EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2011
EMA/555661/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fampyra

fampridine

Procedure No. EMEA/H/C/002097

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

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biogen Idec Ltd. submitted on 23 December 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Fampyra, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 May 2009.

The applicant applied for the following indication:

Fampyra is indicated for the treatment of adult patients with Multiple Sclerosis for the improvement of walking ability.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/213/2010 for the following condition:

- Treatment of multiple sclerosis with walking disability

on the granting of a product-specific waiver.

Information relating to orphan market exclusivity:

Not applicable

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Barbara van Zwieten-Boot

Co-Rapporteur: Martina Weise

- The application was received by the EMA on 23 December 2009.
- The procedure started on 21 January 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 April 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 April 2010.
- During the meeting on 20 May 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 May 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 August 2010.
- During a meeting of a Scientific Advisory Group (SAG) on 8 September 2010, experts were convened to address questions raised by the CHMP.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 October 2010.
- During the CHMP meeting on 21 October 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP a list of outstanding issues on 15 November 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues on 1 December 2010.
- During the CHMP meeting on 15 December 2010, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 20 January 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion.

1.3. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Cristina Sampaio

Co-Rapporteur: David Lyons

- The applicant submitted written notice to the EMA on 7 February 2011 to request a re-examination of Fampyra CHMP opinion of 20 January 2011.
- During its meeting on 17 February 2011, the CHMP appointed Cristina Sampaio as Rapporteur and David Lyons as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 23 March 2011. The re-examination procedure started on 24 March 2011.
- During its meeting on 11-14 April 2011, the CHMP adopted the List of Questions to the SAG on Neurology to be held on 20 April 2011.
- The Rapporteur's re-examination Assessment Report was circulated to all CHMP members on 18 April 2011. The Co-Rapporteur's re-examination Assessment Report was circulated to all CHMP members on 18 April 2011.

- During a meeting of the SAG on 20 April 2011, experts were convened to consider the grounds for re-examination.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 9 April 2011.
- During the CHMP meeting on 17 May 2011, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 19 May 2011, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that the applicant satisfied the criteria for authorisation and recommended the granting of the conditional marketing authorisation.

2. Scientific discussion

2.1. Introduction

MS is an inflammatory condition that damages the myelin of the Central Nervous System and causes neurologic impairment and, frequently, severe disability. It is a common neurological disease with prevalence rate ranging from more than 100 per 100,000 in Northern and Central Europe to 50 per 100,000 in Southern Europe. The aetiology of MS remains unknown. It is generally assumed that MS is mediated by some kind of autoimmune process triggered by an infection and superimposed upon a genetic predisposition.

Most patients present with relapsing-remitting multiple sclerosis (RRMS), characterised by unpredictable acute episodes of neurological dysfunction or relapse, followed by variable recovery and periods of clinical stability. Within ten years more than 50% of patients who presented with a relapsing-remitting (RR) form eventually develop sustained deterioration with or without relapses superimposed, i.e. secondary progressive multiple sclerosis (SPMS). Around 15% of patients develop a sustained deterioration of their neurological function from the beginning, i.e. have primary progressive multiple sclerosis (PPMS). About 5% of the patients have a steady progression of clinical neurological damage with superimposed relapses, i.e. progressive relapsing multiple scleroses (PRMS).

In general, relapses are considered the clinical expression of acute inflammatory focal lesions whereas progression is considered to reflect the occurrence of demyelization, axonal loss and gliosis.

Current therapeutic approaches in multiple sclerosis include: symptomatic treatment (i.e. mainly treatment of complications), treatment modifying the outcome of acute relapses (corticosteroids), treatments aimed to modify the course of the disease (immunomodulators e.g. beta-interferons, glatiramer, nataluzimab and immunosuppressants, e.g. mitoxantrone, azathioprine). Potential future therapies focus on pursuing neuroprotection or restoration of neurological function (e.g. promotors of remyelinisation).

The indication claimed for fampridine was treatment of adult patients with multiple sclerosis for the improvement of walking ability.

Fampridine (4-aminopyridine) is a selective potassium channel blocker. It is a lipid-soluble drug which readily crosses the blood-brain barrier. Fampridine is formulated as a prolonged-release tablet and the recommended dose was one 10mg tablet twice daily, taken 12 hours apart. A prolonged-release tablet has been developed to reduce peak plasma concentrations associated adverse events.

By blocking potassium reflux the hyperpolarisation phase of an action potential is reduced. Consequently the relative refractory period of the action potential is shortened, allowing the action potential to propagate along the cell membrane. This, according to the applicant, especially applies for unmyelinated axons where the action potential dampens quickly below a depolarisation threshold too low for activating the adjacent membrane.

The K+ channels are located primarily in the paranodal and internodal membrane of the axon where they are not significantly activated by the passage of an action potential because the myelin sheath acts as an electrical shield. In demyelinated axons the internodal membrane and its ion channels become exposed to larger electrical transients during the action potential. Under these conditions, leakage of ion current through the K+ channel can contribute to action potential conduction block. Fampridine at low concentration may prolong nerve action potentials by blocking these exposed channels and inhibiting repolarisation, subsequently improving axon potential propagation.

Considering the mechanism of action of fampridine, there is a plausible biological rationale to evaluate the usefulness of fampridine in symptomatic treatment in multiple sclerosis.

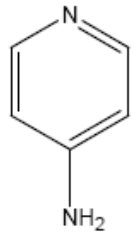
2.2. Quality aspects

2.2.1. Introduction

The finished product concerns a 10 mg prolonged release film coated tablet containing fampridine as active substance. It is packaged in HDPE bottles containing a desiccant and polyester coil.
The active substance fampridine (4-aminopyridine) is a potassium channel blocker. The maximum daily dosage is 20 mg.

2.2.2. Active Substance

Information on the active substance 4-aminopyridine is presented in form of an Active Substance Master File (ASMF) dated December 2009 and submitted by the manufacturer.
The chemical name of the active substance is pyridine-4-amine. The molecular formula of active substance is $C_5H_6N_2$, its relative molecular mass 94.12 and its structural formula is shown below.



Fampridine is a white to off-white non hygroscopic powder, practically soluble in water. No evidence of polymorphism has been found. Fampridine has no stereochemical centers. Its pKa is 9.17 (protonated free base) and its logP is 0.76 and the pH of its solution (50 mg/mL in water) is 11.

Manufacture

Sufficient information on each step of the synthesis of the active substance, including reagents and solvents has been provided. The specifications of the intermediates are acceptable. No critical steps have been determined.

Specification

The drug substance specification includes tests for appearance (visual), identification (IR, Ph.Eur., HPLC), water content (Ph.Eur.), residue on ignition (Ph.Eur.), heavy metals (Ph.Eur.), particle size (laser diffraction), assay (HPLC), related substances (HPLC) and residual solvents (GC).
Sufficient batch analysis data have been presented for three pilot scale batches, the three validation batches and 18 earlier commercial scale batches. All results complied with the specification. Earlier batches comply with the specifications that were active at the time of release. The data generated demonstrate consistency in manufacturing. The purity of the drug substance has been improved over the years.

Stability

The primary stability study has been performed on the three commercial scale validation batches stored at long term (25°C/60% RH) for 60 months and accelerated conditions (40°C/75% RH) for 6 months.

Additionally, batch results of four commercial batches used in the annual stability study tested at long term (25°C/60% RH) up to 48 months for all four batches and accelerated conditions (40°C/75% RH) for 6 months for one of the commercial batches have been presented.
Both the validation batches and the annual stability batches met the specification at all storage conditions and testing intervals and no trends were observed over time.
Forced degradation studies were performed under photo, thermal, acidic, basic and oxidative conditions. No degradation was observed after exposure to photo, thermal, acidic or basic conditions. Degradation was observed after exposure to oxidative conditions. The results also indicate that the in house HPLC method for related substance determination is stability indicating.
The light sensitivity has been tested within the forced degradation studies. Under conditions which are in line with the Note for Guidance on Photostability Testing of New Active Substances and Medicinal Products no degradation has been observed. It can be concluded that fampridine is not sensitive to light.
The stability data support the proposed re-test period for fampridine when packaged in the original container.
In accordance with EU GMP guidelines[*], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The drug product corresponds to a prolonged release (PR) tablet dosage form. A controlled release dosage form was favoured in order to minimise potential plasma peak related adverse events. Drug release is controlled by a hydrophilic matrix-forming polymer, hydroxypropyl methylcellulose (HPMC), which is incorporated into the tablets. When in contact with the contents of the gastrointestinal tract, the polymer absorbs liquid and swells forming a viscous gel. The controlled release of 4-aminopyridine occurs by diffusion out through the viscous mass and/or by erosion of the polymer as it is exposed to the gastrointestinal fluids.
Various immediate and prolonged release capsule formulations have been tested during development. The PR matrix tablet formulations offered a more favourable stability profile while demonstrating comparable pharmacokinetic properties relative to the PR capsule formulation used in the clinical trials.
The final formulation of the film-coated tablet was studied in all Phase 2 and Phase 3 clinical trials. Various tablet dosage strengths of the final formulation were evaluated during clinical development. However, only the 10 mg strength is proposed for commercialisation. The qualitative and quantitative composition of the 10 mg strength used in pivotal clinical trials is the same as those proposed for commercial production..
The selected tablet formulation went through further steps of optimization.
The drug substance is highly soluble and permeable. Particle size distribution is not relevant for dissolution and is not considered critical regarding *in vivo* properties.
Studies on polymorphism were performed. The results of the polymorphism studies show, that only one crystal form exists..
Compatibility studies between 4-aminopyridine and the excipients were performed and presented. All excipients, with the exception of the Opadry, are compendial. The components of Opadry Y-1-7000 are compendial excipients that meet the respective Ph.Eur. monograph requirements.

[*] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

Development of the *in vitro* release method was adequately described. Tablets produced at either manufacturing site have similar dissolution profiles in the pH range 1.2 to 7.2. Moreover, bioequivalence was confirmed in a clinical study.
The potential for dose dumping due to an interruption of the modified release mechanism with alcohol has been investigated. There was no evidence of dose dumping at any time point, under the conditions studied. It is therefore concluded that the drug product is compatible with alcohol.
The development of the manufacturing process has been described. The critical formulation attributes were defined and the critical processing parameters at the different stages of manufacture were studied.
Process scale up was performed and included the evaluation of a number of manufacturing parameters and the optimal settings/ ranges have been established and process robustness was demonstrated.
Additionally, the transfer of the drug product manufacturing process to a second commercial manufacturer has been evaluated. The data show that the manufacturing process was robust for the manufacture of fampridine prolonged release tablets. All tests met the acceptance criteria and quality attributes of the tablet strengths tested.

Adventitious agents

No materials of human or animal origin are used in the manufacture of fampridine tablets.

Manufacture of the product

The manufacturing process of fampridine 10 mg prolonged release film coated tablets, consists mainly of three steps at both proposed manufacturing sites: blending, tabletting, coating and packaging. Holding times have been established. The process steps used are well established standard pharmaceutical methods. No critical steps were identified during development that need to be considered for routine manufacture.
There are minor differences in the process approach for each of these steps between the two sites, but these have been demonstrated to have no impact on product performance.
Process validation has been performed on three production scale batches at both proposed manufacturing sites. A summary of the validation results are provided. The results demonstrate consistency within and between the batches. From the results obtained it can be concluded that Fampridine prolonged release tablets, 10 mg manufactured at both manufacturing sites consistently meet all routine analytical test specifications and validation acceptance criteria.

Product Specification

The release and shelf-life specifications of the drug product include tests and limits for appearance (visual), identification (HPLC, UV - at release only), assay (HPLC, UV), related impurities (HPLC), uniformity of dosage units (Ph Eur - at release only), dissolution (Ph Eur), and moisture (KF) and microbial test (Ph.Eur).
Batch analysis data were provided for four production scale validation batches manufactured at one manufacturer and three production scale validation batches manufactured at the other. The batch analyses data are acceptable. All results are within the proposed specifications.

Stability of the product

Stability studies on the drug product were carried out on four batches up to 36 months at 25°C ± 2°C/60%RH ± 5%RH, 30°C ± 2°C/65%RH ± 5%RH, and 40°C ± 2°C / 75%RH ± 5%RH according to ICH guideline. All batches for which stability data are submitted were manufactured according to the

intended commercial process and comparable equipment. The results presented show that all parameters are well within the proposed shelf-life specification for all conditions investigated. The observed slightly increase of two impurities has been adequately considered in the drug product specification. No other significant tendencies are observed.
A photostability test was performed according to ICH. Results indicated that special precautions for light protection of the marketed drug product are not required for drug product in the proposed commercial package.
An in-use stability study was conducted on two batches. The conditions were mimicking patient use. All results were within specification and no significant trends observed except for moisture content. The provided data show that the proposed in-use period can be granted.
Shipping stability performance of bulk tablets was investigated with three lots. The results demonstrate the continued stability performance following product having been shipped in bulk.
Based on the available stability data the proposed shelf-life and the storage condition can be accepted.
In accordance with EU GMP guidelines†, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.4. Discussion and conclusion on chemical, pharmaceutical and biological aspects

The quality of Fampyra 10 mg prolonged-release film coated tablets is considered to be acceptable. Information on development, manufacture and control of the drug substance has been presented in a satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data. Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug product has been presented. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2.3. Non-clinical aspects

2.3.1. Introduction

Compliance with GLP

Of the four safety pharmacology studies performed with fampridine, three studies investigating cardiovascular safety were compliant with GLP. The pharmacokinetic studies, which were conducted over a course of several decades, were not generally conducted in compliance with GLP standards; however, they were considered adequate by design and their findings were supported by literature publications. During fampridine development, studies analysing toxicities after single- and repeated-dose administration, reproduction toxicity, genotoxicity and carcinogenicity were conducted. These studies formally adhered to GLP standards; however, the pivotal repeated-dose toxicity study, reproduction toxicity study and carcinogenicity study lacked concomitant toxicokinetic evaluations of fampridine or its metabolites. This deficiency was later compensated for by conducting toxicokinetic bridging studies compliant with GLP.

† 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

2.3.2. Pharmacology

Primary pharmacodynamic studies

Aminopyridines are well known for their reversible inhibition of potassium channels and fampridine has been extensively used as an experimental tool to block specific potassium channels *in vitro* or to induce seizures in laboratory animals. Therefore, the applicant mainly referred to pertinent literature regarding the primary pharmacodynamic properties of fampridine.

The existing information was complemented with an *in vitro* study on cloned Kv1.1, Kv1.2 and Kv1.4 channels expressed in HEK 293 cells at concentrations of 50, 500, 5 000 and 50 000 µM, testing the activity of fampridine and also its two primary metabolites (3-OH-4-AP and 3-OH-4-AP-sulphate). The study results suggested that the potassium channel subtypes Kv1.1, Kv1.2 and Kv1.4 might mediate the pharmacodynamic effects of fampridine, because their distribution coincides with changes in fampridine sensitivity of demyelinated fibres. The two primary metabolites showed about 30-fold lower inhibitory effect on the specific potassium channel subtypes and thus, they did not appear to contribute to the pharmacological activity of fampridine.

Improvements of neurological functions or effective dose ranges were not evaluated in an animal model in *in vivo* studies. The CHMP noted that the widely used animal models of experimental autoimmune encephalomyelitis mimic only particular aspects of MS and are hence of limited predictive value to determine the clinical efficacy of a compound. Thus, the CHMP acknowledged challenges of generating relevant non-clinical *in vivo* data and concluded that the pharmacodynamic properties of fampridine would need to be sufficiently substantiated by clinical evidence.

Secondary pharmacodynamic studies

The applicant did not perform any secondary pharmacodynamic studies. Based on a detailed review of Bowman and Savage 1981, the applicant described that the secondary pharmacodynamic effects of fampridine are thought to depend on an increased synaptic transmission and neuromuscular tension, without summarizing the potential secondary pharmacodynamic actions of fampridine.

Safety pharmacology programme

Adverse reactions that were elicited by fampridine in toxicological investigations as well as in MS patients mainly involved excitatory effects on the CNS like paraesthesia, dizziness, anxiety, insomnia, confusion and seizures. The existing knowledge of the CNS effects of fampridine was complemented with an *in vivo* study analysing EEG changes in Sprague-Dawley rats. The safety pharmacological effects of fampridine were investigated at i.v. doses of 0.5, 1, 2 and 4 mg/kg compared to saline. Blood samples were harvested at different time-points and EEG activity was recorded at baseline and post-injection every 13 minutes for 3 hours. Administration of fampridine significantly changed EEG activity with a threshold concentration of 109-135 ng/mL, which was in accordance with an increased risk of seizures reported in humans at fampridine plasma concentrations above 100 ng/mL.

The effects of fampridine on the cardiovascular system, in particular the arrhythmic risk, were evaluated in *in vitro* studies in HERG-expressing HEK293 cells and dog Purkinje fibres and in *in vivo* study in Beagle dogs. Both *in vitro* studies were indicative of a potential of fampridine to extend the QT interval, although only at concentrations exceeding levels clinically relevant (at least 2000x higher). No effects on the ECG were apparent in dogs *in vivo* when fampridine was analysed at concentrations more than 50x higher than the max determined in healthy subjects. Hence, based on the cardiovascular safety pharmacology studies, occurrence of QT prolongation following treatment with fampridine was considered not very likely. This lack of sizable arrhythmic risk at therapeutic levels was

in agreement with absence of arrhythmic effects of fampridine in toxicity studies in dogs. However, the results of a QT clinical study in humans were inconclusive as the confusing results questioned the reliability of this study (described in greater detail in the Clinical part of the assessment report).

Table 1 Overview of safety pharmacology studies performed with fampridine

System	Study No.	Type of study	Concentration/dose	GLP
CNS	pk-pd-1994	EEG changes in Sprague-Dawley rats	0, 0.5, 1, 2, 4 mg/kg i.v.	No
Cardiovascular	hERG4AP102003	Inhibition of HERG current in HEK293 cells in vitro	0, 0.1, 0.3, 1, 10, 30 mM	Yes
	Purk4AP102003	Action potential parameters in dog Purkinje fibres in vitro	0, 0.5, 5, 50, 500 µM	Yes
	TPS468A-501-510-93 / IRDC 684-017 (TK)	Cardiovascular safety in Beagle dogs	0, 0.5, 1, 1.5 mg/kg i.v.	Yes

TK = Toxicokinetic

The results of the safety pharmacological studies demonstrated that fampridine had an acceptable pharmacological safety profile in animals.

Pharmacodynamic drug interactions

The applicant did not perform any drug-drug interaction studies.

2.3.3. Pharmacokinetics

Fampridine concentrations were determined in tissue, plasma and microsomes by a validated High Performance Liquid Chromatography (HPLC) method, while ^{14}C-labelled fampridine was measured in samples of blood, tissues or urine by liquid scintillation counting (LSC). Corresponding metabolites of radioactively labelled fampridine (3-OH-4-AP, 4-AP-N-oxide, 1-methyl-4-pyridone, 4-amino-2-pyridone) were also identified by LSC or HPLC in urine following separation by thin layer chromatography. Analyses of dose formulations and toxicokinetic parameters were performed using validated HPLC with tandem mass spectrometry (LC-MS/MS) to detect 4-AP, 3-OH-4-AP and 3-OH-4-AP-sulphate.

Absorption

Following oral administration of a single dose of fampridine at doses of no more than 2 mg/kg, the PK parameters of fampridine were similar across the non-clinical species tested (rat and dog), and were generally also similar to those observed in humans. Fampridine was rapidly absorbed with peak systemic exposure occurring within 1.5 hours.

Oral bioavailability of fampridine was only measured in rats and appeared to be moderate in both females (55%) and males (67%). Approximately 36% of the parent drug was removed by hepatic first-pass metabolism. Fampridine was neither a substrate for P-gp *in vitro*, nor did it inhibit the P-gp transport of other compounds. In humans, the bioavailability was higher, 95%, which was consistent with the fact that fampridine is not a P-gp substrate.

Fampridine peak (C_{max}) and total systemic exposure (AUC) increased with increasing dose in CD-1 mice, Sprague-Dawley rats, New Zealand White rabbits and Beagle dogs. However, in all species tested the increase was less than dose proportional. Similar results were observed after single- and repeated doses.

Sex differences were not observed in rats and dogs. However, in mice both peak concentrations and exposure were higher in males than in females.

No accumulation of fampridine, as demonstrated by the lack of increase in peak and total systemic exposure values (<2-fold), was observed following repeated dose administration of fampridine at multiple doses for multiple days in CD-1 mice, Sprague-Dawley rats, New Zealand White rabbits, Beagle dogs and humans. Thus, accumulation in plasma after repeated administration was not anticipated.

The effect of food was only examined in dogs. Although the observed effect was small, the C_{max} and AUC values were lower in fed versus fasted dogs.

Toxicokinetic data showed that systemic exposure to fampridine increased less than dose proportionally in mice (2-80 mg/kg/day) and rats (1-18 mg/kg/day), while it was dose proportional in pregnant rabbits (1-5 mg/kg/day) and in dogs (0.75-3.0 mg/kg/day). This interspecies difference could be explained by the dose range, which was higher in mice and rats compared to rabbits and dogs.

Distribution

The volume of distribution at steady state was high in rats (3.4 L/kg in male, 3.3 L/kg in female), which suggested extensive tissue distribution. One hour post-dose, highest concentrations were found in bladder, kidneys and liver. Fampridine related material crossed the blood-brain barrier, since radioactivity was observed in the cerebellum and cerebrum until 8 hours post-dose.

Binding of fampridine to plasma proteins was low with a high free fraction of >75% in rats and dogs and >90% in humans. Protein binding was dependent on the concentration, especially in rat and dog plasma (17% increase of the free drug at 500 ng/mL compared to 5 ng/mL).

The distribution of fampridine across the placenta and into milk is not known as such studies were not identified in the literature nor were any conducted by the applicant.

Metabolism

The specific enzymes involved in the metabolism of fampridine were not identified in laboratory animals, but based on human microsome studies; it was suggested that CYP2E1 could be responsible for hydroxylation in man.

In rat, approximately 36% of the parent drug was removed by hepatic first-pass metabolism. Fampridine was metabolized primarily by hydroxylation, followed by sulfate conjugation. Two circulating metabolites were detected in mouse, rat, rabbit, dog and human plasma: 3-hydroxy-4-AP and 3-hydroxy-4-AP sulfate. Although these metabolites were identified in all species, more extensive metabolism was determined in rats and dogs than in humans. In mouse and rat plasma, it was demonstrated that 4-AP-N-oxide was also a circulating metabolite. In human plasma, two unidentified metabolites were present; however, these metabolites accounted for <2% of the radioactivity.

Fampridine mediated CYP-dependent drug-drug interactions taking place through inhibition or induction of CYP activity in humans appeared to be unlikely. Of three drugs commonly used by patients with multiple sclerosis (amitriptyline, baclofen and caffeine), only baclofen showed a significant interaction with fampridine in rats. This attenuated elimination of fampridine seen in baclofen-treated rats seemed to be irrelevant for human therapy, since it could not be substantiated by clinical data.

Excretion

In rats and dogs, as compared with humans, the clearance rate was higher and the elimination half-life ($t_{1/2}$) was shorter; otherwise, the basic PK parameters of fampridine were similar between species. Elimination of fampridine was in a similar range between rats and dogs with a plasma half-life of 1-2 h, but was slightly prolonged in humans. The predominant route of elimination of radioactivity in rat and

dog following oral administration was via urine with a negligible contribution eliminated in faeces (<2%).
Between 75 to 92% of the dose was detected in urine within the first 12 hours in rats and dogs, approximately 40% of which accounted for unchanged parent compound.

2.3.4. Toxicology

Single dose toxicity

In a single dose toxicity study in rats, approximate median lethal oral doses (LD_{50}) ranged between 14 (males) and 22 (females) mg/kg, but raised to 40 mg/kg (both sexes) when the once daily drug administration was instead separated into 4 sub-doses given every 6 hours. In rabbits, the median lethal dose was 23 mg/kg (both sexes). In dogs, no toxicities were evident at total daily doses of up to 5 mg/kg four times a day. In general, death occurred short after administration (on the day of dosing).
It was noted that findings of the single dose toxicity studies coincided with the short half-life of fampridine and suggested that toxicity is related to peak plasma levels rather than overall exposure. Most notable treatment related acute clinical observations were CNS effects and included excessive salivation, tremor, seizures, convulsions, ataxia, dyspnoea, dilated pupils, prostration, abnormal vocalisation, increased respiration, excess salivation, gait abnormalities and hyper- and hypo-excitability. These findings were in line with those described in overdose reports in humans, including confusion, tremulousness, diaphoresis, seizure, amnesia and rare cases of hallucinations.

Repeat dose toxicity

A full package of GLP-compliant toxicological studies has been submitted. Studies have been performed in mice, rats, rabbits and dogs, and fampridine was dosed via the oral route (gavage, dietary, capsules).
In mice, the signs of toxicity included effects on body weight and food consumption. The main species in repeated dose studies were rats (studies of duration up to 26 weeks) and dogs (studies of duration up to one year). In both species, the findings revealed CNS associated events that included tremor, trembling, convulsions, ataxia, decreased activity, prostration, ptyalism, dilated pupils, increased respiratory rate and laboured breathing. A clear cause of death could not be identified for most animals that died during the studies; however, CNS toxicity and multiple organ failure were regarded as most likely reasons. In both species, decrease in body weight was seen; in rat also a decrease in food consumption and effects on the locomotor system were observed, such as impaired righting reflex or uncoordinated aerial righting, splay of (hind) limbs and hind limb grip strength. In addition, some effects on the behaviour were noted in rats, such as increased activity, arousal, and aggressive behaviour especially in the long studies. In dogs, a behavioural change (anxiety) was noted in the one-year oral toxicity study. This effect may correlate to clinical finding of anxiety which was reported as a common adverse reaction. The observed effects, especially on food consumption and body weight were more pronounced in males than females. In rats urogenital tract was identified as a target for fampridine toxicity. Urinary tract obstruction caused death of two males at the dose of 9 mg/kg/day in a 13-week oral toxicity study. Bladder distension and slight bilateral dilation of the renal pelvis was observed in a male at the dose 15 mg/kg/day in a 28-day oral gavage study. Some small effects in clinical pathology endpoints (haematology, serum chemistry) were recorded in both species in some studies. However, being of mild nature and not seen in all studies, they were considered of limited toxicological and clinical relevance. No effects were noted in ophthalmology and urinalysis in either species. ECG was recorded in most of the dog studies, no changes were observed.

The no observed effect level (NOAEL) from repeated dietary dosing in mice (13 weeks) was 12 mg/kg/day. In the pivotal 26-week study in rats (dietary administration) the NOEL for fampridine was <2 mg/kg/day. At the NOAEL of 0.75 mg/kg in the pivotal 1 year chronic toxicity study in dogs, corresponding C_{max} and AUC_{0-24} h exposure ratios compared to maximum recommended human dose (MRHD) were around 3.4 and 1.1 each (see the Table 2 below).

Table 2 Exposure Ratios for Multiple Dose Administrations Compared to Fampridine Dosing in Rats and Dogs

Species	4-AP total daily dose [mg/kg/day]	Steady state 4-AP AUC0-24 [ng*h/mL]	AUC ratio, compared to human MRHD	Steady state Cmax (ng/mL)	Cmax ratio, compared to human MRHD	Study number
Beagle dog	0.75	536	1.07	107	3.42	7338-106
	1.5	1063	2.13	194	6.20	
	3.0	2071	4.15	325	10.4	
Human	0.33 mg/kg 4-AP	499	--	31.3	--	AN751-102

Despite availability of further exposure levels from toxicokinetic bridging studies in mice and rats, safety factors on basis of C_{max} were not submitted for these species. Nevertheless, as C_{max} values from these bridging studies at the respective NOAEL were related to the maximum plasma concentration in MS patients, exposure ratios of ~2.4 (74.1/31.3) for male and ~1.6 (51.3/31.3) for female mice and of ~1.5 (47.1/31.3) for male rats could be deduced. These levels were comparable to exposures calculated on the basis of AUC. Overall, it was concluded that safety factors derived from non-clinical toxicity investigations were rather low or even not existent, which was taken into consideration in terms of clinical safety.

Genotoxicity

The genotoxic potential of fampridine was tested in standard *in vitro* (AMES test, mouse lymphoma assay) and cytogenetic *in vivo* tests in mouse and rat. All tests were performed in compliance with GLP and fampridine was not shown to have a relevant genotoxic potential.

Carcinogenicity

Fampridine was tested in two long-term carcinogenicity studies over two years in mice and rats as summarized in the table 3 below:

Table 3 – Carcinogenicity studies

Study ID /GLP	Species/ Strain	Dose [mg/kg/d] / Route	Mean (n=10) plasma conc. [ng/ml]	Major findings
MPI 684-022 / yes	Mouse	0, 2, 12.5, 80 / Dietary	Week 52 M/F: 3.89/12*, 40.4/40.7, 239/404 Week 104 M/F: 8.59/13.2, 67/84.3, 365/243**	significantly reduced BW and survival in high dose group due to low survival rate remaining high dose females were sacrificed at week 100 no significant differences in neoplastic lesions between control and treatment groups
MPI 684-023 plus amendment / yes	Rat	0, 2, 6, 18 / Dietary	Week 26 M/F: 40.2/26.4, 131/92.7, 319/268 Week 52 M/F:	BW reduced in mid and high dose groups dose-dependent increase in foot inflammatory ulceration

			39.8/39.7, 110/97.7, 362/249 Week 104 M/F: 24.4/29.3, 117/85.3, 387/265	slight significant increase in uterine polyps at high dose no significant differences in neoplastic lesions between control and treatment groups

* n=8 ; ** due to low survival plasma levels were measured during week 100; M = male; F = female; BW = body weight

Comparing control and treatment groups, no significant differences in clinical parameters were observed in either of the studies. Differences in neoplastic changes between treatment and control groups were only observed in female rats in a slight increase in benign uterine polyps. In addition, a dose-dependent increase in ulceration of the foot was observed in rat. These observations were considered not to be of clinical relevance. There was no other evidence for a treatment-related increase in neoplastic changes in mice or in rats.

No medium- and short-term studies were performed.

Reproduction Toxicity

Studies investigating the effects of fampridine on male and female fertility in rats, embryo-foetal development in rats and rabbits and pre- and post-natal development in rats were performed.

