the LIBERATE study (218MS401) (Fall, Insomnia, Balance disorder, Dizziness, Tremor, Sleep disorder, Anxiety, Irritability, Dysaesthesia, Neuralgia, Paraesthesia and Sensory disturbance).

Table 1 shows the number of patients in each group who experienced events which may suggest Central Nervous System (CNS) overstimulation (24% vs. 23% vs. 18%). There are similar proportions in each of the fampridine groups. The most commonly reported events were fall (9% vs. 7% vs. 6%) and insomnia (7% vs. 2% vs. <1%), both of which occurred more frequently in the responder group. There were proportionally fewer reports of dizziness, fatigue, muscle spasm and spasticity, anxiety, paraesthesia, sensory disturbance and trigeminal neuralgia in the responder group compared with the non-responder. Overall there is no indication that the responder group is at more risk of events related to potential overstimulation compared to the non-responder or placebo groups.

Table 1: Incidence of treatment-emergent adverse events - potential overstimulatio

	Fampridine		Placebo
	Responder	Non-responder	
Adverse events of interest: Potential overstimulation			
Number of subjects with an event (%)	32 (24)	42 (23)	57 (18)
Fall	12 (9)	12 (7)	19 (6)
Insomnia	9 (7)	3 (2)	3 (<1)
Asthenia	4 (3)	5 (3)	7 (2)
Balance disorder	4 (3)	1 (<1)	2 (<1)
Dizziness	4 (3)	7 (4)	7 (2)
Gait disturbance	4 (3)	1 (<1)	7 (2)
Muscular weakness	4 (3)	4 (2)	2 (<1)
Tremor	3 (2)	1 (<1)	1 (<1)
Fatigue	2 (1)	6 (3)	9 (3)
Muscle spasticity	2 (1)	6 (3)	2 (<1)
Sleep disorder	2 (1)	1 (<1)	0
Anxiety	1 (<1)	3 (2)	3 (<1)
Irritability	1 (<1)	0	1 (<1)
Muscle spasms	1 (<1)	3 (2)	2 (<1)
Dysaesthesia	0	0	1 (<1)
Neuralgia	0	0	1 (<1)
Paraesthesia	0	2 (1)	1 (<1)
Sensory disturbance	0	1 (<1)	2 (<1)
Trigeminal neuralgia	0	3 (2)	3 (<1)

SOURCE: 218MS/MAA/MAA/T-AE-PT-SLINTERST-EXCL513-RESP.SAS DATE: 20JAN2017

Cardiovascular Disorders

AEs using the predefined classification of events related to dysrhythmias were reported for 4 subjects (3%) in the responder group, 2 subjects (1%) in the non-responders and 2 subjects (<1%) treated with placebo. The events included palpitations (2 subjects, responders vs. 2 subjects, non-responders vs. 1 subject, placebo), tachycardia (2 subjects, responder), bundle branch block right (1 subject, non-responder), and arrhythmia (1 subject, placebo).

Summary / Conclusion

The incidence and severity of AEs in the two fampridine groups, responder and non-responder, are well balanced and both consistent with the established safety profile of fampridine. There is no indication that the fampridine responder group had a higher incidence of AEs related to the pharmacodynamics of fampridine (e.g. overstimulation).

There were occasional differences between the fampridine responder and non-responder groups in some cases of individual AEs. The incidence of Serious Adverse Events (SAEs), AEs leading to dose interruption or discontinuation and AE severity are similar and compatible with the known safety profile of fampridine and do not represent any new safety findings.

The analysis of the safety data for the patients receiving fampridine by responder and non-responder groups supports the overall established safety of fampridine as observed in clinical trials and post-marketing use. The numbers in the two groups are relatively small (136 responders and 179 non-

responders), however, the safety profile in the two groups appears to be well balanced with no new safety issues identified.

