Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Fampridine

Proprietary Product Name: Fampyra

Sponsor: Biogen Idec Australia Pty Ltd

June 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	13 May 2011
Active ingredient(s):	Fampridine
Product Name(s):	Fampyra
Sponsor's Name and Address:	Biogen Idec Australia Pty Ltd Suite 1 Level 5 123 Epping Road North Ryde NSW 2113
Dose form(s):	Modified release tablet
Strength(s):	10 mg
Container(s):	High density polyethylene (HDPE) bottle
Pack size(s):	14 tablets per bottle, 4 bottles to a carton
Approved Therapeutic use:	The symptomatic improvement of walking ability in adult patients with Multiple Sclerosis who have shown improvement after 8 weeks of treatment.
Route(s) of administration:	Oral
Dosage:	One tablet every 12 hours
ARTG Number:	170002

Product Background

This AusPAR describes the evaluation of a submission to register fampridine (Fampyra) by Biogen Idec Australia Pty Ltd (the sponsor). Fampridine (4-aminopyridine [4-AP]) is the first compound of its class for treatment of multiple sclerosis (MS). It is a selective potassium channel blocker and a lipid-soluble drug which readily crosses the blood-brain barrier. Unlike conventional MS medicines which aim to attenuate the demyelination process, 4-AP offers support in restoring and maintaining the function of damaged nerves in MS patients as a neurofunctional modulator. It acts by blocking the potassium channels in demyelinated nerves which reduces the leakage of current from the axons restoring neuronal conduction and action potential formation.

A common disabling clinical manifestation of damaged nerve function in people with MS is impairment of walking ability caused by disseminated demyelinating lesions in the central nervous system (CNS). The lesions prevent the normal conduction of nerve impulses that control the muscles of posture and movement. By improving conduction of nerve impulses in damaged pathways, fampridine has the potential to lead to better conduction of nerve impulses to, for example, the muscles used in gait. This can be demonstrated by improvement in walking ability. Restoration of, or improvement in, the ability to walk is therefore a measurable and available marker of the benefit of 4-AP.

There is no experience with the prolonged release (PR) formulation of 4-AP. There is extensive literature describing the use of 4-AP compounded by dispensing pharmacists. The main safety concern reported in the literature is risk of seizure.

The indication requested by the sponsor is:

for the treatment of adult patients with MS for improvement of walking ability.

The recommended dose is one PR 10 mg tablet taken twice a daily, 12 hours apart.

Regulatory Status

A similar application was approved in the USA on 22 January 2010. The indication in the US is:

Ampyra (dalfampridine) is a potassium channel blocker indicated to improve walking in patients with multiple sclerosis (MS). This was demonstrated by an increase in walking speed.

An application was refused in the European Union (EU) on 20 January 2011. The Committee for Medicinal Products for Human Use (CHMP) issued a negative opinion with a concern raised of the clinical benefit, particularly whether there is a clinically meaningful benefit. Following re-examination of its previous negative opinion, the Committee adopted a final positive opinion, recommending the granting of conditional marketing authorisation for Fampyra.[1] The recommended indication is:

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

In Canada, a Notice of Deficiency was issued on 22 December 2010. The major concern from Health Canada was in regards to the clinical meaningfulness of the benefit. In addition, Health Canada had some quality concerns (requiring amendments to specifications and manufacturing processes) and further suggested revisions to the Canadian Risk Management Plan. The sponsor has provided a response, which is currently under review.

The application was submitted in Switzerland on 5 March 2010. The filing in Switzerland was withdrawn on 16 April 2011. The application was submitted in New Zealand on 31 Mar 2010 and evaluation is in progress.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

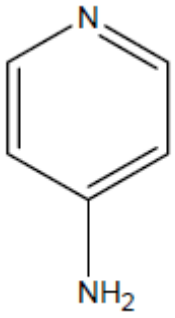
II. Quality Findings

Drug Substance (active ingredient)

Fampridine is 4-aminopyridine (see structure below). It is a crystalline powder with no known polymorphs. It does not exhibit stereoisomerism. It is soluble (> 5%) in aqueous

[1] A conditional marketing authorisation is granted to a medicinal product that fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the risk inherent in the fact that additional data are still required. The marketing authorisation holder is likely to provide comprehensive clinical data at a later stage.

buffers over the entire physiological pH range. It has a pKa of 9.17 and log P (octanol/water) of -0.76. It is classified as BCS Class 1.[2]



Fampridine is manufactured by chemical synthesis. There are no impurities with limits that exceed the applicable International Council on Harmonisation (ICH) qualification threshold. Two potentially genotoxic impurities are controlled to a level of 75 ppm, which corresponds to the Threshold of Toxicological Concern.

The particle size of the drug substance is controlled by laser diffraction.

Drug Product

Fampyra is a matrix type prolonged release tablet formulation. Hypromellose is the rate-controlling excipient. The tablet is film-coated, but the coat does not contribute to the prolonged release properties of the tablet. Due to moisture sensitivity, the tablets are packaged with silica gel desiccant in high density polyethylene (HDPE) bottles. Each bottle contains just 14 tablets so that the contents can be used within one week after the bottle is opened. The product is proposed for supply in cartons of four bottles.

Two significant impurities arise which can be attributed to a reaction of fampridine with derivatives of excipients that are used in the tablets. Both of these impurities are limited at expiry and upon request the corresponding batch release limits were tightened. The proposed limits have been cleared by the Medicines Toxicology Evaluation Section of the TGA.

The applicant also agreed, upon request, to tighten the limits for assay at expiry in order to comply with Therapeutic Goods Order 78.

Adequate stability data have been submitted to support a proposed shelf life of 3 years with storage below 25°C.

Biopharmaceutics

Clinical results using an immediate release capsule showed fampridine to have a narrow therapeutic index. The doses of fampridine required to maintain therapeutic plasma concentrations were linked to serious adverse events (most notably tonic-clonic seizures at plasma levels greater than 100 ng/mL). Therefore, fampridine was developed as a prolonged release tablet formulation. The formulation has remained unchanged through

[2] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

all Phase II and Phase III clinical studies. This formulation is proposed for registration with the addition of the debossed identifier 'A10' on one side of the tablet.

The absolute bioavailability of fampridine immediate release and enteric coated tablets has been reported in the literature as 95%. An absolute bioavailability study has not been performed using the prolonged release tablet because of poor tolerance to intravenous administration.

The 10 mg prolonged release tablet was shown to be bioequivalent to an oral solution of fampridine in terms of the area under the plasma concentration time curve (AUC) (Study BE10-25F-SR10OS122003). As expected, the time to maximal plasma concentration (T_{max}) was longer (3.7 hours [h] compared to 1.1 h) and the maximal plasma concentration (C_{max}) lower (by 57%) for the tablet compared to the solution.

Study FeFa10F-SR-2008 showed that a high fat meal had no significant effect on the extent of absorption of fampridine from the 10 mg prolonged release tablet, although the mean C_{max} was increased by 23%. The highest individual C_{max} result in the fed state was 51 ng/mL (compared to 42 ng/mL fasted), which is still well below the 100 ng/mL level at which serious adverse events occur. The proposed Product Information (PI) indicates that the tablets may be taken without regard to meals.

Study BE10F-SR22004 demonstrated that tablets manufactured at either of the two proposed manufacturing sites are bioequivalent.

In an attempt to establish an *in vitro in vivo* correlation (IVIVC) (Study 0497-010), four batches of 15 mg prolonged release tablets were manufactured with 20%, 40%, 60% and 80% hypromellose. The 60% tablet was a direct scale of the 10 mg tablet proposed for registration. The four tablets showed a rank order correlation in dissolution rate, with greater levels of hypromellose giving slower dissolution rates (for example, 17.5% in one hour for the 80% tablet compared to 30.5% in one hour for the 20% tablet). However, the range of dissolution results was fairly narrow, with the 20%, 40% and 60% tablets all complying with the proposed dissolution specification and the 80% tablet only just failing (48.4% dissolved at the 4 h time point compared to the specification of 49-69%). The four tablets showed no significant differences in C_{max} or AUC and so an IVIVC was not pursued further.

All of the submitted bioavailability studies were single dose studies. One clinical multiple dose study (Study TQTc-F-SR001) included pharmacokinetic measurements. After dosing with the 10 mg tablet every 12 hours for 5 days, C_{max} was 25.3 ± 4.0 ng/mL and the minimum (trough) plasma concentration (C_{min}) was 9.34 ± 1.76 ng/mL.

Quality Summary and Conclusions

A number of issues were raised following the initial evaluation of this application. All of those issues were satisfactorily resolved, including minor amendments of the PI.

There were no objections in terms of chemistry, manufacturing and controls to registration of this product.

III. Nonclinical Findings

Introduction

The submission contained a satisfactory set of toxicity studies (acute toxicity, repeat dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity), with all relevant studies being conducted according to Good Laboratory Practice (GLP) except for the two *in vivo*

safety pharmacology studies. Pharmacokinetic and toxicokinetic data were also adequate. Primary pharmacology data were limited.

Pharmacology

Primary pharmacodynamics

Only a single *in vitro* primary pharmacology study was conducted by the sponsor. Literature studies submitted were neither comprehensive nor supported by an adequate expert overview. Three reviews and a drug profile were included in the literature references submitted but two of the reviews were published about 30 years ago.

MS is characterised by areas of demyelination in the central nervous system (CNS) and many of the neurological signs/symptoms of MS have been attributed to conduction deficits, probably associated, at least in part, with leakage of ion current through the potassium channel (see Judge & Bever, 2006).[3] The neurological benefits of fampridine are generally believed to be achieved by its ability to block potassium channels and thereby reduce current leakage and increase conduction of action potentials in demyelinated axons.

The study demonstrated the ability of fampridine to concentration-dependently block cloned human voltage-gated potassium channels (K_v) of the K_v1.1, 1.2 and 1.4 subfamilies. Literature data were provided on the ability of fampridine to inhibit a more extensive range of K_v subfamilies (Gutman *et al*., (2005)/IUPHAR and review by Judge and Bever, 2006).[3,4] Block of the late phase of outward current and an increase in action potential were also reported in studies by Sherratt and colleagues in demyelinated rat axons (Sherratt *et al*., 1980 and Bostock *et al*., 1981).[5,6]

The median inhibitory concentration (IC_{50}) values for fampridine inhibition of K_v1.1, K_v1.2 and K_v1.4 were 242, 399 and 399 µM (about 22,750, 37,500 and 37,500 ng/mL), respectively. The values for K_v1.1 and K_v1.2 were similar to those reported by Gutman *et al*. (2005)/IUPHAR.[44] For K_v1.4, there was a large discrepancy between the IC_{50} value from that reported by Gutman *et al*. (2005)/IUPHAR (399 and 13,000 µM, respectively) but the data compiled by Judge and Bever (2006) showed a wide range of values (647-13,000 µM), with the sponsor-determined value just outside this range. The data from Gutman *et al*. (2005)/IUPHAR and Judge and Bever (2006) reveal that fampridine is a broad spectrum potassium channel blocker, inhibiting a number of differentially localised K_v channels, with IC_{50} values varying over the µM to mM range. The precise channels underlying the beneficial effects of fampridine remain undetermined.

IC_{50} values for fampridine in most identified K_v channels are greater than the plasma C_{max} at the maximum recommended human dose (MRHD) (about 25 ng/mL), with the sponsor-determined values for K_v1.1 and K_v1.2/K_v1.4 being about 900 and 1,500 fold the clinical C_{max}, respectively. These values would also be greater than CNS concentrations, as rat studies with radiolabelled fampridine found the CNS/blood ratio of radioactivity to be 1.5/1, suggesting the absence of any marked preferred distribution into the CNS. As the potassium channel values are not predictive of clinical efficacy, it is possible that

[3] Judge SIV, Bever CT. Potassium channel blockers in multiple sclerosis: Neuronal Kv channels and effects of symptomatic treatment. Pharmacol Ther 2006; 111: 224-259.

[4] Gutman GA, Chandy KG, Grissmer S et al. International Union of Pharmacology. LIII. Nomenclature and molecular relationships of voltage-gated potassium channels. Pharmacol Rev 2005; 57: 473-508.

[5] Sherratt RM, Bostock H, Sears TA. Effects of 4-aminopyridine on normal and demyelinated mammalian nerve fibres. Nature 1980; 283: 570-572.

[6] Bostock H, Sears TA, Sherratt RM. The effects of 4-aminopyridine and tetraethylammonium ions on normal and demyelinated mammalian nerve fibres. J. Physiol 1981; 313: 301-315.

fampridine blocks an as yet unidentified K_v channel or that demyelinated axons are more sensitive to the potassium channel inhibitory effect of fampridine compared with the cloned channels used in the *in vitro* studies. However, available *in vivo* data are also not predictive of efficacy at the MRHD. Thus, in rat non-myelinated nerve fibres *in vitro* (Bostock *et al*., 1981), fampridine induced a maximal increase in the amplitude of action potentials at about 1 mM (94,000 ng/mL or >3,750 fold the clinical C_{max}).[6] The threshold concentration inducing an effect was not determined in this study. In injured guinea spinal cord strips, the threshold for an effect on action potential amplitude was 0.5-1 µM (47-94 ng/mL) in chronically injured and 1-10 µM (94-940 ng/mL) in acutely injured tissue (Shi and Blight, 1997; Shi *et al*., 1997).[7,8] However, these concentrations are still double or more those achieved in MS patients, and the model may not be relevant to MS.

Some of the pharmacological activity of fampridine may be due to increased neuromuscular transmission and muscle contractions (see Hayes, 2007).[9] Thus, in single fibres of an isolated mouse nerve-hemidiaphragm preparation, Molgo *et al*. (1980) found that fampridine increased transmitter release from motor nerve terminals, but mainly at concentrations above about 5 µM (470 ng/mL).[10] Other primary pharmacological mechanisms have been proposed, such as immunomodulation, but are likely to be secondary to increasing conduction of action potentials and synaptic transmission (review by Judge and Bever, 2006).[3]

No studies in *in vivo* animal models of MS, such as experimental autoimmune encephalomyelitis (EAE), were submitted. It is known there are problems with such models and the sponsor claimed that technical difficulties precluded such studies. Overall, the nonclinical primary pharmacology data are not suggestive of efficacy at the proposed clinical dose and clinical data will need to be relied on to support efficacy.

Data suggested that fampridine metabolites, 3-hydroxy-fampridine and 3-hydroxy-fampridine sulfate are unlikely to contribute to the primary pharmacological activity of fampridine as they were, respectively, >30 fold and >50 fold less potent than fampridine at the three potassium channels tested (Kv1.1, Kv1.2 and Kv1.4).

No pharmacodynamic drug interaction studies were conducted.

Safety and secondary pharmacology

Secondary pharmacology

No secondary pharmacology data were submitted. It would be expected that secondary pharmacological activity would be associated with the potassium channel blocking activity of fampridine. The data reported by Gutman *et al*. (2005) show that fampridine inhibits many potassium channels which are located in a wide range of tissues throughout the body and, particularly, in the nervous system.[4] However, as noted above, the concentrations that were effective in inhibiting these potassium channels were generally well above those achieved in the clinic.

[7] Shi R, Blight AR. Differential effects of low and high concentrations of 4-aminopyridine on axonal conduction in normal and injured spinal cord. Neuroscience 1997; 77: 553-562.
[8] Shi R, Kelly TM, Blight AR. Conduction block in acute and chronic spinal cord injury: different dose response characteristics for reversal by 4-aminopyridine. Exp Neurol 1997; 148: 495-501.
[9] Hayes KC. Fampridine-DR for multiple sclerosis and spinal cord injury. Expert Rev Neurotherapeutics 2007; 7: 453-461.
[10] Molgo J, Lundh H, Thesleff S. Potency of 3,4-diaminopyridine and 4-aminopyridine on mammalian neuromuscular transmission and the effect of pH changes. Eur J Pharmacol 1980; 61: 25-34.

Safety pharmacology

Safety pharmacology studies were restricted to a core battery which included an electroencephalogram (EEG) study, 2 *in vitro* cardiovascular studies and one *in vivo* cardiovascular and respiratory study (respiratory investigation was limited to respiratory rate, with other respiratory parameters not examined). These studies were supplemented with electrocardiogram (ECG) and functional observation battery (FOB) or neurological examination data from the repeat dose toxicity studies. Further safety pharmacology studies were not required because the repeat dose toxicity studies did not raise any cause for concern with organ systems such as renal, gastrointestinal or endocrinological.

Excitatory CNS effects, pro-convulsive activity in particular, were the main adverse effects observed in the nonclinical toxicity studies (see below), and the EEG study investigated the threshold concentration of fampridine for CNS toxicity in rats (discussed below). The CNS effects of fampridine are likely to be associated with potassium channel inhibition although the specific potassium channels underlying the pro-convulsive effects of fampridine remain undetermined. Potassium channel openers and blockers play an important role in convulsions, and Chugh *et al*. (1993) showed that the potassium channel opener, BRL 38227 protected against digoxin-induced convulsions in rats, while fampridine antagonised the protective effects.[11]

Given that fampridine blocks potassium channels and that hERG codes for a potassium channel (K_v11.1), it is important that the effect of fampridine on the hERG ion channel was investigated. Fampridine inhibited hERG channel current *in vitro* only at high concentrations, with an IC_{50} of 3.83 mM (360,000 ng/mL) which is 14,400 fold the C_{max} at the MRHD. In dog Purkinje fibres *in vitro*, increases in the action potential duration at 30% (APD_{30}), APD_{50} and APD_{90} values were observed only at 500 µM (47,000 ng/mL), which is nearly 2,000 fold the C_{max} at the MRHD. In the *in vivo* dog cardiovascular study, 15 minutes (min) intravenous (IV) infusions at up to 1.5 mg/kg, repeated after 2 h had no effect on ECG. Peak plasma fampridine concentrations (up to 1960 ng/mL) were nearly 80 fold the C_{max} expected clinically.

The effect of fampridine on ECG parameters was investigated in a number of the repeat dose toxicity studies in dogs (2 week study with 3x/day dosing, both 13 week studies and the 52 week study) but the only study which provided quantitative data and which reported the time of measurement after dosing was one of the 13 week studies. In this study, measurements were made pre-dose and at 1 to 2 h post dose (about the T_{max}). C_{max} value (combined sexes) at the high dose (HD) in dogs was up to 399 ng/mL (about 16 fold the human C_{max} at the MRHD). Minimal/no effects on ECG were observed in the repeat dose dog toxicity studies, in particular there was no evidence for an effect of fampridine in prolonging the QTc interval. Fampridine was also found to have no effect on mean arterial, systolic and diastolic blood pressure during week 13 in the 13 week toxicity study in dogs. Mean C_{max} (combined sexes) during week 13 was 148 ng/mL, about 6 fold the human C_{max} at the MRHD.

Pharmacokinetics and Relative Drug Exposures

Adequate data on absorption, metabolism and excretion (ADME) were presented for rats and dogs, the two main species used in the toxicity studies. Distribution was also investigated in rats. ADME characteristics of fampridine were similar for rats, dogs and humans. Orally administered fampridine was rapidly and completely absorbed, with a T_{max} between about 0.25-1.5 h in all three species. Bioavailability was estimated at about 60%

[11] Chugh Y, Saha N, Sankaranarayanan A, Sharma PL. BRL 38227-a potassium channel opener, antagonizes digoxin-induced convulsions. Pharmacol Toxicol 1973; 73: 1-2.

in rats and 95% in humans (published data for humans; bioavailability not determined in dogs).

Clearance was more rapid in rats (44 mL/min/kg) than in humans (10.2 mL/min/kg; published data), with an intermediate value (21 mL/min/kg; published data) in mongrel dogs. Plasma half-life was short (about 1-2 h) in rats and dogs, and about 2-3 h in humans.

Systemic exposure increased with increasing oral dose in rats, dogs, rabbits and humans, and after dietary administration in mice and rats but was often slightly less than dose proportional. With repeated dosing, there was generally little accumulation of fampridine in any of the test species (except after dietary administration in mice and rats). No clear differences in systemic exposure to fampridine were observed between males and females in mice, rats, dogs or humans.

Fampridine is lipid soluble and widely distributed, with the volume of distribution in rats, dogs and humans being high (3.4, 2.5 and 2.6 L/kg, well above body water; dog and human values from the literature). After oral administration of [^{14}C]fampridine to rats, concentrations of radioactivity in all tissues/organs except fat were higher than those in blood/plasma, and fampridine and/or its metabolites crossed the blood/brain barrier. Tissue:blood ratio was highest in the kidneys and was also high in the urinary bladder, consistent with renal excretion being the major route of excretion in rats, as well as in dogs and humans. In rats and dogs, respectively, 89.1% and 91.0% of orally administered [^{14}C]fampridine was excreted in urine over 72 h, compared to 1.3% and 1.1% in faeces, while in humans 95.85% was excreted in urine over 24 h and 0.51% in faeces. Given the extensive renal clearance of fampridine, accounting for about 90% of total clearance, the sponsor conducted clinical studies in subjects with varying degrees of renal impairment, and the proposed PI contraindicates fampridine in moderate or severe renal impairment. It also suggests caution when fampridine is prescribed concurrently with drugs significantly affecting renal function and notes the possibility of an interaction of fampridine with other drugs that are renally secreted.