An overview of reproduction toxicity studies is provided below:

Table 4 – Reproduction toxicity studies

Study type (Study ID)	Species (strain) Number/ group	Dose (mg/kg/day) (Route)	Study design	Major findings	NOAEL
Fertility (IRDC 684-001)	Rats (CRL: CD VAF/Plus) 5/Group (35/sex/group)	0, 1, 3, 9 a (Oral Gavage)	Male: 6 days pre-mating up to day 58 days post-mating Females: 14 days pre-mating until 58 days post mating. ~ 1/3 uterine examination at GD 13, rest littering group	F0 Male & Female: = 9 death ≥ 3: tremors, convulsions, ↑ salivation, material around the nose, mouth, and/or eye, ↓ BW, FC F1 (GD13): - F1 (littering): ≥ 3 ↓ viability, = 9: BW (lactation period)	Parental tox: 1 Reproductive function: 9 Embryo-fetal development : 1
Embryo-fœtal development Range-finding (IRDC 684-002)	Rats (CRL: CD VAF/Plus) (5/Group)	0, 3, 5, 7, 10, 13a (Oral Gavage)	GD6 to GD15 C-section at GD 20	F0: = 13: death (2/5), tremors, convulsions,. Vocalization F1: -	F0: 10 F1: 13
Embryo-fœtal development (IRDC 684-003)	Rats (CRL: CD VAF/Plus) (30/Group)	0, 1, 3, 10a (Oral Gavage)	GD6 to GD15 C-section at GD 20	F0: = 10 death (13/30), convulsions, vocalization, ↑salivation. ≥ 3: tremors, ↓ BW ≥ 1: ↓ BWG, FC F1: -	Maternal tox: < 1 Embryo-fetal development : 10

Embryo-fœtal development Range-finding (IRDC 684-004)	Rabbit (New Zealand White SPF) (5/Group)	0, 3, 5, 7, 9, 11 a (Oral Gavage)	GDs 6 to 18 C-section at GD 29	F0: ≥ 5: death, tremors, convulsions ≥ 3: ↓ BWG F1: ≥ 3: ↓BW = 5, 7: ↑ post implantation loss = 3,5,7: ↑ pre implantation loss	Maternal tox; < 3 Embryo-fetal development: < 3
Embryo-fœtal development (IRDC 684-005)	Rabbit (New Zealand White SPF) (20/Group)	0, 1, 3, 5 a	GDs 6 to 18 C-section at GD 29	F0: ≥ 3: Death (1/24) =5: convulsion, loss of righting reflex, material around nose and mouth, ↓ BWG, ↑ whole litter resorption, ≥ 3: tremors, laboured breathing, increased activity ≥ 1: ↓ FC, body or anogenital staining F1: -	Maternal tox; < 1 Embryo-fetal development: = 5
Peri & postnatal (MPI 684-006)	Rats (CRL: CD VAF/Plus (30/Group)	0, 1, 3, 9 (6)a, b (Oral Gavage)	GD7 to LD21 F1: 25 pups/sex/ group C-section at GD20	F0: =9: death (8) =6: death (1) =9(6): abnormal gait, labored breathing, vocalization, ↑ lacrimation and salivation, convulsion, material around nose ≥ 3: tremors, ↓ BWG ≥1: ↓ FC F1: Litters preweaning: =9(6): ↓ viability, ≥ 3: ↓ BW post-weaning: =9: ↓ BW(G) pregnancy =9: ↓ BWG F2: -	Maternal tox: 1 F1 tox: 1

M=male; F=female; F0=F0 generation; F1=F1 generation; BW=body weight; FC=food consumption; ↑=increased; ↓=decreased GD:gestation day, LD: lactation day

a: 4-AP was given in distilled water.

b: Due to mortality high dose was reduced to 6 mg/kg/day during the second week of dosing.

Local Tolerance

No local tolerance studies were performed, which was accepted by the CHMP.

Other toxicity studies

Intrathecal administration

A seven-day intrathecal infusion study in Beagle dogs was performed to further investigate the potential CNS activity of fampridine when delivered directly to the spinal fluid. Signs of toxicity were similar to those reported in oral toxicity studies, but at considerably lower cumulative doses.

Studies on impurities

The stability studies revealed that fampridine may react with either Methocel or Avicel in the tablet formulation leading to the formation of an identified impurity called methylene bridge. In order to qualify this impurity up to a content of 2%, the applicant performed two genotoxicity tests (Ames test and a chromosomal aberration assay) and a 28-day repeated dose toxicity study in rat with fampridine spiked with 2% methylene bridge. There was no indication that the methylene bridge had a genotoxic potential.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant submitted an environmental risk assessment (ERA) according to the guideline EMEA/CHMP/4447/00. The Fpen calculation in the ERA was technically correct. The Fpen refinement was supported with published epidemiological data, and was considered acceptable. The Phase I $PEC_{SURFACEWATER}$ for a country exhibiting the highest prevalence of multiple sclerosis in the EU amounted to 6.2 ng/ L, i.e was below the threshold of 0.01µg/L. Fampridine is neither PBT (persistent, bioaccumulative and toxic) (log Kow does not exceed 4.5), nor vPvB (very persistent, very bioaccumulative). Therefore, a phase II assessment did not need to be performed. The risk of fampridine to the environment was assumed to be negligible.

2.3.6. Discussion on non-clinical aspects

Results of the safety pharmacological studies demonstrated that fampridine had an acceptable pharmacological safety profile in animals. However, it was noted that no studies evaluating pharmacodynamic drug interactions were performed by the applicant and the CHMP pointed out that, given the mechanism of action of fampridine, the risk of these interactions with anti-epileptic and anti-arrhythmic agents cannot be excluded.

The pharmacokinetic profile of fampridine was evaluated *in vitro* as well as *in vivo* (in rats and dogs). The toxicokinetic parameters have been determined in mice, rats, rabbits and dogs. The primary routes of administration in rat and dog were intravenous and oral. Overall, the ADME (absorption, distribution, metabolism, excretion) properties of fampridine were similar across species examined including humans.

The toxicological study programme of fampridine comprised oral single-dose toxicity studies in rats, rabbits and dogs, repeat-dose toxicity studies up to three months in mice, six months in rats and 12 months in dogs, *in vitro* and *in vivo* genotoxicity studies, 24-month carcinogenicity studies in rats and mice and a battery of reproductive and developmental toxicity studies in rats and rabbits. These studies were performed in compliance with GLP standards, with the exception of the lack of thorough toxicokinetic evaluation of fampridine and its metabolites within pivotal toxicology, reproductive toxicology and carcinogenicity studies. The toxicokinetic parameters were therefore obtained in bridging studies that mimicked the design of the toxicity studies.

In the repeated dose studies in rat and dog, the safety findings consistently revealed CNS associated events including tremor, trembling, convulsions, ataxia, decreased activity, prostration, ptyalism, dilated pupils, increased respiratory rate and laboured breathing. Gait abnormalities and hyper-

excitability were also observed. These signs were attributed to the pharmacology of fampridine; they were rapid in onset and seemed to alleviate during continued dosing and also to reverse in surviving animals after discontinuation of treatment. Of note, the urogenital tract was identified as a target for fampridine toxicity in toxicity studies in rats leading to cause of death in certain instances. The clinical relevance of the findings of urinary tract obstruction or bladder distention remained unclear. However, taking into account the almost exclusive renal elimination of fampridine, the general susceptibility of MS patients towards bladder disorders and the potential pharmacological activities of 4-AP on urinary tract smooth muscles and/or bladder innervation, the CHMP noted that this issue is not addressed sufficiently.

In a battery of *in vitro* and *in vivo* studies fampridine did not show any potential to be mutagenic, clastogenic or carcinogenic.

In the reproductive toxicity studies no adverse reproductive effects were noted in the segment I (rat) study (IRDC 684-001). Despite this observation, according to published *in vitro* data, fampridine might inhibit steroid hormone production, which could contribute to dysmenorrhoea and infertility. The CHMP noted that steroid hormone profiles were not evaluated pre-clinically or clinically.

In the embryo-foetal development studies (rat and rabbit) malformations were not seen. Effects on embryo-foetal development (reduced body weight) were seen at or above maternally toxic doses. In the rabbit study a possible small treatment-related increase in resorption, pre/post implantation loss was seen, which could indicate that success of pregnancy outcome is reduced. The toxic effects seen in F0 were similar to those observed in the repeated dose toxicity studies. In the peri-post natal study (rat), effects on F0 and F1 were similar to those seen in the embryo-foetal development studies. Reduced body weight gain was seen in F1 of the high dose group during and beyond lactation, and in F1 females during their pregnancy.

2.3.7. Conclusion on the non-clinical aspects

The CHMP did not raise any objections precluding granting of the marketing authorisation based on the provided non-clinical data; however, the issues of potential pharmacodynamic interactions, urinary tract findings and impact of fampridine on steroid hormone production were not addressed sufficiently in the dossier.

2.4. Clinical aspects

2.4.1. Introduction

Fampridine is a selective potassium channel blocker. By blocking potassium reflux the hyperpolarisation phase of an action potential is reduced. Consequently, the relative refractory period of the action potential is shortened, allowing the action potential to propagate along the cell membrane. This, according to the applicant, especially applies to unmyelinated axons where the action potential dampens quickly below a depolarisation threshold too low for activating the adjacent membrane.

The indication applied for was the treatment of adult patients with multiple sclerosis (MS) for the improvement of walking ability.

The applicant developed a prolonged-release tablet formulation (10mg tablets) to reduce the peak plasma concentration associated adverse events. The recommended dosing regimen was one 10mg tablet twice daily, taken 12 hours apart.

GCP

The applicant stated that all trials were conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline. No triggers for the need of an inspection were found in the dossier.

Tabular overview of clinical studies

A tabular overview of the major PK studies is presented in table 5. The PK studies comprised two ADME (absorption, distribution, metabolism, excretion) studies, single-dose (including IR capsule) and multiple-dose studies, one BE (bioequivalence) study (between two manufacturers of Fampridine 10 mg PR tablet), two food-interaction studies, study on renal impairment, and two interaction studies with PR capsule and IR capsule. The influence of intrinsic factors such as gender, race, age, renal function, body mass index and food was evaluated in the Population PK analysis of the three main clinical studies.

Table 5 Clinical PK Studies

Study no. (Dates)	Objectives	Study design	Strength Formulation (Batch no)	N enrolled (M/F) Type	Mean age (range)
BE10-25F-SR10OS122003 (2003)	Relative BA of the two strengths to 10 mg buffered solution. BE between 10 and 25 mg PR Tab.	Single-dose, open-label, randomized, three-way crossover	10, 25 mg FAM PR Tab (22747, 22896)	30 (17/13) Healthy volunteers	25.4 (19 – 42)
BE10F-SR22004 (2004)	BE between FAM PR tablets manufactured by two manufacturers	Single-dose, open-label, randomized, two-way crossover	10 mg FAM PR Tab (R0105F001,22747)	18 (10/8) Healthy volunteers	29.4 (20-45)
FeFa10F-SR-2008 (2008)	Food interaction (high fat)	Single-dose, open-label, randomized, two-way crossover	10 mg FAM PR Tab (51953)	30 (12/18) Healthy volunteers	24.3 (18-49)
FeFa25F-SR112003 (2003)	Food interaction	Single-dose, open-label, randomized, two-way crossover	25 mg FAM PR Tab (22896)	14 (5/9) Healthy volunteers	34 (26-45)
ELA/G-9101 (1991)	Single dose PK, safety, tolerability	Double blind, randomized, four-way crossover, placebo-controlled, single ascending dose; 7 days wash-out	10, 15, 20, 25 mg IR Cap	8 (8/0) Healthy volunteers	22.6 (20-26))
TQTc-F-SR001 (2007)	Multiple-dose PK, "thorough QT' study	Double blind, placebo-controlled, randomized, double dummy, parallel group	10, 30 mg PR Tab bid x 5 days, fed	208 (113/95) Healthy volunteers	25 (18-44)
0496-002 (1996)	Mass balance	Single dose, open label	15 mg oral solution	4 (4/0) Healthy volunteers	20.7 (18-22_

Table 5 Clinical PK Studies

Study no. (Dates)	Objectives	Study design	Strength Formulation (Batch no)	N enrolled (M/F) Type	Mean age (range)
RD-10F-SR0122004 (2004)	Metabolism and Excretion in renal impairment vs. healthy volunteers	Single dose, two-stage, parallel-group	10 mg PR Tab	20 (9/11)	47 (19-57)
AN751-101 (1997/1998)	Single dose PK	Single-escalating dose, open-label study	5, 10, 15, 20 mg FAM PR days	24 (10/14) MS patients	45.4 (29-56)
AN751-102 (1997/1998)	Multiple dose PK	Multiple dose, single arm, extension of AN751-101	20 mg FAM PR Tab bid x 14 days	21 (10/11) MS patients	45.1 (29-57)
1194-001US (1995)	Interaction	Single and multiple dose	FAM IR Cap (Q8h x 4 days) with and without Betaseron (8 Million Units)	12 (4/8) MS patients	43.8 (38-55)
0194-002 (1994)	Interaction	Open-label, three-way, single dose crossover	15 mg FAM PR Cap, 10 mg Baclofen, and 15 mg FAM PR Cap + 10 mg Baclofen	13 (13/0) Healthy volunteers	29.8 (18-40)

The major clinical studies are presented in table 6, i.e. study MS-F202 a dose comparison study (10, 15, 20 mg BID) and the two pivotal studies MS-F203 and MS-F204 (10 mg BID). In all studies the concentration of fampridine was measured at each visit in order to evaluate a plasma level-response relationship. Primary efficacy was based on the Timed 25 Foot Walk test (T25FW) wherein a patient was asked to walk as quickly as he/she can safely, from one end to the other end of a clearly marked, unobstructed, 25-foot course. The time (seconds) was recorded. After a maximum rest of 5 minutes the test was repeated again. The walking speed for a particular study visit was the average of the walking speeds of the two trials performed. If one of the 2 trials could not be fulfilled then the walking speed for that visit was to be the walking speed from the completed trial.

Table 6 Overview of Main clinical studies:

Study ID	Design	Subjects	Study arms/ Procedure	Outcomes
MS-F202 2003-2003 USA/Canada Dose comparison	Rd Db PC PA 24 centres	MS-patients Age: 26-70 yrs T25FW baseline: 8-60 sec No epilepsy No exacerbation	Placebo (n=47) Fampridine-SR 10 mg BID (n=52) Fampridine-SR 15 mg BID (n=50) Fampridine-SR 20 mg BID (n=57) Screening: 1 wk Placebo-run-in 2-3 wks Titration: 2 wks Stable-blind 12 wks Down-titration 1 wk Follow-up of treatment 2 weeks	Primary: Improvement in average walking speed, relative to the baseline period (placebo run-in), using the Timed 25 Foot Walk. Secondary: T25FW derive variable, LEMMT, MSFC-9-Hole Peg Test, MSFC-PASAT 3, MSFC, Ashworth Score, MSWS-12, CCGI, SGI, SSQ, CSQ, OSQ, MSQLI. Safety: AEs, Vital signs, ECG, EEG, Laboratory variables

Table 6 Overview of Main clinical studies:

MS-F203 2005-2006 USA/Canada Efficacy/safety	Rd Db PC PA 33 centres	MS-patients Age: 26-70 yrs T25W baseline: 8-45 sec No epilepsy No exacerbation	Placebo (n=72) Fampridine-SR 10 mg BID (n=229) Screening: 1 wk Placebo-run-in 2 wks Double-blind 14 wks Follow-up of treatment 4 weeks	Primary: Proportion 'consistent' responders defined as a patient who had a faster walking speed for at least three out of four visits during the double-blind period as compared to the maximum value among five of the non- double-blind treatment visits. Walking speed was based on the Timed 25 Foot Walk Test. Secondary: Other T25FW derived variables, MSWS-12, LEMMT, SGI, CGI. Safety: AEs, Vital signs, ECG, EEG, Laboratory variables
MS-F204 2007-2008 USA/Canada Efficacy/safety	Rd Db PC PA 39 centres	MS-patients Age: 18-70 yrs T25W baseline: 8-45 sec No epilepsy No exacerbation	Placebo (n=119 Fampridine-SR 10 mg BID (n=120) Screening: 1 wk Placebo-run-in 2 wks Double-blind 9 wks Follow-up of treatment 2 weeks	Primary: Proportion 'consistent' responders defined as a patient who had a faster walking speed for at least three out of first four visits during the double-blind period as compared to the maximum value among any of the pre treatment visits and post-treatment visit. Walking speed was based on the Timed 25 Foot Walk Test. Secondary: Other T25FW derived variables, LEMMT MSWS-12, SGI, and CGI. Safety: AEs, Vital signs, ECG, EEG, Laboratory variables

Legend: Ashworth-score: Ashworth Assessment of Spasticity, CGI: Clinical global impression, CSsO: Clinician Summary Questionnaires, EDDS: Expanded Disability Status Scale, LEMMT: Lower Extremity Manual Muscle Test, MC: MultiCenter, MS Multiple sclerosis, MSWS-12: 12 item MS walking scale, MSFC: MS Functional Composite, MSFC-PASAT: Paced Auditory Serial Addition Test, MSQLI: Multiple Sclerosis Quality of Life Inventory, OSQ: Observer Summary Questionnaire, PA: Parallel, PC: Placebo Controlled, Rd: Randomised, SGI: Subjects' Global Impression, SSQ: Subject Summary Questionnaires, T25WT: Timed 25 Foot Walk Test.

2.4.2. Pharmacokinetics

The marketing authorisation was applied for the 10 mg prolonged-release tablet. The prolonged release tablet formulation was developed in order to reduce peak plasma concentrations associated with seizures. The proposed dosing was 10 mg twice a day, 12 hours apart. Only one strength of the prolonged-release tablet, i.e. 10 mg was developed.

Absorption

- **Bioavailability**

When administered orally, fampridine was completely absorbed from the gastrointestinal tract. Absolute bioavailability of fampridine prolonged-release tablets was not investigated, but relative bioavailability (as compared to an aqueous oral solution) was 95%.

When a single fampridine prolonged release tablet, 10 mg dose was administered to healthy volunteers while in a fasted state, peak concentrations ranging from 17 ng/mL to 22 ng/mL occurred 3 to 4 hours post-administration (T_{max}). In comparison, C_{max} achieved with the same 10 mg dose of a fampridine oral solution was 43 ng/mL, which occurred approximately 1.3 hours after dose administration. Thus,

from a pharmacokinetic point of view, the choice of retardation principle was considered justified, as C_{max} is significantly lowered and plasma profile is elongated.
An overview of the PK parameter values following a single 10 mg dose administered in the fasting state is given in the table 7 below.

Table 7 Overview of Mean (S.D.) Pharmacokinetic Parameter Values in Healthy Volunteers Following a Single Dose of a 10 mg Fampridine Prolonged Release Tablet

Parameter (unit)	Study				
	BE10.25-FSR10-OS122003	BE10F-SR022004		RD10F-SR012004	BE10.25-FSR10-OS122003 (Oral Solution)
		P10	E10		
N	27	16		5	29
Cmax (ng/mL)	18.7 (3.7)	17.9 (3.2)	21.6 (3.9)	21.6 (3.9)	42.70
AUC 0-t (ng*h/mL)	187.7 (38.6)	168.9 (29.5)	254.1 (35.0)	254.1 (35.0)	214.95
AUC0-inf (ng*h/mL)	218.3 (39.1)	201.9 (33.9)	284.8 (31.8)	284.8 (31.8)	229.48
Tmax (hours)	3.7 (1.3)	4.0(1.5,5.0)	3.0(1.0, 5.0)	3.0 (1.0, 5.0)	1.14
t½ (hours)	5.5 (1.0)	5.2 (1.3)	6.5 (1.3)	6.5 (1.3)	3.249
CL/F (L/hr)	47.3 (9.0)	50.9 (8.7)	35.5 (4.1)	35.5 (4.1)	45.02

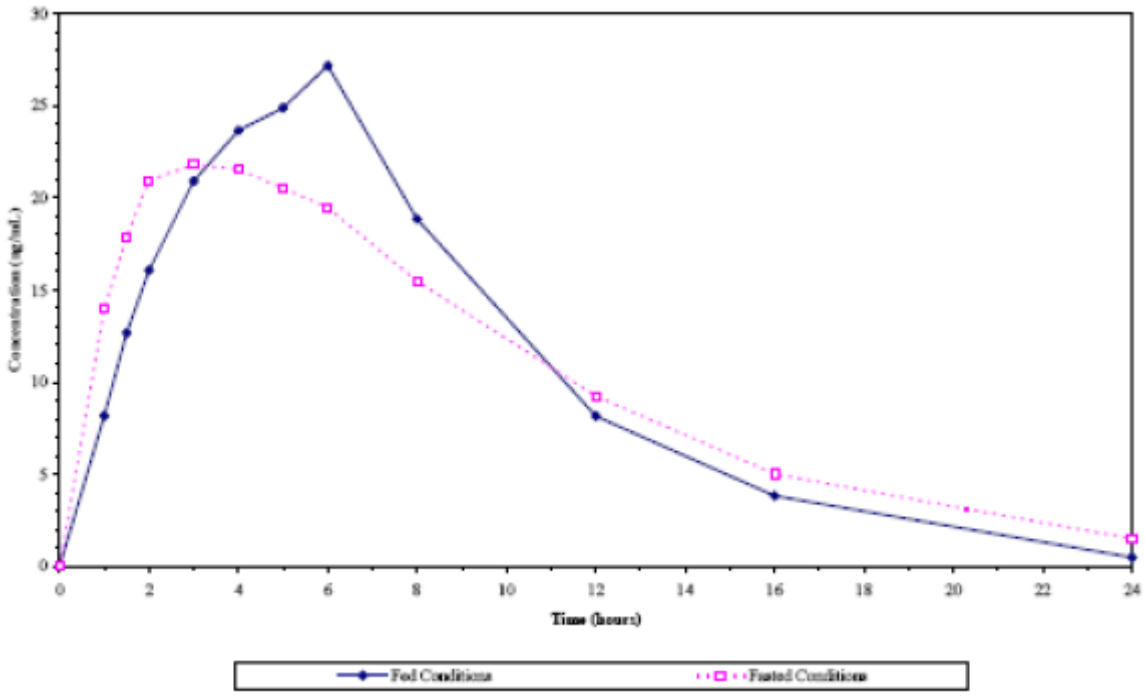
- **Bioequivalence**

The clinical phase II and phase III PR tablet was identical with the proposed commercial tablet, with the exception of a stamp ''A10'' on one side; this was for identification reasons, and should have no consequences on the bioavailability.
Due to minor differences in the manufacturing process at the two proposed manufacturing sites the applicant performed a comparative bioavailability study to demonstrate bioequivalence (Study BE10F-SR022004). This was a single-dose, randomized, open-label, two-way crossover, bioequivalence study of two 10 mg Fampridine-SR Tablets Manufactured by two different manufacturers. A total of 18 healthy subjects were enrolled in the study and 16 subjects completed the study. Blood was collected for up to 36 hours. Analysis of variance was performed on the Ln-transformed parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The 90% CI for the ratio of the test and reference product were within conventional limits and the 100% value was always included. Thus, it was agreed that the applicant established bioequivalence under fasting conditions of 10 mg PR tablet manufactured by two potential manufacturers of the finished drug product.

- **Influence of food**

Two food-interaction studies were submitted by the applicant: one with a 25 mg (FeFa25F-SR112003) and one with a 10 mg (FeFa10F-SR-2008) PR tablet. The tablets were administered under high-fat conditions. In the study with the 25 mg PR tablet, food did not alter AUC, increased C_{max} by 15% and delayed absorption by 2 hours (T_{max} fasted: 3 hours vs. T_{max} fed: 5 hours). In the study with the 10 mg PR tablet (see the figure 1 below), there was no food effect on AUC, but C_{max} increased by 23%. Peak plasma concentration was reached at 3 hours under fasting conditions and at 5 hours under fed conditions. In this context, the CHMP noted that the product should be taken without food.

Fig. 1 Mean (± SD) Plasma Fampridine Concentrations *versus* Time (Fed *versus* Fasting Conditions)



Data Source: Study FeFa10F-SR-2008, Figure 11.1.

No pharmacokinetic data concerning paediatric population were submitted by the applicant.

Distribution

Protein binding of ^{14}C radiolabelled fampridine at concentrations of 5, 50 and 500 ng/mL was investigated in human, dog and rat plasma (HWI 6379-103). After a 4-hour dialysis, when the mean percent of free drug did not increase anymore, the unbound fraction was between 93-97% at all concentrations and was independent of pH. The animal data were in line with the human data. Based on the low level of protein binding, there is no expectation of interactions with highly protein bound drugs.

With administration of a single 20 mg intravenous dose, mean Vd was 2.6 L/kg.

Fampridine is a lipid-soluble drug which crosses the blood-brain barrier. There is no animal/human data on placental transfer or excretion into mother's milk.

Elimination

- **Excretion**

The major route of elimination for fampridine is renal excretion. It appeared that fampridine undergoes active tubular secretion because the renal clearance (clearance: 370 mL/min) is substantially greater than glomerular filtration rate. Following intravenous injection, renal clearance was estimated to represent 90% of total clearance (Uges et al., 1982). A total of 90% of the dose was recovered as parent drug in the urine within 24 hours. In Study 0496-002, following administration of a radiolabelled (^{14}C) oral solution, approximately 94% of the administered dose was excreted in the urine within the first 24 hours post-dose, mostly as parent drug (parent drug accounted for approximately 90% of the excreted radiolabel and the metabolites accounted for about 10%). Faecal excretion accounted for less than 1% of the administered dose. Administration of fampridine prolonged-release tablets resulted in a slower time course of absorption and excretion but the available

data indicated that the excretion in urine is similar, with approximately 90% parent drug and approximately 10% the hydroxylated and sulphated metabolites.
The elimination half-life of fampridine following administration of fampridine prolonged release tablets was 5.2 to 6.5 hours (observed across studies after both single and repeated doses). The plasma half-life of the sulfate conjugate was similar, 7.6 hours; this parameter could not be calculated for the 3-hydroxy-4-aminopyridine metabolite as concentrations for most subjects were close to or below the limit of quantification.

- **Metabolism**

Fampridine was metabolized primarily by hydroxylation followed by sulfate conjugation with 3-hydroxy-4-aminopyridine and its sulfate conjugate as the primary metabolites, although the extent of metabolism was not extensive (approximately 10% of the administered dose). An *in vitro* reaction phenotyping study (Study XT064039) using liver microsomes indicated that the primary CYP enzyme responsible for the limited amount of fampridine metabolism was CYP2E1.
In the main inhibition study (XT075077) investigating direct and time-dependent inhibition of CYPs using fampridine at concentrations between 0.03 to 30μM (2.82 – 2820 ng/mL), there was evidence of direct inhibition of CYP2E1 by fampridine at 30μM (approximately 12% inhibition) which is approximately 100 times the average plasma fampridine concentration measured for the 10 mg tablet.
Treatment of cultured human hepatocytes with fampridine showed little or no effect on induction of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2E1 and CYP3A4/5 enzyme activities in study XT073070 investigating induction of CYP enzymes in human hepatocytes.

Dose proportionality and time dependencies

Fampridine AUC and C_{max} increased in a dose-proportional manner (across the dose range studied) with terminal half-life independent of dose level (linear kinetics). Plasma exposure and peak plasma concentrations of fampridine increased in a dose proportional manner after a single dose (study AN751-101) and at steady state (study TQTc-F-SR001) in MS patients.
Elimination half-life was independent of the dose and did not change with multiple dosing, indicating time-independent pharmacokinetics of fampridine. No accumulation of fampridine was observed after repeated dosing. The steady state was achieved within two days.

Special populations

The influence of intrinsic factors such as renal function, age, gender, weight was evaluated in the Population PK analysis.

Renal impairment

Fampridine exposure was significantly increased in subjects with renal impairment: the mean C_{max} and $AUC_{0\text{-}inf}$ increased by 67% and 75% in mildly impaired subjects, 60% and 105% in moderately impaired subjects, and by 100% and 299% in severely impaired subjects, respectively, when compared to normal subjects. There was a substantial increase in $T_{1/2}$ in severely impaired patients of 14.3 hrs as compared to normal subjects (6.4 hrs). Fampridine was almost completely renally cleared; thus, it was noted that a small decline in renal capacity would result in significant accumulation of fampridine.

Hepatic impairment

The applicant did not conduct studies in patients with hepatic impairment. *In vivo* hepatic metabolism was about 10%. Dose adjustment was not considered necessary for subjects with hepatic impairment.

Elderly

The applicant has neither conducted studies in the elderly nor considered dose adjustment necessary for this patient group. Since renal function declines with age, concerns related to renal impairment were also considered applicable to this patient sub-population.

Paediatrics

Fampridine was granted a full product-specific waiver.

Gender

Clearance of fampridine was approximately 14.5% lower in females. This observation was not considered clinically relevant.

Weight

Body mass index did not affect fampridine pharmacokinetics according to the Population PK analysis.

Pharmacokinetic interaction studies

- ***In vitro***

As mentioned above (in section "Metabolism"), the applicant performed studies to evaluate the extent to which fampridine is metabolized by CYP enzymes, inhibits their activity, or induces their expression. Based on the study results it was concluded that CYP2E1 is the major enzyme responsible for 3-OH-4-AP formation. No direct or time-dependent inhibition of CYP activity was observed at concentrations up to 30 μM (2 820 ng/mL) of fampridine and no induction of CYP activity in human hepatocytes was observed following incubation with fampridine at test concentrations up to 25 μM (2 350 ng/mL) for 3 consecutive days.

The applicant performed *in vitro* studies indicating that OCT-2 (Organic cation transporter) is the transporter mainly involved in the active secretion of fampridine. Given the high contribution of active secretion to the main renal elimination pathway (approximately 60%) and the narrow therapeutic index of fampridine, clinically significant interaction on the level of OCT2 is expected.

- ***In vivo***

Two drug interaction studies with two commonly used drugs in patients with MS (baclofen and interferon-beta) were performed.

Baclofen

Study 0194-002 was a balanced, randomized, single-dose, three treatment period cross-over drug-drug interaction study of fampridine CR, 15 mg capsule and Baclofen, 10 mg tablet under fasted conditions. Twelve healthy male volunteers enrolled into the study with all subjects completing the study and providing PK data. The AUC and C_{max} for both treatments were similar whether they were administered separately or simultaneously. Therefore, it was concluded that PK parameters for fampridine were not affected by coadministration with baclofen.

Interferon

Study 1194-001US was a single center, open-label, single and multiple doses PK and safety drug-drug interaction study of fampridine IR, 7.5 mg and subcutaneous injections of 8 million units of Betaseron.