Assessment of the MAH's response

The conclusion of the Applicant that the data do not support the concern that responders may be at an increased risk of adverse events related to the pharmacological activity of fampridine (overstimulation) is endorsed based on the data provided. There is no large difference of these events between responders and non-responders (see table 1). Moreover, there is no consistent pattern.

Issue resolved

2. The MAH should discuss and propose a strategy to follow-up and investigate the effects in patients that need to terminate treatment with Fampyra. Currently available data seem to suggest that a rebound phenomenon may occur in such cases, and it would be interesting to know whether the patients return to a level of functioning similar to the one before treatment, or if they experience effects of worsening.

Summary of the MAH's response

The MAH believes that effects of fampridine treatment discontinuation have been well characterized across pivotal studies and that there is currently no evidence to support that patients exposed to fampridine experience worsening of function upon treatment interruption. The following results corroborate this observation.

Study MS-F203 and Study MS-F204

The effect of fampridine treatment discontinuation was evaluated during a pre-specified off treatment follow-up visit in studies MS-F203 and MS-F204. This was further complemented by an evaluation of treatment re-initiation effects in patients who chose to participate in phase III extension studies.

In both MS-F203 and MS-F204, a rapid loss of treatment effect but not worsening was observed after fampridine discontinuation. On average, patients assigned to fampridine in the blinded phase of these studies experienced a return to baseline T25FW walking speed values, which was later reversed in patients who re-initiated treatment as part of their participation in the open-label extension phase of these studies (Goodman et al., 2015)

Study 218MS305

Fampridine discontinuation effects were also assessed in Study 218MS305 during a post treatment follow-up visit two weeks after study treatment was completed. The change from baseline MSWS-12 to 2 week off treatment follow-up was -2.61 (95% CI: -4.86, -0.36). These results suggest that, on a population level, fampridine treated patients had a tendency to experience marginal improvements in their reported walking function scores after being exposed to treatment when compared to pre-treatment values.

To further clarify if this analysis on the Intent to Treat (ITT) population could have masked worsening in some subjects, MSWS-12 score changes were also separated into categories of change. Patients who reported worse scores as compared to baseline were then evaluated for the magnitude of their change and its comparison to placebo. Overall, the proportion of fampridine treated patients experiencing a worsening in their MSWS-12 scores at off treatment follow up visit was similar to placebo (49% and 46%, respectively). Likewise, measures of statistical dispersion of the magnitude of increase in MSWS-12

scores was comparable between fampridine treated patients and placebo with mean, median and quartile score changes slightly favoring fampridine as compared to placebo.

For changes in TUG speed similar results are noted. Although placebo treated patients also had an increase in TUG speed at follow-up visit, most fampridine treated patients showed improvements in TUG speed with mean percentage increases of 5.86% (95% CI: 2.80, 8.92) at follow up visit when compared to baseline. When further separating patients by categories of change, comparable proportions of fampridine treated patients and placebo experienced decrease in TUG speed at study completion (35% vs 39%, respectively). Furthermore, measures of statistical dispersion of the magnitude of decrease in TUG speed in this category of patients demonstrated that test performance declined in a similar manner in fampridine and placebo patients, hence suggesting that the observed worsening of function is likely to be disease related rather than treatment related.

Finally, we note that there were no serious falls or other related SAEs reported in fampridine treated subjects during the washout period.

Conclusion
In summary, the MAH believes that effects of treatment discontinuation were adequately studied during the fampridine clinical development program. Results obtained from three distinct phase III clinical trials using objective and patient reported outcome measures were consistent in demonstrating that patients returned to pre-treatment levels of functioning when discontinued from treatment. While some patients reported a worsening compared to baseline, the proportion was nearly identical in the placebo group. Consequently, the MAH believes that further investigation on the possibility for a rebound phenomenon is not warranted at this time.

Assessment of the MAH's response

The conclusion of the Applicant that the data do not support the possibility for a rebound phenomenon is not completely agreed. The long term extension study (MS-F203 & MS-F204) did not specific address rebound. The MSWQ12 may not be sensitive to pick up rebound although it may be argued that if the MSWQ12 does not this up it of limited clinical relevance.