Hydroxylation to 3-hydroxy-fampridine, followed by sulfate conjugation of 3-hydroxy-fampridine was the major route of metabolism in rats, mice, dogs, pregnant rabbits and humans, as revealed by data from studies with [^{14}C]fampridine in rats and dogs (investigation of plasma and urinary metabolite, respectively) and toxicokinetic bridging studies. 3-Hydroxy-fampridine sulfate was a major circulating metabolite in all species, and similarly for 3-hydroxy-fampridine, except in the rat and humans in which it was a minor circulating metabolite. AUC values for 3-hydroxy-fampridine sulfate were about 2-4 fold that of parent drug in mice, dogs and pregnant rabbits, about half that of parent drug in rats and about 43% of parent drug in humans. Corresponding values for 3-hydroxy-fampridine were about 60% in mice, dogs and pregnant rabbits, 6% in rats and 1-9% in humans.

In the rat study with [^{14}C]fampridine, there were two minor unidentified circulating metabolites, both found at similar concentrations to those of 3-hydroxy-fampridine. A subsequent study revealed fampridine-N-oxide to be a major metabolite in mice and a minor metabolite in rats given dietary fampridine. In mice, as well as rats, concentrations were similar to those of 3-hydroxy-fampridine. Levels of fampridine-N-oxide were not determined in dogs. One minor circulating metabolite in rats remained unidentified.

Fampridine was rapidly metabolised, as evidenced by an early T_{max} for 3-hydroxy-fampridine and 3-hydroxy-fampridine sulfate in plasma after oral administration to rats, dogs and pregnant rabbits (T_{max} for both metabolites occurred at about 0.5-2 h in the three laboratory animal species and were similar/slightly longer than the T_{max} for parent drug). Similarly, in humans after administration of prolonged release tablets, T_{max} for metabolites

were similar/slightly longer than the T_{max} for parent drug (3-5 h vs 3 h for parent drug). Fampridine/metabolites were rapidly excreted in rats, dogs and humans, with excretion being largely complete within 24 h. At 24 h post an oral [^{14}C]fampridine dose in rats, <1% of administered radioactivity remained in the animal and concentrations of radioactivity in all tissues were very low or not detectable.

The overall results of studies with human liver microsomes (correlation analysis and chemical inhibition studies) and studies using recombinant human cytochrome P450 (CYP) enzymes suggested that the main P450 cytochrome responsible for the metabolism of fampridine in humans was CYP2E1, although results were not clear cut.

Plasma protein binding was not appreciable (<10% in rats, dogs and humans at concentrations of 50 and 500 ng/mL and <21% at a concentration of 5 ng/mL), being highest in rats, followed by dogs, then humans, at these concentrations. Given the low level of protein binding, it would not be expected that fampridine would interact with highly protein bound drugs.

Extent of absorption was slightly reduced by food in dogs (29 % lower AUC in fed compared with fasted dogs). Similarly, in humans, AUC values tended to be slightly lower in the fed state in several studies but the effect of food on AUC was not marked.

Potential drug interactions are important because of the serious consequences (convulsions) of raised fampridine concentrations. Interactions of intraperitoneal (IP) amitriptyline and baclofen (a commonly used drug in MS patients) and also caffeine, with IV fampridine (fampridine kinetics only were investigated) in rats revealed significant but not marked increases in fampridine AUC (42%, 21% and 30% with the respective drugs). The authors considered that the effects of amitriptyline and caffeine on AUC (and clearance) may have been due to errors in concentration estimation. The routes of administration chosen for this study (for both fampridine and interacting drugs) were not optimal and the reasons for the possible errors were not explained in detail. A follow-up clinical study (oral route) was conducted on baclofen fampridine interactions but no effect on fampridine pharmacokinetics was observed. Additional interaction studies were also conducted in humans.

In studies in human liver microsomes and cryopreserved human hepatocytes, there was little inhibition by fampridine (at concentrations up to 30 μM and 100 μM, in the respective studies; that is >100 and ~375 times, respectively, the clinical C_{max}) of the major CYP isozymes. Fampridine (at concentrations up to 25 μM, ~95 times the clinical C_{max}) had little or no activity in inducing major CYP enzymes in primary cultures of human hepatocytes and limited activity was observed in rats *in vivo* (2 mg/kg IP for 3 days induced a 2.3 fold increase in CYP2B1 which was a considerably smaller increase than that induced by 80 mg/kg/day phenobarbitone IP (about 7.7 fold). Although no pharmacokinetic data were available for IP administration, if it assumed that similar systemic exposure results following IP and IV administration, then the area under the plasma concentration time curve from time zero to infinity ($AUC_{0-\infty}$) achieved would be about 770 ng.h/mL based on the data from study M-2001-03 (IV administration), which is about 3 fold the human AUC. Therefore, it seems unlikely that fampridine would cause any CYP-dependent drug-drug interactions. Fampridine was not found to be a p-glycoprotein substrate or inhibitor. Thus, fampridine is unlikely to affect the pharmacokinetics of drugs that are substrates of p-glycoprotein and the pharmacokinetics of fampridine are unlikely to be affected by drugs that inhibit p-glycoprotein. Detailed exposure comparisons are shown in Tables 1-3.

Table 1: Exposure comparisons

Species (study no.)	Duration (weeks) §	Dose (mg/kg/day) and route	$AUC_{0\text{-}24\ h}$ (ng.h/mL)^	C_{max} (ng/mL)	AUC exposure ratio (ER)*
General toxicity					
Mouse (7338-103)	13	Dietary 2 12.5 80	 226 899 5542	 16 63 319	 0.45 1.8 11
Rat (7338-104)	26	Dietary 2 6 18	 582 1398 4922	 47 107 316	 1.1 2.8 10
Dog (7338-106)	52	PO 0.75 1.5 3	 536 1063 2071	 121# 222# 460#	 1.1 2.1 4

§ duration refers to main study (study numbers refer to toxicokinetic bridging studies); ^ AUC for mice and dogs is combined values for males and females, and AUC data for rats are for males (day 28 for mice and rats dietary route, day 14 for dogs); * $AUC_{0\text{-}24\ h}$ relative to a human value of 508 (derived from multiplying by 2 the $AUC_{0\text{-}t}$ value of 254.1 ng.h/mL obtained in study no. RD10F-SR012004 (section 6.7) with a dose of 10 mg/kg) (this AUC was the highest AUC observed for fampridine given as the 10 mg prolonged release tablet and was similar to the value of 252.2 ng.h/mL observed in MS patients given fampridine as the 10 mg prolonged release tablet in study no. AN751-101); # after second dose.

Table 2: Exposure comparisons for metabolites

Species (study no.)	Duration (weeks) §	Dose (mg/kg/day) and route	3-Hyroxy-fampridine		3-Hyroxy-fampridine sulfate	
			$AUC_{0\text{-}24\ h}$ (ng.h/mL)^	AUC exposure ratio (ER)*	$AUC_{0\text{-}24\ h}$ (ng.h/mL)^	AUC exposure ratio (ER)#
Mouse (7338-103)	13	Dietary 2 12.5 80	 177 715 4401	 3.4 14 84	 520 1896 13891	 2.4 9 65
Rat (7338-104)	26	Dietary 2 6 18	 27 80 361	 0.5 1.5 7	 294 734 2305	 1.4 3.4 11
Dog (7338-106)	52	PO 0.75 1.5 3	 296 596 1192	 6 11 23	 2137 4101 8295	 10 19 39

§ duration refers to main study (study numbers refer to toxicokinetic bridging studies); ^ AUC for mice and dogs is combined values for males and females, and AUC data for rats are for males (day 28 for mice and rats dietary route, day 14 for dogs; * $AUC_{0\text{-}24\ h}$ relative to a human value of 52.6 (derived from multiplying by 2 the $AUC_{0\text{-}t}$ value of 26.3 ng.h/mL obtained in study no. RD10F-SR012004); # $AUC_{0\text{-}24\ h}$ relative to a human value of 213.8 (derived from multiplying by 2 the $AUC_{0\text{-}t}$ value of 106.9 ng.h/mL obtained in study no. RD10F-SR012004).

Table 3: Exposure ratios from reproductive toxicity studies

Species (study no.)	Duration (weeks) §	Dose (mg/kg/day) and route	$AUC_{0\text{-}24\ h}$ (ng.h/mL)^	AUC exposure ratio (ER)*
Rat (7338-105)	Males ~12 weeks	PO 1	517	1.0
		3	1479	2.9
		9	3486	7
Rat (7338-105)	Non-pregnant females	PO 1	601	1.2
		3	1451	2.9
		9	4078	8
Rat (7338-105)	Pregnant females, GD 13	PO 1	666	1.3
		3	1519	3
		9	4168	8
		10	4631&	9
Rat (7338-105)	Pregnant females, GD 20	1	750	1.5
		3	2036	4
		6	3253	6
Rat (7338-105)	Lactating females, PPD 14	PO 1	699	1.4
		3	1813	4
		6	3462	7
Rabbit (7338-107)	GD 13	PO 1	1016	2.0
		3	2538	5
		5	4397	9

§ duration refers to main study (study numbers refer to toxicokinetic bridging studies); ^ day 14 for male and non-pregnant female rat reproductive toxicity; * $AUC_{0\text{-}24\ h}$ relative to a human value of 508 (derived from multiplying by 2 the $AUC_{0\text{-}t}$ value of 254.1 ng.h/mL obtained in study no. RD10F-SR012004 (section 6.7) with a dose of 10 mg/kg); & value extrapolated from AUC at 9 mg/kg/day.

Toxicology

General toxicity

Single dose toxicity studies

Single dose toxicity studies were adequate. The doses administered to dogs (up to a total dose of 5 mg/kg orally [PO], divided into 4 equal doses) failed to cause mortality or clinical signs but two other species (rats and rabbits) were investigated and higher doses in dogs were given in several of the repeat dose studies. The median lethal dose (LD_{50}) was estimated in rats as 14.3 and 22.1 mg/kg in males and females, respectively. Toxicity was reduced when the daily dose was divided into 4 equal doses (LD_{50} for combined sexes of 40.4 mg/kg). LD_{50} in rabbits was similar to that in rats (22.7 mg/kg, combined sexes). Most deaths occurred within 1-2 days after dosing. Neurological clinical signs such as convulsions, tremors, ataxia, hyper- and hypo-activity, increased respiration, dyspnoea, abnormal gait/stance, impaired limb function, prostration, impaired righting reflex, excess salivation, vocalisation, piloerection and dilated pupils were observed in all studies, except in dogs. Clinical signs were first observed soon after dosing, generally within the first hour, consistent with the rapid absorption of fampridine.

Repeat dose toxicity studies

Extensive repeat dose toxicity testing was conducted in rats and dogs by the oral route, with study durations up to 13 and 52 weeks, respectively. Appropriate dose range finding studies for the rat and mouse dietary carcinogenicity studies were conducted using dietary administration, with study durations up to 13 and 26 weeks, respectively.

There was little evidence of target organ toxicity or haematological changes. No consistent clinical chemistry, organ weight, macroscopic or histological changes were observed in the single or repeat dose toxicity studies that were suggestive of target organ toxicity. Changes that were observed in some studies, such as congestion and haemorrhage in various organs, most notably the lungs, appeared to be agonal changes. The most notable non-neoplastic change considered related to treatment was an increased incidence of decubital ulcers (and associated swelling/thickening of the foot observed macroscopically and inflammation observed microscopically) seen in the rat carcinogenicity study. Enlargement of regional lymph nodes (observed macroscopically) and reactive hyperplasia (observed microscopically) was likely to be secondary to the foot ulceration, as was hypercellularity of the femoral and sternal bone marrow. An increased incidence of decubital ulcers was not observed in the 26 week rat study (the same route and similar doses as the carcinogenicity study), so this effect of fampridine was elicited only after long term dosing. The mechanism by which fampridine induces this effect is not clear.

Neurological clinical signs were the most notable findings in the repeat dose toxicity studies in rats and dogs and were similar to those seen in the acute toxicity studies in rats and rabbits. In contrast, clinical signs were not observed in mice, even at lethal doses, possibly due to the particularly extensive (and rapid) metabolism of fampridine to less neuroactive metabolites in this species (see below). The neurological clinical signs observed are likely to be exaggerated pharmacological effects and in most studies, deaths appeared to be associated with the neurological effects. Generally, there were no macroscopic or microscopic changes indicating cause of death.

As in the single dose studies in rats, the dosing regimen employed affected mortality and clinical signs in repeat dose studies in rats and dogs, with these being reduced when administration was as a divided dose (3 or 4 equally divided doses) as opposed to a single larger dose. For example, in most of the repeat dose dog studies from 1 week to 1 year, the threshold dose for producing convulsions lay in the range 1.5-3 mg/kg/day, except when the dose was divided into 3 or 4 equal doses rather than a single daily dose, in which case, the threshold increased to >6 mg/kg/day (this is consistent with the acute toxicity study in dogs in which 5 mg/kg/day divided into 4 equal doses did not induce convulsions). Additionally, clinical signs were observed at a lower dose following an immediate release formulation compared with a sustained release formulation. Thus, mortality and clinical signs appear to be related more to peak plasma drug concentrations than AUC. This might be expected given the neurological nature of the clinical signs and the associated mortality.

It would appear that individual animals that experience convulsions have plasma concentrations above the group mean values. In the study that addressed this issue, plasma fampridine concentrations in samples taken from dogs during seizures were >110 ng/mL, that is > 4 fold the human C_{max} at the MRHD. This is consistent with the threshold plasma concentration for induction of convulsions in rats.

A reduction in body weight gain was a consistent finding in repeat dose toxicity studies in rats and was observed in the 52 week dog study.

Exposure ratios (ER) achieved in the pivotal repeat dose toxicity studies were adequate, being up to >11 in the 13 week dietary mouse study, about 10 in the 26 week dietary rat

study and 4 in the 52 week oral dog study. Due to the more extensive metabolism of fampridine in the mouse and dog than in humans, even higher ERs were achieved for the two major fampridine metabolites in these species, with maximum ERs for 3-hydroxy-fampridine being >84 in the 13 week dietary mouse study, about 7 in the 26 week dietary rat study and 23 in the 52 week oral dog study, and corresponding maximum ERs for 3-hydroxy-fampridine sulfate being >65, about 11 and 39.

Fampridine is proposed for use in adults and no studies were conducted in juvenile animals.

Genotoxicity and carcinogenicity

Genotoxicity

The genotoxicity studies submitted, comprising five *in vitro* tests (two bacterial reverse mutation tests, two forward mutation studies at the $TK^{+/-}$ locus in mouse lymphoma L5178Y cells and a chromosome aberration study in Chinese hamster ovary [CHO] cells) and two *in vivo* micronucleus studies (one in mice and one in rats), exceeded requirements. All these studies were well conducted and in accordance with GLP. The concentrations/doses were selected after appropriate dose-range finding studies and were adequate, except for one study in which percent total growth was 78% and 81% in two of the three trials. However, the other forward mutation study achieved satisfactory levels of cytotoxicity. Although mitotic indices were not measured in one study, adequate cytotoxicity was achieved. The choice of species for S9 metabolic activation (rat) was appropriate, in view of the metabolic profile. None of the genotoxicity studies provided any evidence that fampridine is genotoxic.

Carcinogenicity

Dietary carcinogenicity studies (104 weeks) were conducted in mice and rats. Studies were GLP compliant and adequately conducted, although histological examination was not done on all low dose (LD) and mid dose (MD) animals in the mouse study, which hampered interpretation of the results. There was a significant increase in the incidence of uterine polyps in HD female rats but there was not a well defined dose-response relationship and no evidence of carcinogenic changes in the uterus of either rats or mice. Overall, there was no evidence of a carcinogenic effect of fampridine in either species. ERs (based on toxicokinetic data from the bridging studies) at the HD were adequate in mice and rats, being 11 and 10 for fampridine, 84 and 7 for 3-hydroxy-fampridine, and 65 and 11 for 3-hydroxy-fampridine sulfate, respectively.

Reproductive toxicity

Placental transfer and excretion of fampridine into milk were not investigated. Otherwise, a full set of reproductive toxicity studies was submitted (fertility and early embryonic development, embryofetal development and pre-postnatal studies in rats and an embryofetal development study in rabbits, with toxicokinetic data from bridging studies covering both species and all study segments). Studies were GLP compliant and adequately conducted.

Results of the fertility and early embryonic development study in rats, the embryofetal development studies in rats and rabbits and the pre-postnatal development study in rats showed that there were no effects of treatment on fertility/reproductive performance or embryofetal development (oestrus cycling, mating, pregnancy, gestation length and litter parameters). Systemic exposures to fampridine (AUC) at the HD in the respective animal studies were 7 for males (♂)/8 for females (♀), 9, 9 and 6 times that in humans at the recommended dose. Corresponding ERs for 3-hydroxy-fampridine were 5(♂)/8(♀), 8, 54 and 4, and for 3-hydroxy-fampridine sulfate, 10(♂)/2(♀), 1.4, 33 and 5, respectively. In all

of these studies, maternal toxicity was observed (deaths, clinical signs and/or reduction in body weight gain), with No Observable Effect Level (NOEL) values for maternal toxicity of 1, <1, 1 and 1 mg/kg/day in the respective studies (corresponding to ERs of 1.2-1.3, <1.3, 2 and 1.5, respectively).

Some effects on pups after birth were observed following maternal treatment with fampridine. Thus, at the HD in the fertility and early embryonic development study (which included a littering subsection), pup body weight gain over lactation was reduced and there was a tendency for reduced pup survival from birth to postpartum Day 4. In the pre-postnatal development study, pup survival was reduced from birth to postpartum Day 35 at the HD and pup body weight gain at the MD and HD was reduced from birth to postpartum Day 4 (at the HD, this reduction continued to after weaning). NOEL values for pup developmental effects were 3 and 1 mg/kg/day in the respective studies. ER was 1.4 at 1 mg/kg/day and 4 at 3 mg/kg/day.

Impurities/degradation products

Methylene bridge (N,N-di-4-pyridinyl-methanediamine)

In order to qualify this degradation product, the sponsor conducted two genotoxicity studies (a bacterial reverse mutation test and a chromosome aberration study in CHO cells) and a 4 week PO toxicity study in rats in which fampridine was spiked with 2.0% methylene bridge.[12] This is an acceptable set of studies for qualification of a degradation product. Both the genotoxicity studies were negative. It was disappointing that the 4 week rat toxicity study did not include a comparator group receiving fampridine alone. Doses were similar but not identical in the two studies. In both studies, there were reductions in food consumption and body weight gain at all doses. Convulsions were observed at the HD in the study with spiked fampridine, while only tremors were observed in the study with fampridine alone, however, mortalities were higher in the study with unspiked drug. Overall, there was no clear evidence of greater toxicity of fampridine + methylene bridge than of unspiked fampridine. In the spiked study in rats, the highest dose of methylene bridge was 15 mg/kg/day x 2% = 0.3 mg/kg/day = 1.8 mg/m^2/day, which is about 13x the 'dose' which would be consumed clinically if present at 1% in the product (20 mg/day fampridine dose = 0.4 mg/kg/day (in a 50 kg person) x 1% = 0.004 mg/kg/day = 0.132 mg/m^2/day)[13].

2-HBA (N-(4-pyridyl)-2-hydroxybutyramide)

No studies were conducted to qualify this other degradation product. The intake of fampridine is 20 mg/day, and under the relevant TGA-adopted EMEA guideline, the qualification threshold for a drug with an intake of 10-100 mg/day is 0.5% or 200 µg total daily intake, whichever is lower.[14] The intake of 2-HBA at 0.5% is 100 µg/day, so 0.5% is lower. Thus, the proposed limit is acceptable.

Fampridine-N-oxide

The FDA evaluation report on fampridine queried the potential genotoxicity of the impurity fampridine-N-oxide, based on structural alerts (DEREK assessment was not

[12] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

[13] In the absence of exposure data for the impurity, dose comparisons based on body surface area have been used.

[14] EMEA, ICH Topic Q 3 B (R2), June 2006. Note for Guidance on Impurities in New Drug Products, CPMP/ICH/2738/99.

considered adequate). When queried by the TGA, the sponsor responded that fampridine-N-oxide had been shown to be a metabolite in mice, rats and humans, and the response included an evaluation report in which the plasma AUC values for fampridine-N-oxide from these 3 studies were compared. The exposure to this impurity in mice (640-1043 ng.h/mL) and rats (120 ng.h/mL) was considerably greater than corresponding exposure in the clinical study (4.50-4.56 ng.h/mL). The relevant TGA-adopted EMEA guidelines indicate that impurities that are also significant metabolites in animal and/or human studies are generally considered qualified.[14]

Nonclinical Summary and Conclusions

Primary pharmacology data were limited, with only a single *in vitro* study conducted by the sponsor. Literature studies submitted were neither comprehensive nor supported by an adequate expert overview. The neurological benefits of fampridine are generally believed to be achieved by its ability to block of potassium channels, and thereby reduce current leakage and increase conduction of action potentials in demyelinated axons. Some of the pharmacological activity of fampridine may also be due to increased synaptic transmission and neuromuscular tension. However, fampridine activity *in vitro* and *in vivo* was only observed at much higher concentrations than plasma C_{max} at the maximum recommended human dose (MRHD). No studies in *in vivo* animal models of MS were submitted. Nonclinical data did not predict clinical efficacy, which will need to be adequately demonstrated by the clinical data.

No secondary pharmacology data were submitted. It would be expected that secondary pharmacological activity would be associated with blocking activity at many potassium channels located in a wide range of tissues.

Safety pharmacology studies were restricted to a core battery, which is acceptable. Data from *in vitro* studies (hERG and dog Purkinje fibres) and *in vivo* (IV dog study and ECG in repeat dose dog toxicity studies) did not predict adverse cardiovascular events in the clinic.