A total of twelve MS patients (4 males/8 females) enrolled into the study with 9 patients (3 males/ 6 females) completing the study and providing PK data.

For both treatment options, after single dose administration and at steady state doses, AUC, C_{max} and T_{max} levels for fampridine were comparable following administration of fampridine alone or following coadministration of fampridine and Betaseron. Therefore, it was concluded that there is no PK drug-drug interaction of Betaseron administration on fampridine.

Pharmacokinetics using human biomaterials

In vitro studies on PK aspects of fampridine using human materials are summarised in table 8 below:

Table 8 Fampridine *In Vitro* Studies Using Human Biomaterials

Study no.	Objective
8ACORP1	P-gp transporter
HWI 6379-103	Protein binding
XT064039	Metabolism using human liver microsomes
XT075077	Inhibition of CYP enzymes human liver microsomes
M-2001-029	Inhibition using cryopreserved human hepatocytes
XT073070	Induction of CYP enzymes in human hepatocytes

The results of the studies are presented in the respective sections (absorption, distribution, elimination).

2.4.3. Pharmacodynamics

Mechanism of action

Fampridine (4-aminopyridine) is a selective potassium channel blocker. It is a lipid-soluble drug which readily crosses the blood-brain barrier. The indication claimed was treatment of adult patients with Multiple Sclerosis for the improvement of walking ability. Fampridine is formulated as a prolonged - release tablet and the recommended dose is one 10 mg tablet twice daily, taken 12 hours apart. A prolonged release tablet has been developed to reduce peak plasma concentrations associated adverse events.

By blocking potassium reflux the hyperpolarisation phase of an action potential is reduced. Consequently the relative refractory period of the action potential is shortened, allowing the action potential to propagate along the cell membrane. This, according to the applicant, especially applies for unmyelinated axons where the action potential dampens quickly below a depolarisation threshold too low for activating the adjacent membrane.

The K^+ channels are located primarily in the paranodal and internodal membrane of the axon where they are not significantly activated by the passage of an action potential because the myelin sheath acts as an electrical shield. In demyelinated axons the internodal membrane and its ion channels become exposed to larger electrical transients during the action potential. Under these conditions, leakage of ion current through the K^+ channel can contribute to action potential conduction block. Fampridine at low concentration may prolong nerve action potentials by blocking these exposed channels and inhibiting repolarisation, subsequently improving axon potential propagation.

Considering the mechanism of action of fampridine, there is a plausible biological rationale to evaluate the usefulness of fampridine in symptomatic treatment in multiple sclerosis. Whether fampridine acts on specific K^+ channels and how these K^+ channels are distributed over organs and central nervous system remained unclear.

Primary and Secondary pharmacology

The primary pharmacology of fampridine was not addressed sufficiently in the dossier. In response to the CHMP request, the applicant provided an overview of the type, physiology and tissue distribution of the various K^+ channels in humans and some other species. Main conclusions were that demyelinated fibres show higher susceptibility to K^+ channel blockers, as compared to normal nerve fibres, probably due to morphological changes in the positional and exposure of these channels.

The voltage-gated K^+ channels (target of fampridine) showed expression in excitable cells including neurons, cardiac and skeletal muscle, smooth muscle and lymphocytes. Hence, effects of fampridine could be expected in these tissues and this has been addressed accordingly in the safety questions posed to the applicant. Since the expression of 4-AP-sensitive Kv channel types varied widely across different tissue and cell types and between species, the preclinical findings were of limited value. Therefore the long-term safety data from exposure in humans was considered indispensable by the CHMP.

The PK/PD relationship has been evaluated by the means of modelling and simulation. Based on the clinical data, the model overestimated exposure-response relationship. Based on the clinical data, with doses above 10 mg, there appeared to be no dose-response relationship for doses 10 mg bid and above. Based on the model, there was a clear relationship between AUC and CNS-related adverse events, which was also confirmed by the clinical data. Based on these data, it was expected that there is an even sharper relationship between C_{max} and AEs.

Pharmacodynamic interactions have not been discussed by the applicant. Given the mechanism of action i.e. K^+ channel blocker, fampridine should be considered a narrow therapeutic index drug, unless proven otherwise, as K^+ channels are ubiquitously present in the organism in general and in the CNS in particular. Potential pharmacodynamic interactions are expected with antiepileptic agents and anti-arrhythmic agents influencing sodium-potassium current.

2.4.4. Discussion on clinical pharmacology

Fampridine (4-aminopyridine) is a selective potassium channel blocker. In the CHMP view, the dossier contains a limited overview of the primary pharmacology of fampridine in support of this mechanism. It has not been well-evaluated whether fampridine acts on specific K^+ channels and how these K^+ channels are distributed in the different organs and central nervous systems. It also remains unclear whether the K^+ channels are subject to homologous down/up-regulations like pharmaco-receptors, i.e. whether hypersensitivity or tolerance develops. In addition, electrophysiological data in support of the mechanism of action are not well-presented. In their response to questions raised by the CHMP, the applicant presented a limited overview of the primary pharmacology of fampridine. Importantly, the expression of 4-AP-sensitive K^+ channel types varies widely across different tissue and cell types with a considerable variability of expression between species. Therefore, it was noted that the transferability of preclinical findings to humans is difficult. This emphasises the need of safety data in certain subgroups of MS patients e.g. patients with compromised cardio-vascular function or renal function. With regard to the electrophysiological studies in multiple sclerosis patients, positive data are unexpectedly rare. Most studies referred to were performed in the past (1983 – 2004), were uncontrolled and included a small numbers of MS patients. The data from two controlled cross-over studies in multiple sclerosis subjects provided evidence for improvement of motor evoked potentials (van Diemen et al. 1993, Rossini et al., 2001). These results were however not convincing. Moreover, studies with the current formulation and dose (which is lower) were not performed.

The pharmacokinetics of fampridine is linear; fampridine is absorbed in a dose proportional manner and there is no accumulation after repeated doses. It is unbound to plasma proteins and almost completely eliminated via urinary excretion. Major fraction recovered was contributed to the parent drug. The PK profile in MS patients is not different from that of healthy volunteers. Two minor inactive

metabolites were identified in the urine: 3-hydroxy-4-aminopyridine and its sulphate. Whether 4-AP N-oxide, a metabolite found in rats, is also relevant for humans was not clear. In the response, the applicant clarified that 4-AP N-oxide metabolite is not formed in humans.

Only one strength (10 mg) has been developed which limits the possibility of dose adjustments in special populations and/or intolerant subjects. Fampridine exposure is significantly increased in subjects with renal impairment which also applies to subjects with mild renal impairment. From the clinical data it is clear that subjects with mild renal impairment have more adverse events as compared to subjects with normal renal functioning.

This issue was raised as a major objection and the applicant was asked to evaluate alternative dosing regimes by data simulation for this special population, as it could be more desirable to divide the dose over a day (e.g. 5 mg bid) to prevent an initial high exposure and C_{max} related AEs. The applicant could not address this issue in their response. Because it is expected that once daily dosing would not result in a similar exposure as seen after bid dosing in subjects with normal renal function and because there is a linear relationship between increase in C_{max} and decreasing renal function, the CHMP expressed concerns regarding use of fampridine in patients with mild renal impairment. Further, considering prevalence of mild renal impairment in the elderly, it was noted that use of fampridine would be precluded in a substantial proportion of this population. The applicant has not conducted studies in the elderly and only a limited number of elderly patients have been included in the clinical studies performed.

The CHMP pointed out that PK interactions with renally cleared drugs, transporters involved in the renal excretion and diuretics may be expected. Based on the data provided by the applicant, the CHMP agreed that the risk of interactions with lithium, digoxine, gabapentin and diuretics could be considered small. As indicated in the section "Pharmacokinetic studies – *in vitro*", interactions at the level of OCT-2 is expected, as OCT-2 is the transporter involved in the active secretion of fampridine. With respect to the role of OCT2 polymorphism, the CHMP agreed that it is not expected to play an important role in fampridine clearance.

Further, the CHMP raised a question concerning the rate of glucuronidation, as accumulation was observed in renal impairment; the glucuronidation pathway may be subject to interaction, UGT polymorphism and the glucuronidates may be pharmacologically active. Based on results in humans and from animal species, the CHMP agreed that glucuronidation did not occur and interactions at the UGT level can be excluded.

Potential pharmacodynamic interactions of fampridine were not sufficiently addressed in the dossier. The CHMP noted that potential pharmacodynamic interactions can be expected with antiepileptic agents and anti-arrhythmic agents that affect sodium-potassium current.

With respect to cardiac safety, the data originating in the QTc study were scrutinised by the CHMP. It was noted that, in general, the ECG effects in the moxifloxacine arm were marginal, which questioned the quality and reliability of the entire study. Considering the marginal or no change from baseline values in the moxifloxacine arm (0.0 ms in QTcI, 0.9 ms in QTcF and 4.7 ms in QTcB), it was striking that in most measurements for the fampridine treatment groups, the corresponding values were negative (-4.5 ms in QTcI, -4.3 ms in QTcF and -2.2 ms in QTcB for fampridine 10 mg). Considering this, the study did not reduce concerns with respect to unfavourable cardiac safety of fampridine.

The PK/PD relationship has been evaluated by the means of modelling and simulation. The exposure-response relationship observed was not confirmed in the clinical studies. Based on the model, there seemed to be a clear relationship between AUC and CNS-related adverse events, which was confirmed by the clinical data. Based on these data, it was expected that there is an even more pronounced relationship between C_{max} and AEs. Accordingly, issues concerning AUC variability, which are usually minor, were considered particularly relevant in this context: food intake, intra-individual variability of fampridine and information about reaching the steady-state. As described in section "Absorption – influence of food", due to the significant increase of C_{max} with food intake (by 15-23%), the CHMP

noted that the product should be taken without food. With respect to intra-individual variability, the CHMP agreed that the estimated intra-individual %CV (approximately 20% for both C_{max} and AUC) was established to be low and thus, fampridine was not considered a highly variable drug. The applicant confirmed that a steady-state is reached within 2 days.
The CHMP noted that animal and human data concerning excretion into mother's milk are lacking.

2.4.5. Conclusions on clinical pharmacology

Fampridine is considered a narrow therapeutic index drug, unless proven otherwise. The development of one dose strength allows limited flexibility with dosing which poses problems in patients with renal impairment including the elderly. The CHMP noted that the interaction potential of fampridine needs further evaluation.

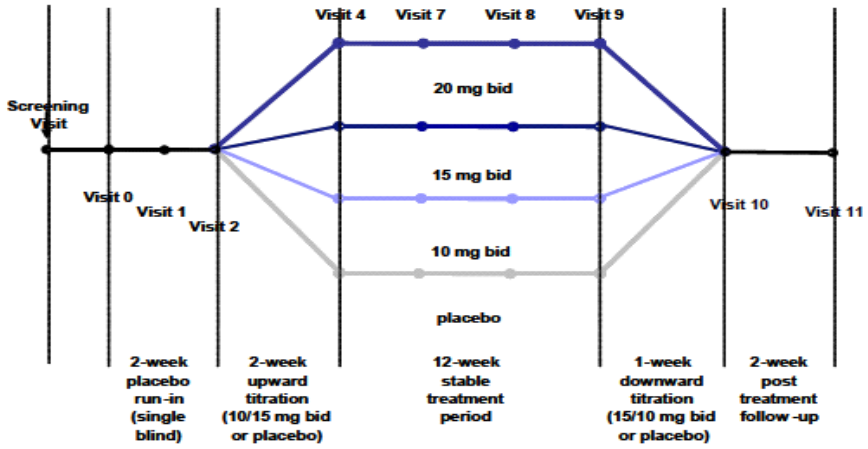
2.5. Clinical efficacy

2.5.1. Dose response study

Study MS-F202

This was a Phase II, double-blind, placebo-controlled, parallel group, 20-week treatment study (one week post screening, two weeks of single-blind placebo, two weeks of double-blind dose escalation, twelve weeks of double-blind stable dose treatment, one week of double-blind down-titration and two weeks of follow-up period) to evaluate safety, tolerability and efficacy of oral fampridine-SR in patients with multiple sclerosis. Patients were randomized to one of four treatment groups: placebo or Fampridine-SR 10 mg, 15 mg, 20 mg b.i.d. The study scheme is presented in the figure 2 below:

Fig. 2 Study MS-F202 Overview of the treatment groups



Subjects included had confirmed multiple sclerosis, were able to perform the test procedures and did not receive background medication other than interferons or Copaxone. Patients had to be able to complete the Timed 25 feet walking test (T25FW) at the Screening Visit in an average of 8–60 seconds (3.1-0.47 ft/sec).
Primary endpoint was the improvement in average walking speed in the stable treatment period relative to the baseline period based on the T25FW. Secondary endpoints included, among others, other T25FW derived variables, the MSFC-9-Hole Peg Test, the MSFC-PASAT 3, the MSFC total, the Ashworth Score, MSWS-12, CCGI, SGI, SSQ, CSQ, OSQ and the MSQLI.

205 patients comprised the ITT population for efficacy analyses. Discontinuation due to adverse events was dose-related; most of the patients withdrew in the Fampridine-SR 20 mg b.i.d. group.

Efficacy results

The main outcomes are presented in the table 9 below:

Table 9 Main outcomes of study MS-F202

	Placebo	10 mg BID	15 mg BID	20 mg BID
n-ITT	47	51	50	57
Baseline values A				
Mean walking speed (ft/sec)	1.87 (0.912)	1.94 (0.874)	2.00 (0.874)	2.04 (0.820)
Average time T25FW (sec by assessor)	13.4	12.9	12.5	12.3
Primary endpoint Percent change (mean)	2.53%	5.53%	8.41%	5.80%
p-valueB		0.82	0.40	0.78
Responders (20% increase of speed)D	12.8%	23.5%	26.0%	15.8%
p-value		0.28	0.14	0.78
LEMMT Score (x, sd) C				
Baseline A	4.07 (0.683)	3.98 (0.661)	3.99 (0.740)	3.96 (0.645)
Stable Dose period	4.02 (0.663)	4.08 (0.636)	4.12 (0.607)	4.00 (0.662)
p-valueB		0.018	0.003	0.212
Ashworth Score (x,sd)C				
Baseline A	1.18 (0.785)	0.88 (0.773)	0.90 (0.816)	0.93 (0.680)
Stable Dose period	1.07 (0.813)	0.83 (0.786)	0.84 (0.776)	0.95 (0.757
p-valueB		0.802	0.826	0.725
MSWS-score C				
Baseline A	75.59 (16.73)	76.31 (16.18)	74.89 (17.65	76.80 (18.13)
Stable Dose period	72.03 (17.52)	70.78 (17.42)	67.66 (21.00)	71.04 (20.72)
p-valueB		0.72	0.45	0.617
Clinician's Global Impression of change				
Any improvement	26.6%	18.0%	18.4%	1.9%
No change	71.1%	80.0%	75.5%	78.8%
Any worsening	2.2%	2.0%	6.1%	5.8%
Subject's Global Impression of change				
Any satisfaction	28.2%	34.0%	42.9%	26.4%
Neutral/mixed	67.4%	54.0%	44.9%	60.4%
Any dissatisfaction	4.3%	12.0%	12.2%	13.2%
MSFC overall (ES)				
Change from baseline	0.08 (0.21)	0.10 (0.31)	0.09 (0.22)	0.06 (0.20)
p-valueB		0.98	>0.99	0.97
MSFC -PASAT (right scores, max 60)				
Baseline (x, sd) A	45.6 (13.1)	51.4 (10.1)	48.6 (11.7)	47.9 (12.3)
Stable dose period	47.8 (11.9)	51.4 (10.1)	49.5 (10.9)	48.5 (11.9)
p-valueB		> 0.99	0.31	0.22
MSFC-Nine-Hole-Peg test (sec)				
Baseline (x, sd) A	33.8 (24.0)	35.8 (28.4)	33.7 (21.0)	35.7 (34.0)
Stable dose period	31.5 (13.3)	31.7 (15.5)	32.2 (19.5)	40.9 (73.1)

Table 9 Main outcomes of study MS-F202

	Placebo	10 mg BID	15 mg BID	20 mg BID
		0.94	> 0.99	0.35
MSQL				
Baseline	32.68	30.93	34.96	30.77
Change at study day 112	1.13 (7.80)	0.26 (6.54)	0.30 (6.72)	1.01 (3.12)
p-valueB		0.95	0.88	>0.99

A Baseline is the average of Study Visits 1 and 2, or the value of last pre-treatment visit. Endpoint is the last observation available during study treatment.
B Overall p-values (not presented here) are based on a test of treatment effect using an ANOVA model with main effects for treatment and centre; pair wise p-values based on Dunnett's test.
C Speed, Asworth Score, MSWS-12 score: Average of 3 (2) visits in the stable treatment period. Average change from baseline of log-transformed walking speeds of two trials of Timed 25-Foot Walk.
D Responders are defined as subjects with a >=20% increase in walking speed from baseline to the average of values obtained during the stable dose period. Subjects who dropped out prior to the stable dose period are considered as non-responders. Overall and pair wise p-values are from the Cochran-Mantel-Haenszel test, stratified by centre.
E LEMMT: Endpoint is the last observation available

In summary, for the primary endpoint and the other T25FW derived variable (% responders) no significant differences compared to placebo were observed. With the exception of the LEMMT, in none of the secondary efficacy variables statistically significant differences between the Fampridine-SR groups and placebo could be shown. Furthermore, a dose-response relationship was not demonstrated. Due to the lack of a clear dose depending effect, absence of investigating the minimal effective dose was considered as a flaw by the CHMP, particularly in the context of the safety profile of fampridine.

A correlation analysis was performed to assess possible relationships between the primary efficacy assessment (walking speed) and changes in two other outcome measures that relate directly to lower extremity function: LEMMT (muscle strength) and Ashworth score (spasticity). Further multiple regression techniques were used to determine the degree to which improvements in walking ability in response to treatment depend on changes in muscle strength and/or spasticity. This was implemented by performing a multiple regression analysis of average walking speed on overall LEMMT and Ashworth scores. None of the linear relationships was statistically significant. Multiple regression techniques to determine the degree to which improvements in walking ability depend on either change in muscle strength and/or spasticity were assessed by estimating the slope for each treatment group. There were no noteworthy findings.

Post Hoc Analysis

It was observed that a proportion of patients (around 30%) seemed to respond with consistently faster walking speeds while on study drug than when off treatment.

Consequently, an alternative responder analysis was performed post hoc. A treatment responder (in terms of consistency of response) was defined as a patient with a faster walking speed for at least three visits during the double-blind treatment period as compared to the maximum value measured in the set of five non-treatment visits. The percentage responder rate according to the new definition was 8.5% for placebo, 35.3% for fampridine 10 mg b.i.d., 36.0% for fampridine 15 mg b.i.d. and 38.6% for fampridine 20 mg b.i.d. Given that there was little difference in responsiveness between the three doses examined, further analyses were performed comparing the pooled Fampridine-SR treated groups against the placebo-treated group. The percentage of patients who met the responder criterion in the combined Fampridine-SR group was 36.7% compared to 8.5% in the placebo-treated group, and this difference was statistically significant ($p<0.001$).

2.5.2. Main studies

The main studies for the clinical development programme for multiple sclerosis comprised two phase III studies:

- Study MS-F203:

A phase 3, double-blind, placebo-controlled, 21-week (one week post screening, two weeks of placebo, 14 weeks of double-blind treatment, and four weeks of no treatment as follow-up), parallel group study to evaluate safety and efficacy of oral Fampridine- SR (10 mg b.i.d.) in subjects with Multiple Sclerosis.

- Study MS-F204:

A multi-center, phase 3, double-blind, placebo-controlled, parallel group, 14-week study (one week post screening, two weeks of single-blind placebo run-in, nine weeks of double-blind treatment, and two weeks of no-treatment follow-up) to evaluate safety and efficacy of oral Fampridine-SR (10 mg b.i.d.) in subjects with Multiple Sclerosis and to explore the duration of effect over the 12-hour dosing interval.

The dose selected was based on previous experience with this patient population; study MS-F202, in particular: doses greater than 10 mg b.i.d. did not appear to provide any additional benefit in efficacy, but were associated with increased incidence of adverse events and discontinuation of treatment.

Both studies MS-F203 and MS-F204 differed in their design with respect to the duration of the double-blind phase (14 weeks against 9 weeks) and the randomisation scheme (3:1 against 1:1), respectively.

Methods

Study Participants

Patients included had clinically confirmed multiple sclerosis as defined by McDonald criteria and had to be able to perform all required study procedures, especially to complete two trials of the Timed 25 feet walking test (F25FW) at the Screening Visit in an average of 8– 45 seconds (3.1- 1.8 ft/sec). Main exclusion criteria were any history of seizures or evidence of epileptiform activity on an EEG, start of new immunomodulatory treatment regime for MS, current exacerbation, receiving corticosteroids, cyclophosphamide or mitoxantrone for MS, presence of significant cardiovascular abnormalities and ECG. Duration of disease and type of multiple sclerosis were not covered in the in-/exclusion criteria. Discontinuation of study treatment was required, if a patient should experience a seizure. Occurrence of an exacerbation, irrespective whether corticosteroids were administered, was no reason for excluding a patient from the study per se.

Treatments

Design of both studies is depicted in the figures 3 and 4 below.

Fig. 3 Study MS-F203

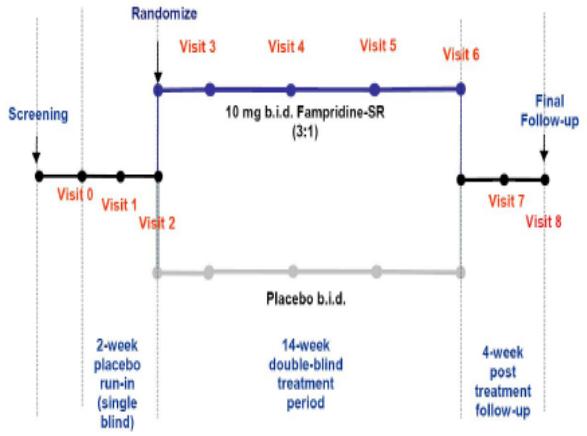
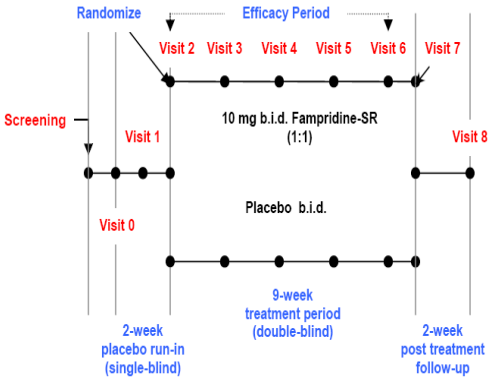


Fig. 4 Study MS-F204



In studies MS-F203/204 patients received placebo or Fampridine-SR 10 mg b.i.d. in a 12 hrs dose interval. Patients were instructed to take one tablet every 12 hours, at approximately the same time each day.

Concomitant Therapy

Patients entering the study were to be stable on any concomitant medication for at least three weeks prior to the screening visit.

Patients were excluded if they started a treatment regimen of Betaseron, Avonex, Copaxone, Rebif, or Tysabri within 90 days prior screening visit or had any change in dose regime of these drugs within 30 days prior to the screening visit. Patients were also to be excluded if they received corticosteroids within 30 days prior to the screening visit, or cyclophosphamide or mitoxantrone for MS treatment within six months prior to the screening visit. These restrictions were imposed with the goal of minimizing concomitant drug-related changes in MS symptoms, particularly motor function, during the trials.

Objectives

The objectives of the pivotal trials MS-F203 and MS-F204 were to assess the efficacy (assessment by walking speed improvements) and safety of Fampridine-SR in patients with multiple sclerosis.

Outcomes/endpoints

Primary efficacy endpoint was the proportion of 'consistent' responders defined as patients with higher walking speed for at least three out of four visits during the double-blind period as compared to the maximum value among the non-treatment visits. Walking speed was based on the T25FW Test, wherein a patient was asked to walk as quickly as possible, safely, from one end to the other end of a clearly marked, unobstructed, 25-foot course. After a maximum rest of 5 minutes the test was repeated again. The walking speed for a particular study visit was the average of the walking speeds of the two trials performed. If one of the 2 trials could not be fulfilled then the walking speed for that visit was to be the walking speed from the completed trial.

Main secondary efficacy endpoints concerned the 12-Item MS Walking Scale, the Lower Extremity Manual Muscle Testing score and the Ashworth Spasticity Examination score. The 12-Item MS Walking Scale is a multi-item rating scale of walking assessed by the patient. The total score ranges from 12 to 60 points and is transformed to a 0 (none) -100 (maximum disability) scale. The Lower Extremity

Manual Muscle Testing (LEMMT) is a muscle strengths score and the Ashworth Spasticity Examination assesses muscle tone. Subject's global impression (SGI) and Clinical global impression (CGI) were assessed to provide secondary measures for validation of the clinical meaningfulness of the walking response criterion.

Sample size

Study MS-F203

A sample size of 180 patients treated with Fampridine-SR, along with 60 placebo-treated patients, was calculated to provide approximately 90% power, at an overall significance level no greater than 0.05 and no less than 0.000125, for the three criteria defined in the statistical analysis plan for the primary measure (see the table 10 below).

Table 10 Assumptions for the Power Calculation

	FMP (N=180)	Placebo (N=60)		Estimated Power *
Responder Rate	35.3%	8.5%		99%
	Responders (N=68)	Non-Responders (N=172)	Common SD	
Avg. Change in MSWS12	-11.8	-2.5	19.0	92%
	FMP-Responders (N=63)	Placebo (N=60)	Common SD	
Change in walking speed (ft/sec) at the last observed visit	0.45	0.04	0.50	99%
Complete primary endpoint				~90%

ABBREVIATIONS: FMP = Fampridine-SR 10mg bid.

*Based on conservative assumptions and the 10mg bid and placebo data from MS-F202.

Study MS-F204

A sample size of 92 patients treated with Fampridine-SR 10 mg b.i.d. and 92 patients treated with placebo would provide approximately 90% power, at an overall significance level of 0.05, to detect the difference between a Fampridine-SR 10 mg b.i.d. response rate of 30% and a placebo response rate of 10%. To ensure that at least 184 patients complete the study, approximately 100 patients were to be randomized to each group. The above calculation was based on assumptions about the response criterion from studies MS-F202 and MS-F203 and the low drop-out rate observed in these two studies.

Randomisation

Patients were randomized to either the 10 mg Fampridine-SR or placebo treatment group in a 3:1 ratio in study MS-F203 and 1:1 ratio in study MS-F204, according to a computer-generated randomization scheme. In study MS-F203 the randomization scheme was blocked and stratified by treatment site.

Blinding (masking)

The first two weeks of the studies was a single-blind placebo run-in phase. The remainder of the study treatment period was double-blind. Placebo tablets were identical in appearance and package to the Fampridine-SR tablets and contained the same set of inactive ingredients. Patient, Clinician and evaluator were not aware of the treatment assigned.

Statistical methods

In studies MS-F202/203/204, the principal analysis of efficacy was based on the ITT population consisting of all randomized patients to whom double-blind study medication was dispensed and who had at least one efficacy (T25FW and MSWS-12) evaluation during the treatment period. Treatment differences in the proportion of responders between Fampridine-SR treated and placebo treated groups were analyzed by the Cochran-Mantel-Haenszel (CMH) test, controlled for centre.

The responder-analysis was the first step in a three stage, stepwise analysis that defined the primary endpoint. The second step of the analysis was to be 'validation of the clinical meaningfulness' of the responder criterion by comparing the changes in MSWS-12 scores in responders and non-responders (without treatment attribution) during the double-blind treatment period. The third and final step was to demonstrate statistically significant improvement in walking speed in Fampridine-SR treated responders compared to the placebo group (responders plus non-responders) at the last visit on treatment to confirm maintenance of effect. In addition to examination of walking speed, data from the individual responder analysis groups (Fampridine-SR responder, Fampridine-SR non-responder and placebo-treated groups) were also to be analyzed with respect to changes in leg muscle strength (LEMMT) and spasticity (Ashworth score). For study MS-F202 the data were re-analyzed in accordance to the statistical analyses plans of studies 203/204, making between study comparisons possible.

In addition to examination of walking speed, data from the individual responder analysis groups (Fampridine-SR responder, Fampridine-SR non-responder and placebo-treated groups) was also to be analyzed with respect to changes in leg muscle strength (LEMMT) and spasticity (Ashworth score).

The overall significance level of the above was to be no greater than 0.05 and no less than 0.000125 (i.e. 0.053) if each test is conducted at the 0.05 level. For the full picture, all nominal p-values were to be presented for every efficacy variable. Additional correction for multiple comparisons of the secondary efficacy variables was pre-specified in the statistical analysis plan.

The average change from baseline in the MSWS-12 score was analysed by an analysis of variance model, with effects for responder status and centre. Similar analyses (responder vs. non-responder) were to be performed on the other two secondary subjective variables, average SGI score during the double-blind period and the CGI score, recorded at the end of the double-blind period.

For the endpoint change from baseline and each of the secondary objective variables, differences between the three responder analysis groups (placebo, Fampridine-SR non-responders, and Fampridine-SR responders) were to be analysed by t-tests of the least-squares means using the mean square error via an ANOVA model with effects for responder analysis group and adjusted for centre. For the pooled analyses study was included as an additional factor controlled for.

Results

Participant flow

Details on participant flow and numbers analysed are given in the following table 11.

Table 11 Patient disposition of studies MS-F203/4

	MS-F Placebo	203 10 mg BID	MS-F Placebo	204 10 mg BID
n of subjects n-Randomised	72	229	119	120
n-safety data base	72	228	119	120
n-ITT(Intention to treat)	72	224	118	119
n-PPP (Per	65 (90.3%)	195 (85.2%)	97 (81.5%)	100 (83.3%)

Table 11 Patient disposition of studies MS-F203/4

	MS-F Placebo	203 10 mg BID	MS-F Placebo	204 10 mg BID
protocol pop.)				
n-Discontinued	1 (1.7%)	17 (7.4%)	5 (4.2%)	7 (5.8%)
AEs	-	11	4	4
Non-compliance	-	-	1	2
Withdrew Consent	-	4	-	-
Lost to follow-up	1	-	-	-
Other	-	2	-	-
	n=72	n=228	n=119	n=120

Recruitment

In study MS-F203, the date of the first patient visit was 7 June 2005; the date of the last patient visit was 28 June 2006. In study MS-F204, the date of first patient visit was 22 May 2007; date of last patient visit was 27 Feb 2008.