Nevertheless the data presented appear compatible with this view that rebound is not an issue although based on circumstantial evidence.

Issue not pursued further

RMP aspects

3. Please include only a brief summary of the SmPC text in the summary table of risk minimisation measures, instead of the exact wording, in order to avoid unnecessary updates of the RMP.

Summary of the MAH's response
The Summary table of the RMMs in the RMP version 11.0, has been updated as requested.

VI.1.4 Summary table of ~~risk minimisation measures~~Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Seizure	**Text in SmPC** **Section 4.2 Posology and method of administration** Treatment with Fampyra is restricted to prescription and supervision by physicians experienced in the management of MS. The recommended dose is one 10 mg tablet, twice daily, taken 12 hours apart.~~(one~~ 1 ~~tablet in the morning and one~~1 ~~tablet in the evening).~~ Fampyra should not be administered more frequently or at higher doses than recommended~~(see section 4.4). The tablets should~~can ~~be taken with or~~without food ~~(see section 5.2)~~ ~~Initial prescription should be limited to 2 to 4 weeks of therapy as clinical benefits should generally be identified within 2 to 4weeks after starting Fampyra~~ ~~A timed an assessment of~~walking test~~ability, e.g. the Timed 25 Foot Walk (T25FW),or MSWS 12, is recommended to evaluate improvement after two weeks~~within 2 to 4 ~~weeks. If no improvement is observed, Fampyra should be discontinued~~ ~~Fampyra should be discontinued if benefit is not reported by patients.~~ ~~If decline in walking ability is observed physicians should consider an interruption to treatment in order to reassess the benefits of Fampyra (see above). The re-evaluation should include withdrawal of Fampyra and performing the an assessment of~~walking test~~ability. Fampyra should be discontinued if patients no longer receive walking benefit.~~ ~~The usual dosing regime regimens~~should always be followed. ~~A double dose should not be taken if a dose is missed.~~ **Section 4.3 Contraindications** Patients with prior history or current presentation of seizure. **Section 4.4 Special warnings and precautions for use** ~~Seizure risk~~ ~~Treatment with fampridine increases seizure risk (see section 4.8).~~ ~~Fampyra should be administered with caution~~Caution in the presence of any factors which may lower seizure threshold. Treatment should be discontinued in patients ~~Fampyra should be discontinued in patients~~ who experience a seizure.~~while on treatment.~~ **Section 4.8 Undesirable effects** ~~**Description of selected adverse reactions**~~ Seizure included as an ADR ~~In post-marketing experience, there have been reports of seizure, the frequency is not known (cannot be estimated from the available data). For further information on seizure risk, please refer to sections 4.3 and 4.4.~~	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4.9 Overdose ~~Symptoms~~ Symptoms of ~~Acute symptoms of~~ overdose with Fampyra include: ~~were consistents with central nervous system excitation and included~~ confusion, tremulousness, diaphoresis, seizure, and amnesia. ~~Central nervous system side effects at high doses of 4-aminopyridine API~~include ~~confusion, seizures, status epilepticus, involuntary and choreoathetoid movements.~~ ~~Management~~ ~~Patients who overdose should be provided supportive care. Repeated seizure activity should be treated with benzodiazepine, phenytoin, or other appropriate acute anti-seizure therapy.~~ Other routine risk minimisation measures **Packaging:** Blister packaging with calendar and design elements to reinforce the required posology of twice daily dosing spaced by 12 hours. This helps to minimize the risk associated with high plasma levels if the twice daily dosing are not spaced adequately, which may increase the risk of seizure. ~~A 'starter pack' for the initial prescriptions will limit to 2 weeks of medication to reinforce the section 4.2 posology of the SmPC that benefit of treatment should be evaluated after 2 weeks and only to be continued in patients responding to fampridine and thereby improving benefit/risk in those continuing therapybe provided to the patients.~~	