The pharmacokinetic characteristics of fampridine in the main species used in the toxicity studies (rats and dogs) were similar to those in humans. Orally administered fampridine is rapidly and completely absorbed. Clearance is rapid and plasma half life is short. Fampridine is lipid soluble and widely distributed, with a volume of distribution well in excess of body water. Fampridine/metabolites cross the blood/brain barrier. Fampridine and its metabolites are rapidly excreted, mainly via urine. Fampridine is contraindicated in renally impaired patients.

Metabolism of fampridine by hydroxylation to 3-hydroxy-fampridine, followed by sulfate conjugation of 3-hydroxy-fampridine, was demonstrated in humans and test species (mice, rats, dogs, rabbits). N-oxidation was also demonstrated in mice and rats. CYP2E1 appeared to be the major enzyme responsible for the 3-hydroxylation of fampridine. Plasma protein binding was not appreciable.

No pharmacodynamic drug interaction studies were conducted. A pharmacokinetic drug interaction study (IP baclofen, amitriptyline and caffeine, with IV fampridine in rats) had some deficiencies. Interaction with baclofen (oral) was further investigated in a clinical study. There was no evidence that fampridine induced or inhibited CYP enzymes. Fampridine was neither a substrate nor an inhibitor of P-glycoprotein. Interactions with other drugs by these mechanisms are therefore unlikely.

Toxicity studies (acute, repeat dose, genotoxicity, carcinogenicity and reproductive toxicity) were adequate, being well conducted and with all relevant studies being GLP

compliant. Bridging toxicokinetic studies provided data for plasma concentrations of fampridine and its two major metabolites in all relevant species by relevant routes.

Single dose oral toxicity studies were conducted rats, rabbits and dogs. Repeat dose toxicity studies by the oral route were conducted in rats (1, 2 and 13 weeks) and dogs (1, 2, 13 and 52 weeks) and by the dietary route in mice (2 and 13 weeks) and rats (2, 4 and 26 weeks). The main feature of these studies was neurological toxicity, with convulsions being the main adverse effect. The threshold plasma concentration for induction of convulsions was about 110 ng/mL in rats and dogs (> 4 fold the human C_{max} at the MRHD). Peak plasma concentrations were reduced for a prolonged release formulation *cf* an immediate release formulation. There was no consistent evidence in either species of target organ toxicity. Adequate systemic exposures to fampridine and its metabolites were achieved in these studies (exposure ratio (ER) up to about 10 and 4 in the 26 week rat study and 52 week dog studies, respectively; corresponding ERs for 3-hydroxy-fampridine were about 5 and 13, and for 3-hydroxy-fampridine sulfate, about 11 and 39). No local tolerance studies were conducted.

The genotoxicity studies comprised five *in vitro* tests (two bacterial reverse mutation tests, two forward mutation studies at the $K^{+/-}$ locus in mouse lymphoma L5178Y cells and a chromosome aberration study in CHO cells) and two *in vivo* micronucleus studies (one in mice and one in rats), exceeding requirements. All tests gave negative results.

Two year carcinogenicity studies were conducted in mice and rats using the dietary route. Exposure ratios of 11 and 10 were achieved at the HD in mice and rats, respectively, and there was no evidence of a carcinogenic effect of fampridine. In HD female rats, there was an increase in the incidence of uterine polyps, but no evidence of any carcinogenic changes in the uterus in rats or mice.

Placental transfer and excretion into milk were not investigated, but a complete set of reproductive toxicity studies was submitted, using the oral route. There was no evidence of an effect of fampridine on fertility in rats or on embryofetal development in rats or rabbits. Fampridine was not teratogenic in rats or rabbits. In a pre-postnatal development study in rats, no effects of fampridine were observed at the LD (exposure ratio about 1.5), but higher doses were associated with reduced pup survival and weight gain. Exposure ratios up to about 6-9 were achieved in all the reproductive toxicity studies.

Proposed limits for degradation products in the product, methylene bridge (N,N-di-4-pyridinyl-methanediamine) and 2-HBA (N-(4-pyridyl)-2-hydroxybutyramide), were NMT 1% and 0.5%, respectively. Methylene bridge was qualified to a level of 2.0% by two genotoxicity studies (bacterial reverse mutation and chromosomal aberration; both with negative results) and a 4 week toxicity study in rats with fampridine spiked with 2.0% methylene bridge. The proposed limit of 0.5% for 2-HBA is at the qualification threshold and no qualification is therefore required. The impurity fampridine-N-oxide is a metabolite in mice, rats and humans and is therefore qualified.

Issues addressable from the nonclinical data

Adequate toxicity studies were submitted. These studies revealed that the main safety issue for fampridine is its pro-convulsive activity. The threshold plasma concentration for induction of convulsions was about 110 ng/mL in rats and dogs (> 4 fold the human C_{max} at the MRHD). There was no evidence of target organ toxicity, genotoxicity, carcinogenicity or cardiovascular safety issues and safety margins were adequate. Reproductive toxicity was observed in neonates of dams administered fampridine (reduced viability and body weight gain) but fampridine was not embryotoxic or teratogenic.

There are no nonclinical reasons that would preclude the registration of fampridine for the proposed indication at a dose of 10 mg twice daily. Six additional nonclinical studies are planned or in progress, at the request of the FDA. When available, final reports of these studies should be submitted to the TGA.

Issues likely to be addressable from the clinical data

Nonclinical data did not predict clinical efficacy, which will need to be adequately demonstrated by the clinical data.

IV. Clinical Findings

Introduction

The clinical evaluator identified 48 biopharmaceutical studies comprising:

- 8 bioavailability (BA) study reports
- 4 comparative BA and bioequivalence (BE) study reports
- 1 *in vitro-in vivo* correlation study report
- 11 reports of bioanalytical and analytical methods for human studies
- 2 reports of hepatic metabolism and drug interaction studies
- 3 reports on healthy subjects pharmacokinetic (PK) and initial tolerability studies
- 10 reports on patient PK and initial tolerability studies
- 1 intrinsic factor PK study report
- 2 extrinsic factor PK study reports
- 3 reports on healthy subject pharmacodynamic (PD) and PK / PD studies
- 3 reports on patient PD and PK/PD studies:

The clinical evaluator identified 11 efficacy and safety studies on multiple sclerosis comprising:

- 4 controlled clinical studies pertinent to the claimed indication
- 5 uncontrolled clinical studies:
- 1 report of analyses of data from more than one study:
- 1 other clinical study report

In addition, there were 12 efficacy and safety studies on spinal cord injury and 2 efficacy and safety studies on Guillain Barré Syndrome.

Pharmacokinetics

Introduction

To support the approval of the application, the clinical pharmacology and biopharmaceutics program for fampridine, consisted of 20 clinical studies, focusing on relative bioavailability of various oral formulations; pharmacokinetic characterization in healthy volunteers, MS patients and special populations; elucidation of the drug-drug interaction potential both *in vitro* and *in vivo* with commonly used concomitant medications; population pharmacokinetic and exposure-response analyses using data from various Phase 1, 2 studies and the pivotal clinical trials.

Methods

Pharmacokinetic data analysis

Pharmacokinetic methods were rigorous. The duration of blood sampling and the washout period are appropriate given the half-life of the parent drug.

Statistical analysis

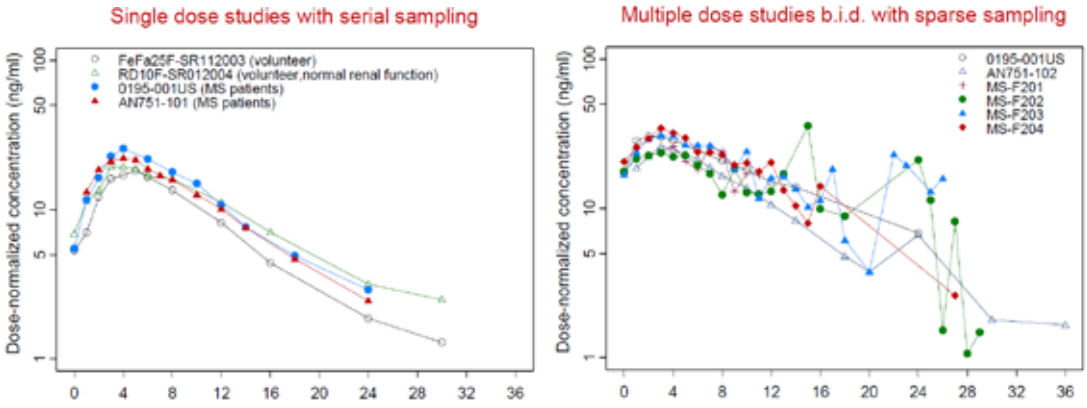
Statistical methodology was appropriate. Where appropriate, pharmacokinetic data for different doses of 4-AP were compared using a two-way analysis of variance (ANOVA). Differences were assessed between mean values for plasma concentrations at each sampling time, AUC, C_{max}, the ratio of peak to trough plasma concentration calculated at 6 h (C_{max} /C(t)), T_{max}, mean residence time (MRT), elimination half-life ($t_{1/2}$), elimination rate constant (k_{el}) and time cover (the duration of time for which plasma concentrations of 4-AP were equal to or greater than four specified values, chosen to represent values from the upper to lower end of the range of plasma 4-AP concentrations in this single dose phase). Ninety percent confidence intervals (CI) were calculated to compare the treatment groups. If the normalised confidence intervals for the dose-dependent parameters (AUC and C_{max}) contained 100%, this was taken as evidence of dose proportionality. The % coefficient of variation (CV) of C_{max} and AUC values was estimated as a measure of intersubject variability. Statistically significant differences between the treatments were detected at a probability level (p) of less than 0.05.

Absorption

Bioavailability

The plasma C_{max} and AUC values of fampridine increased in a dose proportional manner following single-dose administration of 5-25 mg (Figure 1). Dose proportionality was also observed with 5-20 mg administered twice daily (bd) as a tablet in the fasted state and further confirmed with fampridine sustained release (SR) 12.5 mg tablet following multiple-dose.

Figure 1: Plasma concentration-time profile following an oral dose of fampridine SR tablet in healthy volunteers and MS patients normalised to 10mg dose



The steady-state concentrations of fampridine SR in plasma are achieved within 4 days of bd dosing. This is consistent with its apparent elimination half-life in plasma of approximately 5-6 h.

Pharmacokinetic and absorption, distribution, metabolism and excretion studies in animals with an immediate release formulation used in later toxicology studies have shown that absorption occurs mainly in the small intestine. In humans, fampridine is rapidly and almost completely absorbed from gastrointestinal tract following oral administration.

Bioequivalence

The pharmacokinetics of the different fampridine formulations have been evaluated in both healthy subjects and those with MS. Early studies of fampridine were conducted

using an IV formulation (for example, Study Rush-001), after which an IR (immediate release) formulation for oral administration was developed (for example, Study 1091-001). The IR formulation consisted of fampridine powder in a gelatin-based capsule. Administration of the IR capsules resulted in fampridine plasma levels in excess of 100 ng/mL (for example, Study 0494-006 and Study ela/g-9101), which were associated with seizure activity in clinical trial subjects. Additionally, bioavailability of this formulation was shown to be significantly decreased (37% less peak plasma level) when administered to subjects in a fed state compared to a fasted state. Subsequently, a CR (controlled-release) capsule was developed (Study 0492-002). While this formulation yielded longer half-life and lower peak plasma levels following administration, the CR capsules were susceptible to degradation by ambient humidity, and the gelatin-based capsules were found to leech fampridine. A SR (sustained-release) matrix tablet was then developed. Clinical studies have demonstrated that the SR matrix tablets are bioequivalent to the earlier formulations, however, slightly lower peak plasma concentrations are observed following administration (Study 1194-002).

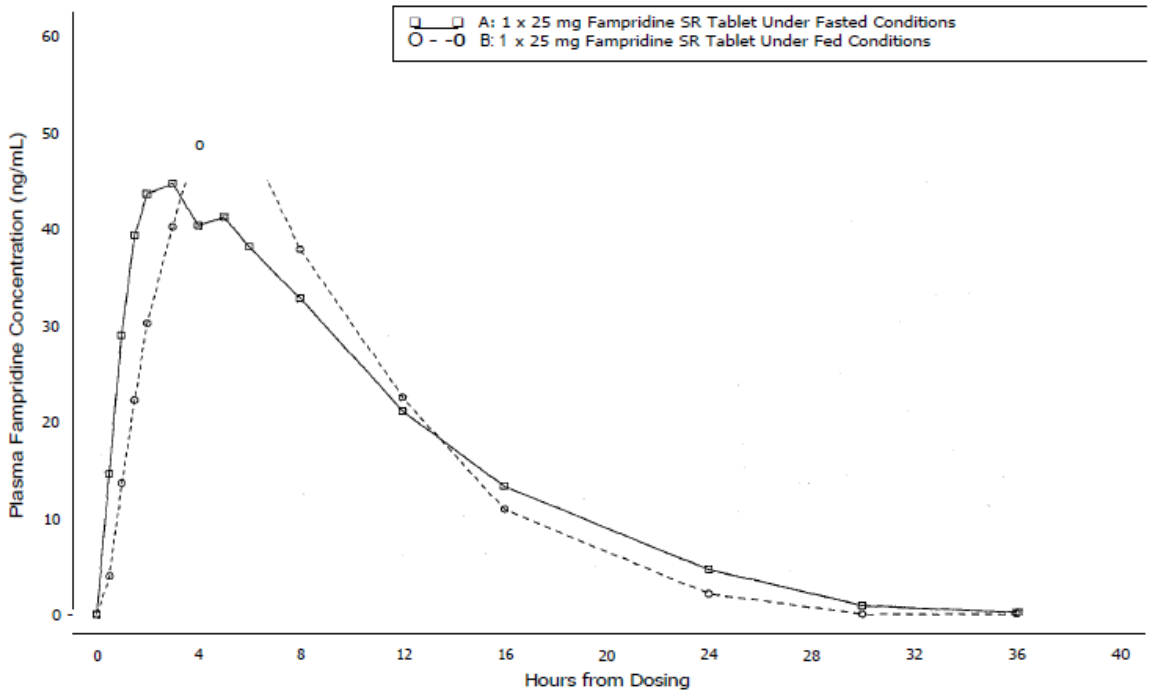
The relative bioavailability of fampridine SR 10 mg dose used in the pivotal Phase III studies MS-F203 and MS-F204 as compared to a 10 mg buffered aqueous oral solution (0.83mg/ml) was 96% when compared to an aqueous oral solution under fasting conditions. The sustained release tablet delays absorption of fampridine relative to the solution formulation characterized by lower C_{max} concentration (approximately 40% of those achieved with the oral solution) and delayed T_{max} (from 3.2 hours for the oral solution versus 5.4 to 5.5 hours on average for the sustained release tablets) (Study BE10-25F-SR10OS122003).

A bioavailability study to assess the bioequivalence of the 10 mg strength of fampridine SR tablets was conducted to support the substitution of the product by an alternate manufacturer.

Influence of food

The commercial formulation of the fampridine SR 10 mg tablet utilizes hydroxypropyl methylcellulose as the release rate controlling polymer. With food, absorption is delayed, with the median peak concentration occurring 3.0 hours post-dose in the fasted state and 5.0 hours post-dose in the fed state (Figure 2). Therefore, food had a relatively small impact on C_{max} and AUC (a slight increase of approximately 17% and approximately 5%, respectively under fed conditions). Since fampridine is indicated for chronic dosing, the delay in T_{max} is not considered clinically significant. The results justify administration of fampridine SR tablets with or without regard to food.

Figure 2: Mean plasma fampridine concentration versus time profile (Study FeFa10F-SR-2008)



Distribution

The apparent volume of distribution of fampridine is 2.6 L/kg (Study 0496-002).

The mean protein binding was 1-3%, evaluated over a range of concentrations (5, 50, and 500 ng/ml) and pH (7.2-7.6) (Study HWI 6379-103). Fampridine was largely unbound and had a high free drug fraction at all three concentrations tested.

Elimination

The elimination half-life of fampridine following administration of SR tablet formulation was 5.2 to 6.5 hours. The plasma half-life of the sulfate conjugate is approximately 7.6 hours and the half-life of 3-hydroxy-4-aminopyridine was not determined as concentrations for most subjects were close to or below the limit of quantitation.

Overall renal clearance of fampridine was 22.2 L/hour (370 mL/min), suggests active tubular secretion since it is much higher than the glomerular filtration rate (GFR).

Excretion

Fampridine is not extensively metabolized and mainly eliminated as unchanged drug in urine. Radiolabelled mass balance and metabolism study indicates that fampridine and metabolites are eliminated nearly completely after 24 hours with 96% of the dose recovered in the urine and 0.5% recovery in faeces. Most of the excreted radioactivity in the 0-4 hour pooled urine was parent drug (90.3%). Two metabolites were identified: 3-hydroxy-4-aminopyridine (4.3%) and 3-hydroxy-4-aminopyridine sulfate (2.6%) (Study 0496-002). These metabolites have been shown to have no pharmacologic activity on potassium channels (sponsor's *Nonclinical Overview*).

Metabolism

In vitro studies with human liver microsomes indicate that CYP2E1 was the major enzyme responsible for the 3-hydroxylation of fampridine based on correlation analysis, chemical

inhibition studies and incubations with recombinant human CYP enzymes. Several other CYP enzymes may be involved in playing a minor role in the 3-hydroxylation of fampridine. The 2 major metabolites 3-hydroxy-4-aminopyridine and 3-hydroxy-4-aminopyridine sulfate were identified and both were inactive (Studies xt075077 and xt064039).

Dose proportionality and Time Dependency

Dose proportionality

The plasma C_{max} and AUC values of fampridine increased in a dose proportional manner following single-dose administration of 5-25 mg (Study ELA/G-9101). Dose proportionality was also observed with 5-20 mg administered bd as a tablet in the fasted state (AN751-102).

Time dependency

Steady state fampridine concentrations are achieved within 4 days confirmed with fampridine SR 12.5 mg tablet following multiple-dose (Study 0195-001).

Intra- and Inter-Individual variability

Analysis of serum fampridine levels in patients with steady state levels of fampridine tested a week apart (Study AN751-102 in 18 patients maintained on 20 mg fampridine SR bd) showed no significant differences in C_{max} and AUC levels (Table 4).

Table 4: Serum fampridine pharmacokinetics repeated a week apart in MS patients (Study AN751-102)

Day 8 Cmax (ng/ml) Mean (SD)	Day 15 Cmax Mean (SD)	Paired t P value	Day 8 AUC Mean (SD)	Day 15 AUC Mean (SD)	Paired t P value
66.73 (11.61)	62.58 (14.62)	0.60	531.0 (159.2)	499.2 (113.8)	0.53

The mean percentage difference in C_{max} from measurements taken at T1 compared to T2 was 0.9% (standard deviation [SD] 24%). The mean percentage difference in AUC from measurements taken at T1compared to T2 was 0.8% (SD 25%). Given that the proposed fampridine SR dosage will be 10 mg bd and given the known pharmacodynamics and pharmacokinetics of fampridine, these values are acceptable. However, there is little pharmacokinetic data from extension studies or outside of trials where medication compliance may be more variable.

Pharmacokinetics in the Target population

In a population pharmacokinetic and pharmacokinetic-pharmacodynamic analysis of fampridine SR tablets (Study fsr-pkpd-2008) body mass index, race, subject status (healthy controls vs MS patients - Figure 2) and the most commonly used concomitant medications did not appear to affect the pharmacokinetics

Pharmacokinetics in Special Populations

Hepatic Impairment

Fampridine has not been studied in patients with hepatic impairment. Since fampridine is primarily excreted unchanged in the urine, hepatic insufficiency may not significantly affect fampridine pharmacokinetics or recommended dosing.

Age

A population pharmacokinetic analysis showed that fampridine clearance decreases with increasing age (49L/hr→39L/hr over 20 years to 80 years) (Study fsr-pkpd-2008).

Body Mass Index

Body mass index (BMI) does not appear to affect pharmacokinetics (Study fsr-pkpd-2008).

Gender

A population pharmacokinetic analysis showed that fampridine clearance was approximately 14.5% lower for females (36 L/hr) at the same age and creatinine clearance (CrCL). Also, the volume of distribution was found to be significantly lower in females as compared to males (Study fsr-pkpd-2008).

Race (Caucasian vs Non-Caucasian)

There were no effects of ethnicity observed on fampridine pharmacokinetics in the analyses. However, data from other races is limited according to the sponsor, although there were a small number of Black, Asian, Hispanic and Other subjects captured in the database and the disease is predominantly occurs in Caucasians (Study fsr-pkpd-2008).

Renal Impairment

The effects of renal impairment on the pharmacokinetic profile were studied in single-dose administration of fampridine SR in subjects with normal renal function, mild, moderate or severe renal impairment (RD10F SR012004). The mean C_{max} and $AUC_{0-\infty}$ of fampridine increased by 67% and 75% in mildly impaired subjects, by 60% and 105% in moderately impaired subjects, and by 100% and 299% in severely impaired subjects, respectively, when compared to normal subjects. The mean C_{max} and $AUC_{0-\infty}$ of 3-hydroxy-4-aminopyridine sulfate increased by 35% and 80% in mildly impaired subjects, by 123% and 216% in moderately impaired subjects, and by 8 fold and 26 fold in severely impaired subjects, respectively, when compared to normal subjects. The apparent total body clearance of the drug from plasma after oral administration (CL/F) and renal clearance (CLr) of fampridine showed significant relationship ($p < 0.0001$ for CL/F and $p = 0.0001$ for CLr) with creatinine clearance. No studies of the effect of renal impairment on steady state pharmacokinetics have been done.