Conduct of the study

Two protocol amendments were issued for the trial MS-F203. In addition, several changes in the planned analyses occurred after the protocol and amendments, but before breaking the blind: addition of another efficacy variable (consistency of improvements in the LEMMT), ordering of secondary endpoints for the trial and clarifications of study outcome expectations. The additions were included in the Statistical Analysis Plan of the study. Two amendments were issued for the trial MS-F204 with regard to efficacy to the original study protocol.

Protocol Deviations

In both studies, the majority of protocol deviations were considered minor (e.g. assessment not performed, out-of-window visits, minor drug compliance issues and plasma sample taken out of protocol-specified time window). None was considered sufficiently significant to affect interpretation of study results.

Baseline data

Baseline patient demographics and disease characteristics are summarised in the table 12 below.

Table 12 Patient disposition and baseline features of study MS-F203/4

	MS-F Placebo	203 10 mg BID	MS-F Placebo	204 10 mg BID
n of subjects				
n-Randomised	72	229	119	120
Baseline features				
Age (x, sd)	50.9 (8.88)	51.5 (8.720	51.7 (9.84)	51.8 (9.67)
MS-type				
RRMS	29.2%	27.2%	33.6%	35.8%
PPMS	19.4%	16.0%	17.6%	8.3%
SPMS	48.6%	53.3%	47.1%	51.7%
PR	2.8%	4.0%	1.7%	4.2%

Table 12 Patient disposition and baseline features of study MS-F203/4

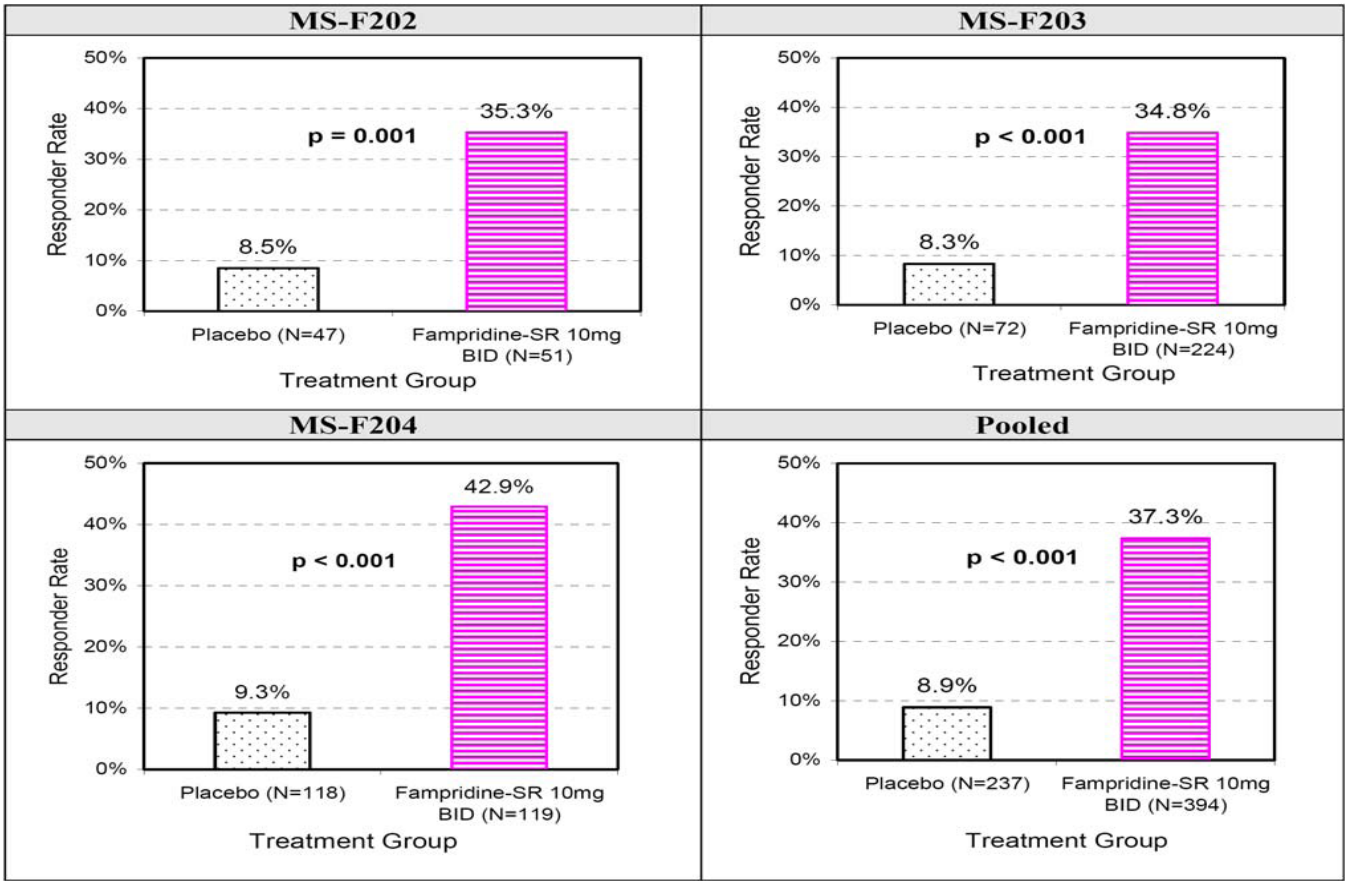
	MS-F Placebo	203 10 mg BID	MS-F Placebo	204 10 mg BID
Duration of disease (yrs, median, range)	10.8 1.4 ; 37.7	11.8 0.4 ; 41.7	12.5 0.1 ; 34.5	12.75 0.5 ; 45.6
EDSS (median, range)	6.00 2.5 ; 6.5	6.00 2.5 ; 7.0	6.00 1.5 ; 7.5	6.00 2.5 ;6.5
Concomitant medication				
Any	97.2%	100%	100%	100%
Interferon-use	44.4%	43.9%	32.8%	36.7%
Glatiramer-use	25.0%	21.9%	26.1%	22.5%
Baclofen	51.4%	48.7%	41.2%	43.3%

Outcomes and estimation

Figure 5 presents responder analyses for studies MS-F202 (post-hoc), MS-F203, MS-F204 and the pooled analysis MS-F202/3/4. For studies MS-F203 and MS-F204 the primary outcome was met, i.e. difference in responder rates (primary endpoint) was statistically significant. The retrospective re-analysis of study MS-F202 was consistent with these results.

Pooling studies MS-F202/3/4, the responder rates were 37.3% for the fampridine group and 8.9% for the placebo group (difference 28.4%, CI95% 22.1%; 34.2%; p<0.001, CI by assessor).

Figure 5



In the table 13 below, the main results for studies MS-F202, MS-F203 and MS-F204 are summarised, including efficacy data on both the primary endpoint and the secondary endpoints. Results of study MS-F202 concerning the fampridine 10 mg arm are presented with respect to consistency evaluation.

Table 13 Main outcomes of study MS-F202/3/4

	MS-F	202	MS-F	203	MS-F	204
	Placebo	10 mg BID	Placebo	10 mg BID	Placebo	10 mg BID
n-ITT	47	51	72	224	118	119
Walking speed (ft/sec, LSM)						
Baseline	1.80	1.83	2.04	2.02	2.21	2.12
Endpoint	1.84	1.92	2.15	2.32	2.39	2.43
Change (LSM, SE)D	0.04 (0.077)	0.09 (0.077)	0.11 (0.066)	0.30 (0.040)	0.18 (0.046)	0.31 (0.046)
p-valueB		0.635		0.010		0.038
Percentage change (LSM) D	2.30%	10.11%	5.24%	13.88%	7.74%	14.36%
		0.035		< 0.001		<0.007
RespondersA	8.5%	35.3%	8.3%	34.8%	9.3%	42.9%
Risk-Diff-by assessor		26.8%		26.5%		33.5%
CI95%		10.5% ; 41.4%		16.0% ; 34.3%		22.7% ; 43.4%
OR		9.39		6.77		9.22
CI95%		2.41 ; 36.53		2.71 ; 16.92		5.23 ; 16.27
p-valueC		0.001		<0.001		<0.001
LEMMT Score (x, sd)						
Baseline	4.04 (0.666)	3.97 (0.655)	3.97 (0.737)	4.06 (0.586)	3.96 (0.580)	3.91 (0.603)
Average change	-0.04 (0.031)	0.11 (0.030)	0.05 (0.024)	0.13 (0.014)	0.05 (0.024)	0.10 (0.024)
p-valueB		< 0.001		0.003		0.106
Ashworth Score (x,sd)						
Baseline	1.18 (0.768)	0.93 (0.779)	0.95 (0.670)	0.90 (0.713)	0.80 (0.672)	0.91 (0.611)
Average change	-0.11 (0.053)	-0.15 (0.051)	-0.09 (0.037)	-0.18 (0.022)	-0.07 (0.033)	-0.17 (0.032)
p-valueB		0.533		0.021		0.015
MSWS-12-score (x, sd)						
Baseline	76.51 (16.57)	74.31 (16.19)	68.48 (22.30)	70.98 (18.55)	67.68 (22.56)	73.80 (17.75)
Average change	-1.84 (2.40)	-4.63 (2.22)	-0.08 (1.46)	-2.84 (0.878)	0.87 (1.22)	-2.77 (1.20)
p-valueB		0.383		0.084		0.006
Subject's Global Impression						
Least square mean (SE)	4.19 (0.15)	4.34 (0.14)	4.51 (0.12)	4.60 (0.07)	4.30 (0.11)	4.38 (0.11)
Median	4.00	4.00	4.25	4.50	4.00	4.25
Range	2.5 ; 6.0	1.5 ; 7.0	1.5 ; 6.8	2.0 ; 7.0	1.0 ; 7.0	1.3 ; 6.8
		0.451		0.477		0.607
nwith SGI assessment	-	-	72	224	118	119

Table 13 Main outcomes of study MS-F202/3/4

	MS-F 202		MS-F 203		MS-F 204	
	Placebo	10 mg BID	Placebo	10 mg BID	Placebo	10 mg BID
7=delighted } 6= pleased }	-	-	6.9%	12.5%	9.3%	9.2%
5=mostly satisfied	-	-	27.8%	24.1%	14.4%	18.5%
4=neutral/mixed	-	-	51.4%	44.2%	54.2%	50.4%
3= mostly dissatisfied	-	-	9.7%	13.8%	16.9%	16.0%
2=unhappy	-	-	2.8%	0.0%	4.2%	4.2%
1=terrible	-	-	1.4%	5.4%	0.8%	1.7%
OR (CI95%)	-		1.91 0.71 ; 5.16		0.99 0.41 ; 2.39	
RR (CI95%)	-		1.93 0.77 ; 4.81		0.99 0.45 ; 2.20	
RDCI95%)	-		6.01 -2.65% ; 12.20%		0.08% -7.47% ; 7.31%	
p-value	-		0.199		0.983	
Clinical Global Impression						
Least Square Mean (SE)	3.85 (0.13)	3.69 (0.12)	3.79 (0.53)	3.59 (0.06)	3.83 (0.07)	3.54 (0.07)
Median	4.00	4.00	4.00	4.00	4.00	4.00
Range	2.0 ; 5.0	1.0; 6.0	2.0 ; 5.0	1.0; 6.0	2.0 ; 5.0	1.0; 5.0
		0.344		0.065		0.002
nwith CGI assessment			70	213	112	110
1=very much improved } 2=much improved }	-	-	8.6%	11.7%	1.8%	10.9%
3=somewhat improved,	-	-	17.1%	26.8%	21.4%	31.8%
4=no, change	-	-	64.3%	55.4%	73.2%	50.9%
5=somewhat worse	-	-	10.0%	5.6%	3.6%	6.4%
6=much worse	-	-	0.0%	0.5%	0.0%	0.0%
7=very much worse.	-	-	0.0%	0.0%	0.0%	0.0%
OR (CI95%)	-		1.42 0.56 ; 3.61		6.73 1.47 ; 30.84	
RR (CI95%)	-		1.37 0.59 ; 3.20		6.11 1.40 ; 26.67	
RD (CI95%)	-		3.17% -6.45 ; 9.96		9.12% 2.80% ; 15.40%	
p-value	-		0.464		0.014	

A A responder was defined as a patient with a faster walking speed for at least three visits during the double-blind treatment period (out of a possible total of four) as compared to the maximum speed for any of the pre-treatment visits and the first post-treatment visit. A patient who missed a visit was counted as a non-responder for that visit.
B Least squares means, standard errors, p-values, and 95% confidence intervals were obtained from an ANOVA model controlled for centre.
C P-values and 95% confidence intervals for the odds ratios (OR) for the individual studies were obtained from a logistic regression model, controlled for centre.
D Average change over DB period.

Of note, converting walking speed into seconds to bridge a 25 feet distance, the mean at endpoint was 13.6 vs 13 seconds (placebo vs fampridine) in study MS-F202, 11.6 vs 10.8 seconds in study MS-F203 and 10.5 vs 10.2 seconds in study MS-F204.

As presented above, in the pivotal studies MS-F203 and MS-F204, differences between the active treatment and placebo in the average change in LEMMT Score, Ashworth Score and MSWS-12 score (secondary endpoints) were either statistically significant or showed a trend towards statistical significance; however, clinical relevance of these observations was questioned (see Discussion of Clinical Efficacy). The mean changes in these parameters from baseline were small.

For the SGI and CGI there was no or almost no shift in median, indicating that the improvement might not be perceived as substantial.

Within responder analysis

The within responder analysis is described in detail under the "Statistical methods". In this analysis, results were only slightly better i.e. the average number of seconds to bridge 25 feet during the double-blind phase was 11.7 seconds under placebo, 12.0 seconds for fampridine non-responders and 9.8 seconds for fampridine responders.

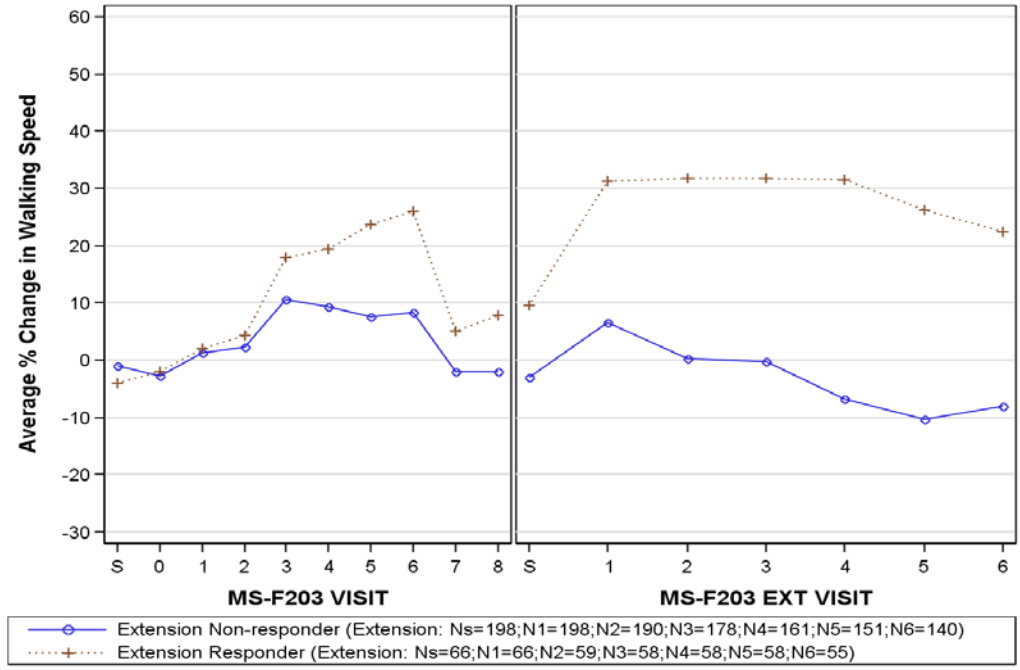
Also the fampridine PR Timed-Walk responders had statistically significant greater average increases (improvement) in LEMMT scores when compared to the placebo group. The average increase in LEMMT score for the fampridine PR Timed-Walk responders was 0.15 units compared to 0.03 units for the placebo group. The baseline score was 4.0 points. Also for the Ashworth score the improvement was statistically significant but small, i.e. 0.19 points in fampridine responders as compared to -0.09 points in the placebo group (baseline score 0.91-0.95 points). For the Subject Global Impression and Clinician Global Impression there was no or almost no shift in median in the within responder analysis.

Maintenance of effect

Three ongoing, long-term, open-label extension studies (studies MS-F202EXT, MS-F203EXT, MS-F204EXT) have enrolled 660 multiple sclerosis patients. Three-hundred three patients have been treated for 2 years or longer. An equivalent Timed-Walk response analysis was performed using a definition of an Extension Timed-Walk responder as a patient with walking speeds at the majority of extension study visits in the first year that are faster than the fastest walking speed at any of the off-treatment visits in the double-blind parent study or the extension study.

The average percent change from baseline walking speed for the Extension Timed-Walk responders and Extension Timed-Walk non-responders is shown for all patients in MS-F203EXT (see figure 6 below). The functional improvement observed during treatment with fampridine PR in the double-blind studies was rapidly lost after cessation of treatment, without evidence of rebound. For Extension Timed-Walk responders, average walking speed at each extension study visit was slightly more than 30% faster than the baseline walking speed from the double-blind study during the first year of the extension study, and slightly decreased to approximately 23% at following two visits.

Figure 6 Average Percent Change from Baseline in Walking Speed for the Extension Timed-Walk Responders and Extension Timed-Walk Non-Responders



Ancillary analyses

Subgroup analyses

Subgroup analyses indicated that response was not influenced by gender, age (≤ 45 yr, 46-64 yr, ≥ 65 yr), MS type (relapsing-remitting MS, primary progressive MS, secondary progressive MS, progressive relapsing MS), duration of disease, Expanded Disability Status Scale score (≤ 5.5, 6, ≥ 6.5), baseline walking speed, baseline LEMMT score, baseline Ashworth Score, baseline MSWS-12 score, baseline SGI score, mild renal impairment (> 80 ml/min, 40-80 ml/min) and use of immunomodulators.

The main results are presented in table 14.

Table 14 Distribution of Responders per subgroup

	Placebo	Fampridine 10 mg BID			
Age			OR	CI-95%	p-value#
≤ 45 yr	4.6%	35.3%	15.25	3.98 ; 58.36	I term
46-64 yr	10.7%	36.6%	7.97	4.12 ; 15.44	0.662
≥ 65 yr	11.1%	54.5%	12.21	1.82 ; 82.01	
Gender					
Male	5.4%	33.9%	4.42	1.10 ; 17.72	0.183
Female	11.1%	38.7%	9.00	2.54 ; 31.86	
MS-Type					
RRMS	2,7%	29,2%	23.13	4.25 ; 126	
PPMS	15,2%	44,2%	7.56	2.25 ; 25.44	0.554
SPMS	10,6%	39,7%	9.59	4.48 ; 20.51	excl PRMS
PRMS	0,0%	40,0%	-	-	
Duration of disease					
≤ Q1	8.3	35.4	≤ Median		
Q1 ≤ Q2	13.3	39.0	7.04	3.32 ; 14.94	0.318
Q2 ≤ Q3	6.6	35.7	> Median		
> Q4	7.1	39.2	12.55	5.32 ; 29.64	
EDSS					
≤ 5.5	7.8	36.1	8.50	2.72 ; 26.54	
6	13.4	35.7	4.67	1.99 ; 10.91	0.103

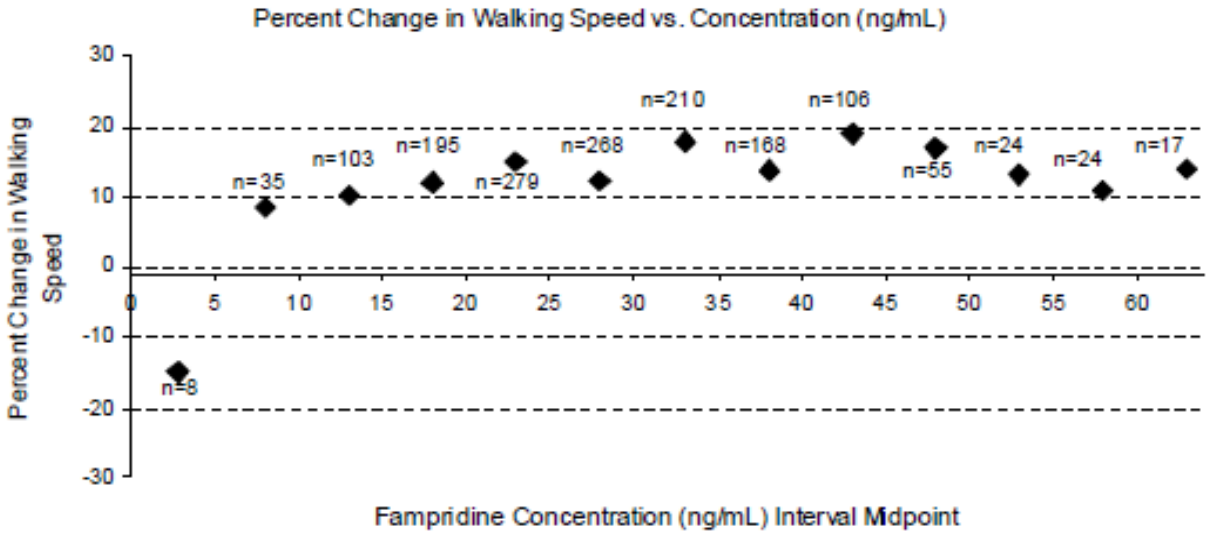
≥ 6.5	5.5	39.6	21.33	7.07 ; 64.38	
Baseline Walking Speed					
≤ Q1	10.0%	31.1%	≤ Median		
Q1 ≤ Q2	5.1%	37.4%	9.05	3.94 ; 20.8	
Q2 ≤ Q3	10.0%	40.4%	> Median		0.93
> Q4	10.3%	40.2%	9.51	4.44 ; 20.38	
Renal impairment status					
Normal (> 80 ml/min)	8.6%	34.7%	8.74	4.64 ; 16.43	
Abnormal (40-80 ml/min)	10.3%	47.6%	10.20	2.96 ; 35.23	0.825

For interaction term

Relationship Between Efficacy and Plasma Concentration of Fampridine

Based on the plasma concentration data sampled in studies 202/3/4 no plasma concentration response relationship could be established, as shown in the figure 7.

Fig. 7 Percent Change From Baseline in Walking Speed versus Fampridine Plasma Concentration (Means per 5 ng/mL Concentration Window)



Analysis performed across trials (pooled analyses and meta-analysis)

In the figures 8a and 8b below, the percentage change in walking speed over studies MS-F202/3/4 is presented. The difference in proportion of subjects with more than 0%, 10%, 20% or 30% improvement between placebo and fampridine 10 mg (figure 8a) was statistically significant.

Figure 8a Percentage change in walking speed: Increase

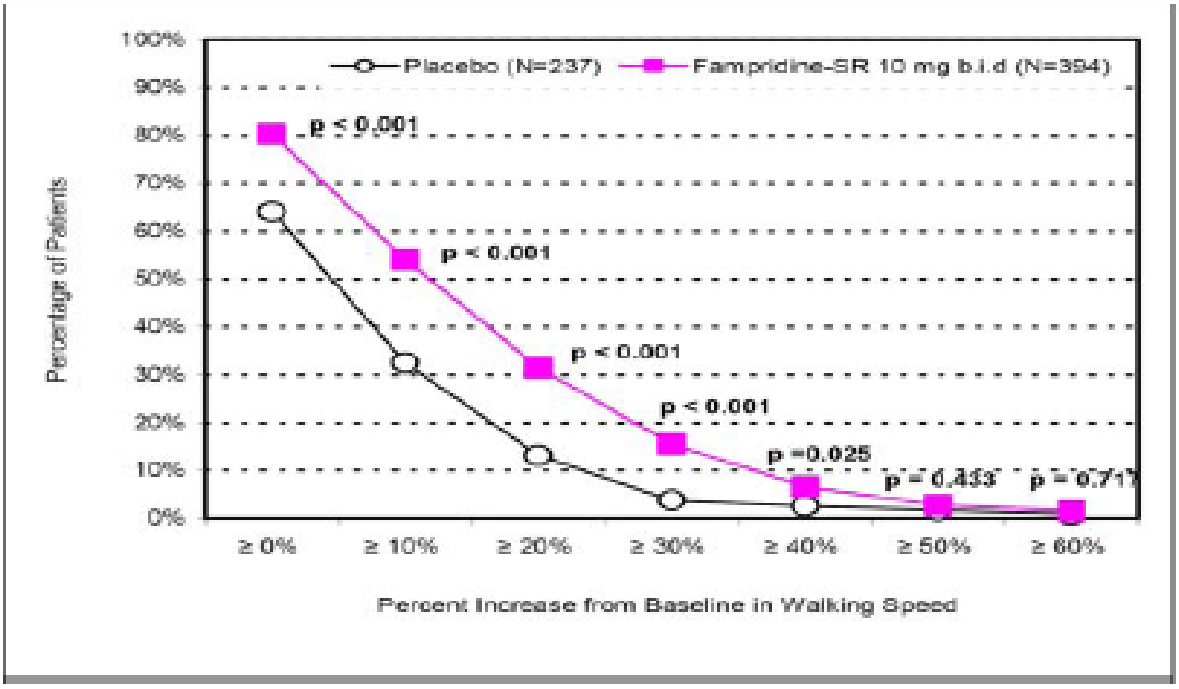
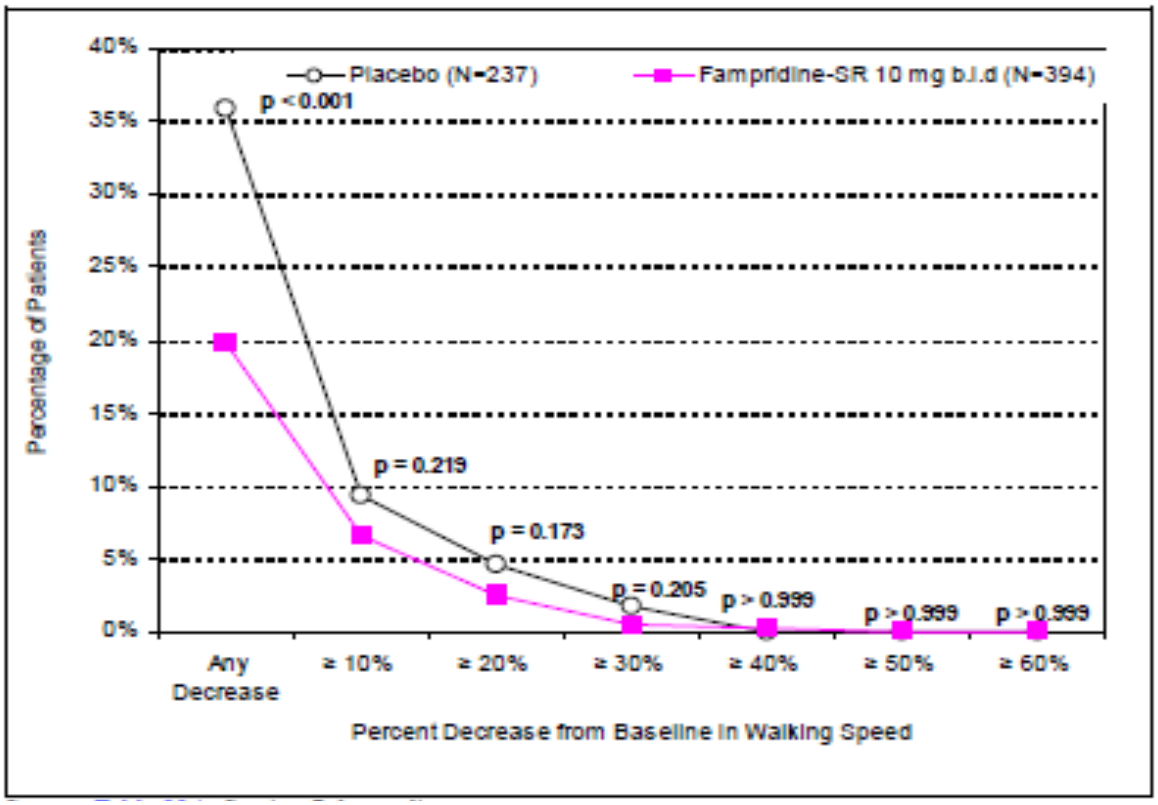


Figure 8b Percentage change in walking speed: Decrease



Further, figure 5 (Responder rates) where results of studies MS-F202/3/4 were pooled is referred to.

Clinical studies in special populations

No studies were performed in special populations. Of note, the studies conducted included only a limited number of the elderly, i.e. 4.9% of the multiple sclerosis patients were older than 65 years. Moreover, the studies did not include patients with compromised cardio-vascular function or seizure prone subjects, as these factors were exclusion criteria.

Supportive studies

Study MS-F20-F201

This was a randomised placebo controlled parallel group dose-ranging study. Patients with multiple sclerosis received placebo (n=11) or fampridine-SR (n=25) in increasing doses from 10 mg to 40 mg. The primary objective was to determine the tolerance of escalating doses of fampridine (10, 20, 30, 40 mg BID). Total treatment duration was 8 weeks. The outcomes concerned fatigue scores, LEMMT, and MSFC. With respect to efficacy, statistical significance as compared to placebo was observed for the LEMMT score, but not for the T25FW. The reciprocal of walking time i.e. walking speed was identified as a suitable transformation to improve the normality of the data. The resulting post-hoc analysis showed statistically significant differences as compared to placebo for walking speed. Statistical significance was not achieved for the other outcome variables.

Three long-term, open-label extension studies with fampridine PR (MS-F202EXT, MS-F203EXT, and MS-F204EXT) are currently ongoing. The efficacy data originating in these trials are reflected in the "Maintenance of Effect section" and in the Discussion on clinical efficacy.

2.5.3. Discussion on clinical efficacy

Introduction

Fampridine is a selective potassium channel blocker. Considering this mechanism of action of fampridine, there is a plausible biological rationale to evaluate the usefulness of fampridine in symptomatic treatment in multiple sclerosis. This view, i.e. that fampridine could potentially be a useful drug for treatment of Multiple Sclerosis (MS) was shared by the Scientific Advisory Group (SAG) for Neurology.

The indication claimed for fampridine was treatment of adult patients with multiple sclerosis for the improvement of walking ability. The CHMP noted that the indication was restricted to what has been observed rather than being conceptual, e.g. symptomatic treatment of neurological dysfunction due to demyelinisation in multiple sclerosis. Although improvement of walking ability may have merits on its own, an improvement of other symptoms caused by demyelinisation would have given more body to the evidence of efficacy.