Serious hypersensitivity	~~**Text in SmPC**~~ Section 4.3 of the SmPC includes hypersensitivity to as a contraindication. Section 4.4 of the SmPC includes a warning for serious hypersensitivity reactions the majority of which have occurred in the first week of treatment. Section 4.8 of the SmPC includes reference to hypersensitivity and anaphylaxis as recognised ~~dverse reactions~~ ADRE~~s~~.	None
UTIs	**Text in SmPC** **4.8 Undesirable effects** UTI is included as a very common ADR.	None
Interaction with OCT2 inhibitors	**Text in SmPC** **Section 4.3 Contraindications**	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Concomitant use of Fampyra with ~~medicinal products that are inhibitors of Organic Cation Transporter 2(~~OCT2~~)~~ inhibitors~~for example, cimetidine.~~.	
Cardiovascular disorders	**Text in SmPC** **4.4. Special warnings and precautions for use** Caution is advised in patients with ~~cFampyra should be administered with caution to aptients with~~ cardiovascular symptoms of rhythm and sinoatrial or atrioventricular conduction cardiac disorders ~~These effects are seen in overdose). There is limited safety information in these patients.~~ **Section 4.9 Overdose** Symptoms seen at high doses include cardiac arrhythmias ~~Other side effects at high doses include cases of cardiac arrhythmias (for example, supraventricular tachycardia and bradycardia) and ventricular tachycardia as a consequence of potential QT prolongation. Reports of hypertension have also been received~~	None
Interaction with OCT2 substrates	**Text in SmPC** **4.4. Special warnings and precautions for use** Caution is required when Fampyra is prescribed concurrently with medicinal products that are substrates of OCT2 for example, carvedilol, ~~propranolol~~ propranolol and metformin.	None
Interaction with drugs with potential to lower seizure threshold	**Text in SmPC** **4.4 Special warnings and precautions for use** Fampyra should be administered with caution in the presence of any factors which may lower seizure threshold.	None
Population not studied: paediatric and adolescent patients	**Text in SmPC** **Section 4.2 Posology and method of administration** ~~Peadiatric populations~~ The safety and efficacy of Fampyra in children aged 0 to 18 years have not been established.~~No data are available.~~ ~~**Section 5.1 Pharmacodynamic properties**~~ ~~The European Medicines Agency has waived the obligation to submit the results of studies with Fampyra in all subsets of the paediatric population in treatment of multiple sclerosis with walking disability (see section 4.2 for information on paediatric use).~~ ~~**Section 5.2 Pharmacokinetic properties**~~ ~~Paediatric Population:~~ ~~No data are available~~	None
Population not studied: aged > 65	**Text in SmPC**	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
years	**Section 4.2. Posology and method of administration** ~~Elderly~~ Older people Renal function should be checked in ~~elderly patients~~ older people before starting treatment with Fampyra and during treatment. ~~Monitoring renal function to detect any renal impairment is recommended in elderly patients~~ older people~~(see section 4.4).~~ **Section 5.2. Pharmacokinetic properties** ~~Special Populations~~ ~~Elderly patients~~Older people: ~~Clinical studies of Fampyra did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients.~~ Fampyra is primarily excreted unchanged by the kidneys, and with creatinine clearance known to decrease with age, monitoring of renal function in ~~elderly~~ older patients should be considered~~ed (see section 4.2).~~	
Pregnancy	**Text in SmPC** **4.6. Fertility, pregnancy and lactation** ~~**Pregnancy**~~ There are no or limited amount of data from the use of fampridine in pregnant women. It is preferable to avoid using fampridine during pregnancy, ~~Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure it is preferable to avoid the use of Fampyra in pregnancy.~~	None