Evaluator's overall comments on pharmacokinetics in special populations

The evaluator advised extreme caution in patients with renal impairment. Safety data on patients with mild renal impairment is too limited to allow specific recommendations for fampridine's use in this population. A daily dosage could be justified in patients with mild to moderate impairment but there are no or limited pharmacokinetic, efficacy or safety data to guide recommendations. Patients with severe renal impairment should not receive fampridine SR on the basis of currently available data.

Interactions

***In vitro* pharmacokinetic interactions**

In vitro data with human liver microsomes showed that fampridine was not a direct or time dependent inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 at concentrations up to 30 µM. This is approximately 10 times the average plasma fampridine concentration measured for the 10 mg tablet caused 12% inhibition of CYP2E1.

Fampridine had had little or no potential to induce CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2E1 or CYP3A4/5 enzyme activities in human hepatocytes at concentrations up to 25 µM.

In vitro studies indicated that fampridine is neither a substrate of the P-gp (MDR1MDCK, MDCK cells), nor an inhibitor of digoxin (Caco-2 cells) transport activity.

***In vivo* pharmacokinetic interactions**

Drug-Drug Interaction with Baclofen

The study of single dose 15 mg fampridine SR co-administered with 10 mg baclofen in 12 healthy male volunteers did not show a PK interaction (Study 0194-002).

Drug-Drug Interaction with Beta-Interferon

The impact of 7.5 mg three times daily (tds) of fampridine immediate release formulation co-administered with 8 million units of interferon beta-1b (Betaseron) in 3 male and 6 female MS patients showed that fampridine kinetics were comparable following administration of fampridine alone (steady state C_{max} of 56.7 ng/mL and the area under the plasma concentration time curve from time zero to 8 hours (AUC_{0-8}) of 216.0 ng·hr/mL) or following coadministration of interferon beta (steady state C_{max} of 50.1 ng/mL and AUC_{0-8} of 207.2 ng·hr/mL). No pharmacokinetic drug-drug interaction of interferon beta1b was observed on fampridine plasma levels. These results were confirmed by population PK analysis of coadministration of fampridine SR 10 mg tablet with Betaseron, showed no effect on PK parameters.

Population PK analysis evaluating the effect of most commonly used concomitant medications in MS patients indicated no change in fampridine plasma levels as result of coadministration of these concomitantly used medications. Common concomitant medications included baclofen, glatiramer acetate, interferon beta, tizanidine, renal transport inhibitors (including ACE inhibitors, nitrofurantoin, trimethoprim-sulfamethoxazole, amoxicillin, and trimethoprim) and diuretics (including hydrochlorothiazides and potassium sparing drugs).

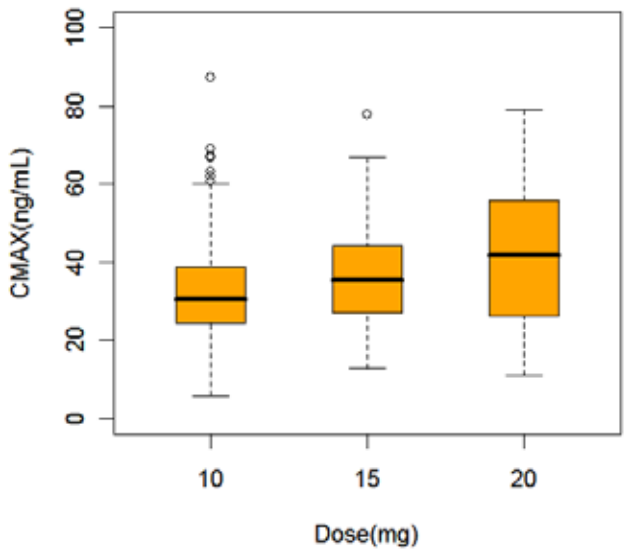
Evaluator's overall comments on pharmacokinetic interactions

The evaluator agreed that there are not likely to be any clinically relevant pharmacokinetic interactions with this drug.

Exposure relevant for safety evaluation

Studies in animals and humans of the adverse effects of fampridine suggest that seizure risk in particular is related to C_{max} rather than AUC. Figure 3 shows the distribution of C_{max} at each dose group.

Figure 3: Distribution of Cmax at each dose group (pooled data from Study MS-F202, 203 and 204)



Evaluator's Overall Conclusions on Pharmacokinetics

In the opinion of the evaluator, the pharmacokinetic program has satisfactorily characterised the key variables for fampridine in MS. However, there are little or no PK data for patients with hepatic or in particular renal impairment; or in children, adolescents, the elderly; or in different racial groups. These issues are adequately reflected in the proposed PI.

Pharmacodynamics

Mechanism of action

Fampridine SR is a sustained-release, orally administered potassium-channel blocker acting in the central nervous system to enhance conduction in demyelinated axons.

Primary pharmacology

MS is a chronic inflammatory disorder of the CNS. It usually first affects people in their 20s or 30s. MS is one of the most common causes of nontraumatic disability among young and middle-aged people. Initially in the disease course, MS involves recurrent bouts of CNS inflammation that result in damage to both the myelin sheath surrounding axons as well as the axons themselves. The majority (85%) of patients with MS initially have a relapsing–remitting disease (RRMS) course characterized by clearly defined alternating episodes of neurologic disability and recovery. Within a period of about 25 years, 90% of patients with RRMS exhibit a secondary progressive disease (SPMS) course characterised by steadily increasing permanent neurologic disability. Approximately 10% of MS patients experience primary-progressive MS (PPMS) characterized by a steady decline in neurologic function from disease onset without recovery and fewer still have initially progressive disease with relapses later – primary relapsing MS (PRMS). Current therapeutic agents for patients with MS are anti-inflammatory or immunomodulatory in nature and only benefit in patients with RRMS.

The pathologic hallmarks of MS lesions include breakdown of the blood–brain barrier, multifocal inflammation, demyelination, oligodendrocyte loss, reactive gliosis and also

axon degeneration. The immune-mediated destruction of CNS myelin and oligodendrocytes is considered the primary pathology in MS. Damage to the myelin insulation of axons results in slowing of impulse conduction, with loss of the capacitative shield and a consequent increase in the time required for the propagating impulse to depolarize downstream portions of the membrane. Conduction block, on the other hand, is due to both loss of myelin's capacitative shielding influence and exposure after demyelination of previously myelinated parts of the axon membrane, which possess only low densities of sodium channels, too low to support high frequency impulse conduction. It is under these conditions that measurable effects on synaptic transmission can be appreciated. Electrophysiological studies of demyelinated axons have shown that abnormal potassium currents decrease action potential duration and amplitude and contribute to action potential failure or conduction block.

Demyelination within the central nervous system can lead to a broad diversity of symptomatic complaints such as visual disturbance, sensory loss, weakness and incoordination; many of which may be heat sensitive. Heat sensitivity is a phenomenon known as Uhthoff's sign. Temporary worsening in MS symptoms can result from even a very slight elevation in core body temperature (one-quarter to one-half of a degree) because an elevated temperature further impairs the ability of a demyelinated nerve to conduct electrical impulses.

Fampridine is a novel symptomatic therapy for MS that is proposed to ameliorate the clinical disability primarily related to demyelination. Early research that documented the ability of 4-AP to increase conduction of action potentials in demyelinated axons, and non-myelinated axons, through inhibition of potassium channels is the rationale for evaluating the clinical efficacy of 4-AP in MS subjects.[3] The concentration dependent ability of 4-AP to block cloned Kv channels has been determined for most members of the Kv1 – Kv4 subfamilies.[5]

In a healthy subject without myelin deficiencies, the blockade of fast, voltage-gated potassium channels plays a minimal role in action potential conduction because the channels are covered by layers of myelin sheath. However, when myelin is destroyed, as is the case in MS, the potassium channels become exposed, shunting local circuit currents and creating impairments in the generation and conduction of action potentials. Demyelination also exposes slow potassium channels, further interrupting normal hyperpolarization and blunting repetitive impulse release from the presynaptic terminal.[15]

However, the major cause of permanent neurologic disability is in fact axon loss which is evident even in early disease stages.[16] Disability related to axonal loss would not be expected to improve with fampridine treatment. Once axon loss surpasses the compensatory capacity of the CNS, irreversible neurologic disability becomes clinically evident and the disease transitions to the SPMS phase.

It is not possible to determine the extent to which the neurological disability of an individual relates to either demyelination or axonal loss. Early clinical trials of fampridine employing a variety of clinical biomarkers reported often marked clinical and electrophysiological responses in the target population. Interestingly, due to the proposed mechanism of action of fampridine, these clinical trials were often restricted to patients

[15] Korenke AR, Rivey MP, Allington DR. Sustained-release fampridine for symptomatic treatment of multiple sclerosis. Ann Pharmacother 2008; 42:1458-1465.

[16] Dutta R, Trapp BD. Pathogenesis of axonal and neuronal damage in multiple sclerosis. Neurology 2007; 68: S22-S31.

displaying temperature sensitive symptoms (thought to be reflective of a significant symptomatic burden linked to demyelination).

Pilot efficacy studies of the effect of fampridine in MS showed significant improvements in a variety of biologically plausible subjective and semiquantitative measures of neurologic function as well as physiologic measures of visual function (contrast sensitivity, critical flicker fusion frequency, visual evoked potentials, visual acuity measurements, saccade peak velocities).[17,18,19]

Early randomised, double blind placebo-controlled, crossover design trials of 4-AP in MS attempted to relate these biomarkers of fampridine's effect to clinically meaningful outcomes. In 1992, Van Diemen and colleagues reported a randomised double blind crossover design trial of oral 4-AP in 69 MS patients. They confirmed effects on visual evoked potentials (VEP) latencies and eye movements as well as finding significant improvements during the 12-week period in Expanded Disability Status Score (EDSS).[20] Later studies with fampridine, however, found no change in the EDSS despite some apparent efficacy with lower limb strength.[17,21]

MS is a disease of profound heterogeneity in clinical course and manifestation. Considerable controversy exists as to the best measures of disease disability and progression.[22] In the TGA-adopted EU guideline on clinical investigation of medicinal products for the treatment of MS, the use of the EDSS is recommended in order to facilitate comparisons with other studies.[23] It should be noted that clinical development of symptomatic therapies (such as fampridine) is acknowledged to be outside the scope of this guideline. However, the EDSS is a widely used and known scale to assess changes in disability in MS. Acceptable efficacy parameter endpoints are time to reach progression or the proportion of individuals who have shown progression at a pre-specified time. The shortcomings of the EDSS as a measure are well known but the guideline recommends additional neurological rating scales, quantitative neuro-performance tests (for example Multiple Sclerosis Functional Composite [MSFC]) or patient and neurologist global opinion as (secondary) measures of disability. The EDSS has a more useful role in detecting progression of disease rather than a patient's perception of disability. It has also been found to have poor relative responsiveness to change when compared to instruments such as the MS Walking Scale 12-item (MSWS-12) and Timed 25 foot walk (T25FW). However,

[17] Bever CT, Jr., Young D, Anderson PA et al. The effects of 4-aminopyridine in multiple sclerosis patients: results of a randomized, placebo-controlled, double blind, concentration-controlled, crossover trial. Neurology 1994; 44: 1054-1059.

[18] Davis FA, Stefoski D, Rush J. Orally administered 4-aminopyridine improves clinical signs in multiple sclerosis. Ann Neurol 1990; 27: 186-192.

[19] Van Diemen HA, Polman CH, van Dongen MM, et al. 4-Aminopyridine induces functional improvement in multiple sclerosis patients: a neurophysiological study. J Neurol Sci 1993; 116: 220-226.

[20] Van Diemen HA, Polman CH, van Dongen TM, et al. The effect of 4-aminopyridine on clinical signs in multiple sclerosis: a randomized, placebo-controlled, double blind, cross-over study. Ann Neurol 1992; 32: 123-130.

[21] Rossini PM, Pasqualetti P, Pozzilli C, et al. Fatigue in progressive multiple sclerosis: results of a randomized, double blind, placebo-controlled, crossover trial of oral 4-aminopyridine. Mult Scler 2001; 7: 354-358.

[22] Foley JF, Brandes DW. Redefining functionality and treatment efficacy in multiple sclerosis. Neurology 2009; 72: S1-11.

[23] EMEA, Committee for Medicinal Products for Human Use (CHMP), 15 September 2005. Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis, CPMP/EWP/568/98 Rev 1.

in cross sectional studies and longitudinal studies, the EDSS has been found to show strong correlation with the T25FW and moderate correlation with the MSFC.[24,25]

Two trials examined the relationship of serum levels to side effects and efficacy.[26] In 1993, it was reported that efficacy was related to total drug exposure whereas toxicity was related to peak serum levels.[17] This observation was supported by a serum concentration-controlled trial of oral 4-AP in 8 MS patients (Study1091-001). Serum levels measured every 4–6 h showed that outcomes were related to the area under the serum concentration curve but that toxicities were related to peak serum levels. In particular, a grand mal seizure and an episode of confusion occurred in patients at the time of peak serum levels (with measured serum levels of >100ng/mL). These results showing that toxicity was related to peak serum levels whereas efficacy was related to total drug exposure suggested that controlled release formulations of 4-AP might have reduced toxicity.

Because of the conclusions reached from the studies of the relationship of the pharmacokinetics of 4-AP to toxicity and efficacy, a slow release formulation of 4-AP was developed. This formulation was tested in a randomized, double blind, placebo-controlled, crossover design trial (Study 0995-001US).[27] Ten MS patients were treated for a week with active drug and for a week with placebo. Outcome measures included timed ambulation, timed stair climbing, quantitative isometric motor testing, manual motor testing, grip strength, and disability as scored by the EDSS and patient subjective responses. Treatment-related improvements were seen in all measures, which were statistically significant only for timed ambulation. Adverse events were limited to mild nausea, dizziness, paraesthesias and insomnia. These results supported the idea that the controlled release formulation retained its efficacy while reducing toxicity.

This subsequently led to a large randomised clinical trial to compare three doses of fampridine (Study MS-F202).[28] Results of the planned portions of the trial were negative. Comparison of each dose group with placebo yielded nonsignificant results on the primary endpoint (percent change in walking speed on the timed 25-foot walk) as well as on seven of the eight secondary endpoints, despite the fact that the sample size was increased from 38 to a minimum of 50 per dose group to meet the requirements of the US Food and Drug Administration (FDA) on the issue of preserving the type I error rate when comparing multiple doses with placebo. Consistent with much of the pilot literature, the endpoint attaining significance was the change from baseline in lower extremity strength, which showed an improvement of roughly 15% over placebo in both the 10 mg and 15 mg dose groups.

Goodman et al. defined a responder *a priori* to be a patient with a greater than 20% improvement from baseline in walking speed averaged over the treatment period.[28] Although the proportion of responders in the 10 and 15 mg dose groups nearly doubled

[24] Cohen JA, Fischer JS, Bolibrush DM, et al. Intrarater and interrater reliability of the MS functional composite outcome measure. Neurology 2000; 54: 802-806.
[25] Cohen JA, Cutter GR, Fischer JS, et al. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. Neurology 2002; 59: 679-687.
[26] Van Diemen HA, Polman CH, Koetsier JC, Van Loenen AC, Nauta JJ, Bertelsmann FW. 4-Aminopyridine in patients with multiple sclerosis: dosage and serum level related to efficacy and safety. Clin Neuropharmacol 1993; 16: 195-204.
[27] Schwid SR, Petrie MD, Murray R, et al. A randomized controlled study of the acute and chronic effects of cooling therapy for MS. Neurology 2003; 60: 1955-1960.
[28] Goodman AD, Cohen JA, Cross A, et al. Fampridine-SR in multiple sclerosis: a randomized, double blind, placebo-controlled, dose-ranging study. Mult Scler 2007; 13: 357-368.

the proportion for placebo (23.5% and 26.0% vs 12.8%), neither comparison attained significance due to lack of statistical power.

In allowing a responder analysis to promote drug approval, the FDA recognizes that "there may be situations when it is more reasonable to characterize the meaningfulness of an individual's response to treatment than a group's response, and there may be interest in characterizing an individual patient as a responder to treatment, based upon pre-specified criteria."[29] Given the current understanding of the biology of MS (that is, the admixture of disability due to demyelination vs axonal loss) a responder analysis may be reasonable.

It is also well know that when clinical trial results do not attain significance, the investigators are prone to searching the database for a subset of patients who might benefit from the therapy.[30] Based on the data Goodman retrospectively defined a responder to be a patient who walks faster than baseline on at least 3 of 5 visits while undergoing therapy. The investigators reported that 36.7% of patients given the drug will be responders (95% CI 33.3– 40.1%). This represents a nontrivial subset of patients that is significantly larger than 8.5%, the proportion of responders to placebo. The clinical relevance of the responder criterion was justified by examining the difference between responder and nonresponder groups, irrespective of treatment, on the MSWS-12, the Subject Global Impression of Change (SGI) and the Clinician Global Impression of Change (CGI). Timed walk responders showed greater improvements than nonresponders in MSWS-12 (p =0.020) and SGI (p = 0.004). The change in CGI scores showed a trend in favour of the responder group (p = 0.056). However, responders cannot be identified beforehand based on demographic data.

The FDA allowed this responder analysis with minor modifications for MS-F203 and noted that, if positive, it could be one of the adequate and well controlled studies that demonstrate efficacy. FDA emphasised that "as usual, the division will evaluate the risk and benefits of the treatment to determine approvability."

Secondary pharmacology

In the literature, the secondary pharmacodynamic effects of 4-AP are also thought to depend on an increased synaptic transmission and neuromuscular tension providing the basis for other clinical indications that have been considered for 4-AP including Eaton-Lambert syndrome, myasthenia gravis, botulism and ketamine antagonism.[31] Enhanced synaptic transmission mediated by 4-AP is thought to result from the abnormal influx of calcium (Ca^{2+}) ions at presynaptic terminals that is generated from the prolonged action current. The presence of increased Ca^{2+} at the synapse then increases transmitter release that, in turn, eventually leads to enhanced neuro-neuronal or neuromuscular transmission.[32] Most studies of effects on autonomic transmission have used concentrations of 5 µM (0.47 µg/mL) and higher within *in vitro* preparations so the extent that this mechanism contributes is not known.[31] However, this mechanism is likely to play a role in generating the adverse effects of 4-AP that are observed at higher doses (for example, seizures).

[29] Kryscio RJ. Fampridine for MS responders: clinically relevant or hypothesis generating? Neurology 2008; 71: 1130-1131.
[30] Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ 2006; 332: 1080.
[31] Bowman WC, Savage AO. Pharmacological actions of aminopyridines and related compounds. Rev Pure Appl Pharmacol Sci 1981; 2: 317-371.
[32] Hayes KC. Fampridine-SR for multiple sclerosis and spinal cord injury. Expert Rev Neurother 2007; 7: 453-461.

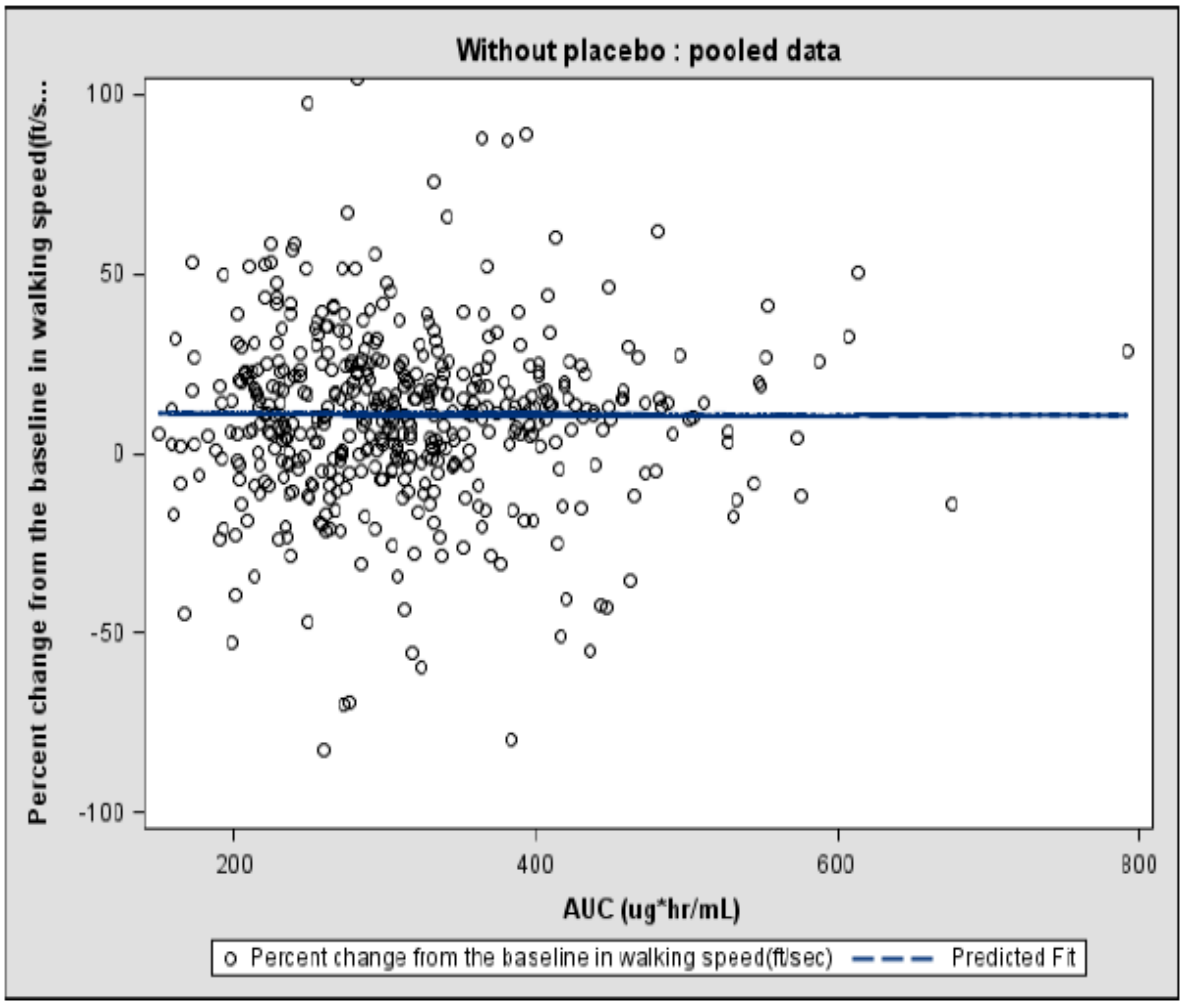
Relationship between plasma concentration and effect

A linear regression analysis has been done for the pooled data of Study MSF202, MS-F203 and MS-F204 to explore the relationship between exposure (AUC) and the percent change from the baseline in walking speed. That analysis included data collected with patients receiving 10 mg bd, 15 mg bd or 20 mg bd.