Three studies were indicated as being relevant by the applicant, i.e. a dose comparison study MS-F202 and two pivotal studies MS-F203 and MS-F204.

Design and conduct of clinical studies

Timed-25 Foot Walk test / responder definition

The primary endpoint in the pivotal studies was the proportion of responders based on the Timed 25 feet walking test (T25FW), i.e. the time in seconds it takes to walk 25 feet.

The walking speed for a particular visit was derived by calculating the average of two walking tests separated by at least 5 minutes. If one test was missed then the walking speed from the completed

test was taken. If both trials were missed, the walking speed for the visit was to be considered slower than the maximum speed recorded during the non-double-blind period. In principle, the failure of two walking tests in the same visit should be considered a failure. The applicant submitted additional data indicating that missing a second walk was rare. Hence, it is unlikely that this affects the outcome substantially.

A responder was defined as a patient with a higher walking speed for at least three visits during the double-blind treatment period (out of a possible total of four) as compared to the maximum speed for any of the pre-treatment visits and the first post-treatment visit. This responder definition was questioned by the CHMP. In principle, a responder analysis was considered useful, as in general it incorporates a clinically significant improvement on an individual patient level. In this case however, the CHMP was of the view that the definition focused more on consistency of the effect, i.e. persistence of any improvement above the maximum off-treatment speed, not taking into account the magnitude of the improvement.

Further, the T25FW test measures essentially the speed of walking. It was argued by the applicant that walking speed alone is a meaningful treatment goal, since a limited walking speed impacts everyday activities and social participation. The CHMP acknowledged that a certain walking speed in daily life is needed e.g. for crossing a street safely. However, it was also noted that if 2.6 ft/sec is needed to cross a street safely, as argued by the applicant, under fampridine treatment on the average, this velocity would not be reached.

In the CHMP view, it remained unclear whether the T25FW test reflects walking sufficiently as walking also requires muscle strength, sensory feedback and coordination. In this respect, the T25FW was considered a pharmacodynamic endpoint rather than a clinically relevant outcome. That the T25FW is frequently used may indicate its convenience of use, but this was not considered by the CHMP the same as being clinically relevant for walking ability.

These issues were put forward to the SAG, as they are related to the interpretation of clinical relevance of the observed effect discussed below.

The SAG considered the T25FW to be acceptable as a pharmacodynamic endpoint. The submitted studies, according to the SAG, have demonstrated that fampridine had a small, but statistically significant effect on the speed of walking over a short distance. However, the majority of the SAG was concerned that a significant effect across the broader aspects of walking has not been shown, which makes the test unacceptable as a clinically relevant outcome measure. The SAG also expressed concerns regarding the reliability of correlating the effect on walking speed with other walking parameters as a predictor of an overall treatment effect. Further, it was acknowledged that to be able to walk at a certain speed, motor and sensory function needs to be involved. However, walking speed does not provide information with regard to the quality of walking. There are several different aspects of walking that can be affected by MS, including coordination, balance and stamina. Outcome measures that would address these aspects specifically have not been presented. It was noted that endurance is considered by patients more important than the speed to bridge a short distance, as it determines the range of action.

The view of the SAG is supported by an independent multidisciplinary consensus conference by the Consortium of Multiple Sclerosis Centres (Hutchinson et al 2007). The aim of this consensus meeting was to determine the most appropriate outcome measures for gait and fatigue in people with MS. In this consensus paper it is stated that gait is not a unitary entity but encompasses many independent and interdependent variables and a single measure of gait would not suffice. Thus, in this paper it is agreed that the T25FW is useful, but as part of a test battery, not as single item. In addition, it was recognised that gait disorder in MS is highly heterogeneous as it can occur for many different reasons. Hence, the extrapolation of results based on the T25FW in other conditions with less heterogeneous walking patterns was not justified, although the applicant argued that for Friedreich's ataxia this might be different.

Efficacy data and additional analyses

Clinical relevance of presented data

In the pivotal studies, a statistically significant difference in responder rates was observed in favour of active treatment i.e. fampridine 10 mg b.i.d. The same held for study MS-F202 where this analysis was performed post hoc.

Converting walking speed into seconds to bridge a 25 feet distance, the mean at endpoint was 13.6 seconds versus 13.0 seconds (placebo versus fampridine) in study MS-F202, 11.6 versus 10.8 seconds in study MS-F203 and 10.5 versus 10.2 seconds in study MS-F204. In the "within responder analysis", results were only slightly better, i.e. the average number of seconds to bridge 25 feet during the double-blind phase was 11.7 seconds under placebo, 12.0 seconds for fampridine non-responders and 9.8 seconds for fampridine responders. As stated above, it was considered of greater importance whether this speed can be maintained for a while, increasing the range of action. The CHMP highlighted that this was not assessed by the applicant.

For the main studies, a statistically significant difference in responder rates was observed in favour of active treatment. Pooling the results of studies MS-F202/3/4, the responder rates were 8.9% for the placebo group versus 37.2% for the fampridine group (Difference 28.4%, CI95% 22.1%; 34.2%). For the secondary endpoints, the mean changes from baseline in MSWS-12, LEMMT and Ashworth scores within the study groups were small, let alone the difference in change from baseline between the study groups, although statistical significance or a trend to statistical significance was observed. For the Subject Global Impression and Clinician Global Impression there was no or almost no shift in median indicating that the improvement might not be perceived as substantial. The majority of subjects perceived no satisfaction or improvement, let alone a substantial improvement.

Hence, the responder definition increases the sensitivity to show statistical significance, but the clinical significance of the observed effect was not addressed sufficiently. The CHMP considered the justification of the responder definition by the applicant unsatisfactory. The choice of consistency above incorporating the degree of improvement remained disputable. In agreement with this, the SAG considered the applicant's responder definition arbitrary, in that it was not defined as a clinically relevant outcome of defined magnitude. It was pointed out by the SAG that tests such as the T25FW could be useful for monitoring patients in everyday clinical practice, but it has not been shown that improvement in responders, defined according to the responder definition in the clinical trials, is of general benefit for this group of MS patients.

Analysis within responders

The CHMP questioned the appropriateness of the "within responder analysis", because a circular line of reasoning in establishing improvement in improvers was noted; responders are first defined based on a walking test (in terms of any improvement) then it is evaluated whether responders do better on the same walking test (in terms of walking speed) and other aspects of walking function (MSWS-12, LEMMT, Ashworth score). This approach was considered to be self-fulfilling and was not considered a validation of the responder definition. Hence, the overall analysis has been given more weight by the CHMP than the within responder analysis. In their response, the applicant failed to demonstrate that there is no circular argument. Even if accepting this analysis, the CHMP noted that the clinical relevance of the effect sizes in responders remained questionable.

Clinical meaningfulness of 20% improvement in walking speed

The applicant argued that a 20% improvement in walking speed is clinically meaningful. Overall, the difference in proportion of >20% responders was 13% versus 31% for placebo and fampridine, respectively.

However, the clinical relevance of >20% improvement in walking speed remained questionable. The analysis presented by the applicant was based on aggregated data instead of analysing the data on individual level, i.e. plotting changes in walking speed to changes in MSWS-12, SGI and CGI per patient. In the oral hearing these data were graphically presented as scatter plots. The plots showed a large variability and large overlap. There was no visual separation between placebo and fampridine.

The CHMP noted that, even if the above aspect is disregarded, a 20% improvement translates into an average improvement of 2.08 seconds to bridge a 25 feet distance, i.e. from 12.5 seconds at baseline to 10.4 sec under treatment. Such small improvement may be of relevance if one is able to walk longer distances; however, data supporting assumption that the speed can be maintained were not available. The T25FW provides no information concerning quality of walking, maintenance of this speed over longer distances or endurance of walking.

Based on the published literature the CHMP acknowledged that there is a relationship between walking speed and walking distance. However, in these published studies the range of walking speed or seconds to walk 25 feet evaluated was much larger than the range that was observed in studies MS-F202/3/4. In fact, the observed walking speed in studies MS-F202/3/4 was in the outer lowest range where this relationship collapses, i.e. the range of walking speed that does not affect the range of action.

Moreover, the difference in proportion of >20% responders, i.e. 13% (placebo) versus 31% (fampridine), shifted neither the overall mean scores in MSWS-12 nor the median scores of SGI and CGI.

Regarding the MSWS-12, the relevance of the 6 point change in the MSWS-12 (as specified in a paper by Hobart 2010) was questioned by the CHMP. The paper referred to by the applicant was an abstract of a poster presented and appeared to be based on the current fampridine studies and not on independent data. In addition, it was stated in the paper that a change of > 6.9 points is clinically relevant, while the applicant presented 4.23-6.02 points.

Regarding the SGI, the percentage of patients being satisfied by treatment was equal for subjects on placebo and fampridine, i.e. 35% in study MS-F203 and 26% in study MS-F204. If the difference in proportion of >20% responder, i.e. 13% (placebo) versus 31% (fampridine) was considered clinically significant, it would be expected that these figures would have been different.

Regarding the CGI, in study MS-F204 but not in study MS-F203 the proportion of patients with a shift in CGI category separated from placebo. However, this was inconsistent with the SGI that the clinician perceives an improvement that is not perceived at all as an improvement by the patient.

As stated above the scatter plots presenting the percentage change in walking speed versus change in MS-F20-score, CGI and SGI categories showed a large variability and large overlap and no visual separation between placebo and fampridine study arm.

In summary, the CHMP did not agree on the clinical relevance of the 20% improvement in walking speed. The effect on walking speed was not perceived as a relevant and consistent improvement by patient and physician.

The CHMP concluded that the applicant was not able to link the improvement in walking speed, or 20% improvement in walking speed to relevant improvements in walking function (MSWS-12), spasticity (Ashworth) and leg weakness (LEMMT) and SGI/CGI. The question to which extent walking speed, especially the walking speed observed in the studies, represents walking ability, walking quality and endurance, was not addressed sufficiently by the applicant.

Maintenance of effect

The CHMP noted that maintenance of effect was unclear, although at treatment cessation, a drop in walking speed was observed. However, this was over a relatively short treatment period of a maximum of 14 weeks. The result presented was a within responder analysis, that is, the average percent change

in walking speed over time, presented for responders and non-responders, whereas the responder definition was based on the walking speed. Thus, the analysis was not accepted by the CHMP.
With regard to maintenance of effect there were two additional issues of concern. Firstly, the product had minor effect on walking speed in about one third of the exposed subjects. Following review, it remained questioned whether this minor effect is clinically relevant as discussed above. Secondly, it remained unclear whether the decline in walking speed over time is due to progression of disease or lack of maintenance of effect. This would require periodical T25FW tests while off treatment. The long term efficacy assessments were insufficient in this respect.

Supportive evidence for efficacy

Supportive evidence for efficacy was scarce, i.e. a dose-response relationship, a plasma-concentration relationship, efficacy on sign/symptoms of other demyelinated areas were not observed.
Progression in multiple sclerosis is believed to be due to an increased axonal loss and damage. Apparently, the response to fampridine was not influenced by MS type, duration of disease and Expanded Disability Status Scale score. This was considered unexpected. An explanation for this could be that patients were selected based on walking function, i.e. they had sufficient amount of functional axons. Alternative explanations may be that the responder analysis (any improvement) masked larger improvements observed in e.g. RRMS as compared to SPMS or that the effect was too small for showing such differences. Further evaluation by the applicant reinforced that the effect of fampridine was similar despite differences in duration of disease, EDSS stage or MS-type. However, this was regarded not as a strength but as a weakness of arguments, i.e. the presence of such effects would have strengthened the concept of mechanism of action of fampridine.

2.5.4. Conclusions on the clinical efficacy

In summary, there is a biological rationale for evaluating the usefulness of fampridine in symptomatic treatment in multiple sclerosis. In the pivotal studies, an effect was shown on walking speed indicating pharmacological activity. The key question, i.e. the clinical relevance of the effect observed for walking speed has not been demonstrated. The applicant was not able to relate the effect on walking speed, or 20% improvement in walking speed to relevant improvements in walking function (MSWS-12), spasticity (Ashworth) and leg weakness (LEMMT) and SGI/CGI. The question to which extent walking speed, especially the walking speed as observed in the studies, represents walking ability, walking quality, endurance and range of action has not been addressed. Long term efficacy remained an issue of concern at the end of the review.

2.6. Clinical safety

Patient exposure

A total of 1952 subjects were exposed to any dose/formulation of fampridine during the clinical development program of fampridine (46 pooled and 11 non-pooled studies).
The overall safety of fampridine was evaluated in 57 clinical studies (total of 2282 subjects) with the use of different doses, strengths, duration and formulations. The studies were performed in healthy volunteers, patients with multiple sclerosis (MS), spinal cord injury (SCI), and Guillain-Barré Syndrome (GBS). 46 studies were included in an integrated pooled data analysis (2144 subjects), while the remaining 11 studies were presented as non-pooled data (138 subjects). The non-pooled studies were open label cross-over studies in non-patients performed in the early stages of development of the

product and allowed no statistical analysis due to incomplete data. This was considered an indication of GCP deficiencies in the early development of the product.

A summary of subjects exposed to fampridine (prolonged-release or other formulations) and placebo treatment in the 46 pooled studies is presented in the table 15 below. A total of 652 subjects were randomized to receive placebo and 1509 subjects received fampridine of any dose or formulation.

Table 15 Total number of MS and SCI patients exposed to fampridine

	Placebo	Clinical Pharmacology Studies (Duration of ≤1 Week)	Fampridine Any Dose/ Formulation	Uncontrolled Studies (Duration of >1 Week)	Total Fampridine Any Dose/ Formulation
n MS patients	330	94	621	693	916
n SCI patients	322	18	372	369	593

The mean dose administered to the SCI patients was higher (25 mg b.i.d.) as compared to the dose administered to MS patients (14 mg b.i.d.). The safety profile of fampridine in the SCI patient population was not different from the one observed in MS except for higher incidence related to the higher dosing of fampridine. Therefore, the current safety assessment focused on the indication applied for i.e. multiple sclerosis.

With regard to gender distribution, the demographic characteristics of the MS patient population were representative of the general MS population. The mean age was higher than that of the general MS population, since the proposed indication patients had to have walking disability. Of note, the safety database of MS subjects included only 5% patients older than 65 years. A prior history of seizure or presence of epileptiform activity on a screening EEG was an exclusion criterion for most of the clinical studies in the fampridine development program. Patients with presence of significant cardiovascular abnormalities were also excluded from the studies. The ethnic distribution of the studied population (93% Caucasians) was considered acceptable for the purpose of an EU registration.

In the summary of clinical safety the applicant focused on data from the three placebo-controlled studies MS-F202, MS-F203 and MS-F204. In addition, supporting safety data were presented from the fampridine-PR 10 mg b.i.d open-label extension studies (MS-F202 EXT, MS-F203 EXT and MS-F204 EXT), other MS studies, 12 SCI studies, and 14 non-patient studies. Exposure data with cut-off date August 2009 are presented in the table below.

Table 16

Summary of Extent of Exposure to Fampridine (Any Dose/ Any Formulation) in 46 Trials as of August 2009

Exposure	Non Patients[a]	Multiple Sclerosis	Spinal Cord Injury	Total
Number of patients with exposure				
Exposure to any dose/formulation	313	916	593	1822
Duration of exposure				
Mean (SD) duration of exposure to any dose or formulation (weeks)[b]	0.41 (0.487)	105.98 (91.883)[c]	22.40 (24.154)	-
Number of patients with exposure >6 months	0	628	191	819
Number of patients with exposure >12 months	0	577	51	628
Number of patients with exposure >24 months	0	370	11	381
Number of patients with exposure >36 months	0	312	0	312
Number of patients with exposure >48 months	0	106	0	106

a. Non patients are all patients from the healthy volunteer studies and the renal deficiency studies.
b. Patients could have been exposed to multiple doses.
c. Note that the mean duration of exposure given in this table includes data from the short-term studies as well as uncontrolled extension studies. The mean is lower than the mean of exposures in the uncontrolled extension studies in Part III of this response that follows.

Adverse events

Safety data for the dose-finding study MS-F202 and the pooled safety data for the 10 mg b.i.d. over studies MS-F202, MS-F203 and MS-F204 were presented separately by the applicant.

The overall incidence of treatment related AEs (TEAEs) and specific adverse events observed in study MS-F202 are presented in the table 17. There was an increased incidence of nervous system disorders, mainly tremor and paresthesia. A high incidence of asthenia was observed already in the 10 mg fampridine group.

This data set indicated that some AEs might be dose-related, such as infections and infestations, in particular the urinary tract infections; nervous system disorders, particularly headache, paresthesia and balance disorders; psychiatric disorders particularly insomnia; respiratory, thoracic and mediastinal disorders.

Table 17 STUDY MS-F202 TEAEs with incidence ≥ 5%

	Fampridine-PR				10 mg fampridine PR versus Placebo		
	Placebo	**10 mg b.i.d.**	**15 mg b.i.d.**	**20 mg b.i.d.**	**Diff >5%**	**Diff >10 %**	RR>2
	N=47	N=52	N=50	N=57			
Patients with at least one TEAE	80.9	86.5	94.0	91.2	*		
Patients with Serious TEAE	4.3	0.0	8.0	12.3			
Patients with TEAE Leading to withdrawal	2.1	0.0	2.0	8.8			
Patients at least with one severe TEAE	14.9	17.3	24.0	29.8	*		
Patients at least with one related TEAE	36.2	42.3	18.0	54.4	*		
System Organ Class Preferred Term							
Kind of adverse events							
Eye Disorders	**6.4**	**5.8**	**12.0**	**10.5**			
Gastrointestinal Disorders	**23.4**	**23.1**	**32.0**	**26.3**			
Constipation	2.1	1.9	4.0	5.3			
Diarrhea	4.3	5.8	6.0	1.8			
Dyspepsia	0.0	7.7	2.0	0.0	*		*
Nausea	4.3	9.6	8.0	10.5	*		***
Vomiting	0.0	1.9	6.0	1.8			
General Disorders and Administration Site Conditions	**25.5**	**48.1**	**46.0**	**42.1**	*	*	
Asthenia	2.1	19.2	18.0	5.3	*	*	***
Chest discomfort	0.0	0.0	0.0	5.3			
Difficulty in walking	0.0	5.8	0.0	7.0	*		**
Fatigue	10.6	15.4	14.0	8.8			
Oedema peripheral	6.4	7.7	12.0	5.3			
Infections and Infestations	**17.0**	**28.8**	**28.0**	**36.8**	*	*	
Gastroenteritis viral	0.0	0.0	2.0	5.3			
Upper respiratory tract infection	2.1	1.9	4.0	10.5			
Urinary tract infection	4.3	11.5	10.0	15.8	*		***
Injury. Poisoning and Procedural Complications	**14.9**	**30.8**	**30.0**	**17.5**	*	*	***
Contusion	0.0	1.9	6.0	1.8			
Fall	10.6	19.2	20.0	8.8	*		
Metabolism and Nutrition Disorders	**8.5**	**3.8**	**2.0**	**5.3**			
Decreased appetite	6.4	1.9	2.0	5.3			
Musculoskeletal and Connective Tissue Disorders	**31.9**	**26.9**	**24.0**	**35.1**			
Musculoskeletal stiffness	10.6	3.8	2.0	3.5			
Pain in extremity	6.4	1.9	2.0	12.3			
Nervous System Disorders	**44.7**	**38.5**	**50.0**	**63.2**			
Balance disorder	0.0	5.8	8.0	8.8	*		**
Coordination abnormality	0.0	0.0	0.0	5.3			
Dizziness	10.6	3.8	20.0	12.3			
Headache	8.5	11.5	14.0	14.0			

Hypoesthesia	6.4	1.9	2.0	7.0			
Multiple sclerosis	4.3	1.9	10.0	8.8			
Multiple sclerosis relapse	0.0	0.0	0.0	5.3			
Muscle spasticity	2.1	5.8	0.0	1.8			***
Paresthesia	6.4	7.7	6.0	14.0			
Tremor	0.0	1.9	0.0	8.8			**
Psychiatric Disorders	**12.8**	**17.3**	**26.0**	**21.1**			
Insomnia	8.5	9.6	20.0	12.3			
Renal and Urinary Disorders	**6.4**	**9.6**	**6.0**	**12.3**			
Pollakiuria	2.1	0.0	2.0	5.3			
Urinary incontinence	0.0	5.8	0.0	5.3	*		**
Respiratory, Thoracic and Mediastinal Disorders	**6.4**	**9.6**	**14.0**	**19.3**			
Cough	0.0	0.0	2.0	5.3			
Skin and Subcutaneous Tissue Disorders	**14.9**	**15.4**	**20.0**	**19.3**			
Vascular Disorders	**2.1**	**7.7**	**8.0**	**7.0**	*		***

* flag if difference between 10 mg and placebo ≥ 5%
* flag if difference between 10 mg and placebo ≥ 10%
*** = RR ≥2
** = RR not calculated, however % in placebo group is 0, % in 10 mg group is ≥2

The overall incidence of AEs observed during treatment with fampridine 10 mg b.i.d. in studies MS-F202/203/204 is presented in the table 18. Overall, the incidence of TEAEs was higher in the fampridine-PR than in the placebo group. AEs occurring during the treatment with fampridine and which were twice or more frequently reported in the fampridine groups were: vertigo; gastrointestinal disorders – abdominal pain, dyspepsia, nausea and vomiting; infections and infestations – nasopharyngitis, pneumonia, viral infections; back pain; sensory disturbances; psychiatric disorders – anxiety and insomnia; pharyngolaryngeal pain; polakiuria; pruritus.

Table 18 Summary of AEs occurring during treatment with incidence ≥ 1% in placebo controlled studies 202/203/204 (truncated)

	Placebo	Fampridine PR 10 mg b.i.d.	Difference Fampridine-PR vs Placebo			
	%	%	%			
	N = 238	N = 400		>5	>10	RR>2
Patients with any TEAE during active treatment	71	81.8	10.7	*	*	
Patients with Serious TEAE	1.7	4.7				*
Patients with TEAE Leading to withdrawal	0.4	1.8				*
Patients at least with one severe TEAE	2.1	2.8				
Patients at least with one severe TEAE	21.4	27.8		*		
System Organ Class Preferred Term						
Kind of adverse events						
Blood and Lymphatic System Disorders	1.3	0.8	-0.5			
Cardiac Disorders	1.3	2.5	1.2			
Ear and Labyrinth Disorders	1.3	1.8	0.5			
Vertigo	0.4	1	0.6			***
Eye Disorders	4.6	3	-1.6			

Vision blurred	1.7	0.3	-1.4			
Gastrointestinal Disorders	16	18.5	2.5			
Abdominal pain	0.4	1.3	0.9			***
Constipation	2.1	3.3	1.2			
Dyspepsia	0.8	2	1.2			***
Nausea	2.5	7	4.5			***
Vomiting	0.4	1.8	1.4			***
General Disorders and Administration Site Conditions	18.1	19.3	1.2			
Asthenia	3.8	6.8	3			
Difficulty in walking	1.3	1.5	0.2			
Fatigue	4.6	4.8	0.2			
Gait disturbance	1.3	0.8	-0.5			
Pain	0.8	1.3	0.5			
Pyrexia	0.8	1.5	0.7			
Infections and Infestations	24.8	31	6.2	*		
Gastroenteritis viral	1.7	1.5	-0.2			
Influenza	0	1.5	1.5			
Nasopharyngitis	1.7	3.5	1.8			***
Pneumonia	0.4	1	0.6			***
Upper respiratory tract infection	6.3	5	-1.3			
Urinary tract infection	8.4	12	3.6			
Viral infection	0.4	1.5	1.1			***
Injury.Poisoning and Procedural Complications	18.9	18.8	-0.1			
Contusion	3.4	3	-0.4			
Fall	15.1	12.5	-2.6			
Investigations	9.7	10.5	0.8			
Metabolism and Nutritional Disorders	2.9	3	0.1			
Musculoskeletal and Connective Tissue Disorders	18.9	23	4.1			
Arthralgia	5.9	3.3	-2.6			
Back pain	2.1	5	2.9			***
Muscle spasms	2.5	3.3	0.8			
Musculoskeletal stiffness	3.4	2.5	-0.9			
Myalgia	0.8	1	0.2			
Neck pain	0.8	1	0.2			
Pain in extremity	5	3.5	-1.5			
Shoulder pain	1.3	1	-0.3			
Nervous System Disorders	21.4	28.8	7.4	*		
Balance disorder	1.3	4.8	3.5			***
Dizziness	4.2	7.3	3.1			
Headache	3.8	7	3.2			
Hypoesthesia	3.4	2.3	-1.1			
Memory impairment	1.3	0	-1.3			
Multiple sclerosis relapse	3.4	4	0.6			
Muscle spasticity	0.8	1	0.2			
Paresthesia	2.5	4	1.5			
Sensory disturbance	0.4	1	0.6			***
Tremor	0	1	1			
Psychiatric Disorders	5.5	12.3	6.8	*		***
Anxiety	0.4	1.5	1.1			***
Depression	0.8	1	0.2			

Insomnia	3.8	8.8	5	*		***
Renal and Urinary Disorders	4.6	5.5	0.9			
Micturition urgency	1.7	0.8	-0.9			
Pollakiuria	0.8	1.8	1			***
Reproductive System and Breast Disorders	1.3	0.3	-1			
Respiratory.Thoracic and Mediastinal Disorders	8	7.8	-0.2			
Pharyngolaryngeal pain	0.8	2	1.2			***
Skin and Subcutaneous Tissue Disorders	8	7.8	-0.2			
Pruritus	0.4	1.5	1.1			***
Vascular Disorders	2.1	2.8	0.7			

* flag if difference between 10 mg and placebo ≥ 5%
* flag if difference between 10 mg and placebo ≥ 10%
*** = RR ≥ 2
** = RR not calculated. however % in placebo group is 0. % in 10 mg group is ≥ 2

Severe TEAEs

Overall, the incidence of severe TEAEs increased with increasing fampridine-PR doses (17.3%, 24.0% and 29.58% respectively in 10, 15, and 20 mg) versus 14.9% in the placebo group. Outstanding severe AEs in the 10 mg group were diarrhoea (3.8%), asthenia (5.8%), fatigue (5.8%), UIT (1.9%) and falls/contusions (1.9%). Nervous system disorders showed a clear trend towards an increase with dose, with confusion, balance disorder, confused state, convulsion, coordination abnormal, headache, hypoesthesia, paresthesia, migraine, MS, transient ischemic attack particularly observed in the 20 mg dose group. This general trend that incidence of TEAEs increased with dose raised concerns particularly with respect to intentional or incidental overdose.

In the pooled data (studies MS-F202/203/204) for exposure to 10 mg there were more events of anxiety (0.3%), asthenia (1.8%), balance disorder (0.5%), dizziness (0.3%), headache (0.8%) and UTI (1.0%) in the fampridine arm as compared to placebo. In this dataset, the incidence of paresthesia was similar in both groups – 0.4% in placebo vs 0.3% in fampridine 10 mg b.i.d.

Treatment related AES

Overall, in study MS-F202 the incidence of related TEAEs was higher in the 10 mg b.i.d treatment group (42.3%) as compared to placebo (36.2%) and increased with increasing fampridine-PR doses (48.0% and 54.4% at 15 mg b.i.d and 20 mg b.i.d, respectively).

In the pooled data (studies 202/203/204) for 10 mg b.i.d., the related TEAEs in the placebo group were 21.4% vs 27.8% in the fampridine group. Adverse events which occurred more than twice more frequently in the fampridine group vs placebo were nausea (3.3% vs 1.3%), asthenia (2.8% vs 1.3%), balance disorder (2.3% vs 0.4%), headache (2.8% vs 0.8%), and paresthesia (2.8% vs 0.8%).

Serious adverse event/deaths/other significant events

The overall incidence of serious TEAEs in study MS-F202 showed a dose-response relationship with reported incidences of 4.3% (placebo), 0.0% (10 mg b.i.d), 8.0% (15 mg b.i.d) and 12.3% (20 mg b.i.d). The majority of reported serious TEAEs were in the Nervous System Disorders SOC and all showed dose-dependency (0%, 4.0%, 10.5% in the 10, 15 and 20 mg groups respectively versus 0% in placebo).

In studies MS-F202/203/204, the overall incidence of serious TEAEs was higher in the fampridine-PR treatment group (5.5%) than in the placebo treatment group (2.1%). More serious TEAEs in the fampridine-PR treatment group compared to placebo were registered in the Infections and Infestations SOC (2.3% vs 0.8%), e.g. bacterial pyelonephritis, influenza, pneumonia, sepsis, UTI, viral and wound

infection; Nervous System Disorders SOC and Injury, Poisoning and Procedural Complications SOC, while no clear or significant differences were observed in the remaining SOCs.

Cardiac disorders were slightly higher in the fampridine-PR group (3.0%) compared to the placebo group (1.3%). There was one case with chest pain (0.3%) and one with coronary artery disease (0.3%) in the fampridine group; in the placebo, one myocardial infarction (0.4%) was reported. Bundle branch block, tachycardia, and palpitations were all reported slightly more often with fampridine PR compared to placebo (data from 10 mg b.i.d. studies MS-F202/203/204).

There were no suicide ideations or events in the short term studies and there were four in the extension studies: two completed suicides, one attempt and one ideation. In view of the generally increased risk of suicidal ideations and completed suicides in the MS patient population, no conclusion could be drawn whether the treatment with fampridine 10 mg b.i.d. is associated with increased incidence of suicidal ideations and events.

Deaths

During the clinical programme a total of eight deaths were reported, all occurring during the open-label extension studies (MS-F202 EXT, MS-F203 EXT, and MS-F204 EXT). These included seven patients receiving fampridine-PR at 10 mg b.i.d and one patient receiving a dose of 15 mg b.i.d (before dose titration to 10 mg b.i.d). One death occurred five weeks after the last dose of study medication (patient taking part in the study MS-F203).

The 8 cases reported during the extension studies occurred in 4 male patients and 4 female patients. Causes of death included two suicides and one accidental oxycodone toxicity, two cases of intracranial haemorrhage, one in a patient with brain aneurysm, one case of ruptured aorta, one case of coronary heart disease and one case with unknown cause of death.

All 8 cases were considered unrelated to the fampridine treatment by the investigator. However, at least in two cases (unknown cause of death and coronary heart disease) the contribution of fampridine to cardiac events could not be excluded. In addition, contribution of fampridine to the depressive mood followed by suicide could not be excluded in the two reported cases.