Population with renal impairment	**Text in SmPC** **Section 4.2 Posology and methods of administration** ~~**Patients with renal impairment**~~ Fampyra is contraindicated in patients ~~mild, moderate or severe~~ renal impairment ~~Creatinine clearances <80 ml~~ml/min)~~.(see section 4.3)~~ **Section 4.3 Contraindications** Patients with ~~mild, moderate or severe~~ renal impairment Concomitant use with OCT2 inhibitors.~~ Creatinine clearances <80 ml/min).~~ ~~**Section 4.4 Special warnings and precautions for use**~~ ~~Renal impairment~~ ~~Fampyra is primarily excreted unchanged by the kidneys. Patients with renal impairment have higher plasma concentrations which are associated with increased adverse reactions, in particular neurological effects.~~	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	~~Determining renal function before treatment and its regular monitoring during treatment is recommended in all patients (particularly the elderly~~in older people ~~in whom renal function might be reduced). Creatinine clearance can be estimated using the Cockroft-Gault formula.~~ ~~Fampyra should not be administered to patients with renal impairment (creatinine clearance <80 ml~~mL/min~~) (see section 4.3).~~ ~~Caution is required when Fampyra is prescribed concurrently with medicinal products that are substrates of OCT2 for example, carvedilol, propanolol, and metformin.~~ ~~**4.5 Interaction with other medicinal products and other forms of interaction**~~ ~~Fampridine is eliminated mainly via the kidneys with active renal secretion accounting for about 60% (see section 5.2). OCT2 is the transporter responsible for the active secretion of fampridine. Thus, the concomitant use of fampridine with medicinal products that are inhibitors of OCT2 for example, cimetidine are contraindicated (see section 4.3) and concomitant use of fampridine with medicinal products that are substrates of OCT2 for example, carvedilol, propanolol, and metformin is cautioned (see section 4.4.)~~ **Section 5.2 Pharmacokinetic properties** Fampridine is eliminated primarily by the kidneys as unchanged medicinal product and therefore renal function should be checked in patients where renal function might be compromised. ~~Elimination~~ ~~The major route of elimination for fampridine is renal excretion, with approximately 90% of the dose recovered in urine as parent medicinal product within 24 hours. Renal clearance (CLR 370 ml~~ mL~~/min) is substantially greater than glomerular filtration rate due to combined glomerular filtration and active excretion by the renal OCT2 transporter. Faecal excretion accounts for less than 1% of the administered dose.~~ ~~Fampyra is characterized by linear (dose proportional) pharmacokinetics~~PKs ~~with a terminal elimination half-life of approximately 6 hours. The maximum plasma concentration (~~ The ~~C_{max}) and, to a smaller extent, area under the plasma concentration time curve (AUC) increase proportionately with dose. There is no evidence of clinically relevant accumulation of fampridine taken at the recommended dose in patients with full renal function. In patients with renal impairment accumulation occurs relative to the degree of impairment.~~ ~~Patients with renal impairment:~~ ~~Fampridine is eliminated primarily by the kidneys as unchanged medicinal product and therefore renal function should be checked in patients where renal function might be compromised. Patients with mild renal impairment can be expected to have approximately 1.7 to 1.9 times the fampridine concentrations achieved by patients with normal renal function. Fampyra must not be administered to patients with mild, moderate and severe renal impairment (see section 4.3).~~	
Interaction with	None	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
anti-epileptic agents affecting sodium-potassium current		
Long-term safety	None	None
~~Lack of efficacy~~	~~None~~	~~None~~

Assessment of the MAH's response
The summary table of the RMMs was amended as requested.

Issue resolved.

Product Information
4. Please see section 4.5 of this AR for comments relating to the SmPC. In addition the Applicant is requested to consider these comments, where relevant, also in relation to the PL.

Summary of the MAH's response

See section 4.5. SmPC section 4.8. p 45

Assessment of the MAH's response

See section 4.5. SmPC section 4.8. p 45

Conclusion

☒ No need to update overall conclusion and impact on benefit-risk balance

7. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 23 March 2017.