Figure 4 shows a flat relationship between exposure and change in walking speed (p=0.935), that suggests that the response reached a plateau at 10 mg bd and did not improve with increased exposure.

Figure 4 indicates that a lower dose may be as efficacious as 10 mg bd and the lowest effective dose has not been identified by the development program. The identification of the lowest effective drug is important for drugs with narrow therapeutic index, such as fampridine. Based on this the FDA has requested testing of 5 mg bd fampridine.

Figure 4: Dose-response analysis for efficacy



Evaluator's overall conclusions on pharmacodynamics

A role for aminopyridines in reducing conduction block in multiple sclerosis was first proposed in 1978 long after their epileptogenic properties were described.[33] Pilot studies using biologically plausible biomarkers showed encouraging responses but investigators found it difficult to translate these effects into clinically meaningful endpoints; such as the widely used EDSS. This was partly due to the narrow therapeutic window of the immediate release formulation. In the early 1990s, observations linking clinical toxicity of fampridine to peak serum levels led to the development of a slow release formulation with good stability and better pharmacokinetic properties.[17,26] Subsequent studies with fampridine SR using a range of neurologic measures suggested that improvements in timed walking may be a useful therapeutic effect.[34] This effect was further refined to dichotomise patients into responders and nonresponders based on consistently faster walking during treatment.[28] Clinical meaningfulness was proposed on the basis of group differences between responders and nonresponders (including fampridine and placebo treated subjects in each group). Criticisms of this methodology include its proneness to bias and the conceptual similarity between the T25FWT and the MSWS-12. In the evaluator's opinion, it is biologically plausible that a subgroup of MS patients with established disease could consistently respond to fampridine and show improved timed walking and lower limb strength while on treatment. Therefore, a responder analysis in this case is appropriate.

Dose response analysis for efficacy indicates that the lowest effective dose of fampridine has not been identified by the development program.

Efficacy

Introduction

The clinical program consisted of the following studies:

Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

- **Study No. MS-F201**. A Double Blind, Dose-Ranging Study of Fampridine SR in Subjects with Multiple Sclerosis
- **Study No. MS-F202**. Double blind, Placebo-Controlled, 20-Week, Parallel Group Study to Evaluate Safety, Tolerability and Activity of Oral Fampridine SR in Patients with Multiple Sclerosis
- **Study No. MS-F203**. Double blind, Placebo-Controlled, 21-Week, Parallel Group Study to Evaluate Safety and Efficacy of Oral Fampridine SR (10 mg bd) in Subjects with Multiple Sclerosis
- **Study No. MS-F204**. Double blind, Placebo-Controlled, Parallel Group Study to Evaluate Safety and Efficacy of Oral Fampridine SR (10 mg bd) in Patients with Multiple Sclerosis.

[33] Sears TA, Bostock H, Sheratt M. The pathophysiology of demyelination and its implications for the symptomatic treatment of multiple sclerosis. Neurology 1978; 28: 21-26.

[34] Schwid SR, Petrie MD, McDermott MP, Tierney DS, Mason DH, Goodman AD. Quantitative assessment of sustained-release 4-aminopyridine for symptomatic treatment of multiple sclerosis. Neurology 1997; 48: 817-821.

Study Reports of Uncontrolled Clinical Studies

- **Study No. 0195-001USEXT**. Pharmacokinetic and Tolerability Evaluation of Single Dose Fampridine SR Tablets Under Fed and Fasted Conditions, Single Dose Fampridine SR Capsules Under Fasted Conditions, and Multiple Dose Fampridine SR Tablets in Patients with Multiple Sclerosis [Open Label Extension Phase]
- **Study No. 1293-001USEXT**. An Open Label Dose Tolerability Study of Slow Release Fampridine in Multiple Sclerosis Patients (Extension Phase)
- **Study No. MS-F202EXT**. Open-Label Extension Study to Evaluate the Safety, Tolerability and Activity of Oral Fampridine SR in Subjects with Multiple Sclerosis - Interim Report
- **Study No. MS-F203EXT**. Open-Label Extension Study to Evaluate the Safety, Tolerability and Activity of Oral Fampridine SR in Subjects with Multiple Sclerosis who Participated in the MS-F203 Trial - Interim Report
- **Study No. MS-F204EXT**. Open-Label Extension Study to Evaluate the Safety, Tolerability and Activity of Oral Fampridine SR in Patients with Multiple Sclerosis who Participated in the MS-F204 Trial

Reports of Analyses of Data from More Than One Study

- **Study No. MS-F202-203 Meta**. Validation of a Criterion for Consistency of Response in Walking Speed on the Timed 25 Foot Walk as a Measure of Clinically Meaningful Change for Patients Diagnosed with Multiple Sclerosis

Other Clinical Study Reports

- **Study No. MS-F200**. Randomized, Double blind, Placebo-Controlled Trial of Sustained-Release Fampridine (4-aminopyridine) in Multiple Sclerosis Patients with Internuclear Ophthalmoplegia (INO)

Reports of Efficacy and Safety Studies (Spinal Cord Injury)

Study Reports of Uncontrolled Clinical Studies

- **Study No. SCI-F201EXT**. Open-Label Extension of Double blind, Placebo-Controlled, Parallel Group Study To Evaluate Safety, Tolerability and Activity of Oral Fampridine SR in Subjects with Chronic, Incomplete Spinal Cord Injury
- **Study No. SCI-F300EXT**. Open-Label Extension of Double blind, Placebo-Controlled, Parallel Group Study to Evaluate Safety, Tolerability and Activity of Oral Fampridine SR in Subjects with Chronic, Incomplete Spinal Cord Injury

Other Clinical Study Reports

- **Study No. SCI-001**. A Pilot Phase I Safety and Pharmacokinetic/Pharmacodynamic Study of Oral 4-Aminopyridine in Spinal Cord Injury
- **Study No. SCI-101**. Open Label, Single Dose Study to Determine Pharmacokinetics of Fampridine SR in Patients with Spinal Cord Injury
- **Study No. SCI-102**. Open Label Study to Determine Pharmacokinetics of Fampridine SR after Multiple Doses in Patients with Spinal Cord Injury
- **Study No. SCI-103**. Open Label Study to Determine Multiple Dose Pharmacokinetics of Fampridine SR at Higher Dose Levels in Patients with Chronic Spinal Cord Injury

- **Study No. SCI-200**. Phase II, Double blind, Placebo-Controlled, Dose Escalating Study to Evaluate Safety and Efficacy of Oral Fampridine SR in Patients with Spinal Cord Injury
- **Study No. SCI-F201**. Double blind, Placebo-Controlled, Parallel Group Study to Evaluate Safety, Tolerability and Activity of Oral Fampridine SR in Subjects with Chronic, Incomplete Spinal Cord Injury, and to Evaluate a New Subject Diary/ Questionnaire
- **Study No. SCI-F203**. The Effect of Oral Fampridine SR on Pulmonary Function in Subjects with Chronic Tetraplegia.
- **Study No. SCI-F301**. Double blind, Placebo-Controlled, 12-Week Parallel Group Study to Evaluate Safety and Efficacy of Oral Fampridine SR in Subjects with Moderate to Severe Spasticity Resulting from Chronic, Incomplete Spinal Cord Injury
- **Study No. SCI-F302**. Double blind, Placebo-Controlled, 12-Week Parallel Group Study to Evaluate Safety and Efficacy of Oral Fampridine SR in Subjects with Moderate to Severe Spasticity Resulting from Chronic, Incomplete Spinal Cord Injury
- **Study No. 0295-001US**. A Randomized, Double blind, Placebo-Controlled, Cross-Over Dose-Titration Study of Fampridine SR Administered BID to Patients with Incomplete Spinal Cord Injury

Reports of Efficacy and Safety Studies (Guillain Barré Syndrome)

Other Clinical Study Reports

- **Study No. CGBS Phase 2a**. Assessment of Improvement of Motor, Sensory and Functional Status of Chronic Guillain- Barré Syndrome with the Use of 4-Aminopyridine (Phase IIA)
- **Study No. CGBS Phase 2b**. Assessment of Improvement of Motor, Sensory and Functional Status of Chronic Guillain- Barré Syndrome with the Use of 4-Aminopyridine (Phase IIB)

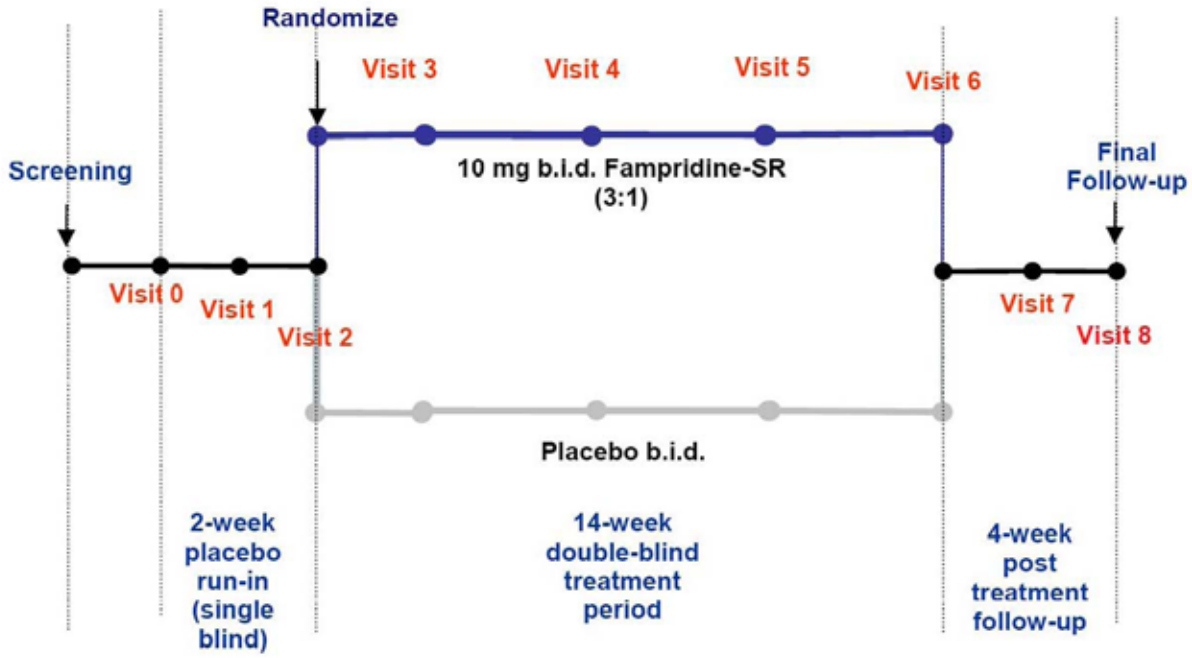
Pivotal studies

MS-F203

Methods

MS-F203 was a Phase III, double blind, placebo-controlled, parallel group, 21 week study (one week post screening, two weeks of single blinded placebo run-in, 14 weeks of double blind treatment and four weeks of no treatment as follow-up) in patients diagnosed with MS. The scheme of the study design is shown in Figure 5.

Figure 5: Scheme of the overall study design



Objectives

The objectives were to assess the safety and efficacy of 10 mg bd fampridine SR in patients diagnosed with MS, in a double blind, placebo controlled, parallel group study

Study Participants

The study involved 240 patients from approximately 30 centres in the US and Canada who:

- Had clinically defined MS
- Were able to complete 2 trials of the T25FW in an average time of 8-45 seconds (s) at screening
- Had no exacerbations within 60 days (d) of screening
- Had no history of seizures or evidence of epileptiform activity on a screening EEG

Treatments

Participants were randomised 3:1 fampridine SR 10 mg bd to placebo

Outcomes/endpoints

1. The primary measure of efficacy was based on changes in walking speed (in feet per second) as measured by the T25FW from the MSFC: a response analysis was performed to determine the numbers of subjects who show a consistent improvement while on drug. A responder was defined as a subject with a faster walking speed for at least three visits during the double blind treatment period (Visits 3 through 6) as compared to the maximum speed for any of the pre-treatment visits (Screening Visit, Visits 0, 1 and 2) and the first post-treatment visit (Visit 7).

2. The clinical significance of this improvement was examined by comparison of changes from baseline in average score on the MSWS-12 for those subjects who show consistent improvement compared to those who do not
3. The maintenance of improvement over the course of treatment was examined by comparing the walking speed at the last on drug visit with the baseline walking speed for those subjects who show a consistent improvement while on fampridine SR compared to subjects on placebo treatment.

Related secondary measures of efficacy were:

· Lower Extremity Manual Muscle Testing (LEMMT)

· Ashworth Score for spasticity

· SGI

· CGI

Statistical Considerations

A sample size of 180 subjects treated with fampridine SR, along with 60 placebo subjects, will provide approximately 90% power, at an overall significance level no greater than 0.05 and no less than 0.000125 to detect the necessary differences for this study to be considered positive with regard to demonstration of efficacy. Assumptions for power calculation –

1. Responder rate fampridine 35.3% vs 8.5% placebo
2. Average Change in MSWS12 responders -11.8 vs -2.5 nonresponders
3. Change in walking speed (ft/sec) fampridine responders 0.45 vs 0.04 placebo

Patients were randomised to either 10 mg fampridine SR or placebo treatment group in a 3:1 ratio according to a computer generated randomisation scheme. The randomisation scheme is blocked and stratified by treatment site and was created prior to the study.

The trial primary efficacy variable was responder status, based on consistent improvement in walking speed on the Timed 25-Foot Walk. A Timed-Walk responder was defined as a subject with at least three of the four on-treatment walking speeds faster than the fastest walking speed achieved among five off-treatment visits (that is, the four pretreatment visits and the two week post treatment visit).

The sponsor justified the use of responder status variable. Clinicians previously noted a subset of MS patients appeared to respond to fampridine treatment. The selective responsive may be related to the restoration of conduction in demyelinated axons through blockade of voltage-dependent potassium channels. The variability of MS pathology may mean that only proportion of the patients have axons that are susceptible to fampridine's effects. The sponsor further supported the existence of the subset of consistent fampridine responders among MS patients with results of *post hoc* analyses of earlier trials.

Based on the responder status, the sponsor proposed a multi-stage primary endpoint for the MSF203 trial. The three stage, stepwise analysis served two purposes: to establish a positive outcome on the primary endpoint, and to establish its clinical meaningfulness with respect to overall walking ability.

The ***first step*** was to show a significantly greater proportion of Timed Walk responders in the fampridine SR group as compared to the placebo group.

The ***second step*** was to register a significant improvement in MSWS-12 score for the Timed Walk responders when compared to Timed-Walk nonresponders.

The ***third step*** was to demonstrate statistically significant improvement in walking speed in fampridine-treated responders compared to the placebo group (responders plus nonresponders) at the last visit on treatment. The sponsor suggested the third step to confirm maintenance of effect by testing whether those patients who responded to fampridine SR on the T25FW would still register a significant improvement in walking speed relative to placebo treated patients at the last observed double blind visit (that is, the change from baseline in walking speed at the double blind endpoint).

The intent to treat (ITT) population was based on all randomized subjects who received treatment and had at least one efficacy (T25W and MSWS-12) evaluation during the double blind treatment period.

The Cochran Mantel Haenszel (CMH) test was used to analyse treatment differences in the proportion of responders between fampridine treated and placebo treated groups while controlling for centre.

The sponsor compared the average change from baseline in the MSWS-12 score over the double blind treatment period between responders vs nonresponders (that is, responder status) using an analysis of variance model with effects for responder status and centre. The sponsor performed similar analyses for responders compared to nonresponders on the secondary subjective variables, average SGI score during the double blind period and the CGI score recorded at the end of the double blind period.

The trial secondary efficacy variables were the following:

- Percent change from baseline in walking speed at each double blind visit
- Change from baseline in LEMMT at each double blind visit
- Change from baseline in the Average Ashworth Score at each double blind visit Subjective Variables
- Average SGI score during the double blind period
- The CGI score, recorded at the end of the double blind period

In April 2006, the sponsor made the following changes to the statistical analysis plan before breaking the blind:

- Addition of consistency of improvement in the LEMMT.
- Ordering of secondary endpoints (in order to maintain the overall alpha level less than or equal to 0.05). On meeting the primary endpoint, the secondary endpoints were to be analysed in the following stepwise order:

1. Fampridine SR responders had to be statistically superior to the placebo group with respect to the average change from baseline in LEMMT during the double blind period;
2. Fampridine SR nonresponders had to be statistically superior to the placebo group with respect to the average change from baseline in LEMMT during the double blind period;
3. Fampridine SR had to be statistically superior to placebo with respect to the percentage of patients with consistent improvements in LEMMT;
4. The clinical significance of the consistent improvement in LEMMT was to be validated by demonstrating that patients who had consistent improvements significantly perceive this improvement (via the average SGI score during the double blind) compared to those who did not;

5. Fampridine SR responders had to be statistically superior to the placebo group with respect to the average change from baseline in Ashworth score during the double blind period;
6. Fampridine SR nonresponders had to be statistically superior to the placebo group with respect to the average change from baseline in Ashworth score during the double blind period.

The secondary subjective variables (SGI, CGI) were not part of the stepwise procedure, but were to serve as additional support to the validation of the responder criteria.

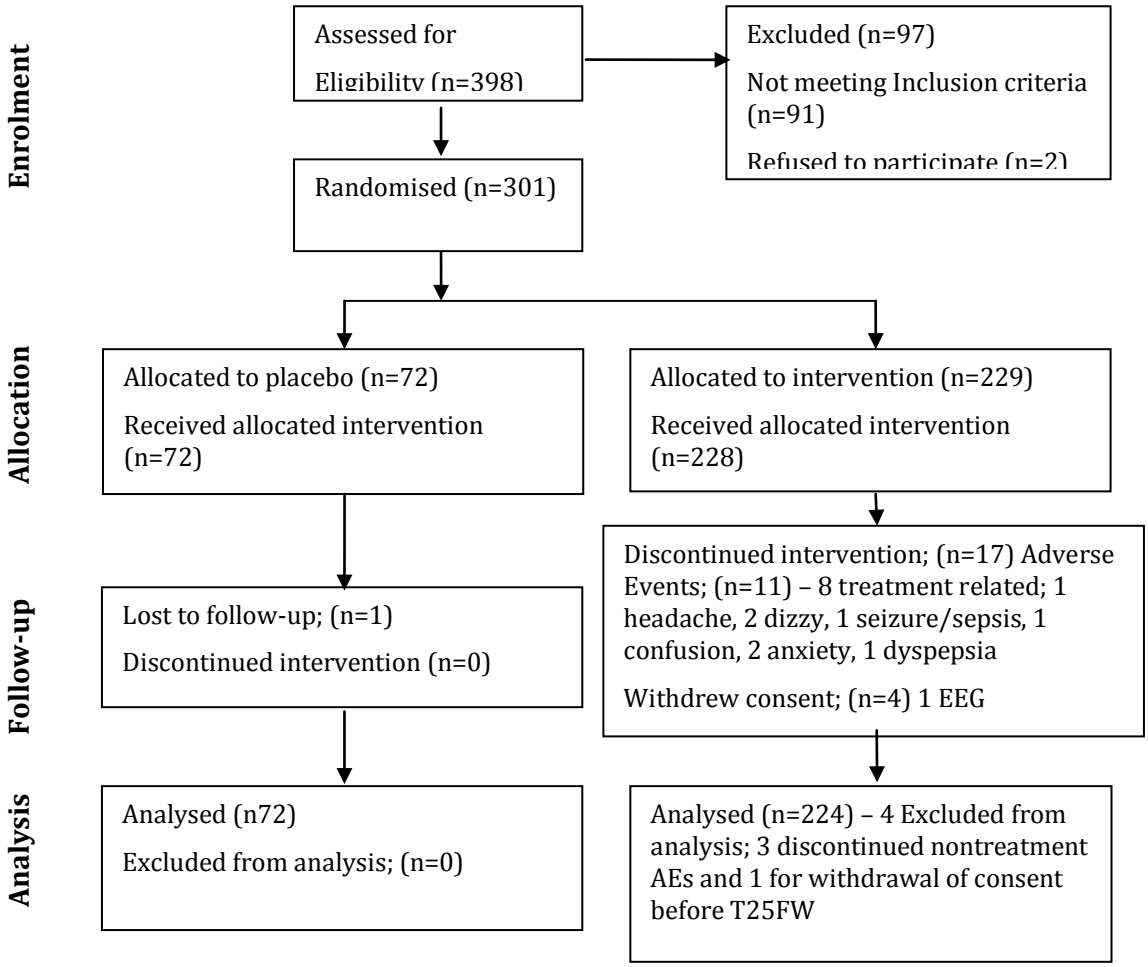
The sponsor added the following clarifications of study outcome expectations: Hypotheses to be tested

- The response rate on the primary endpoint for the fampridine SR treated patients would be significantly higher than that for the placebo treated patients;
- The clinical significance of the response criterion would be validated by the MSWS12, and potentially other subjective measures, comparing responders with nonresponders;
- The walking speed improvement among fampridine SR responders, compared to placebo treated patients, would be maintained at the last treatment visit;

Results

The participant flow is shown in Figure 6.