Safety data from the long term extension MS studies MS-F202EXT, MS-F203EXT, MS-F204EXT

In the open-label MS studies (MS-F202 EXT, MS-F203 EXT, and MS-F204 EXT), 660 patients began or continued treatment with fampridine-PR; 464 of 660 patients remained on treatment at the time of data cut-off (i.e. 30 November 2008). From March 2005, all patients were being treated with the 10 mg b.i.d. fampridine-PR, while prior to that date, some of the patients received 15 mg b.i.d (175 patients) or 20 mg b.i.d (10 patients).

TEAEs had the highest incidence in the first six months of treatment (83.0%) and then levelled off between 6 and 54 months of treatment (range: 40.3% to 67.3%). The incidence of serious TEAEs was in the range of 1.6% to 9.6%. The incidence of severe TEAEs and TEAEs leading to withdrawal was also highest during the first six months and lower in the subsequent treatment periods.

Events of nausea, asthenia, back pain, headache, dizziness and insomnia occurred at their highest incidence during the first six months. In comparison to incidences in the first six months of treatment (range: 5.3% to 10.9%), these TEAEs were reported at very low levels after 6 months (range: 0.9 to 5.7%), with no further reports after 54 months of treatment.

The higher incidence of TEAEs in the first 6 months and its decline later could be due to several reasons: discontinuation of patients with AEs in the first months, patients not reporting AEs repeatedly as they get used to the AE, and AEs disappearing.

The TEAEs of urinary tract infection remained relatively consistent irrespective of the duration of treatment, with exceptions for period 30-36 months and 54-60 months, with incidences of 5.2% and 1.8%, respectively.

Thirty-four cases of serious TEAEs were reported, which included massive pulmonary saddle embolus, active tuberculosis, splenic rupture, septic shock, acute renal failure, overdose (accidental) and suicide.

Cardiovascular disorders were seen in 2% of the patients in the first 6 months, then this percentage was lower with another peak of 2.1% for >24-30 months and 2.9% for >42-48 months. Since the number of subjects is decreasing with time, these percentages were not interpreted as absolute measures of incidence, but as a signal that cardiac events are persistently observed adverse events in patients on long term treatment with fampridine.

There were no major differences in the clinically significant ECG findings between placebo and fampridine treated patients, although it was noted that not all patients had an ECG assessment. Pulse rate was measured in few patients; therefore, no conclusions could be drawn for this parameter. Fluctuations in systolic and diastolic blood pressure were observed in about one third of the patients, with similar proportions in the placebo and fampridine group.

Peripheral oedema was observed also in patients treated for longer time (i.e. 4.3% in >36-48 months). No temporal relation between oedema and heart failure, renal impairment or electrolyte imbalance was found.

In study MS-F202 EXT, two patients receiving > 10 mg fampridine b.i.d. and one patient on 10 mg b.i.d. had a seizure. In Study MS-F203 EXT four patients experienced a seizure and there were no cases in MS-F204 EXT. Of the five patients (one male and four females) with any type of seizure while treated with fampridine-PR 10 mg b.i.d, four experienced generalized seizures and one patient a partial complex seizure. The seizures could be attributed to the use of tolterodine or to the concomitant use of tolterodine with fampridine in one patient, since tolterodine is known to block K^+ channels and increase the duration of the action potential.

Furthermore, gastrointestinal disorders such as constipation, diarrhoea and nausea, as well as fatigue and asthenia were relatively prominent in the first six months.

Infections and infestations were observed with high incidence (mainly upper respiratory tract infections and particularly urinary tract infections). In the long term open label studies it was difficult to distinguish the proportion of AEs related to the treatment and the AEs related to the disease itself. In any case the high incidence of infections was considered to represent an additional risk factor for the MS patient population and was reflected in the final benefit/risk balance.

Injuries and particularly falls were relatively frequent, suggesting that these events may be related to the AEs in the nervous system such as dizziness, balance disorder and abnormal sensory feedback, which were frequent as well. Other AEs related to the nervous system were paraesthesia, tremor, hypoesthesia and headache. There was a decrease in the incidence of these AEs with time. Given the mechanism of action of fampridine, this was considered due to the fact that patients got used to these AEs and did not report them any more rather than due to a real decrease in these AEs with time.

Insomnia appeared to be frequent in the first six months of treatment, but was less reported later.

Laboratory findings

The percentage of MS patients with clinically significant haematology values was ≤13.6%. Changes in haematology parameters were consistently observed both in short term and long term in fampridine patients: low haematocrit (6.6%), low haemoglobin (4.0%), low lymphocytes (5.2%) and low white blood cells (3.4%). No data on erythrocyte counts were available.

The comparison of low white cell blood counts and lymphocytopenia between fampridine (any dose) and placebo only from the controlled studies indicated a greater % of cases in the fampridine group

(4.5% vs 2.2% lymphopenia for fampridine vs placebo). On the basis of the presented data it was not possible to exclude the effect of fampridine on haematopoiesis.
A slightly higher incidence of elevated levels of bilirubin was observed in the fampridine treated patients. The laboratory results for these subjects did not show concurrently elevated levels of transaminases. Thus, the data did not indicate liver toxicity in subjects exposed to fampridine 10 mg b.i.d. in the MS studies.

Safety in special populations

Renally impaired patients

A comparison of the incidence of AEs in fampridine treated patients with and without renal impairment, indicated an increased frequency of AEs in the group with abnormal renal function: ear and labyrinth disorders (1.3% vs 3.5%); eye disorders (3.5% vs 8.1%); infections and infestations (33.1% vs 43%); nervous system disorders (29.6% vs 43%); psychiatric disorders (11.8% vs 18.6%) and renal and urinary disorders (6.1% vs 9.3%).
This is an indication that fampridine, being a drug with narrow therapeutic window, cannot be applied safely in patients with renal impairment. The proposed dose of 10 mg b.i.d. does not give room for dose adjustment if necessary.

Paediatric population

Fampridine was granted a full product-specific waiver.

Elderly

The number of elderly patients included in the short term studies was rather low – 11 in the placebo and 18 in the fampridine group. Since fampridine is eliminated from the body via the kidneys, due to the physiological reduction in renal function with age, elderly patients might be exposed effectively to a much higher dose of fampridine and therefore be exposed to more risks. Moreover, the pharmacodynamics in the elderly might be different due to different sensitivity to CNS adverse events.
Due to the small number of subjects, no firm conclusions could be drawn whether AEs increase with age. However in the 10 mg fampridine subgroup of patients ≥65 years, the incidence of AEs was rather high (78.3%).

Concomitant immunomodulating therapy

No immunological events have been discussed by the applicant. A comparison of patients receiving concomitant immunomodulating therapy with patients without showed that more AEs were observed in the group without immunomodulating treatment and those events seemed to be related to fampridine, i.e. in the domains of CNS and psychiatry. In the subsequent subgroup analysis, concomitant therapy with immunomodulators did not seem to increase the risk of adverse events in the categories Blood and lymphatic system disorders and Infections and infestations.
However, both fampridine groups (with and without concomitant immunomodulatory therapy) showed higher percentage of AEs than placebo (with the concomitant treatment). Therefore, there is an indication that fampridine itself might have an effect on the immune system leading to leucopenia and infections.

Safety related to drug-drug interactions and other interactions

Drug interactions with other commonly used drugs in MS (interferon beta and baclofen) were studied without observing negative impact on the AE profile or frequency of AE reports. During the fampridine

PR clinical programme, concomitant use of routinely prescribed MS drugs was allowed. The most commonly used concomitant medications, by therapeutic class, in fampridine-treated patients in placebo-controlled studies MS-F202/203/204 were nervous system (86.2%), musculoskeletal system (78.3%), alimentary tract and metabolism (71.2%), antineoplastic and immunomodulating agents (68.6%), and genitourinary system and sex hormones (58.2%). There were no consistent differences in AEs reported by patients taking concomitant medications versus not taking concomitant medications.
Given the mechanism of action of fampridine, the risk of fampridine interactions with anti-epileptic and anti-arrhythmic agents could not be excluded.

Discontinuation due to adverse events

In the dose finding study MS-F202 a total of seven patients (one patient in the placebo group and six patients in the fampridine-PR treatment groups) withdrew from the study due to AEs. The overall incidence was highest in patients receiving fampridine-PR 20 mg b.i.d. (8.8% vs 2.1% in the placebo). The majority of TEAEs leading to withdrawal were in the Nervous System Disorders SOC (balance disorder 1.8%, complex partial seizures and convulsions – 1.8% each), abnormal coordination 3.5%, headache 3.5%, paresthesia 1.8%).
In the pooled data for 10 mg b.i.d. from studies MS-F202/203/204 there were 2.8% of patients withdrawing due to AEs, versus 2.1% in the placebo arm. The most prominent AEs leading to withdrawal were infections (pneumonia 0.3%, sepsis 0.3%), CNS disorders (balance disorder 0.5%, dizziness 0.5%, headache 0.5%) and psychiatric disorders (anxiety 0.3%, confusional state 0.3%).

Post-marketing experience

During the oral explanation post-marketing safety data (USA) with respect to seizure risk were submitted. The data were considered insufficient for an assessment of seizure risk. No other additional post-marketing safety data were submitted.

2.6.1. Discussion on clinical safety

Exposure

The overall evaluation of the safety of exposure to fampridine is based on the data presented from the application of the product in 57 clinical studies, where different doses, strengths, duration and formulations have been used. These studies have been performed in healthy volunteers, in patients with multiple sclerosis (MS), spinal cord injury (SCI), and Guillain-Barré Syndrome (GBS).
The main source of safety information are three placebo-controlled studies MS-F202, MS-F203 and MS-F204 performed in MS patients and with the use of the PR formulation. This was completed with some preliminary data from the ongoing extension studies and from studies in SCI patients.
The majority of studies have been included in an integrated pooled data analysis, so the missing statistical analysis of the remaining 11 studies was not considered as critical for obtaining the overall picture about the safety profile of the drug.

Mechanism of action

Given the mechanism of action, i.e. blocking K^+ channels, fampridine should be considered a narrow therapeutic index drug, unless proven otherwise. Positive arguments for a narrow therapeutic index were AEs and CNS-AEs related to higher C_{max} and AUC of fampridine as observed in the PK studies, which was a reason for developing the prolonged-release formulation. In addition, the main elimination route of fampridine was renal excretion and active secretion. An increased frequency of AEs was

observed in the patients with abnormal renal function as compared to normal renal function. The applicant did not challenge that fampridine should not be considered as a narrow therapeutic index drug.

Special populations

Related to the mechanism of action of fampridine effects on the cardiovascular system were predicted. The incidence observed in the short term studies did not confirm these expectations. However, since patients with cardiovascular disorders were excluded from the studies, the safety data in the dossier were not considered to reflect the real risk for the total patient population. In response to the request for additional information, the applicant stated that no increase in cardiovascular events was observed in the unselected patient population after the marketing in the USA.

Furthermore, the applicant stated that there was no temporal effect of exposure to fampridine, since in the exposure period between day 1 and 98 in the controlled studies, there were only 4 cardiac events not related to the drug. The definition of serious cardiovascular events as proposed by the applicant included only cardiomyopathy, coronary heart disease and ventricular hypertrophy, which logically would not be considered as related to treatment by the investigator. The applicant has not provided arguments why arrhythmias and conduct disorders were not considered to be serious cardiac events, while it is well known that such AEs could lead to a fatal outcome.

Further, additional data from the QTc study provided by the applicant did not make it clear whether the study performed was sensitive to evaluate QTc changes as the response in the moxifloxacine arm was unexpectedly low.

Despite the exclusion of subjects with cardiac symptoms from the short term placebo controlled studies, it appeared that about 40% of the subjects included had cardiac symptoms reported at baseline. These data were not considered sufficient for confirming or rejecting the concerns about cardiac safety. The range of seriousness of this co-morbid condition remained unclear. In principle, patients with major cardiovascular diseases have been excluded from the trials and for these, an altered sensitivity of K^+ channels cannot be excluded.

The proposal of the applicant to monitor cardiac safety in an observational study was not considered sufficient. From the description provided, it was not clear whether this study would be suitable to study cardiovascular adverse events, especially those related to potential QT prolongation, QT shortening and conduction disorders.

The proposal of the applicant to register cardiac events in the post marketing phase was not considered sufficient, either. In the dossier, patients with cardiovascular disease were excluded from the studies, therefore the true magnitude of the cardiovascular risk could not be estimated from the short term safety data and the long term data were insufficient.

Another concern was related to the elderly patients with MS. Very few elderly patients were included in the studies, so the data available were insufficient to judge the safety in this population. Two aspects were considered in this context. Firstly, the physiologically decreased renal function in the elderly means that these patients might be exposed to higher C_{max} and AUC, leading to increased risk of AEs. Secondly, in general the elderly are more sensitive to CNS adverse events. It is not known whether the pharmacodynamics of fampridine is different in the elderly due to different quantitative and qualitative distribution or response of the K^+ channels in the CNS and elsewhere. The lack of alternative dose regimens was considered a deficiency of the dossier.

Specific adverse events

Based on the mechanism of action, an increased risk of seizures is expected. In general, the seizure risk increased with dose and was not much higher than placebo in the 10 mg b.i.d. dosing of fampridine. However, the patients included in the studies were not completely representative of the MS patient population, since subjects with history of seizures or increased epileptiform activity on a screening EEG were excluded. Due to the disease itself, MS patients have an increased risk of seizures

and therefore, the safety of fampridine in seizure susceptible subjects might be different. In addition, because of the relatively narrow therapeutic window of fampridine and almost complete renal clearance of the product, the risk of seizures might also be increased in patients taking the recommended dose of 10 mg b.i.d., but who present with mild renal impairment due to the disease or in the elderly, where renal function is physiologically decreased.

Further, an increased frequency of UTI, respiratory tract infections and constipation was observed in the fampridine arm. This raised several questions, in particular with respect to the effect of fampridine on the motility of the urogenital, respiratory and gastrointestinal tract and its effect on haematopoiesis and immunological response.

The applicant did not provide sufficient evidence as to whether fampridine could have an influence on the motility of the urogenital, respiratory and gastrointestinal tract. There seemed to be dose-dependent increase in constipation, dyspnoea and UTI. The applicant claimed that the UTI cases were not real infections, because they were not confirmed by cultures. Since very few cases of UTI were tested with urine cultures, this statement was not supported with evidence. Moreover, if the UTI symptoms were due to the direct and indirect neurological effect of fampridine on bladder motility, as stated by the applicant, this would suggest that fampridine does have an effect on motility. In conclusion, the question about the effect of fampridine on motility was not addressed sufficiently.

A compromised immune response may form an alternative explanation for the differences in infection rates. The applicant commented on publications, where some authors suggested that fampridine may modulate the immune response and inhibit T-cell proliferation by blocking 4-AP-sensitive Kv channels expressed in lymphocytes. In animal studies, fampridine treatment did not induce experimental allergic encephalitis in rats and therefore it was concluded by the applicant that the clinical effects of fampridine on MS patients at therapeutic doses are not mediated through effects on the immune system and that fampridine is unlikely to increase the risk of infection through effects on T-cells. The applicant's responses were considered incomplete and an effect of fampridine on haematopoiesis could not be excluded. Hence, it seemed that fampridine as monotherapy or in combination with immunomodulators was related to increase in infections of various types. Moreover, whether the UTI symptoms are based on an infection or not, these are considered severe inconvenient events.

There was an indication of overstimulation of the sensory nerves, expressed in increase in events of dizziness, balance disorder, paraesthesia, pain, suggesting an abnormal sensory feedback which might also be the reason for the increased incidence of falls and injuries. For better interpretation of these safety results, the applicant was asked to provide a separate analysis of AEs related to the sensory nerves. This additional analysis did not show relation between coordination disorders and falls/injuries. However, the approach of the applicant to combine all AEs suggesting stimulation of the sensory nerves and compare the combined percentages between fampridine 10 mg b.i.d. and placebo arms was not appropriate and therefore the applicant's conclusions were not considered convincing. In any case, the exposure to 10 mg BID fampridine was related to increased incidence of nervous system AEs; in particular pain, paraesthesia and dysaesthesia, abnormal coordination with balance disturbance, and sensory abnormalities were observed more frequently. The applicant argued that most of these events were transient i.e. lasting less than 8 weeks. The events were apparently partially transient, but it is not clear whether patients may get used to them. In a substantial proportion of patients these events persisted. Moreover, considering the efficacy, the CHMP questioned whether the increased percentage of events, even if transient e.g. persisting for 0-4 weeks or 4-8 weeks, is acceptable. These aspects were taken into consideration in the overall benefit/ risk assessment.

There were more reports of multiple sclerosis relapse in the fampridine treated patients as compared to placebo. The CHMP was of the opinion that some of these exacerbations might have been misclassified, meaning that symptoms of over-stimulation of the sensory nerves (pain, paraesthesias, etc.) could have been defined as exacerbation of MS, while in fact these were adverse events related

to the treatment with fampridine. In addition, the incidence of MS in the long term open label study was compared to the background rates, but such historical comparisons have several deficiencies. Overall, the applicant did not provide sufficient evidence to conclude on whether fampridine does or does not worsen MS related symptoms. In light of uncertainties on treatment duration, the recurrence of MS symptoms remained an important issue in the benefit/risk assessment.

A higher incidence of anxiety, depressive mood and insomnia was observed in the fampridine treated patients. While for the depressive events and the suicide events it is rather difficult to judge if these were related to the fampridine treatment or to the MS itself, the signals of increased anxiety and insomnia were easier to distinguish. This might present a serious problem in the long run, as the drug was intended for a chronic administration.

Long-term safety

The data regarding long term safety were considered insufficient by the CHMP. Although the statement that no serious adverse events were reported appeared reassuring, lack of details was pointed out by the CHMP. The withdrawal rate of 35 % (lost to follow-up, non-compliance, consent withdrawal etc.) was considered substantial and was indicative of underlying motives that suggest the benefit/risk is not persisting.

2.6.2. Conclusions on the clinical safety

The safety profile of fampridine poses some serious concerns related mainly to the fact that the drug appears to have a narrow therapeutic window and CNS AEs increase with relatively small increase in exposure. In the dossier the applicant proposed only one dose regimen, which might prove unfavourable for a major part of the MS patient population, such as renally impaired patients, the elderly, or in cases of increased dose intake. Moreover, the safe use in patients at risk of seizures including epileptic patients and with cardiac co-morbidity remains unknown, as these patients were excluded from the studies. The magnitude of the cardiovascular risk could not be estimated. In addition, the magnitude of the problem with UTI and other infections remains unknown, since most patients with infections (UTI and other) were treated symptomatically, but no bacteriological tests were performed to confirm or reject the diagnosis.

Major safety concerns are related to the increased risk of seizures, infections (particularly UTIs), anxiety and insomnia, and of symptoms of abnormal sensory feedback interfering with walking ability. Long-term safety data did not allow an assessment of long term safety. In the elderly population, generally sensitive to CNS adverse events, the safety remains unclear.

2.7. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The MAA submitted a risk management plan. The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

2.8. Benefit-Risk Balance

Benefits

- Beneficial effects

In the clinical studies MS-F202/203/204, a statistically significant difference in responders was observed. The results of the three studies were similar, overall the responder rate was 8.9% for the placebo group versus 37.2% for the fampridine group (difference 28.4%, CI95% 22.1%; 34.2%). The responder definition was based on the walking speed assessed in the Timed 25 feet walking test (T25FW), i.e. the time in seconds it takes to walk 25 feet. A responder was defined as a patient with a faster walking speed for at least three visits during the double-blind treatment period as compared to the maximum speed for any of the off-treatment visits. Overall efficacy in terms of responders appeared homogenous across subgroups identified. Also the difference in proportion of subjects with a 20% improvement in walking speed i.e. 13% versus 31% for placebo and fampridine was statistically significant.

In the main studies MS-F203/204, the differences in mean changes from baseline in walking questionnaire, muscle strength and spasticity were either statistically significant or showed a trend in favour of fampridine.

The pharmacokinetics of fampridine is linear; fampridine is absorbed in a dose proportional manner and there is no accumulation after repeated doses. Moreover, it is unbound to plasma proteins and almost completely eliminated via urinary excretion. The major fraction recovered was contributed to the parent drug.

- Uncertainty in the knowledge about the beneficial effects

The main uncertainties concern the value of the Timed 25 Foot Walk test and value of the responder definition derived from it, as no experience exists in the evaluation of treatments for symptomatic treatment in multiple sclerosis so far. Further, the clinical meaningfulness of the observed statistically significant differences has not been established.

The Timed 25 feet walking test (T25FW) in essence measures the speed of walking. The T25FW is considered more a pharmacodynamic endpoint rather than a clinically relevant outcome. The submitted studies have demonstrated the proof of concept, i.e. that fampridine has a small, but statistically significant effect on the speed of walking over a short distance. The significance across broader aspects of walking has not been shown, which makes the test unacceptable as a clinically relevant outcome measure. The use of walking speed as a surrogate of walking ability is uncertain.

The clinical relevance of the effect observed is highly uncertain. Any improvement in the speed of walking over a short distance is hard to interpret in terms of clinical relevance. As stated above more important is whether speed can be maintained for a while, increasing the range of action. For the secondary endpoints, the mean changes from baseline in MSWS-12, LEMMT and Ashworth scores within the study groups were small, let alone the differences in change from baseline between the study groups, although statistical significance or a trend to statistical significance was observed. For the Subject Global Impression and Clinician Global Impression there is no or almost no shift in median indicating that the improvement might not be perceived as substantial. The majority of subjects perceived no satisfaction or improvement let alone a substantial improvement. This confirms the picture that emerges from the scatter plots presented by the applicant at the oral hearing. The change in walking speed versus the MSWS-12 score, CGI and SGI categories showed a large overlap. Visually there was no separation between the placebo and fampridine study arm.

In agreement with this, the Scientific Advisory Group (SAG) concluded that a significant effect across the broader aspects of walking has not been shown, which makes the test unacceptable as a clinically relevant outcome measure. Walking speed does not provide information with regard to the quality of walking. There are several different aspects of walking that can be affected by MS, including coordination, balance and stamina. Outcome measures that address these aspects specifically have not been presented. It was noted that patients consider endurance as more important than the speed to bridge a short distance, as this determines the range of action.

Based on the literature submitted the range of walking speeds observed in the fampridine studies does not affect the range of action.

The applicant has argued that a 20% improvement in walking speed, as measured by the T25FW, results in clinically relevant changes in the clinical outcome. This was questioned by the CHMP, as the difference in proportion of a 20% responder, i.e. 13% (placebo) versus 31% (fampridine) did neither shift the overall mean scores in MSWS-12 nor the median scores of SGI and CGI. Regarding the MSWS-12, the validation of the 6 point change in the MSWS-12 as defined was questioned as the data were limited (based on a poster) and not based on independent studies. Importantly, the percentage of patients being satisfied by treatment was equal for subjects on placebo and fampridine i.e. 35% in study MS-F203 and 26% in study MS-F204. If the difference in proportion of 20% responder, i.e. 13% (placebo) versus 31% (fampridine) was considered clinically significant, it would be expected that these figures would be different. Regarding the CGI, in study MS-F204 but not in study MS-F203, the proportion of patients with a shift in CGI category separated from placebo. However, this was inconsistent with the SGI that the clinician perceives an improvement that is not perceived at all as an improvement by the patient (SGI).

The applicant suggested identifying responders and continuing treatment only in responders and proposed a treatment algorithm in the SmPC. However, no conclusion could be drawn with respect to the clinical relevance of the 20% improvement in walking speed as stated above. Although responder definitions are inherently arbitrary, it has not been shown that improvement in responders, either defined according to the responder definition in the clinical trials or defined as 20% improvement, is of general benefit for this group of MS patients. Hence, the suggestion by the applicant to resolve the issue in the SmPC was not considered acceptable.

Supportive evidence for efficacy was scarce, e.g. PD studies (electrophysiological studies), a dose-response relationship, a plasma-concentration relationship, efficacy on sign/symptoms of other demyelinated areas, was not observed. Further, the effect of fampridine was similar despite large differences in duration of disease, EDSS stage or MS-type.

Maintenance of effect remains unclear. The observed decline in effect may be attributed to disease progression or lack of effect or both. This has not been evaluated appropriately by the applicant.

Hence, it remains uncertain to which extent improvement in walking speed, and particularly the walking speed as observed in the studies, is indeed a benefit for the patient with respect to walking ability, walking quality, endurance and increase in range of action.

Risks

- Unfavourable effects

Fampridine is a selective potassium channel blocker, which acts on subtypes of K channels expressed in excitable cells such as neurons, cardiac and skeletal muscle, smooth muscle and lymphocytes. Hence, effects of fampridine in these tissues could be expected and this has been addressed correspondingly in the safety questions posed to the applicant. Given this mechanism of action and the PK data so far, fampridine should be considered as a narrow therapeutic index drug, unless proven otherwise.

In the PK-PD models AEs and CNS-AEs were related to higher C_{max} and AUC of fampridine. This was confirmed in the clinical studies, i.e. an increased frequency of AEs was observed in the patients with abnormal renal function as compared to normal renal function. Hence, the safe use in patients with mild renal impairment was questioned by the CHMP. This highlights drawback of having just one dose strength of 10 mg, which limits dosing flexibility and poses problems in patients with renal impairment including the elderly. The MAH could not justify a safe dose in the elderly.

Identified risks concern possible coordination abnormalities, anxiety, depressive mood, insomnia and an increased risk for infections.

A prominent signal is the higher incidence of dizziness, pain of various types, paraesthesia, balance, coordination disorders and falls, which all indicate a possible over-stimulation of the afferent nerve tracts, i.e. an abnormal sensory feedback affecting motor coordination. Related to this is the excess of MS symptoms and MS relapses in the fampridine group which might include misclassifications of symptoms of over-stimulation of the sensory fibres. Although most of these events were apparently transient, as patients may get used to them, in a substantial proportion of patients these events persisted. Moreover, considering the efficacy, it was questioned whether the excess in events, even if transient, i.e. persisting 0-8 weeks, is acceptable.

A higher incidence of anxiety, depressive mood and insomnia was observed in the fampridine treated patients. While for the depressive events (and also the suicide events) it is rather difficult to judge if these were related to the fampridine treatment or to the MS itself, the signals of increased anxiety and insomnia were easier to distinguish. For a drug which would be applied chronically, this might present a serious problem in the long run.

Further an increased frequency of UTI, respiratory tract infections and constipation was observed in the fampridine arm. This raises the question whether fampridine does affect the motility of the urogenital, respiratory and gastrointestinal tract. Since there are some changes in the blood counts indicative for suppression of haematopoiesis, a compromised immune response may form an alternative explanation for the differences in infection rates.

- Uncertainty in the knowledge about the unfavourable effects

Pharmacodynamic interaction of fampridine with anti-epileptic and anti-arrhythmic agents is expected, based on the mechanism of action of fampridine. This was not investigated sufficiently and therefore remained a point of concern.

Cardiovascularly compromised patients were excluded from the trials. Given the mechanism of action, the safety in cardiovascularly compromised patients remains to be established. As a matter of fact, even in the absence of these patients in the MS population studied, these events have already been observed with higher incidence in the fampridine group than in the placebo group. Hence, the true

magnitude of the cardiovascular risk could not be estimated from the short term safety data, and long term data so far are insufficient. The benefit/risk in this population is therefore uncertain.

Another uncertainty is related to the benefit/risk in the elderly multiple sclerosis patients, since very few elderly patients were included in the studies. Adverse events may be a specific issue in the elderly, as the product is eliminated renally, but also because this population might be more sensitive to CNS effects.

Long term safety data are insufficient for a conclusive assessment of long term safety. 35% drop-out rates suggest that the benefit/risk balance changes over time.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

A statistically significant effect in terms of a consistent improvement in walking speed in the short-term studies is considered established. However, the value of the T25FW and the responder definition derived from it is questioned. The clinical relevance of the statistically significant differences is highly uncertain. The applicant was not able to relate the observed changes in walking speed to clinical meaningfulness. In particular, neither patients nor physicians perceived the change in walking speed as an improvement, whereas overstimulation may impair walking quality and the range of action. Supportive evidence of efficacy is limited and whether the decline in effect under long term treatment is due to disease progression or lack of effect or both remained unclear. Hence, maintenance of efficacy is unclear.

Identified risks include coordination abnormalities, but also anxiety, pain, insomnia and an increased risk of infections. There are uncertainties concerning the long term safety, safe use in the elderly, cardiovascularly compromised patients, patients at risk of seizures including epileptic patients and patients with mild renal impairment.

- Benefit-risk balance

The benefit / risk of fampridine is considered unfavourable.

2.8.1. Discussion on the benefit-risk balance

Concerning the quality and non-clinical data, no major objections remained at the end of the review.

However, regarding the clinical data too many uncertainties concerning both benefit and risk, preclude a recommendation for a positive opinion.

Basically, these refer to the need to substantiate the clinical relevance of the effect observed on walking speed. With respect to safety, the observed abnormal coordination may counterbalance a positive effect on the walking speed. Long term efficacy and safety remains unclear. In addition, relevant issues related to the mechanism of action of fampridine need further attention for a positive recommendation, i.e. the safety in cardiovascularly compromised patients, patients at risk of seizures including epileptic patients, the elderly and patients with mild renal impairment.

The proposal of the applicant to resolve these problems in the SmPC was not considered acceptable by the CHMP. The lack of relationship between the walking test and clinical benefit precludes a recommendation of accepting this symptomatic treatment. The efficacy on a clinical outcome remains questionable, long-term efficacy declines and long-term safety data are insufficient, precluding accepting a risk of overstimulation affecting walking ability.

One member of the CHMP expressed a divergent position to the outcome of the benefit-risk assessment and considered the benefit-risk balance of fampridine for improvement of walking ability favourable. In particular, this member was of the view that results of fampridine in the pivotal trials were consistent with a clear symptomatic effect that might be of importance in a subgroup of multiple

sclerosis patients, for whom there are no alternatives besides physiotherapy. With respect to the safety profile of the product, namely the risk of seizures, the member considered that these are manageable as their frequency is low and specialised prescribers will supervise use of the product.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the benefit-risk balance of fampridine in the treatment of adult patients with multiple sclerosis for the improvement of walking ability was unfavourable and therefore did not recommend the granting of the marketing authorisation.