Figure 6: Participant flow for MS-F203



Fampridine and placebo participants were well matched for demographic characteristics with 296 subjects analysed.

The proportion of timed walk responders was higher in the fampridine group (78/224 or 35%) than in the placebo group (6/72 or 8%; p<0·0001).

Improvement in walking speed in fampridine treated timed walk responders, which was maintained throughout the treatment period, was 25·2% (95% CI 21·5% to 28·8%) and 4·7% (1·0% to 8·4%) in the placebo group.

Compared to Timed Walk nonresponders, Timed walk responders showed a

1. Greater improvement in 12 item multiple sclerosis walking scale scores (–6·84, 95% CI –9·65 to –4·02) than timed walk nonresponders (0·05, –1·48 to 1·57; p=0·0002).
2. Significant improvements in the SGI and CGI (p < 0.001 for each).

Also there was

· Significant increases in LEMMT score were seen in both the fampridine SR Timed Walk responders (p < 0.001) and the fampridine SR Timed Walk nonresponders (p=0.046) compared to placebo.

Despite achieving significance for the primary outcome measures, the average walking speed during double blind treatment was not significantly different between fampridine and placebo (Table 5).

Table 5: Analyses of Study MS-F203

	Placebo (N=72)	Fampridine (N=224)	P value
Baseline walking speed (ft/sec)	2.12	2.14	0.88
Visit 6 Walking speed (ft/sec)	2.16	2.35	0.19
Walking speed change Visit 6 vs baseline (ft/sec)	0.05	0.21	0.03
Walking speed change Visit 6 vs baseline (%)	5.58	10.9	0.24
Walking speed on drug (average)	2.16	2.34	0.17
Walking speed change (ft/sec) on drug (average) vs baseline	0.1	0.28	0.0004
Walking speed change (%) on drug (average) vs baseline	4.71	13.63	0.0003
MSW12 change on drug (average) vs baseline	0.62	-2.72	0.084
MSW12 change Visit 6 vs baseline	3.59	-1.56	0.063
SGI change on drug vs baseline	-0.1967	-0.0045	0.12
LEMMT change on drug vs baseline	0.04	0.13	0.003
Ashworth change on drug vs baseline	-0.07	-0.16	0.021

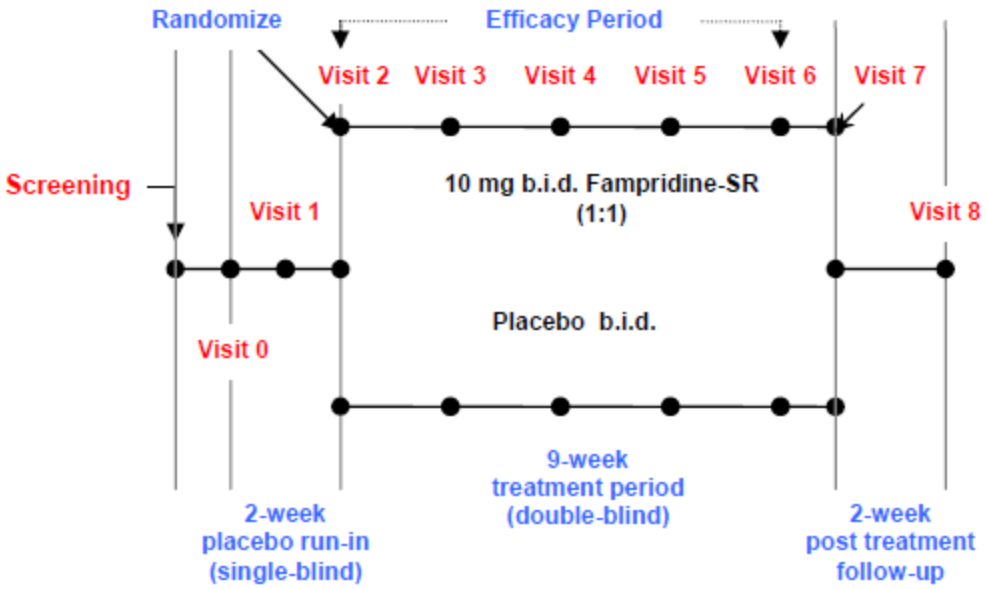
No formal subgroup analyses were performed. Increased response rate on the T25FW was seen across all four major types of MS. The proportions of responders among the four types were: RRMS - 15 of 62 (24.2%); PPMS - 11 of 31(35.5%); SPMS - 48 of 125 (38.4%); PRMS - 4 of 10 (40%). Therefore, the response rate on the timed walk among patients with progressive forms of the disease may be slightly higher than that in the relapsing-remitting patients.

MS-F204

Methods

MS-F204 was a Phase III, double blind, placebo controlled, parallel group, 14 week study (one week post screening, two weeks of single blind placebo run-in, 9 weeks of double blind treatment, and two weeks of no treatment follow up) shown schematically in Figure 7 .

Figure 7: Scheme of Overall Study Design



Objectives

The objectives of this study were to assess the safety and efficacy of 10 mg bd fampridine SR in patients diagnosed with MS, as well as to explore the duration of effect over the 12 hour dosing interval

Study Participants

The study involved 239 patients with MS ranging between 18-70 years of age who were able to complete the T25FW in an average of 8-45 secs at the screening visit

Treatments

The treatments were fampridine SR (10 mg), 1 tablet orally every 12 hours (bd) or placebo 1 tablet orally bd.

Outcomes/endpoints

The primary endpoint was:

1. To demonstrate that more patients treated with fampridine SR 10 mg bd experienced consistent increase in walking speed while on drug versus patients treated with placebo. Walking speed at each visit were based on the average of two T25FW assessments made within 5 minutes of each other

Secondary endpoints were:

1. To demonstrate improved leg strength in:

a. Fampridine SR 10 mg bd patients who experience consistent improvements in walking speed versus placebo; and

b. Fampridine SR 10 mg bd patients who do not experience consistent improvements in walking speed versus placebo.

2. To measure the maintenance of efficacy towards the end of the dosing interval (10-12 hours post dose at steady state) as measured by walking speed and leg strength.

Additional measurements were:

· Ashworth Assessment of Spasticity,

· MSWS-12

· SGI

· CGI

Statistical Considerations

The planned sample size was approximately 200 evaluable patients. There were 240 subjects enrolled, 239 subjects randomized and 227 completed. There were 237 patients evaluable for efficacy and 239 patients evaluable for safety.

Patients were randomized to one of two treatment groups, 10 mg bd fampridine SR or placebo, in a ratio of 1:1

The ITT population included all randomized patients to whom double blind investigational drug was dispensed and who had at least one T25FW evaluation during the eight week double blind treatment period. The Safety Population included all patients randomized and treated with double blind investigational drug.

The primary efficacy variable was responder status, based on consistency of response in walking speed on the T25FW. A Timed Walk responder was defined as a patient with a faster walking speed for at least three of the first four double blind visits (Visits 3 through 6) as compared to the maximum walking speed for any of the pretreatment visits (Screening Visit, Visits 0, 1 and 2) and the post-treatment visit (Visit 8). As mentioned, the purpose of the last double blind visit (Visit 7) was to obtain data on efficacy and drug plasma concentration from near the end of the normal 12 hour dosing interval; therefore, Visit 7 was not part of the responder criterion.

The treatment difference between fampridine SR-treated and a placebo treated group in the proportion of Timed Walk responders was analysed by the CMH test, controlling for centre.

The differences in the average change from baseline in LEMMT between the three Timed Walk responder analysis groups (placebo, fampridine SR Timed Walk responders, and fampridine SR Timed Walk nonresponders) were 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 centre.

Descriptive statistics (sample size, mean, median, standard deviation, range) were presented for the additional variables:

· Average change from baseline in the Ashworth Score by Timed Walk responder analysis group;

· Average change from baseline in the MSWS-12 by Timed Walk responder status (Timed Walk responder or Timed Walk nonresponder, independent of treatment);

· Average SGI score during the double blind period by Timed Walk responder status;

- The CGI score recorded at the end of the double blind period by Timed Walk responder status

Descriptive statistics were presented by Timed Walk responder analysis group as well as for the overall fampridine SR group. Descriptive statistics and 95% confidence intervals for each responder analysis group were computed for the following:

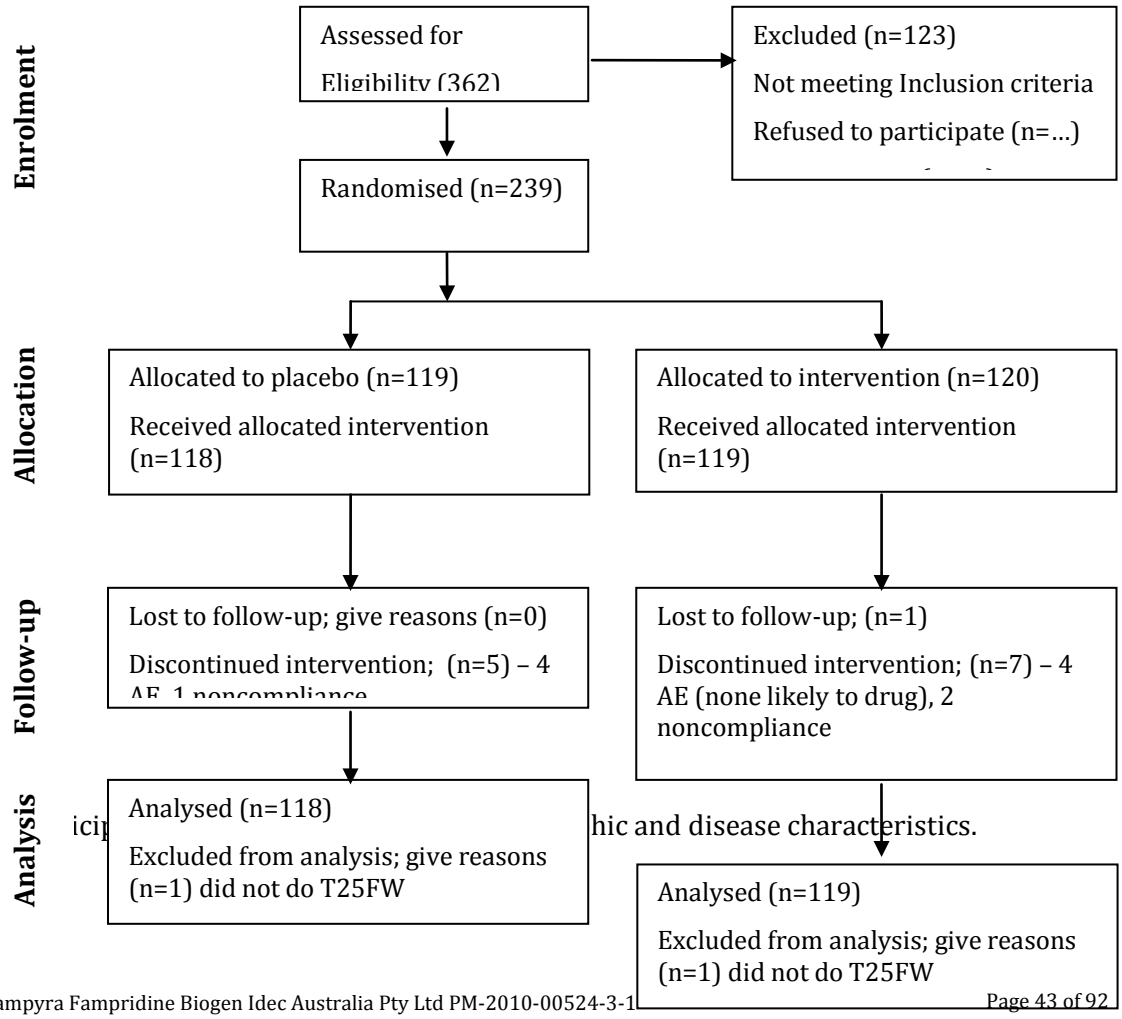
- percent changes from baseline in walking speed by the analysis window of time from last dose as defined above;
- changes from baseline in LEMMT score by the analysis window of time from last dose as defined above;
- plasma fampridine concentration (ng/ml) by the analysis window of time from last dose as defined above.

The secondary efficacy variable was the average change from baseline in LEMMT during the 8 week, double blind treatment period, considered separately and sequentially for fampridine SR-treated Time Walk responders and Time Walk non responders vs placebo treated patients. Additional variables were the average change from baseline in the Ashworth Score and the MSWS-12, the average SGI score during the double blind period, and the CGI score at the end of the double blind period.

Results

The participant flow is shown in Figure 8.

Figure 8: participant flow for Study MS-F204



Stud icip hic and disease characteristics.

The primary efficacy endpoint for this study was met: the percentage of patients who met the Timed Walk responder criterion was 42.9% in the fampridine SR treated group compared with 9.3% in the placebo treated group. This difference was highly statistically significant (p<0.001), and consistent with the results of study MS-F203.

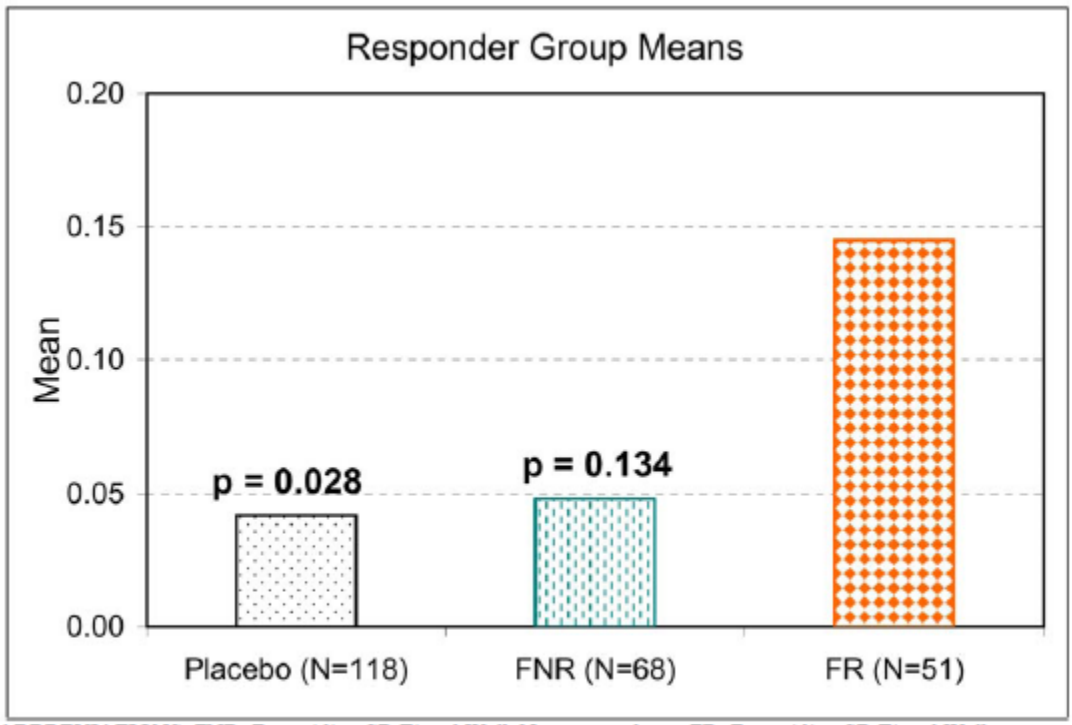
The increased response rate in the fampridine SR group was observed across all four major types of MS disease course.

The average improvement in walking speed for the fampridine SR responders during the double blind period was 25% compared to 6% for the fampridine SR nonresponders and 8% for the placebo group (the *post hoc* statistical comparison between the fampridine SR responders and placebo group was significant, p<0.001).

There was a small decrease in the magnitude of walking speed improvement in the fampridine SR responder group at the end of the normal dosing interval from hours 10-12, the response at hour >12 of about 20% walking speed improvement for the Timed Walk responders, is still considered a meaningful level of change.

The secondary efficacy endpoint of greater leg strength improvement in the fampridine SR Timed-Walk responders compared with placebo treated patients was also met (p=0.028). However, the change in leg strength for fampridine SR Timed Walk nonresponders was not statistically significantly different from either placebo treated patients or fampridine SR Timed Walk responders (Figure 9).

Figure 9: Average Change from Baseline LEMMT Score during the double blind treatment period by responder analysis group



ABBREVIATIONS: FNR=Fampridine-SR Timed Walk Non-responders; FR=Fampridine-SR Timed Walk Responders

Note: each p-value reflects comparison with Fampridine-SR Timed Walk responder (FR) group.

Fampridine SR Timed Walk responders showed a numerically greater mean improvement than the placebo group in average change from baseline in the Ashworth score, a measure of spasticity.

In *post hoc* statistical comparisons, Timed Walk responders (independent of treatment) showed a greater improvement than Timed Walk nonresponders (independent of treatment) for the three summary subjective outcomes in this study: average change from baseline in the MSWS-12 (responders -6.04 SD 13.9, nonresponders 0.8 SD 10.5; p<0.001), average SCI score over the double blind period (responders 4.8 [SD 1.0], nonresponders 4.2 [SD 1.0]; p<0.001), and CGI at end of the double blind period (responders 3.4 [SD 0.8], nonresponders 3.8 [SD 0.6]; p<0.001).

However, the average walking speed and average change in LEMMT on drug vs baseline during the double blind treatment were not different between fampridine and placebo (Table 6).

Table 6: Analysis of Study MS-F204

Study MS-F204	Placebo	Fampridine	p value
Baseline walking speed (ft/sec)	2.28	2.21	0.5463
Visit 6 Walking speed (ft/sec)	2.39	2.42	0.7284
Walking speed change Visit 6 vs baseline (ft/sec)	0.11	0.22	0.0425
Walking speed change Visit 6 vs baseline (%)	4.87%	10.64%	0.0392
Walking speed on drug (average)	2.37	2.41	0.7135
Walking speed change (ft/sec) on drug (average) vs baseline	0.17	0.29	0.0089
Walking speed change (%) on drug (average) vs baseline	7.67%	13.99%	0.0072
MSW12 change on drug (average) vs baseline	0.73	-2.62	0.0213
MSW12 change Visit 6 vs baseline	0.72	-3.12	0.0264
SGI change on drug vs baseline	-0.04	0.09	0.1939
LEMMT change on drug vs baseline	0.04	0.09	0.1059
Ashworth change on drug vs baseline	-0.06	-0.18	0.0153

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

The same primary efficacy variable for both Phase III trials was used in this pooled efficacy analysis. The variable was Timed Walk responder status, based on consistent improvement in walking speed on the T25FW. A Timed Walk responder was defined as a patient with a faster walking speed on this test for at least three of the four (efficacy) visits during the double blind treatment period, as compared to the maximum walking speed achieved among any of the four pre-treatment visits and the two week post treatment visit. The treatment periods differed between MS-F203 and MS-F204 but participants had the same number of double blind treatment evaluations. The sponsor analysed the primary efficacy variable by comparing the proportion of responders in the treatment groups.

Pooling all studies (F202, F203, and F204), Timed Walk Response rates were 37.3% in the fampridine SR 10 mg bd group and 8.9% in the placebo group (*P*<0.001).

The effect of fampridine SR on Timed Walk response was highly consistent across subgroups.

Clinical characterisation of Timed Walk responders (irrespective of treatment allocation) were as follows:

- Mean change in MSWS-12 was -7.19 in Timed Walk responders vs -0.006 in Timed Walk nonresponders (P<0.001)

- Mean CGI rated significantly better in Timed Walk responders vs Timed Walk nonresponders (P<0.001)
- Mean SCI significantly better in Timed Walk responders vs Timed Walk nonresponders (P<0.001)

The effects of fampridine SR on Objective and Subjective measures (irrespective of responder status) are given in Table 7.

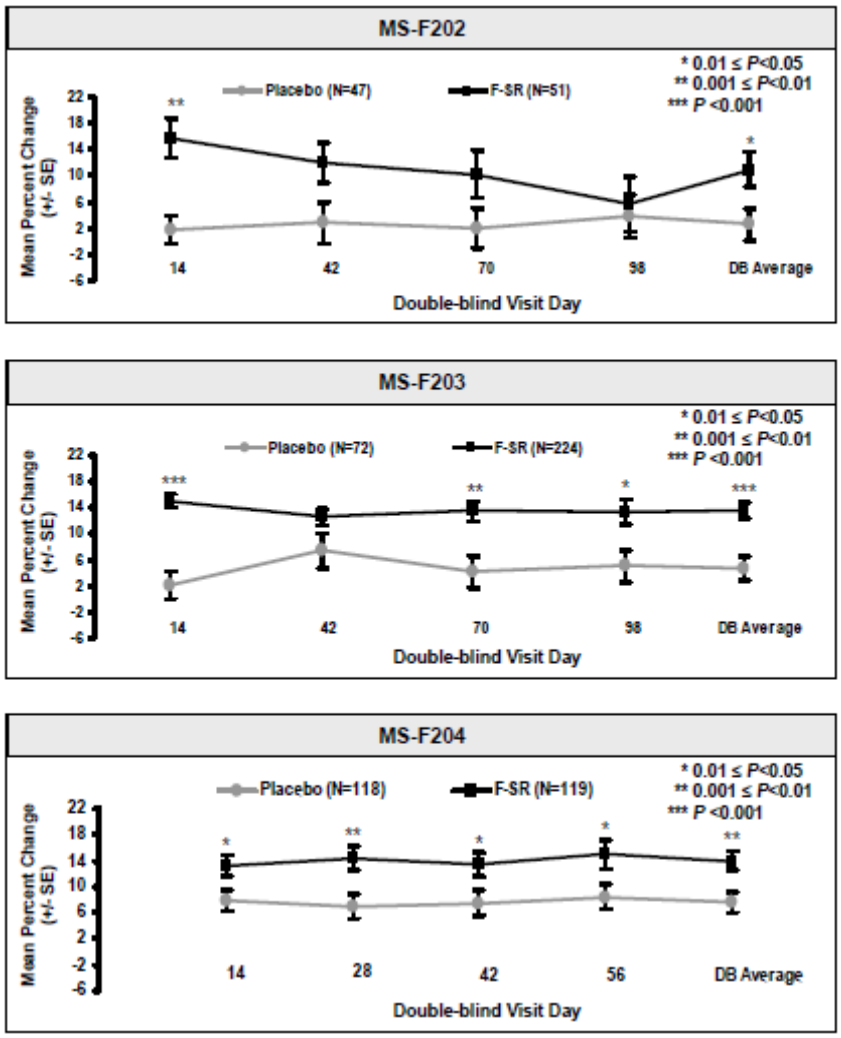
Table 7: Additional variables in the Pooled ITT population

Efficacy Endpoint	Placebo [a]	Fampridine PR 10 mg b.i.d. [a, b]	p-Value [a]
Timed-Walk responders	8.9%	37.3%	<0.001
Walking speed change at end of treatment vs. baseline (ft/sec)	0.05 0.10 0.19	0.10 (MS-F202) 0.29 (MS-F203) 0.30 (MS-F204)	0.635 0.010 0.038
Walking speed change, on-drug average vs. baseline (%)	5.76%	13.38% 25.3% (Timed-Walk responders)	<0.001 <0.001
Subjects with ≥20% walking speed change on-drug average vs. baseline	13.1%	31.5%	<0.001
MSWS-12 improvement, on-drug average vs. baseline [c]	0.2%	9.9% (Timed-Walk responders)	<0.001
LEMMT change, on-drug average vs. baseline (5-point scale)	0.03	0.12 0.16 (Timed-Walk responders) 0.09 (Timed-Walk non-responders)	<0.001 <0.001 0.006
Ashworth reduction, on-drug average vs. baseline (4-point scale)	0.07	0.16 0.15 (Timed-Walk responders) 0.16 (Timed-Walk non-responders)	<0.001 0.003 0.009
SGI change, on-drug average vs. baseline (7-point scale) [c]	4.35	4.83 (Timed-Walk responders)	<0.001
CGI at end of treatment period (7-point scale) [c]	3.79	3.31 (Timed-Walk responders)	<0.001

a Results are based on pooled data from MS-F202, 203, and 204, unless specified otherwise.
b Results are for fampridine PR-treated patients overall (disregarding responder status), unless specified otherwise.
c MSWS-12, SGI, and CGI data were analyzed with Timed-Walk responders versus non-responders from both treatment groups to validate the clinical meaningfulness of the Timed-Walk response criteria. The results showed correlation of MSWS, SGI, and CGI with Timed-Walked response status.

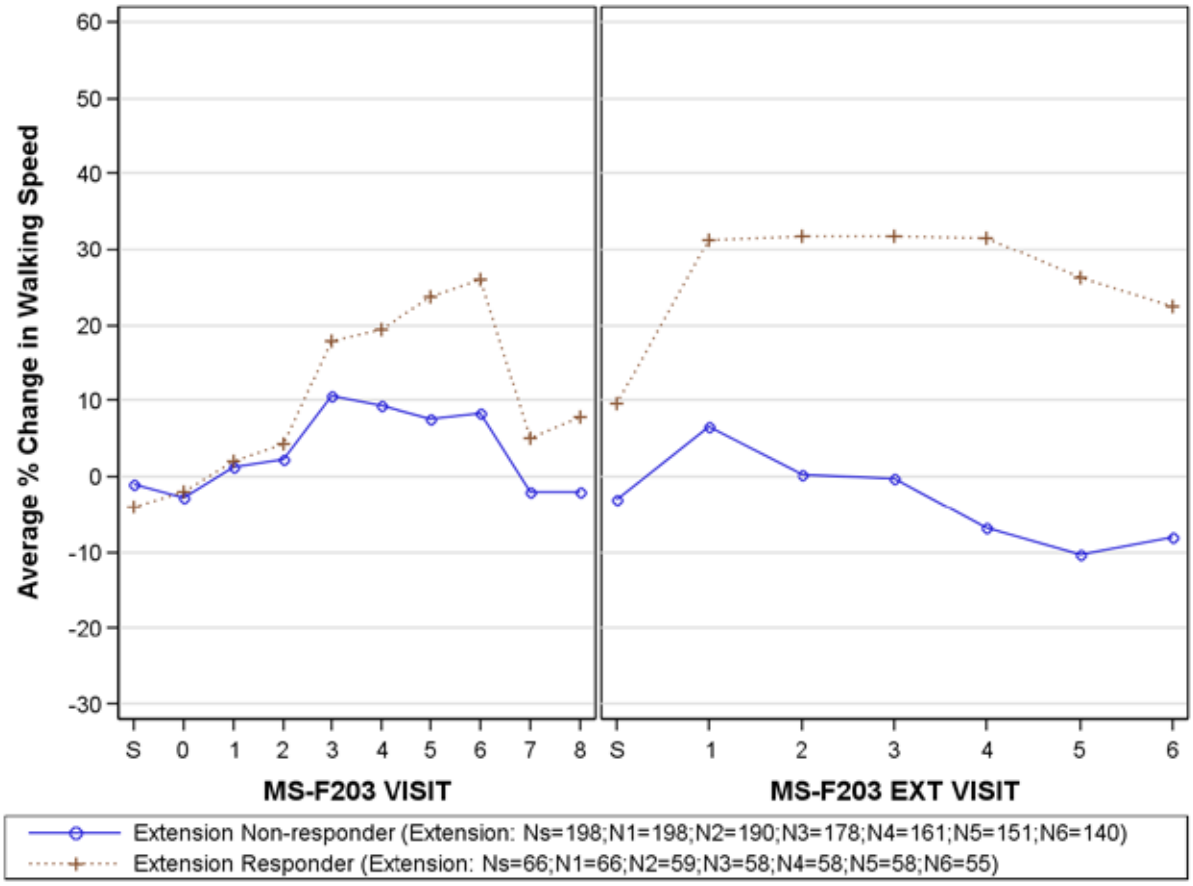
Maintenance of effect is shown in Figure 10.

Figure 10: Percent Change in walking speed at each double blind visit



Loss of Efficacy occurred after discontinuation of treatment (Figure 11).

Figure 11: Average percent change from baseline in walking speed for the extension timed walk responders and extension timed walk nonresponders in sudies MS-F203 and MS-F203EXT



Evaluator's overall conclusions on clinical efficacy

Problems exist with the use of the sponsor's primary endpoint. It has not been used often as a primary endpoint in MS clinical trials of other drugs. The first study to use MSFC (of which the T25FW is a component) as the primary clinical outcome measure was a Phase III placebo controlled randomized trial of interferon-b1a for SPMS. The primary outcome specified in advance was between-group difference in two-year MSFC change. Secondary outcome measures included EDSS, relapse rate, magnetic resonance imaging (MRI) lesion load, and patient self reported Quality of Life (QOL). Treatment with interferon-b1a was associated with 40% less worsening on MSFC (median change for IFNb-1a, 0.096; for placebo, 0.161; p=0.03). MSFC component changes were in favour of treatment for 9HPT (p=0.024) and Paced Auditory Serial Addition Test (PASAT) (p=0.061) but not for T25FW (p=0.378). Treatment effects on secondary outcome measures supported the MSFC effect. There were statistically significant benefits on relapse rate, T2 and gadolinium enhancing lesions, and the MS Quality of Life Inventory. However, no benefits on the T25FW were observed.[25] It could be argued that,

a. in cross sectional studies and longitudinal studies, the EDSS has been found to show strong correlation with the T25FW and the EDSS and T25FW show moderate correlation with the total MSFC score.[24,25]

b. the T25FW shows greater responsiveness to change than does the EDSS.[35]

2. In MS patients, it is not clear what extent of improvement in walking speed improves walking ability or quality of life, that is, the responder variable does not adequately explain the importance of the extent of improvement in walking speed. It has been suggested that doctor rated measures such as the T25FW do not examine disease effects as measured by patient reported measures.[36] Furthermore, the mean improvement in walking speed in fampridine responders was 0.51 ft/second. That change translated into approximately a 2.3 second improvement in T25FW. This effect is modest in comparison to the change reported in a group of patients with similar baseline T25FW scores who were treated with steroids for a MS relapse. These patients recorded an improvement of 2.9 seconds (>30%).(32) Conversely, walking ability (measured in a different way) forms the major component of the most widely scale of disability for MS.[37] In addition, independent scientific literature supports that a change of 20% or more in Timed Walk is clinically meaningful.[38,39,40]

3. In the study design, if step one of the analysis was found positive then it was highly likely step 3 would also be positive, proving maintenance of treatment effect, that is, there would be statistically significant improvements in walking speed in fampridine treated responders compared to the placebo group (responders plus nonresponders) at the last visit on treatment. This is because responders were identified on the basis of showing consistently improved walking speeds compared to baseline or pre-treatment visits. In support of the maintenance of treatment effect, it was reported that the efficacy results of three ongoing open label extension studies (MS-F202EXT, MS-F203EXT, and MS-F204EXT) have enrolled 660 MS patients, of which more than 333 patients have been treated for 2 years or longer (up to 5 years, as of 30 November 2008). Data from these studies on Timed-Walk response provide additional support for sustained benefits; the functional improvement observed during treatment with fampridine SR 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. In contrast Extension Timed Walk nonresponders had a slight decrease from baseline walking speed at the end of the first and second year.

4. Supportive endpoints such as dimensions assessing Activities of Daily Living (ADLs) or QoL could be helpful. The difference shown in MSWS-12 between responders and nonresponders does provide additional information and it has

[35] Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). Neurology 2003; 60: 31-36.

[36] Costelloe L, O'Rourke K, McGuigan C, Walsh C, Tubridy N, Hutchinson M. The longitudinal relationship between the patient-reported Multiple Sclerosis Impact Scale and the clinician-assessed Multiple Sclerosis Functional Composite. Mult Scler 2008; 14: 255-258.

[37] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33: 1444-1452.

[38] 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; 12: 594-598.

[39] Kaufman M, Moyer D, Norton J. The significant change for the Timed 25-foot Walk in the multiple sclerosis functional composite. Mult Scler 2000; 6: 286-290.

[40] Schwid SR, Goodman AD, McDermott MP, Bever CF, Cook SD. Quantitative functional measures in MS: what is a reliable change? Neurology 2002; 58: 1294-1296.

good psychometric properties but it is conceptually very similar to the T25FW. Only baseline EDSS was performed in the sponsor's trials. Moreover, the magnitude of the difference in average improvement in the MSWS-12 of 6.79 for timed walk responders compared to timed walk nonresponders, (although significant - p=0.0002) seems quite modest, in the validation study of the MSWS-12 by Hobart and colleagues, treatment with steroids to patients with an MS relapse resulted in an improvement of 20.0 (SD 22.2) in patients with a mean baseline MSWS score of 78.0 (SD21.5). In the evaluator's opinion, statistical significance has been achieved but clear clinical significance may not have been achieved.

5. In both MS-F203 and MS-F204, Visit 6 absolute walking speed was not significantly different between fampridine and placebo patients. In MS-F203, changes in the walking speed in the fampridine group as a whole vs placebo did reach significance but were of small magnitude; walking speed increased 0.21 ft/sec for fampridine group between baseline and Visit 6, and the placebo group increased 0.05 ft/sec increase for placebo group (p=0.03). That change translated into a 0.88 second difference between fampridine and placebo groups overall to complete the 25 foot walk. This does not preclude a subgroup gaining a significant benefit from fampridine treatment. However, it indicates that patients receiving fampridine outside of clinical studies possibly should not continue the treatment if they have not shown an early clinical benefit (such as possibly >20% increase in walking speed which is considered the minimum clinically relevant change), especially considering potential toxicity issues.[41]
6. There is insufficient data to make recommendations regarding patients with moderate or severe renal impairment. It would be ideal if fampridine levels could be monitored in patients with mild renal impairment.

Safety

Introduction

Clinical studies of 4-aminopyridine have been conducted by several different sponsors examining its use in various indications including MS, spinal cord injury (SCI), and Guillain-Barré syndrome. Acorda became the sponsor for fampridine SR in 1998 and conducted Phase III trials in MS patients for the indication of improving walking ability. There are several approved treatments for MS but fampridine SR would be the first approved treatment for improvement of walking ability in MS patients.

Data contained within the submission reports on the evaluation of 57 clinical studies accounting for a total of 2283 subjects and using various formulations and dose strengths of fampridine in healthy volunteers and patients with MS, spinal cord injury (SCI), and Guillain-Barré Syndrome (GBS), with the majority of studies in MS and SCI.

The two pivotal trials are also reported.

Patient exposure

In three extension studies (MS-F-202EXT, MS-F203EXT, and MS-F204EXT), 660 patients received fampridine SR 10 mg bd for a total of 1325 patient-years of exposure; 594 having been exposed for >6 months; 441 for >12 months; and 333, 115, and 98 for >24, >36, and >48 months, respectively, as of November 2008 (Table 8). Total numbers in all studies are shown in Table 9.

[41] Bosma LV, Kragt JJ, Brieva L, et al. Progression on the Multiple Sclerosis Functional Composite in multiple sclerosis: what is the optimal cut-off for the three components? *Mult Scler* 2010; 16: 862-867.

Table 8: Summary of the Extent of Exposure to fampridine as of November 2008

Exposure	Non Patients	MS Patients	SCI Patients	Total
Number of Subjects with Exposure				
Exposure to any dose/formulation	412 [a]	917 [b]	593 [c]	1922
Exposure to 10 mg of any formulation	-	789	-	-
Exposure to PR formulation (any dose)	-	807	-	-
Duration of Exposure				
Mean (SD) duration of exposure to any dose or formulation (weeks)	0.47 (0.436)	87.30 (81.049)	22.40 (24.154)	-
Number of subjects with exposure >6 months	0	627 [d]	191	818
Number of subjects with exposure >12 months	0	503 [d]	51	554
Number of subjects with exposure >24 months	0	350 [d]	11	361
Number of subjects with exposure >36 months	0	178 [d]	0	178
Number of subjects with exposure >48 months	0	105 [d]	0	105
Exposure in Patient-Years	-	1534	-	1792

[a] 397 healthy volunteers and 15 subjects with renal deficiency from 14 studies.
[b] MS patients from 20 studies.
[c] SCI patients from 12 studies.
[d] Of these patients, a subset was from Studies MS-F202EXT, MS-F203EXT, and MS-F204EXT: 594 patients for >6 months; 441 for >12 months; and 333, 115, and 98 for >24, >36, and >48 months, respectively.

Table 9: Total number of patients exposed to fampridine and placebo in all clinical trials (cutoff date of 30/11/2008)

Trial Population	Trial Category	Trial Number	Placebo	Fampridine SR	Fampridine Other	Fampridine Total
Multiple Sclerosis	Clinical Pharmacology	All	56	67	89	145
	Placebo Controlled	All	330	532	89	621
	Uncontrolled	All		208		974
		Total	386	807	178	974
Spinal Cord Injury	Clinical Pharmacology	All		14	4	18
	Placebo Controlled	All	322	372		372
	Uncontrolled	All		203		203
Renal Deficiency	Clinical Pharmacology	RD10FSR 012004		20		20
Guillain-Barre	Guillain-Barre	CGBS Phase 2A#	7		8	8
		CGBS Phase 2B#	17		16	16
Healthy Volunteers	Clinical Pharmacology	All	113	205	147	311
All	All	Total from all studies with available data	797	1621	224	1793
		Grand Total	845	1621	353	1922

In the entire development program, 1922 subjects received at least one dose of fampridine (1793 in the integrated safety database and 129 from trials not included in the integrated safety database). This total includes 1621 subjects that were exposed to fampridine SR, the formulation Acorda intends to market. For the population with the indication being considered for approval, subjects with MS, Acorda exposed 917 subjects to fampridine (807 to SR formulation).

Adverse events

In these trials, 86.4% (438/507) of fampridine SR subjects experienced one or more adverse events (AEs) compared to 73.5% (175/238) of placebo subjects. Table 10 reports the AEs occurring in at least 1% of fampridine SR subjects and that occurred more frequently compared to placebo.

Table 10: Treatment Emergent AEs (TEAEs) occurring in>=1% of fampridine SR subjects and more frequently compared to Placebo, Adequate and well controlled MS trials

AE Preferred term	Placebo (n=238)	Fampridine Total (n=507)	Fampridine 10mg bid (n=400)	Fampridine 15mg bid (n=50)	Fampridine 20mg bid (n=57)
Subjects with 1 or more AEs	73.5% (175)	86.4% (438)	84.8% (339)	94% (47)	91.2% (52)
UTI	9.2% (22)	14.3% (72)	14.5% (58)	10% (5)	15.8% (9)
Insomnia	3.8% (9)	10.5% (53)	9.3% (37)	18% (9)	12.3% (7)
Dizziness	4.2% (10)	9.5% (48)	7.8% (31)	20% (10)	12.3% (7)
Headache	4.2% (10)	8.9% (45)	7.5% (30)	14% (7)	14% (8)
Asthenia	4.2% (10)	8.7% (44)	8.3% (33)	18% (9)	3.5% (2)
Nausea	2.5% (6)	7.7% (39)	7% (28)	10% (5)	10.5% (6)
Fatigue	4.6% (11)	7.5% (38)	6.5% (26)	14% (7)	8.8% (5)
MS relapse	3.8% (9)	6.5% (33)	5.3% (21)	8% (4)	14% (8)
Balance disorder	1.3% (3)	6.3% (32)	5.8% (23)	8% (4)	8.8% (5)
Paraesthesia	3.4% (8)	5.7% (29)	4.8% (19)	6% (3)	12.3% (7)
Back pain	2.1% (5)	5.3% (27)	5.5% (22)	4% (2)	5.3% (3)
Muscle spasms	3.4% (8)	4.1% (21)	3.8% (15)	6% (3)	5.3% (3)
Nasopharyngitis	2.9% (7)	4.1% (21)	4.3% (17)	6% (3)	1.8% (1)
Constipation	2.1% (5)	3.7% (19)	3.5% (14)	4% (2)	5.3% (3)
Diarrhoea	2.5% (6)	2.8% (14)	2.5% (10)	6% (3)	1.8% (1)
Difficulty walking	1.3% (3)	2.8% (14)	2.5% (10)	0	7% (4)
Pharyngolaryngeal pain	0.8% (2)	2.6% (13)	2.3% (9)	4% (2)	3.5% (2)
Gastroenteritis viral	1.7% (4)	2.4% (12)	2% (8)	2% (1)	5.3% (3)
Pollakiuria	0.8% (2)	2.4% (12)	2% (8)	2% (1)	5.3% (3)
Vomiting	0.4% (1)	2.4% (12)	2% (8)	6% (3)	1.8% (1)
Pyrexia	0.8% (2)	2.2% (11)	1.8% (7)	4% (2)	3.5% (2)
Rash	0.8% (2)	2.2% (11)	1.8% (7)	2% (1)	5.3% (3)
Anxiety	0.4% (1)	2% (10)	1.8% (7)	2% (1)	3.5% (2)
Cough	1.7% (4)	2% (10)	1.5% (6)	2% (1)	5.3% (3)
Tremor	0	2% (10)	1.3% (5)	0	8.8% (5)
Dyspepsia	0.8% (2)	1.8% (9)	2% (8)	2% (1)	0
Influenza	0	1.8% (9)	2.3% (9)	0	0
Muscle spasticity	1.7% (4)	1.8% (9)	2% (8)	0	1.8% (1)
Pain	0.8% (2)	1.8% (9)	1.3% (5)	6% (3)	1.8% (1)
WBC urine positive	0.8% (2)	1.8% (9)	1.8% (7)	2% (1)	1.8% (1)

Depression	0.8% (2)	1.6% (8)	1.3% (5)	2% (1)	3.5% (2)
Urinary incontinence	0	1.6% (8)	1.3% (5)	0	5.3% (3)
Viral infection	0.4% (1)	1.6% (8)	1.5% (6)	4% (2)	0
Abdominal pain	0.4% (1)	1.4% (7)	1.3% (5)	0	3.5% (2)
Cystitis	0.8% (2)	1.4% (7)	1.5% (6)	2% (1)	0
Dyspnoea	0	1.4% (7)	1% (4)	4% (2)	1.8% (1)
Joint swelling	1.3% (3)	1.4% (7)	1.3% (5)	2% (1)	1.8% (1)
Myalgia	0.8% (2)	1.4% (7)	1% (4)	4% (2)	1.8% (1)
Pruritis	0.4% (1)	1.4% (7)	1.5% (6)	2% (1)	0
Shoulder pain	1.3% (3)	1.4% (7)	1.3% (5)	2% (1)	1.8% (1)
Skin laceration	0	1.4% (7)	1.3% (5)	2% (1)	1.8% (1)
Back injury	0.8% (2)	1% (5)	1.3% (5)	0	0
Bronchitis	0.8% (2)	1% (5)	0.8% (3)	4% (2)	0
Chest pain	0.4% (1)	1% (5)	0.8% (3)	2% (1)	1.8% (1)
Diplopia	0.4% (1)	1% (5)	0.8% (3)	2% (1)	1.8% (1)
Dry mouth	0.8% (2)	1% (5)	0.8% (3)	0	3.5% (2)
Hypertension	0.4% (1)	1% (5)	0.8% (3)	0	3.5% (2)
Muscular weakness	0	1% (5)	0.3% (1)	2% (1)	5.3% (3)
Neck pain	0.8% (2)	1% (5)	1% (4)	0	1.8% (1)
Sensory disturbance	0.4% (1)	1% (5)	1% (4)	0	1.8% (1)
Stomach discomfort	0.8% (2)	1% (5)	0.8% (3)	2% (1)	1.8% (1)
Vertigo	0.4% (1)	1% (5)	1% (4)	0	1.8% (1)
WBC count decreased	0.4% (1)	1% (5)	1% (4)	2% (1)	0

UTI: urinary tract infection

MS-F203

A majority of patients in each treatment group had at least one treatment emergent AE (TEAE) during the double blind period (84% and 81% of patients in the fampridine SR and placebo groups, respectively). The most common AEs seen with fampridine SR treatment were falls (reported by 15.8% of the patients), urinary tract infection (UTI; (13.6%), dizziness and insomnia (each 8.3%), fatigue, nausea and upper respiratory tract infection (each 6.1%), and asthenia, back pain, balance disorder and headache (each 5.7%). Falls and UTIs were seen at comparable rates across the fampridine SR and placebo treated patients. Insomnia, fatigue, back pain and balance disorder were reported in the fampridine SR treated patients at rates more than 50% higher than in the placebo treated subjects.