The CHMP considered that:

- The statistically significant but small improvements in walking speed could not be related to meaningful improvements in walking ability e.g. walking quality, endurance and increased range of action. Furthermore, the improvement in walking speed was not accompanied by a clear and consistent overall benefit, as assessed by doctors and patients.
- The small uncertain benefit does not outweigh the increased incidence of adverse events e.g. anxiety, insomnia, seizures, infections and events indicating an abnormal sensory feedback/overstimulation that may negatively affect walking ability.
- The long-term efficacy as well as long-term safety have been insufficiently established.
- The benefit/risk in relevant subpopulations, such as the elderly, cardiovascularly compromised patients and epileptic patients is unclear.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Re-examination of the CHMP opinion of 20 January 2011

Following the CHMP conclusion that Fampyra was not approvable for the following indication:

"Treatment of adult patients with Multiple Sclerosis for the improvement of walking ability"

the applicant submitted detailed grounds for the re-examination of the opinion.

Detailed grounds for re-examination submitted by the applicant

The applicant presented their detailed grounds for re-examination in writing and at an oral explanation to the CHMP. Following a request from the applicant at the time of the re-examination, the CHMP convened Scientific Advisory Group (SAG) Neurology inviting the experts including patient representatives to provide their views on the CHMP questions in relation to the marketing authorisation application, taking into account the applicant´s response to the grounds for refusal.

Ground 1: *The statistically significant but small improvements in walking speed could not be related to meaningful improvements in walking ability e.g. walking quality, endurance and increased range of action. Furthermore, the improvement in walking speed was not accompanied by a clear and consistent overall benefit, as assessed by doctors and patients.*

Applicant´s position:

The applicant considered that the CHMP questioned both the magnitude of the treatment effect and the breadth of the data collected on overall walking ability in the Fampridine-PR studies. These concerns were raised in the context of a lack of confidence in certain aspects of the trial design and analysis plan.

The applicant focused on the following key concerns raised by the CHMP during their review:

1. The nature of the definition of a responder on the Timed 25 Foot Walk (T25FW): There were concerns regarding the limitations of the T25FW as a measure of walking ability in MS. There was concern that the definition of a responder did not appear to define a clinically meaningful magnitude of change in walking speed.

2. The use of a subgroup analysis for the key secondary endpoint of patient-reported walking disability (MSWS-12), which was performed based on the T25FW responder categories. The statistical validity of this approach was questioned.

3. The weakness of changes in global impression scores in those patients experiencing consistent changes in walking speed. Given the concerns with points 1 and 2, the CHMP did not further evaluate the significance of the MSWS-12 data but concentrated instead on the "small" changes in the global impression measures in those patients identified as showing consistent improvement in walking speed. These changes did not appear to support clinical meaningfulness. In addition, the T25FW without the support of the MSWS-12 appeared to be too narrow an evaluation of walking ability overall.

The applicant emphasised that the clinician and subject global impression scores were neither adequate nor intended to be used to support a specific effect on improvement of walking. On the contrary, the scales were intended to determine whether there might be some negative effect of treatment in another, unexpected domain of patient experience that might offset the ambulatory improvements measured with the focused ambulation measurements: the T25FW and the MSWS-12. Moreover, the applicant mentioned that it was not reasonable to expect that the outcomes on these scales could be compared to indications like pain or psychiatric indications where treatment may make patients return to "normal". Patients in the Fampridine-PR development had severe walking disability and many non-walking disabilities that are not expected to "overall improve".

To address the CHMP concerns, the applicant presented the clinical and scientific justification for the endpoints chosen and the analyses used in the subsequent evaluation of the clinical meaningfulness of the treatment effects:

Rationale for Timed 25-Foot Walk Test

The objective for the development of a Responder definition was to use a clinically relevant method to identify patients whose walking improves with treatment. In the applicant´s view, independent scientific literature supports the appropriateness of using the T25FW as the primary outcome measurement for walking in the intended MS patient population. Maximum walking speed over short distances is sufficient to assess walking quality and walking capacity, especially in severely disabled people with MS. The T25FW has proven methodological strengths, is a validated test for walking ability in MS, is considered in the field to be among the most sensitive and reproducible of tests for walking, and has known responsiveness and established thresholds for what is a reliable change. There are ethical and feasibility reasons that hinder the use of long-distance walk tests in severely disabled people with MS, such as those studied in this programme.

During the initial review, the CHMP was of the opinion that the T25FW as "a single item" would not be sufficient to assess walking and that in particular endurance was very important to patients with MS and should have been evaluated. The applicant clarified that walking was not assessed by a "single

item". The patient-reported outcome (MSWS-12) was applied to complement the objective assessment of walking speed with elements like endurance, balance, distance, effort to walk, etc.; and Fampridine-PR was superior to placebo (group comparison) on all domains except running.

The CHMP referenced a report of a Multidisciplinary Consensus Conference by the Consortium of Multiple Sclerosis Centres claiming that the T25FW does not adequately reflect walking ability. [The authors] support the use of T25FW as a measure of walking ability in the clinical research setting; therefore, the applicant argued that the conclusion reached by the CHMP did not accurately reflect the proposals from this consortium and the context in which these recommendations were made – the clinical *management* of patients.

The applicant also commented on the CHMP reasoning that gait speed would not give information on "muscle strength, sensory feedback and coordination" and suggesting that these parameters might in fact be negatively impacted by Fampridine-PR treatment. The applicant argued that this opinion is not intuitive because it is hard to imagine how coordination problems and weakness would *not* realistically impact walking speed. Further, the applicant objected that the CHMP opinion was not in line with the existing literature, which showed that gait speed in people with MS is related to leg strength and sensory impairment. In both the aforementioned studies the correlation between strength parameters and gait velocity was modified by sensory impairment. The applicant stated that gait speed is defined by and reflects the complex interplay of strength, sensory impairment and coordination.

The applicant pointed out that despite the acknowledged methodological strengths of the T25FW, the CHMP questioned whether the "T25FW test sufficiently reflects walking" with regard to the "range of action." In the detailed grounds for re-examination, the applicant referred to new scientific literature published since the original MAA demonstrating that the T25FW can predict, in large part, the range of daily activities (i.e. habitual walking as measured by number of steps) in patients with higher level of disability (EDSS 4.5 to 6.5) [Gijbels et al 2010]; longer timed-walking tests (2-Minute Walk Test and 6-Minute Walk Test [6MWT] both unvalidated at the time of this development) did not predict habitual walking significantly better in patients with higher disability [Gijbels et al 2010], the authors highlighted the value of the T25FW to predict range of action "particularly if it is not possible or perhaps somehow unethical to evaluate walking for an extended period, for example, in more severely affected patients."; the study by Barry et al. [2009] underscores that the 6MWT was indeed not feasible for patients with progressive MS.

The applicant concluded that the T25FW has been validated across numerous studies as an objective clinical assessment of walking disability and the ideal walking assessment in a trial with severely disabled MS patients.

The Timed Walk Responder Definition

As MS symptoms and walking ability fluctuate widely within a given individual from day to day an effective responder definition should only identify "real" change on an *individual basis* that is beyond natural fluctuation that may occur on any clinical assessment of walking.

In the Fampridine-PR programme, a responder was defined as someone who had consistent improvement in walking speed, i.e. walked faster on the majority of on-treatment visits (3 or 4 out of 4) than the fastest of 5 off-treatment visits (4 before and 1 after treatment). This clinical definition selected individuals who demonstrated walking speeds during treatment that were consistently faster than the best that they had achieved without treatment.

In theory, this approach could have selected patients as responders who had relatively small but consistent changes from baseline; however, the applicant claimed that their data showed that this was not the case: the effect was in fact large and meaningful in patients that responded to the drug. In fact, small changes on this criterion would only be possible in patients with very little variability in

walking speed at baseline, where the best walking speed was little different from the average walking speed, and this is rare in MS; the applicant also considered worth noting that even small, but consistent improvement over the patients' best speed is in itself a worthy outcome for the severely affected patients with high variability in their day to day walking abilities.

The applicant highlighted that this approach was not new, for example in clinical studies assessing disease modifying therapies in MS, there is a definition of consistent change in disability, defined as a sustained change in EDSS score at two time points. The Fampridine-PR development programme adopted a similar model and assessed sustained increases in speed over time.

More conventional responder analyses tend to use a response definition based on a selected threshold of average change from baseline. However, such a definition was not considered optimal for MS because it ignores the temporal variability of MS symptoms. The underlying assumption in selection of a predefined magnitude of response is that a change is believed, *a priori*, to be "meaningful", whether or not it is related to treatment. In the presence of significant variability, this is susceptible to a high rate of false positive responses created by random fluctuations in MS symptoms.

Using the reasoning above, the applicant concluded that a clinical responder definition based on consistency appropriately identified real improvement of walking speed on T25FW from natural baseline fluctuations in patients with heterogeneous, severe walking disability. In addition to the clinical assessment of walking with the T25FW, the MSWS-12 was used as a patient-reported outcome to complement the clinical assessment with the patient perspective of different aspects of overall daily walking ability (distance walked, effort to walk, balance, concentration, etc.).

MSWS-12 and Validity of the Statistical Analysis

The MSWS-12 is a patient-reported outcome scale that was developed from qualitative research in people with MS to define the most relevant aspects of walking from the patient's perspective. The MSWS-12 assesses 12 different domains of walking function and quality (11 of the 12 are not "speed"). They include:

• Function: walking, running, climbing stairs, standing, and balancing

• Quality: distance, effort, need for support outdoor/indoor, speed, smoothness, required mental concentration.

MSWS-12 is a validated tool developed specifically to assess walking ability in MS patients. There are established methods that can be used to determine meaningful changes in the MSWS- 12. Standard error of measurement (SEM): mean estimate using data from 7 studies (two of which used fampridine) is 5.0 points (range: 4.2 to 6.0 points). The minimal important difference (MID) was 4.9 points (range 3.5 to 6.2 points). International standards on guidelines for clinically important change on patient-reported outcome measures are met by defining meaningful changes through both SEM and MID and (IMMPACT consensus criteria).

The applicant concluded that the MSWS-12 complements the T25FW for the assessment of overall walking ability, as it measures different aspects of global walking ability from a different perspective. In their initial review, the CHMP considered that a circular line of reasoning had been presented by the applicant, given that non-randomized groups of responders and non responders were formally compared for their changes in MSWS-12 score and also with respect to the magnitude of change in walking speed in these groups.

In light of the CHMP comments, the applicant further reviewed the use of the responder analysis in this context. The applicant concluded that while the responder analysis alone is useful, it is not sufficient to establish that the observed treatment difference in walking speed translates into a clinical benefit of Fampridine-PR, the clinical benefit can be established by examining the totality of the data.

Moreover, the applicant also concluded that the within-responder analysis provides useful information that allows characterization of the magnitude of effect in patients who responded to Fampridine-PR treatment. In their grounds for re-examination the applicant acknowledged that the original presentation of these data may have incorrectly given the impression that the within-responder analysis was to be interpreted as an inferential statistical result to further establish efficacy. An analysis of this kind would not have been valid for a comparison of non-randomized groups. This analysis was intended only as a correlation of the key objective and subjective measurements in order to further characterize the extent to which Timed Walk Responders experienced clinically meaningful improvements in their walking ability, as reflected in their MSWS-12 scores. The applicant specified that this step was necessary to examine the clinical relevance of the primary endpoint but did not in itself serve to demonstrate efficacy; efficacy was established by the treatment group comparison of the primary endpoint itself, supported by the totality of evidence from similar comparisons of all the other available endpoint measures.

Primary Analysis of Timed-Walk Response

The pre-specified primary efficacy endpoint was the Timed Walk Response, defined as consistent improvement in walking speed. In each of the two pivotal studies there were substantially more Fampridine-PR-treated patients who experienced consistent improvements in walking speed when compared to placebo-treated patients. The applicant reiterated that the results were highly statistically and clinically significant, in the individual studies as well as in the pooled data from the two studies.

Table 19 Number (%) of timed walk responders by study and treatment

	Placebo	Fampridine
Study 203	6/72 (8.3)	78/224 (34.8)
Study 204	11/118 (9.3)	51/119 (42.9)
Pooled 203 & 204	17/190 (8.9)	129/343 (37.6)

In study MS-F203 a three stage stepwise analysis was pre-defined to establish a positive outcome on the primary endpoint and to establish its clinical meaningfulness with respect to overall walking ability. Step 1 was to show a significantly greater proportion of Timed Walk Responders in the Fampridine-PR group as compared to the placebo group. Step 2 was to register a significant improvement in the MSWS-12 score for the Timed Walk Responders when compared to Timed Walk Non-Responders. Step 3 was to confirm maintenance of effect by testing whether those patients who responded to Fampridine-PR treatment on the T25FW would still register a significant improvement in walking speed relative to placebo-treated patients at the last observed double-blind visit. The second step in the pre-specified primary analysis showed that those patients who were responders (in both treatment groups combined) according to the primary endpoint improved in terms of the key clinical endpoint (average change from baseline in the MSWS-12 score over the double-blind period) than the corresponding non-responders.

The applicant agreed with the CHMP that this correlation of itself was not sufficient to establish that the observed treatment difference in the primary endpoint translates into a clinical benefit of Fampridine-PR. In order to demonstrate that this is indeed the case it was considered of outstanding importance to show two things: Firstly, that amongst the responders in the Fampridine-PR group, the average change from baseline in the MSWS-12 score is similar to the corresponding average change from baseline amongst the responders in the placebo group. Secondly, that amongst the non-responders in the Fampridine-PR group, the average change from baseline in the MSWS-12 score is similar to the corresponding average change from baseline amongst the non-responders in the placebo group. The applicant stated that both pivotal studies MS-F203 and MS-F204 showed that these assumptions hold true, as shown in the table below. The applicant chose to present these data in the detailed grounds

for re-examination in order to clarify that the treatment effects seen in responders were clinically meaningful. In the applicant´s view, this additional analysis supports that the highly significant differences seen in the primary endpoint translate into clear differences on a scale which has direct clinical meaning.

Table 20 - Change from baseline in MSWS-12 by responder status and clinical study

	Timed walk responders		Timed walk non-responders	
	Fampridine	Placebo	Fampridine	Placebo
Study 203	-6.97 (n = 78)	-7.47 (n = 6)	-0.55 (n =146)	+ 1.36 (n = 66)
Study 204	-6.33 (n = 51	-4.73 (n = 11)	+ 0.16 (n = 68)	+1.29 (n = 107)
Pooled	-6.61 (n = 129)	- 5.69 (n = 17)	-0.32 (n = 214)	+1.32 (n = 173)

Treatment Comparisons for the Secondary Endpoints

The applicant pointed out that in assessing the statistical significance for secondary endpoints, one must remember that the power and sample size calculations for the pivotal studies were based on the primary endpoint and not specifically the secondary endpoints. Achieving statistical significance for these endpoints therefore should not be expected in the individual studies. According to the applicant, the pooled analysis provides the most complete information with regard to these endpoints, and supports the robustness of the conclusions through the consistency of effect across the individual studies. The table below presents results of treatment comparison for the secondary endpoints both for the individual studies and for the pooled (meta) analyses.

Table 21 Comparison of secondary efficacy endpoints by study and treatment

		Placebo	Fampridine	p- value
Change in Walking Speed at Endpoint ft/sec	Study 203	0.10	0.29	0.01
	Study 204	0.19	0.30	0.38
	Pooled	0.15	0.30	0.001
Change in Average Walking Speed ft/sec	Study 203	0.10	0.28	0.001
	Study 204	0.17	0.29	0.009
	Pooled	0.14	0.29	0.001
% Change in Average Walking Speed	Study 203	4.71	13.63	0.001
	Study 204	7.67	13.99	0.007
	Pooled	6.54	13.76	0.001
Subjects with ≥20% Change in Average Walking Speed	Study 203	11.1%	31.7%	0.001
	Study 204	15.3%	34.5%	0.001
	Pooled	13.7%	32.7%	0.001
Change in Average MSWS-12 (negative change equals improvement)	Study 203	0.62	-2.72	0.084
	Study 204	0.73	-2.62	0.021
	Pooled	0.69	-2.68	0.004
Change in Average Ashworth Spasticity Score (negative change equals improvement)	Study 203	-0.07	-0.16	0.021
	Study 204	-0.06	-0.18	0.015
	Pooled	-0.07	-0.16	0.001
Change in Average Lower Extremity Manual Muscle Test (LEMMT) (5-point scale)	Study 203	0.04	0.13	0.003
	Study 204	0.04	0.09	0.106
	Pooled	0.04	0.12	0.001
Average SGI (7-point scale)	Study 203	4.48	4.58	0.447
	Study 204	4.32	4.38	0.607
	Pooled	4.38	4.51	0.387
Average SGI ≥ 6 (pleased/delighted) (7-point scale)	Study 203	6.9%	12.5%	0.133
	Study 204	9.3%	9.2%	0.983
	Pooled	8.4%	11.4%	0.371
CGI at End of Treatment Period (7-point scale)	Study 203	3.76	3.55	0.065
	Study 204	3.79	3.52	0.002
	Pooled	3.77	3.54	0.001

CGI ≤ 3 (improved) at End of Treatment Period (7-point scale)	Study 203 Study 204 Pooled	25.7% 23.2% 24.2%	38.5% 42.7% 39.9%	0.033 0.003 0.001

Patients Perceived Walking Speed Improvement as Meaningful

The applicant claimed that the Timed Walk Responders showed a marked reduction from baseline in MSWS-12 score. In comparison, Timed Walk Non-Responders showed an average score that was quite stable between baseline and treatment periods in the individual studies and in the pooled analysis:

• The change from baseline score was -6.50 for Timed Walk Responder versus +0.41 for Timed Walk Non-Responders, respectively (pre-defined analysis)

To contextualize what an improvement of 6.5 points means, the applicant attributed the claimed meaningfulness of this change to the fact that

• it exceeds the threshold for minimally important change as described above and also exceeds the clinically-meaningful change estimated from seven studies, of which two include Fampridine-PR,

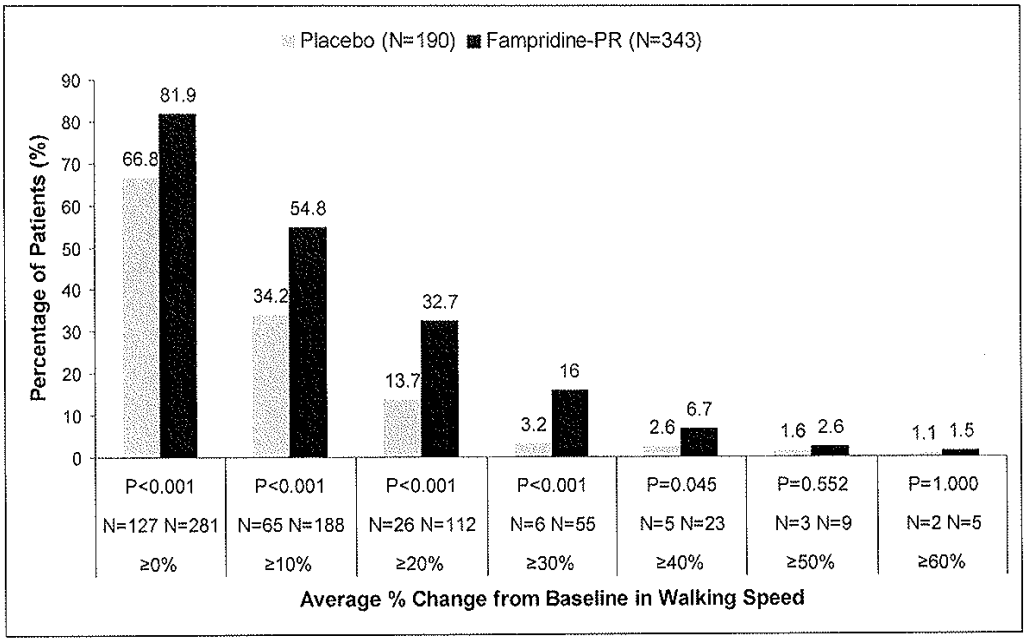
• there is a 6.7 point difference in baseline MSWS-12 score between patients with EDSS 5.5 and 6.5 at baseline in the pivotal studies. A difference of 6.5 MSWS-12 points illustrates the difference between being able to walk with two canes (EDSS 6.5) or without walking aid (EDSS 5.5).

Meaningfulness of Improvements of 20% on T25FW

The applicant also used post-hoc sensitivity analyses that explored alternatively-defined response criteria based on magnitude of walking speed improvement, concluding that the outcomes provided strong support for conclusions of the original analysis. In the analysis below (figure 9), the applicant looked at the proportion of Fampridine-PR-treated patients who achieved threshold changes in walking speed from no change to ≥60% improvement. At any chosen threshold up to 40%, Fampridine-PR was nominally significantly better than placebo which would have demonstrated statistical significance if these thresholds had been used to prospectively define response.

Figure 9

Cumulative Percentage of Patients with Increasing Levels of Walking Speed Improvement



Further, the applicant pointed out that an average improvement of ≥20% on the T25FW (without regard to Timed Walk Responder status) was associated with meaningful improvements on the MSWS-12 (average improvement 8.4 points), mentioning this was in agreement with the literature that has consistently demonstrated that the change on the T25FW of approximately 20% is clinically meaningful.

Applicant's Overall Conclusion to Grounds for Refusal 1

The applicant mentioned that in their initial review, the CHMP was of the opinion that the small improvements in walking speed could not be related to meaningful improvements in walking ability and that the improvement was not accompanied by a clear overall benefit. The applicant concluded that the magnitude of improvement in patients responding to treatment with Fampridine-PR was sizeable and clinically meaningful, giving emphasis on the fact that the result was obtained in patients with severe walking ability for whom walking over short distances is critically important.

In their response the applicant claims to have shown that:

- The clinical responder definition and the walking assessment were appropriate especially given the severity of walking disability in patients in this development
- The objective, physician-measured improvement in the time to walk 25 feet was supported by the patient's own subjective assessment of 12 parameters of overall walking ability
- The correlative analyses of objective and subjective measures within responders is valid and not circular
- The clinical responder definition alone, although useful, was not sufficient to prove clinical meaningfulness of the data
- The totality of evidence demonstrates clinical significant improvements with Fampridine-PR

The applicant also reiterated that the pre-defined responder analysis was further supported by an alternative post-hoc analysis demonstrating an increase of walking speed of ≥20% in 33% of patients treated with Fampridine-PR compared with 14% of patients in the placebo-group and that the benefit demonstrated on 11 of the 12 domains of the MSWS-12 confirmed the clinical meaningfulness of a 20% improvement for the patient population within this programme.

CHMP position

The CHMP re-discussed the acceptability of the primary endpoint of the pivotal trials, considering that timed walk tests, and the T25FW in particular, are tools to evaluate walking in multiple sclerosis in clinical practice. In their initial review, the choice of the T25FWT was regarded by the CHMP as a pharmacodynamic endpoint only, which was supported by the SAG Neurology (1st SAG in September 2010). During the re-examination the CHMP considered that the result on MS Walking Scale-12, which is a validated patient reported outcome measure specifically developed to assess walking ability in MS patients, contributed to supporting the primary endpoint of the pivotal studies, i.e. the T25FW test. The relevance of the primary endpoint itself was further re-discussed in terms of clinically meaningful improvement in walking speed. The CHMP noted that the SAG Neurology concluded in its second meeting (May 2011) by majority that a 20 % difference compared to placebo is probably clinically relevant. Of note, in the second SAG Neurology meeting during the re-examination procedure, clinical relevance was considered and discussed in the context of a "% improvement" rather than with respect to the outcome measure as such, and improvement of a certain magnitude (cut-off), i.e. 20%, was

considered meaningful (see section SAG Neurology). Also in literature*[1-4], scientific evidence was available supporting the difference of 20% in walking speed as clinically relevant.

Furthermore, following the applicant´s presentation of the new correlation analyses (tables 22-24 below) in the re-examination oral explanation, the CHMP considered that improvement in walking speed and subjective perceptions of change (MSWS-12) were related in the pivotal trials. Correlation of the two scales was about 0.4. Overall, the CHMP was of the opinion that T25FW with the support of MSWS-12 was an acceptable evaluation of walking ability. The CHMP also took into consideration that there was only a minor proportion of patients (about 5 % in the fampridine group) experiencing improvement only subjectively (on the MSWS-12) and having no increase in walking speed at the same time (Table 23). This finding was considered re-assuring by the CHMP.

Table 22

Correlation Between ***Change*** on MSWS-12 and T25FW

All Patients, Active and Placebo, ITT population

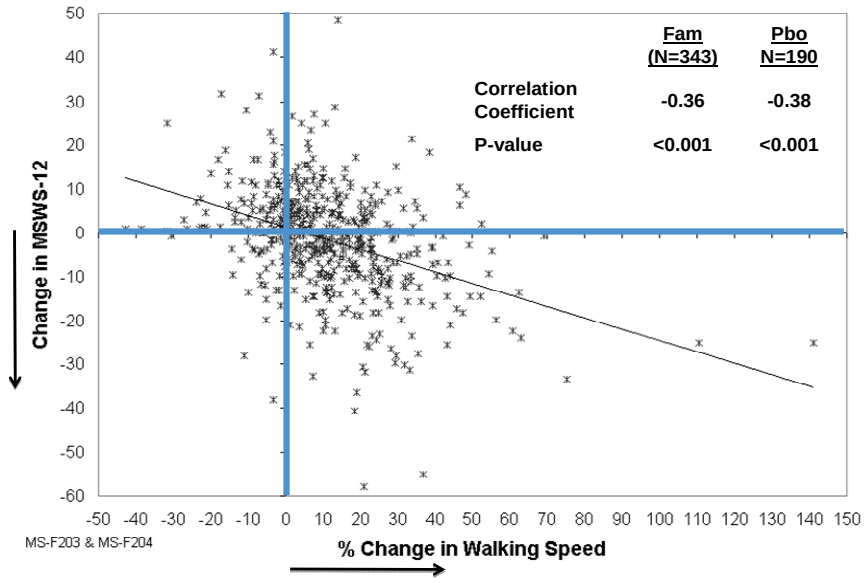


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Table 23

* [1]Kaufman M, Moyer D, Norton J. The significant change for the Timed 25-foot Walk in the multiple sclerosis functional composite. Mult Scler. 2000 Aug;6(4):286-90.

[2]Schwid SR, Goodman AD, McDermott MP, Bever CF, Cook SD Quantitative functional measures in MS: what is a reliable change? Neurology. 2002 Apr 23;58(8):1294-6.

[3]NILSAGARD et al. Clinical relevance using timed walk tests and 'timed up and go' testing in persons with Multiple Sclerosis. Physiother. Res. Int. 12(2) 105–114 (2007)

[4]Kragt JJ, van der Linden FA, Nielsen JM, Uitdehaag BM, Polman CH. Clinical impact of 20% worsening on Timed 25-foot Walk and 9-hole Peg Test in multiple sclerosis. Mult Scler. 2006 Oct;12(5):594-8.

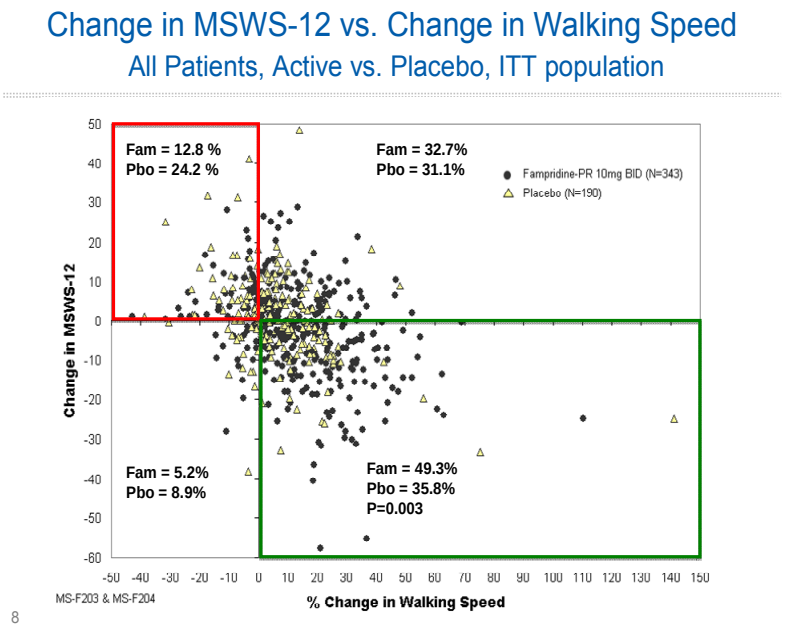

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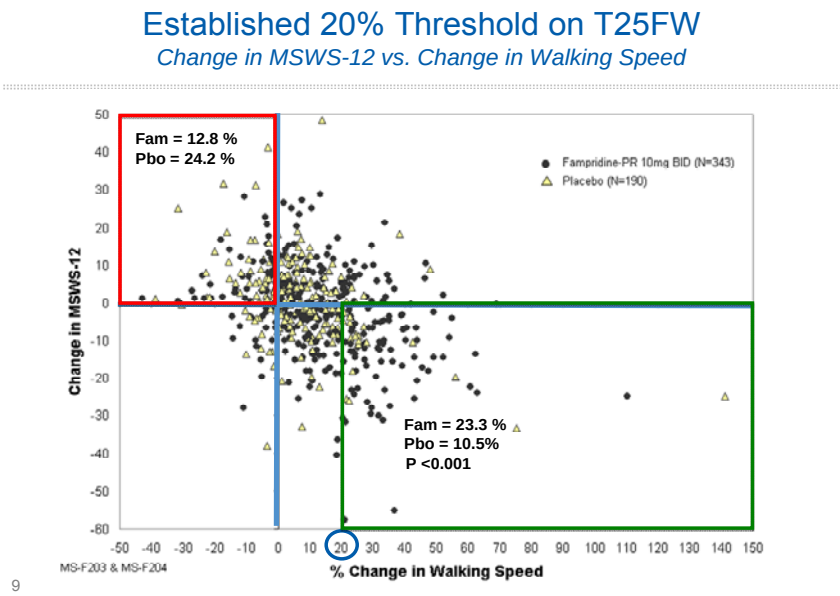
Table 24



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Taking results on the primary (T25FW) and the MSWS-12 secondary endpoint together, it was considered possible to define a patient population benefiting from the treatment in both scales, i.e. select the responders and conclude on a positive-benefit risk balance.

In view of the oral explanation, the CHMP agreed to the modification in the section 4.2 (Posology) proposed by the applicant, which was elaborating on criteria for selecting responders and on discontinuation criteria in case patients stop exhibiting response. This approach was in line with the re-examination SAG Neurology, which suggested that improvement on a walking test with clinical utility and simple to use in clinical practice should be evaluated in an interval of two weeks after starting treatment to guide further treatment:

Section 4.2

"Starting and Evaluating Fampyra Treatment

- *Initial prescription should be limited to 2 weeks of therapy as clinical benefits should generally be identified within 2-weeks after starting Fampyra.*
- *A timed walking test, e.g. the Timed 25 Foot Walk (T25FW), is recommended to evaluate improvement after two 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. Fampyra should be discontinued if patients no longer receive walking benefit."

Nevertheless, the CHMP considered that the understanding of benefit provided by fampridine is not completely explained by the data currently available; in particular, other important aspects of walking such as balance, endurance and walking distance that constitute additional evidence of improvement in the overall walking ability were regarded relevant. The CHMP considered that further data obtained in a controlled setting of a clinical trial are needed and that the validity of the currently proposed criteria for identification of responders should be further evaluated. Therefore, the CHMP requested that the marketing authorisation should be 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. The study report is to be submitted by 30 June 2016."

Given the CHMP view that T25FW with the support of MSWS-12 was an acceptable evaluation of walking ability, the results concerning the CGI and SGI scores were no longer considered of relevance for efficacy.

The CHMP concluded that the ground for refusal No.1 was resolved with the condition specified above.

Ground 2: *The small uncertain benefit does not outweigh the increased incidence of adverse events e.g. anxiety, insomnia, seizures, infections and events indicating an abnormal sensory feedback/overstimulation that may negatively affect walking ability.*

Applicant´s position:

The applicant argued that the benefits to responders were significant and neither uncertain nor small and commented that the side effects of Fampridine-PR identified from the placebo-controlled clinical trials, including seizures, are recognised symptoms or complications of MS itself, and there is no evidence that they adversely affect the improved walking ability.

Of the adverse events (AEs) observed in the placebo-controlled studies (Phase 2 Study MSFS202, Phase 3 Studies MS-F203 and MS-F204), which included anxiety and insomnia, 94% were assessed as either mild or moderate in intensity and rarely caused withdrawal of treatment. Those events subsequently recognized as adverse drug reactions (ADRs) usually resolved with continued therapy and led to withdrawal in only 1.75% of the safety population. In the active treatment group, withdrawals caused by ADRs were balance disorder 0.5%, dizziness 0.5%, headache 0.5%, and anxiety 0.3% (notably there was no withdrawal due to insomnia). In the placebo group, a complex partial seizure led to withdrawal in one patient (0.4%). Spontaneous data emerging from the US

marketplace are reassuring and strongly support the current understanding of the safety profile. The anticipated increase in urinary tract effects has not been confirmed.

Non-Seizure CNS events

The ADRs occurring with Fampridine-PR treatment were identified from an integrated safety analysis and are presented in the table below. The incidence of events in the placebo group indicates how commonly these complications are seen in MS patients.

Table 25 Psychiatric and non-seizure CNS events by treatment.

MeDRA term	Placebo n= 238	Fampridine 10 mg b.d. n = 400	TEAEs > 1% Difference vs. placebo
Insomnia	9 (3.8)	35 (8.8)	5.0%
Anxiety	1 (0.4)	6 (1.5)	1.1%
Balance disorder	3 (1.3)	19 (4.8)	3.5%
Dizziness	10 (4.2)	29 (7.3)	3.0%
Headache	9 (3.8)	28 (7.0)	3.2%
Parasthesia	6 (2.5)	16 (4.0)	1.5%
Tremor	0	4 (1.0)	1.0%

The applicant emphasised that the AEs recognised as treatment group side effects represent only a relative increase in some common symptoms of MS and that they occurred in a small percentage of patients. As shown in the table above, the excess of anxiety in the treatment group compared to placebo is only 1.1%, although that of insomnia is 5%.

The analysis of data from the trials using the recommended 10 mg BD dosage of Fampridine-PR showed that the rates of AEs of falling and/or injuries sustained as a result of falling were actually less in the Fampridine-PR treated patients (12.5%) compared with placebo-treated patients (15.1%). In addition, the reported falls (and any injuries likely to have been sustained in falling) were not associated with concurrent or preceding events indicative of CNS excitation.

Seizures

Pre-clinical animal pharmacology has shown a dose and plasma concentration dependent risk of seizure.

Seizure in Pre-Marketing Development of Fampridine-PR

History of seizure or presence of epileptiform activity on a screening EEG was an exclusion criterion for the clinical studies in the Fampridine-PR development programme. Dose finding studies with Fampridine-PR showed evidence of a dose-dependent risk of seizure. However, the Phase 3 double-blind placebo-controlled studies did not show any elevated risk of seizure with Fampridine-PR treatment at the therapeutic dose of 10 mg BD when compared to placebo (incidence of seizure/convulsion was 0.19% for Fampridine-PR and 0.4% for placebo). The incidence rate of reports of seizure/convulsion in the long-term open-label trials was 4.1/1000 patient years (95% confidence intervals 0.13, 0.96) which most likely represents the background incidence in MS patients. The report of seizure in the placebo group in the trials demonstrates that patients with advanced MS are at risk of seizures. The rate of seizure in the placebo group was 0.4% over a period of 3 months, suggesting an incidence of around 16/1000 patient years, but of course with very wide 95% confidence intervals (0.00, 46.6). These results from clinical trials are reassuring, but patients were carefully selected and specific exclusion criteria ensured a low-risk population.

Seizure Reports from US Post-Marketing Surveillance

Fampridine-PR has been available on the US market since March 2010, and up until 21st January 2011, an estimated 39,600 patients had been supplied with the drug. In the USA, cases of seizure and convulsion are specifically solicited as part of the marketing authorisation risk-management commitments, making under-reporting unlikely. As of 28th February 2011, 64 reports of seizure had been reported or confirmed by a healthcare professional. The mean age of the patients was 52 years (range 26 to 73, median 52). Sixteen patients (25%) were male and 46 (72%) female, for two the gender was not known. Duration of treatment prior to the event varied between one dose and 236 days (mean 54 days, median 21 days) and in four cases it was unknown. Seventeen patients (27%) suffered a seizure within three days of starting treatment with fampridine. The descriptions of the 64 reports of seizure were given as 26 convulsions, 16 seizures, 13 Grand Mal episodes, 4 status epilepticus, 3 tonic/clonic episodes, one confusional state/convulsion, and one nocturnal seizure. The seizures were generally of short duration, although four reports described a period of status epilepticus.

Of the 64 case reports, 44 had a potential risk factor for seizure, 17 did not, and the remaining 3 cases had insufficient available detail for assessment. Two of the seizure events were associated with dosing errors. The first case report described a 66-year-old female patient who took her evening tablet of fampridine after several weeks of uneventful treatment. Her husband, not realising she had already taken the evening dose, gave her a further tablet some 30 minutes later. Five hours later, she experienced a generalised tonic/clonic seizure. The second case report describes a 47-year-old female patient who experienced a seizure following only the second tablet of fampridine taken 6 hours after the first.

In three cases aetiologies for seizure other than fampridine are more likely. One case described off label use in a child with a high seizure-risk medical condition (adrenoleucodystrophy). In a second case, a seizure was reported in a patient with progressive multifocal leucoencephalopathy (PML) who experienced a further seizure after fampridine had been stopped. The third patient was a previously diagnosed epileptic and was taking prophylactic topiramate treatment.

Analysis of the 59 remaining cases identified a history of previous seizure in 10 patients. Thirty-five case reports described the use of at least one concomitant medication with a labelled seizure risk. Of these 35 case reports, patients in 21 cases were taking one medication with labelled seizure risk, 11 were taking two and 3 patients were taking a combination of three other medications with labelled seizure risk. One patient had suffered a head injury and subdural haematoma five months previously. Seventeen cases had neither a history of previous seizure or risk factor, nor were taking concomitant medications with a seizure risk labelled, and three had insufficient information reported to make an assessment.

CHMP position

The CHMP considered that a higher rate of CNS adverse events with active treatment as compared to placebo was observed. This observation was not completely unexpected and was regarded as related to the mechanism of action – through alteration (acceleration) of nerve impulse transmission. The CHMP was of the view that the type and frequency of these adverse events, i.e. anxiety, insomnia, dizziness, tremor, etc. should not be assessed isolated from efficacy; with resolving the efficacy-related ground for refusal number one, these adverse events were no longer considered a safety concern precluding granting the marketing authorisation but rather an issue of tolerability. Furthermore, the CHMP noted that in clinical trials, despite being more frequent in the treated group, these adverse events were of mild and transitory nature and rarely led to discontinuation.

The potential of fampridine to cause seizures was considered of a main safety concern by the CHMP. In studies MS-F201 and MS-F202 where doses greater than 10 mg twice daily were used 2 out of 25 and 2 out of 159 fampridine treated patients experienced seizures respectively – an overall rate of 2.2%.

In the double blind phases of studies MS-203 and MS-204 where the proposed dose of 10 mg twice daily was used one placebo treated patient experienced an absence episode, but no fampridine treated patients experienced seizures. In study MS F-203EXT an un-blinded extension study, 5 out of 269 (1.9%) fampridine treated patients experienced seizures. In study MS F-204EXT 0 out of 214 patients experienced seizures giving an overall rate in the two extension studies of 1.04%.

In the post authorisation experience in the US there have been 64 reports of seizures in 39,600 treated patients. Three of these were in patients with serious neurological problems predisposing to seizures that should probably not have been treated; if these are excluded, the seizure rate is 0.15%.

In their meeting, the re-examination SAG Neurology discussed the seizure risk and recognized that seizures occur rarely in patients treated with fampridine, further data presented by the applicant suggesting that occurrence of seizures is not a major concern for the overall benefit-risk balance of the product. In conclusion, the SAG Neurology recommended that pre-existing seizure disorder should be a contraindication to treatment with fampridine, which was agreed by the CHMP.

At the time of the oral explanation, the applicant presented data on seizures as observed in the controlled clinical trials (MS-F202/3/4), open-label extension studies and post-marketing seizure reports. The applicant estimated that the added risk of fampridine to seizures is less than 1/1000 patients. The CHMP considered that this was further supported by literature[‡] and the applicant´s data from clinical studies with other multiple sclerosis products (disease-modifying drugs) providing evidence on the background incidence of seizures in MS patients. The CHMP regarded this re-assuring in terms of fampridine´s low level of the added risk. The applicant also recognized the dose-related association of fampridine with seizures and highlighted that the prolonged release formulation was developed to minimise this risk.

The CHMP was of the opinion that the data presented during the re-examination oral explanation were re-assuring, but did not allow for quantifying the true incidence of seizures associated with fampridine. However, the added risk level was considered low and dose-dependent (some of the events observed were related to medication errors associated with overdose). The CHMP considered that the therapeutic dose is border-line and that any increase (e.g. overdose) might put patients at higher risk of seizures. In this context, the CHMP considered that an observational study further quantifying the risk of seizure will be conducted, as described in the Risk Management Plan.

The CHMP concluded that the ground for refusal No. 2 was resolved with the measures implemented in the RMP.

Ground 3: *The long-term efficacy as well as long-term safety have been insufficiently established.*

Applicant´s position:

Clinical efficacy with Fampridine-PR was demonstrated by the ITT analysis of improvement in walking speed compared with placebo over the double-blind duration of the pivotal studies of up to 12 weeks. The analyses demonstrated that the effect of Fampridine-PR 10 mg BD was maintained throughout the treatment period in both studies.

Current CHMP guidelines for long-term symptomatic treatment and maintenance of effect within the nervous system class of compounds vary widely depending on disease area, treatment objectives, and intended treatment duration. For other symptomatic treatments, such as for neuropathic pain, three months double-blind treatment, followed by open label extension (for issues with tolerance) is considered adequate (Guideline on clinical medicinal products intended for the Treatment of Neuropathic Pain: CPMP/EWP/252/03 Rev. 1). The length of the double blind treatment periods in the

[‡] Eriksson M, Ben-Menachem E, Andersen O. Epileptic seizures, cranial neuralgias and paroxysmal symptoms in remitting and progressive multiple sclerosis. Mult Scler 2002; 8 (6):495-9

Fampridine-PR studies served the additional purpose of reducing concerns that expected disease-related decline in walking speed would interfere with interpretation of the results. Approximately 5% decrease in walking speed over 6 months can be expected in patients with progressive MS and high disability. This medicine [fampridine] has rapid symptomatic effects and can be adequately and safely assessed by a neurologist to confirm continued benefit. To optimize the benefit risk equation the SmPC recommends re-assessing the benefits through an interruption in treatment if a decline in walking ability is noted in patients who initially respond to treatment and receive long-term therapy.

Long-term open-label study data allow the assessment of long-term safety of Fampridine-PR treatment. A full analysis of data in August 2009 showed that the AE profile remained consistent over time, with no evidence of emergence of AEs not seen in the short-term trials. An analysis investigating effects of long-term Fampridine-PR treatment on progression of MS has shown that the decline in disability expected with a progressive disease such as MS in patients treated with Fampridine-PR is not different to that seen in an historical control group of patients treated with the disease modifying therapy Avonex.

Patients in the open-label extension study in USA were followed until drug was available on the market and in Canada, long-term treatment is still continuing. As of December 2010, 547 patients had been treated for one year, 480 for two years, 288 for three years, 235 for four years, 83 for five years, and 48 for six years. SAE data and data on AEs causing discontinuation from this further extension have been analysed and no suggestion of any new risk has been identified.

At the time of the oral explanation, the applicant further clarified the concept of re-evaluating efficacy if walking deteriorates during the treatment with the options of a temporary interruption and re-exposure to fampridine or permanent discontinuation in patients losing walking benefit.

CHMP position

The CHMP considered that there was no evidence of fampridine efficacy loss or increasing toxicity over time and that there were sufficient data from open-label extensions of the Phase III studies to satisfy the standard regulatory criteria for long-term clinical safety and efficacy data. According to the response more than 1,400 patients were treated in clinical trials for at least one year. Moreover, based on the clinical pharmacology it would seem unlikely that there would be increasing toxicity or decreasing pharmacodynamic activity over time. On the other hand, loss of clinical benefit over time can unfortunately be anticipated due to disease progression, but unrelated to the changes in the pharmacological properties of fampridine. The CHMP also considered the long-term safety data collected post-authorisation in the US and was of the opinion that these did not suggest any change in the safety profile defined in the double-blinded trials and thus, was supportive of the clinical study data. The CHMP considered that in the absence of a CHMP guidance, clinical monitoring of effects for three months could be accepted for a symptomatic treatment and should not preclude granting of a marketing authorisation, particularly in the context of the supportive post-marketing data from the US.

The concept of re-evaluating efficacy using the walking test, as implemented by the applicant in the revised product information was considered acceptable by the CHMP.

Section 4.2

"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. Fampyra should be discontinued if patients no longer receive walking benefit."

The CHMP concluded that the ground for refusal No. 3 was resolved.

Ground 4: *The benefit/risk in relevant subpopulations, such as the elderly, cardiovascularly compromised patients and epileptic patients is unclear.*

Applicant´s position:

Elderly

The number of elderly MS patients included in the adequate and well-controlled studies was small. In the placebo-controlled trials MS-F202, MS-F203, and MS-F204, there were 23 patients in the 10 mg group (5.8%) aged over 65 years and 18 (7.6%) in the placebo group. Analysis of AEs by age in the 10 mg BD Fampridine-PR placebo-controlled trials is reassuring in that there was no suggestion of any increase in overall reporting rates of AEs in the elderly age group.

There is however, no evidence either from the limited exposure in the studies, or from the exposure in the US marketplace, that the risk for the elderly from taking Fampridine- PR is increased. No safety signals have emerged of problems relating to either renal function or greater age.

Table 26 Overview of treatment emergent AEs by age and treatment

	Placebo patients with TAE	Famrpidine patients with TAE
Aged ≤ 45 years	n = 65 46 (70.8%)	n = 86 74 (86.0%)
Aged 46 to 64 years	n = 155 118 (76.1%)	n = 291 247 (84.9%)
Aged ≥ 65	n = 18 11 (61.1%)	n = 23 18 (78.3%)

Cardiovascular

There is a theoretical risk based on the K+ blockade of fampridine to modify the cardiac conduction at high concentration, which could lead to sinoatrial or atrioventricular conduction abnormalities

The cardiac data have been reviewed by an independent expert who has concluded that:

• There is little to suggest that fampridine will result in QT interval prolongation or in consequent arrhythmias.

• Clinical cardiovascular events are relatively rare compared with neurological AEs. No particular pattern of cardiovascular AE is seen. There is little to suggest that arrhythmia and conduction disturbances are specific problems.

• Clinical overdose has sometimes been associated with cardiovascular incidents, but these have not been at all consistent or particularly disturbing.

Clinical Development

A thorough QT/QTc study did not detect any signal of pharmacological effects on cardiac repolarization at doses of Fampridine-PR of up to 30 mg twice a day, which suggests that at therapeutic doses in man, fampridine has a low potential for inducing cardiac arrhythmias based on QT-prolongation.

Comparison with placebo in the controlled studies using Fampridine-PR at 10 mg BD showed a slight excess of cardiovascular events in the active treatment group; 10 events in 400 patients (2.5%) compared to placebo three events in 283 patients (1.3%). Exposure to fampridine in patients with cardiovascular disorders was limited, as subjects with clinically significant cardiovascular disease (abnormal ECG, angina, uncontrolled hypertension, clinically significant cardiac arrhythmias or any

other clinically significant cardiovascular abnormality) were excluded from the studies. However, cardiac symptoms were reported in approximately 40% of subjects at baseline in both the placebo and active treatment groups.

A full analysis of data concerning seizures has been presented as part of the applicant´s response to ground for refusal No. 2.

CHMP position

The CHMP considered that multiple sclerosis is predominantly a disease of young and middle aged adults. The applicant presented an analysis of adverse events by age (Table 26) showing there was no evidence of increasing frequency of events by age. The CHMP considered this finding unexpected as in the clinical trial setting, adverse events tend to be more common in the elderly; in addition, older patients would be expected to have more advanced disease and therefore more events whether treatment related or not. The CHMP considered that the data base was too small to provide a robust analysis. Nevertheless, with precautions concerning a diminished renal function specified in the Product Information (see below) and measures described in the RMP (study to evaluate the effect of a dose lower than 10 mg twice daily), the issue was considered to be resolved.

SmPC Section 4.2:

"Elderly

Renal function should be checked before starting treatment with Fampyra. Monitoring renal function to detect any renal impairment is recommended (see section 4.4)."

SmPC Section 4.4

"Determining renal function before treatment and its regular monitoring during treatment is recommended in all patients (particularly the elderly in whom renal function might be reduced)."

During the re-examination procedure, the CHMP considered that with respect to patients with cardiovascular disease a study evaluating potential effects on the ECG (i.e. conduction effects) did not identify any safety concerns and also in clinical trials there was only a small excess of cardiovascular events with active treatment. The CHMP agreed that the wording proposed by the applicant in section 4.4 of the SmPC was appropriate:

"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."

Nevertheless, the CHMP also considered that given the known mechanism of action, patients with cardiovascular diseases were (as a precautionary measure) excluded from trials. As a result, there is currently limited exposure in patients with known cardio-vascular diseases. The CHMP considered that the applicant´s approach to closely monitor these events in a post-authorisation safety study and in a clinical trial including safety assessment in patients with cardiovascular compromise, as described in the Risk Management Plan, was acceptable.

The issue regarding risk of seizures was discussed under Ground for refusal No. 2, i.e. prior history or current presentation of seizure was agreed by the CHMP to be included as a contraindication. This approach was also supported by the SAG. In this context, the CHMP considered that an observational study further quantifying the risk of seizure will be conducted, as described in the Risk Management Plan.

The CHMP considered the ground for refusal No. 4 was resolved with the measures implemented in the RMP.

Scientific Advisory Group (SAG) Neurology

General comments to the CHMP:

1) The applicant should formulate an indication best reflecting the target population for treatment with fampridine, taking into consideration the level of disability; and formulate responder selection criteria.

2) Evaluation of efficacy in the clinical studies is difficult because there is no CHMP guideline available which the applicant can use for an assessment of symptomatic treatment.

SAG input on the CHMP questions:

1. Walking speed is an outcome that has been correlated with disability in MS. Could you comment on the significance of walking speed as a marker of global MS induced disability? What would constitute a clinically relevant difference, compared to placebo, for this marker?

SAG response: It is self-evident that in a population with multiple sclerosis, the global disability will correlate with a reduction in walking speed. The SAG has not seen evidence for any clear correlation between the T25FW and quality of life or ADL related measures, and therefore cannot make any reliable conclusion. Of the neurological clinicians in the group, the majority accepted that a 20 % difference compared to placebo is probably clinically relevant. One member of the group did not consider 20 % as clinically relevant, since there was no robust evidence for an associated improvement in disability or quality of life-related measures.

2. In MS gait and walking are important determinants of disability. The most used scale, EDSS, is heavily weighted by these items. In the fampridine development patients were mostly at the severe end of the spectrum of EDSS, i.e, their score was >6. In your opinion, what are the treatment expectations for improvement for this severely disabled patient population e.g. in terms of preservation of mobility?

SAG response: The applicant presented data on small subgroups showing that the EDSS did not influence the outcome of the responder analysis. Nevertheless, the drug should not be prescribed without the patients having a significant level of walking impairment, which the applicant should define.

In severely disabled patients, impairment is at least in part due to axonal loss. If this prevails there is probably little room for any clinical improvement due to any pharmacological effect on K+ channels of the residual fibers (see also answer to question 4).

3. The fampridine trials included, as a secondary endpoint, a patient oriented outcome the Multiple Sclerosis walking scale-12. We would like to have your comments about the validity of this outcome as measurement in MS.

SAG response: The group regarded MSWS-12 as the best available tool for patients to record subjective aspects of a range of their walking abilities. The correlation between the responder analysis for T25FW and a definition of response on MSWS-12 should be shown by the applicant.

4. Would you consider it practical to evaluate the response to treatment at an individual level based on monitoring of response by means of the timed walking test. In the event of lack of response when should treatment be stopped; is a delayed response likely?

SAG response: The group recognized that any such test must have clinical utility, and should be simple to use in clinical practice. In general, the T25FW before and within 2 weeks after starting

treatment was considered acceptable. The group has not seen any data on the timing of withdrawal of treatment to assess continued efficacy.

The SAG considered that the development of clinical and/or biological profiles to improve identification of responders (e.g. correlating electrophysiological variables to treatment response) would be desirable.

5. Fampridine was associated with the occurrence of neurological adverse effects, in particular seizures. Could you comment on the impact of this risk and on the contraindication for fampridine patients with known seizures?

SAG response: Although the SAG recognized that seizures occur rarely in patients treated with fampridine, the further analyses presented by the applicant suggest that occurrence of seizures is not a major concern for the overall risk/benefit balance of the product. Pre-existing seizure disorder should be a contraindication to treatment with fampridine.

Overall conclusion on grounds for re-examination

The CHMP assessed the detailed grounds for re-examination and argumentation presented by the applicant in writing and in the oral explanation and considered the views of the re-examination Scientific Advisory Group Neurology.

The latest modified indication applied for by the applicant was

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

With the re-examination, the CHMP considered whether the application for Fampyra would meet the requirements for a conditional marketing authorisation, taking into account the public health interest and the fact that Fampyra is a medicinal product which aims at the treatment of a seriously debilitating disease.

The risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/Ec, is positive.

At the end of the re-examination procedure the CHMP concluded on a favourable benefit-risk balance of Fampyra. The CHMP considered that approximately one third of patients may benefit from the treatment. The CHMP recognised that the product demonstrated benefits in terms of improving walking speed together with improvement on MSWS-12 (multiple-sclerosis walking scale score), i.e. a patient reported outcome measure. Using these two efficacy outcome measures, for which a certain level of relationship was observed, the CHMP considered that it was possible to define a patient population benefiting from treatment with fampridine on both scales. As described above (CHMP position on ground for refusal No. 1), new elements were brought in by the re-examination SAG Neurology; in particular, the 20% improvement based on walking speed was suggested to be of potential relevance, if correlated to patient-reported outcome measures. Furthermore, practical approach to evaluating response to treatment on an individual level, based on monitoring of response by means of a walking test as suggested by the SAG Neurology, was accepted by the CHMP during the re-examination procedure.

Nevertheless, the CHMP was of the opinion that the understanding of benefit provided by fampridine is not completely explained by the data currently available; in particular, other important aspects of walking such as balance, endurance and walking distance that constitute additional evidence of improvement in the overall walking ability were regarded relevant. The CHMP considered that further data obtained in a controlled setting of a clinical trial are needed and that the validity of the currently

proposed criteria for identification of responders should be further evaluated. Therefore, the CHMP requested that the marketing authorisation should be 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. The study report is to be submitted by 30 June 2016."

The CHMP considered that the safety profile of fampridine is dominated by adverse events related to the expression of CNS overstimulation, which is concordant with fampridine´s mechanism of action and that these adverse events are dose-dependent. The CHMP noted that although the adverse events were more frequent in the treated group in the clinical trials, they rarely led to discontinuation and were rated as mild and transitory. The CHMP considered that the main safety issue among events related to overstimulation were seizures, because of the level of seriousness as a health event.

The data presented by the applicant did not allow for quantifying the true incidence of seizures associated with fampridine, but the added risk level was considered low and dose-dependent (some of the events observed were related to medication errors associated with overdose). In their meeting, the re-examination SAG Neurology discussed the seizure risk and recognized that seizures occur rarely in patients treated with fampridine, further data presented by the applicant suggesting that occurrence of seizures is not a major concern for the overall benefit-risk balance of the product. The SAG Neurology recommended that pre-existing seizure disorder should be a contraindication to treatment with fampridine. The CHMP took the SAG Neurology recommendation into account and furthermore, also considered that literature[§] and the applicant´s data from clinical studies with other multiple sclerosis products (disease-modifying drugs) providing evidence on the background incidence of seizures in MS patients were re-assuring in terms of fampridine´s low level of the added risk.

The CHMP concluded that the current therapeutic dose is border-line and that any increase (e.g. overdose) might put patients at higher risk of seizures. In this context, the CHMP considered that an observational study further quantifying the risk of seizure will be conducted, as described in the Risk Management Plan.

Unmet medical needs will be fulfilled

The CHMP considered that the benefits of Fampyra were observed in the field of symptomatic treatment of multiple sclerosis, where there is no other drug approved. In this context, Fampyra was considered to address an unmet medical need by providing symptomatic treatment for walking impairment in patients with MS.

The CHMP further considered that given the lack of symptomatic treatment in MS, extemporaneous formulations of 4-aminopyridine are in use, which might be of lower quality standards and also pose safety problems linked to limited control over their dosing. The formulation of Fampyra, i.e. prolonged-release tablets, was considered to tackle these problems. Thus, the CHMP concluded that placing Fampyra on the market would help address the unmet medical need.

The benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

The CHMP considered that overall, approximately one third of patients treated might get a relevant benefit from the treatment and, in the context of the unmet medical need described above, concluded on a benefit of the immediate availability of Fampyra on the market. The CHMP also considered that patients benefiting form the treatment can be identified on the basis of their response at an early stage

[§] Eriksson M, Ben-Menachem E, Andersen O. Epileptic seizures, cranial neuralgias and paroxysmal symptoms in remitting and progressive multiple sclerosis. Mult Scler 2002; 8 (6):495-9

and that treatment can be discontinued in patients not benefiting, hence preventing unnecessary exposure. The CHMP was of the opinion that data currently not available and required additionally, i.e from *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* do not preclude concluding on a positive benefit-risk balance for the target population.

At the time of the CHMP opinion, there was a quality issue that will be resolved as Follow-up Measure within an agreed timeframe. This issue relates to confirming the in-use period to product close to the end of the shelf-life. However, this issue was not expected to have a negative impact on the benefit-risk balance of the product.

In conclusion, the CHMP confirmed that the criteria needed for granting a Conditional Marketing Authorisation have been met.

Risk Management Plan

SUMMARY of the EU risk management plan

Safety concern	**Proposed Pharmacovigilance activities**	**Proposed risk minimization activities**
Significant Known Risk		
Seizure	Routine pharmacovigilance Observational Study Preclinical seizure threshold study	Routine risk minimization by referencing safety concerns in SmPC and PIL:- Contraindication of fampridine in patients with prior history or current presentation of seizure (SmPC 4.3); Special warning on cautious use of fampridine in the presence of any factors which may lower seizure threshold and on discontinuation of fampridine in patients who experience a seizure while on treatment (SmPC 4.4); Seizure is reported as uncommon adverse reaction in randomised controlled clinical studies, in open label long term studies and in the post marketing setting (SmPC 4.8); Seizure is listed as one of the acute symptoms of overdose with fampridine (SmPC 4.9). Indication to limit continued use of fampridine to those patients showing response early in treatment (SmPC 4.2). Calendar blister packaging Prescribing limited to specialist neurologist
Potential Risk		
Cardiovascular Risk	Routine Pharmacovigilance Clinical study to include assessment of safety in patients with cardiovascular	Precaution and warning in SmPC Section 4.4. about use of fampridine in patients with cardiovascular compromise

	compromise Observational Study	
Effect on steroid hormones (from pre-clinical studies)	Preclinical study and collection of clinical data to assess the presence of any effect	None required
Missing Information		
Special population groups: Patients >65 years Renal function impairment	PK study to evaluate the effect of a dose lower than 10mg BD in subjects with renal impairment, in view of the development of lower dosage form Routine Pharmacovigilance Observational Study	Routine risk minimization by referencing safety concerns in SmPC and PI. SmPC 4.4: Special warning and precautions for use: "Fampyra should not be administered to patients with renal impairment" SmPC 5.2: Pharmacokinetic properties - Special populations: "Fampyra must not be administered to patients with mild, moderate and severe renal impairment" "Fampyra is primarily excreted unchanged by the kidneys, and with creatinine clearance known to decrease with age, monitoring of renal function in elderly patients should be considered"
Special population groups: Pregnancy Children and adolescents	Pregnancy Registry	Routine risk minimization by referencing safety concerns in SmPC and PI. SmPC 4.6: Fertility, pregnancy and lactation: "There are no 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".
Potential interaction with anti-epileptic medications	Preclinical seizure threshold study	None required

The MAA submitted a revised risk management plan.

The CHMP, having considered the data submitted in the application, was of the opinion that no additional risk minimisation activities are required beyond those included in the product information, calendar blister packaging and restricting prescription to specialist neurologists.

Recommendation following re-examination

Based on the CHMP review of data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the benefit-risk balance of Fampyra in the following indication:

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

was favourable and that the application satisfied the criteria for authorisation and recommended the granting of the conditional marketing authorisation.