Most AEs were mild to moderate in severity. A similar percentage of patients in each treatment group (26-27%) had AEs that were considered possibly or probably related to treatment. Dizziness, insomnia and paraesthesia were the AEs most frequently judged treatment related in the fampridine SR group, again consistent with previous studies. Eight patients (3.5%), all in the fampridine SR group, were withdrawn from the study due to a TEAE.

MS-F204

The two most frequent individual TEAEs in both the treatment groups were urinary tract infections and falls. UTIs occurred at a higher rate in the fampridine SR group compared with the placebo group (17.5% vs 8.4%), whereas falls occurred at higher rate in the placebo group (16.8% vs 11.7%). Other common AEs in patients treated with fampridine SR were insomnia (10.0%), headache (9.2%), asthenia, dizziness, nausea (each 8.3%), back pain, balance disorder, upper respiratory tract infection (each 5.8%), and arthralgia, nasopharyngitis and paraesthesia (each 5.0%). Other common events in the placebo group included upper respiratory tract infections (6.7%), contusion (5.0%), asthenia, arthralgia, nasopharyngitis and peripheral oedema (each 4.2%). Most AEs were rated mild or moderate in intensity and did not prevent patients from continuing to take the investigational drug. No trend emerged for events considered severe in intensity since no single type of event was rated severe in more than one patient. Dizziness, nausea, insomnia, balance disorder, headache and asthenia occurred at rates more than 50% higher in the fampridine SR group than in the placebo group and also were among the more common investigator assessed 'treatment related' adverse events.

There were relatively few adverse events leading to study discontinuation in either treatment group: 3 patients (2.5%) in the fampridine SR group did not complete the study due to a TEAE or serious adverse event, including patellar fracture, symptomatic hypotension and headache and 4 (3.4%) in the placebo group did not complete the study due to arrhythmia, worsening ataxia, gastric reflux/chest tightness, and a possible complex partial seizure.

Selected AEs

Dizziness

The median time to onset was 12 days and the duration was 7 days. The outcome for 43 of the 48 patients reporting dizziness was resolved.

Insomnia

The median time to onset was 15 days and the median duration was 26 days.

Asthenia

The risk increased with fampridine SR dose. The median time to onset was 44.5 days and the median duration was 14 days.

Anxiety

In the adequate and well controlled MS trials, the risk for anxiety among placebo subjects was 0.4% (1/238) compared to 1.8% (7/400) for fampridine SR 10 mg bd, 2% (1/50) for fampridine SR 15 mg bd and 3.5% (2/57) for fampridine SR 20 mg bd. One anxiety event (fampridine SR) was an SAE in these trials and one anxiety AE (fampridine SR) led to discontinuation. The finding of increased risk of anxiety AEs with fampridine SR was replicated in the SCI adequate and well controlled trials.

Other

The following AEs also showed evidence of a dose response: insomnia, dizziness, headache, nausea, fatigue, MS relapse, balance disorder, paraesthesia, muscle spasms, balance disorder, paraesthesia, muscle spasms, constipation, pharyngolaryngeal pain, pyrexia, rash and cough.

Serious adverse events and deaths

There were no deaths in either group during the three placebo-controlled studies (MS-F202, MS-F203, and MS-F204). The reported causes of death in other fampridine clinical trials (oxycodone overdose, aortic dissection, suicide, unknown/found dead in bed, intracerebral haemorrhage and fall) did not appear related to fampridine. Serious adverse events (SAEs) are shown in Table 11.

Table 11: All Serious TEAEs in Placebo Controlled Studies 202/203/204

	Placebo-Controlled Studies 202/203/204	
System Organ Class Preferred Term	Placebo (N=238)	Fampridine-PR 10 mg b.i.d (N=400)
Patients with any serious TEAE	5 (2.1%)	22 (5.5%)
Cardiac Disorders	**1 (0.4%)**	**2 (0.5%)**
Chest pain	0 (0%)	1 (0.3%)
Coronary artery disease	0 (0%)	1 (0.3%)
Myocardial infarction	1 (0.4%)	0 (0%)
Gastrointestinal Disorders	**1 (0.4%)**	**1 (0.3%)**
Colitis	0 (0%)	1 (0.3%)
Reflux gastritis	1 (0.4%)	0 (0%)
General Disorders and Administration Site Conditions	**1 (0.4%)**	**1 (0.3%)**
Catheter related complication	0 (0%)	1 (0.3%)
Chest discomfort	1 (0.4%)	0 (0%)
Hepatobiliary Disorders	**0 (0%)**	**1 (0.3%)**
Cholelithiasis	0 (0%)	1 (0.3%)
Infections and Infestations	**2 (0.8%)**	**9 (2.3%)**
Bacterial pyelonephritis	0 (0%)	1 (0.3%)
Cellulitis	1 (0.4%)	1 (0.3%)
Influenza	0 (0%)	1 (0.3%)
Pneumonia	0 (0%)	2 (0.5%)
Sepsis	0 (0%)	1 (0.3%)
Urinary tract infection	1 (0.4%)	2 (0.5%)
Viral infection	0 (0%)	1 (0.3%)
Wound infection	0 (0%)	1 (0.3%)
Injury, Poisoning and Procedural Complications	**0 (0%)**	**4 (1%)**
Foot fracture	0 (0%)	1 (0.3%)
Fracture	0 (0%)	1 (0.3%)
Neck injury	0 (0%)	1 (0.3%)
Patella fracture	0 (0%)	1 (0.3%)

System Organ Class Preferred Term	Placebo-Controlled Studies 202/203/204	
	Placebo (N=238)	Fampridine-PR 10 mg b.i.d (N=400)
Musculoskeletal and Connective Tissue Disorders	**0 (0%)**	**1 (0.3%)**
Aseptic necrosis bone	0 (0%)	1 (0.3%)
Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps)	**0 (0%)**	**1 (0.3%)**
Breast cancer	0 (0%)	1 (0.3%)
Nervous System Disorders	**1 (0.4%)**	**4 (1%)**
Complex partial seizures	1 (0.4%)	0 (0%)
Multiple sclerosis relapse	0 (0%)	1 (0.3%)
Spondylitic myelopathy	0 (0%)	1 (0.3%)
Syncope	0 (0%)	2 (0.5%)
Psychiatric Disorders	**0 (0%)**	**1 (0.3%)**
Anxiety	0 (0%)	1 (0.3%)
Vascular disorders	0 (0%)	1 (0.3%)
Deep vein thrombosis	0 (0%)	1 (0.3%)

Seizure risk

In open-label trials, the seizure risk at 10 mg bd was similar to the risk seen in controlled trials. The results from this open label population must be considered carefully since this was a highly selected population. These patients were screened by history and EEG prior to the controlled studies, and those with exposure to fampridine in the controlled studies (roughly two thirds of open label trial participants) survived a trial of therapy without seizure and then all subjects were screened with EEG again prior to entering the open-label trial.

In the controlled trials MS 201/202/203/204 the reported seizures typically occurred on higher doses of fampridine. The one subject with focal seizure on 10 mg occurred in the context of sepsis.

A total of 660 patients continued treatment in the extension studies MS-F202 EXT, MS-F203 EXT and MS-F204 EXT. In these studies 464 of 660 patients remained on treatment at the time of cutoff. Seizure rates are given in Table 12. Of the five patients (one male and four females) who experienced some form of seizure while taking fampridine SR 10 mg bd in the extension studies, four experienced generalized seizures and one patient a partial complex seizure. All five patients had EDSS scores of 6 or 6.5; three were diagnosed as relapsing-remitting MS and two as primary progressive MS.

Table 12: Seizures in the Open-Label Extension MS Studies

	MS-F202EXT >10 mg b.i.d	MS-F202EXT 10 mg b.i.d	MS-F203EXT 10 mg b.i.d	MS-F204EXT 10 mg b.i.d	Total at 10 mg b.i.d
Patients exposed (N)	175	177	269	214	660
Patient-years	115	453.3	576.1	186.5	1215.9
Patients with any seizure (n)	2	1	4[1,2]	0	5
% patients	1.14%	0.56%	1.5%	0	0.76%
Incidence/100 patient years (95% CI)	1.7 (0.21-6.28)	0.22 (0.005-1.23)	0.69 (0.18-1.78)	0 (0, 1.61)	0.41 (0.13-0.96)

Source: Table 1.8.

[1] One of these cases was a patient taking a very high dose of DetrolLA (tolterodine) 12 mg b.i.d at the time of the seizure. She discontinued from both fampridine and DetrolLA and experienced another seizure one year later, on resuming Detrol treatment.

[2] One additional patient (#23015) experienced seizure at 22 days following discontinuation from Study MS-F203 EXT due to an MS relapse. This patient was not included here as the event, given the length of time off treatment, the rapid clearance of fampridine, and the lack of any known association between withdrawal and seizure. The event was evaluated by the investigator as unlikely related to treatment.

One 47 year old woman experienced prolonged status epilepticus requiring admission to the intensive care unit. The plasma concentration of fampridine recorded in this patient during treatment ranged between 23.0 and 40.3 ng/mL.

Other seizures during the development program were more convincingly related to high serum levels of fampridine.

Overall, the incidence rate observed during the long term, open label treatment with fampridine SR 10 mg bd was also consistent with the rates reported for placebo groups in long-term studies of other MS drugs (0.0 to 1.1 per 100 patient years). This incidence rate also aligns with the findings in a prospective study of first seizure onset among 255 Swedish MS patients.[42] Based on 6,375 patient-years of data, the investigators reported an incidence rate for first seizure of 0.35 per 100 patient-years, with 95% confidence intervals that overlap the fampridine SR observed rate of 0.41 (95% confidence interval: 0.13–0.96). The conclusions of this report support other epidemiological studies showing a higher rate of seizure in the MS population and also confirm that the risk of first seizure increases with age and progression of disease.[43]

Suicidality

Four patients in the open-label studies reported events of suicidal ideation, suicide attempt and suicide.

Urinary tract infections (and ? symptoms)

Urinary tract infections were increased in fampridine groups. The majority of urinary tract infections were diagnosed and treated on the basis of symptoms rather than after investigations to confirm infection. The sponsors propose that this is due to the excitatory effect the drug may have on the urinary symptom.

Cardiovascular disorders

At the recommended dose of 10 mg bd TEAEs in the *Cardiac Disorders* System Organ Class (SOC) occurred at slightly higher rates (2.5% vs 1.3%) but only 2 cases (0.5%) were classified as serious. There were no reports of clinically significant arrhythmia.

[42] Eriksson M, Ben-Menachem E, Andersen O. Epileptic seizures, cranial neuralgias and paroxysmal symptoms in remitting and progressive multiple sclerosis. Mult Scler 2002; 8: 495-499.

[43] Koch M, Uyttenboogaart M, Polman S, De KJ. Seizures in multiple sclerosis. Epilepsia 2008; 49: 948-953.

Laboratory findings

Analysis of laboratory values from placebo controlled Studies 202/203/204 and the long term extension studies consistently found clinically significant values to be very low. Hypertriglyceridaemia and reduced white cell count are reported in 1% of fampridine subjects but are not likely to be clinically significant.

Safety in special populations

Ethnicity

There was no evidence for demographic interactions with TEAEs except the relative risk for TEAEs was higher among non-Caucasians than Caucasians, based on a small number of non-Caucasian subjects in these trials (non Caucasian fampridine subjects n=37). This difference was driven by lower TEAE risks among the non-Caucasian placebo subjects.

Renal function

For all TEAEs, the relative risk for subjects with abnormal renal function (relative risk [RR] 1.35; fampridine SR 89.8%, placebo 66.7%) was higher than the relative risk for subjects with normal renal function (RR 1.14; fampridine 85.6%, placebo 74.9%). For the TEAEs occurring in at least 5% of fampridine SR subjects and at least twice as commonly compared to placebo, fampridine SR subjects with abnormal renal function had higher risks and RR for nausea, balance disorder, dizziness and insomnia.

Age

The relative risk for insomnia was higher for subjects aged <45 years (RR 3.6; fampridine SR 11.2%, placebo 3.1%) than 45-≤65 years (RR 2.5; fampridine SR 9.6%, placebo 3.9%). Subjects 45-≤65 years had a higher relative risk for back pain (RR 3.6; fampridine SR 4.7%, placebo 1.3%) compared to subjects <45 years (RR 1.9; fampridine SR 6.0%, placebo 3.1%).

Safety related to drug-drug interactions and other interactions

When considering antispasticity medications and TEAEs that occurred in at least 5% of fampridine SR subjects and at least twice as commonly compared to placebo in the adequate and well controlled MS trials, balance disorder was the only TEAE where the RR among subjects using antispasticity medications (RR 6.1; fampridine SR 4.9%, placebo 0.8%) was notably higher compared to subjects not using antispasticity medications (RR 4.4; fampridine SR 7.9%, placebo 1.8%)

For antidepressants, when examining the TEAEs that occurred in at least 5% of fampridine SR subjects and at least twice as commonly compared to placebo in the adequate and well controlled MS trials, back pain was the only TEAE where the risk among subjects using antidepressants (fampridine SR 7.2%, placebo 0) was notably different compared to subjects not using antidepressants (RR 1.4; fampridine SR 4.5%, placebo 3.2%)

Discontinuation due to Adverse Events

In MS controlled trials, 3.4% of 507 fampridine-treated subjects had one or more AEs leading to discontinuation compared to 2.1% of 238 placebo subjects (Table 13).

Table 13: AEs leading to withdrawals in MS-F202/203/204

System Organ Class Preferred Term	Placebo-Controlled Studies 202/203/204	
	Placebo (N=238)	Fampridine-PR 10 mg b.i.d (N=400)
Patients with any TEAEs leading to study discontinuation	5 (2.1%)	11 (2.8%)
Cardiac Disorders	**2 (0.8%)**	**1 (0.3%)**
Coronary artery disease	0 (0%)	1 (0.3%)
Myocardial infarction	1 (0.4%)	0 (0%)
Ventricular extrasystoles	1 (0.4%)	0 (0%)

System Organ Class Preferred Term	Placebo-Controlled Studies 202/203/204	
	Placebo (N=238)	Fampridine-PR 10 mg b.i.d (N=400)
Endocrine Disorders	**0 (0%)**	**1 (0.3%)**
Thyroid cyst	0 (0%)	1 (0.3%)
Gastrointestinal Disorders	**1 (0.4%)**	**0 (0%)**
Reflux gastritis	1 (0.4%)	0 (0%)
General Disorders and Administration Site Conditions	**1 (0.4%)**	**0 (0%)**
Chest discomfort	1 (0.4%)	0 (0%)
Infections and Infestations	**0 (0%)**	**1 (0.3%)**
Pneumonia	0 (0%)	1 (0.3%)
Sepsis	0 (0%)	1 (0.3%)
Injury, Poisoning and Procedural Complications	**0 (0%)**	**1 (0.3%)**
Patella fracture	0 (0%)	1 (0.3%)
Musculoskeletal and Connective Tissue Disorders	**0 (0%)**	**1 (0.3%)**
Neck pain	0 (0%)	1 (0.3%)
Nervous System Disorders	**2 (0.8%)**	**5 (1.3%)**
Balance disorder	0 (0%)	2 (0.5%)
Complex partial seizures	1 (0.4%)	0 (0%)
Coordination abnormal	1 (0.4%)	0 (0%)
Dizziness	0 (0%)	2 (0.5%)
Headache	0 (0%)	2 (0.5%)
Psychiatric Disorders	**0 (0%)**	**2 (0.5%)**
Anxiety	0 (0%)	1 (0.3%)
Confusional state	0 (0%)	1 (0.3%)
Skin and Subcutaneous Tissue Disorders	**0 (0%)**	**1 (0.3%)**
Cold sweat	0 (0%)	1 (0.3%)
Vascular Disorders	**0 (0%)**	**1 (0.3%)**
Hypotension	0 (0%)	1 (0.3%)

Evaluator's overall conclusions on clinical safety

In terms of safety, adequately controlled studies of 10 mg fampridine SR bd have demonstrated that the majority of side effects are mild or moderate in severity and usually self-limiting. Nervous system disorders (balance disturbance, dizziness, headache, paraesthesia, and tremor), psychiatric disorders (insomnia and anxiety), minor cardiac symptoms, constipation, dyspepsia, nausea and vomiting, asthenia, flu-like symptoms, nasophyaryngitis, urine infections, back pain and pruritis occur ≥1% more frequently compared to placebo arm. In the MS controlled trials, 3.4% of 507 fampridine treated subjects had one or more AEs leading to discontinuation compared to 2.1% of 238 placebo subjects. Many AEs are dose dependent. Relatively high retention rates are reported in long term extension studies with fampridine.

Fampridine has been shown to potentiate seizures in a dose dependent fashion in preclinical and clinical studies. In the early development phase of fampridine, higher doses (>10 mg bd) and immediate release forms (which produced higher plasma C_{max} levels) that were associated with plasma fampridine levels >100 ng/mL were associated with increased risk of seizure. Although the number of subjects receiving these higher doses was relatively small, 2.4% of MS patients treated with fampridine SR 20 mg bd had seizures as did approximately 4% of patients at 30 and 35 mg bd. This dose dependence was also observed for CNS events in general in the dose-ranging MS-F202 study. The narrow therapeutic window of fampridine in this regard is reflected in the observation that some seizures were triggered by patients inadvertently doubling up on dosing during earlier clinical studies.

It has been estimated that seizures occur in 2-3% of all MS patients and may be more common in progressive disease.[43,44] Fampridine may potentiate the risk of seizure even at doses of 10 mg bd. The data of extension studies suggest that seizures occurred at exposure levels within the range expected for the 10 mg bd dose, as the maximum fampridine concentration observed for the 10 mg bd dosing regimen was 87.3 ng/mL. More than 333 patients have been followed for a period of more than 2 years in open labelled extension studies using 10 mg fampridine SR bd but there are no data available from controlled studies with this dose beyond 14 weeks. Moreover, the population studied in long term extension studies has been carefully screened for EEG abnormalities and past seizure, closely observed and their follow up has been relatively short given the potential for long term symptomatic treatment. Therefore a significant effect on seizure risk with fampridine cannot be ruled out. Current observational extension data with fampridine for MS disability puts the incidence of new seizures at 0.4 per 100 patient years which puts it on a par with rather limited prospective studies.[42]

More post marketing experience is required to assess whether there is a possible association between fampridine and other potentially serious effects such as suicidality.

In the light of the pharmacodynamics of the efficacy data, the evaluator concurred with the FDA's request for additional efficacy studies using a lower dose of fampridine.

Clinical Summary and Conclusions

The sponsor is seeking approval of fampridine as a treatment to improve walking speed in MS patients. It has recently been approved by the FDA to improve walking in MS patients.

To support the approval of the application, the clinical pharmacology and biopharmaceutics program for fampridine, consisted of a large number of clinical studies,

[44] Martinez-Juarez IE, Lopez-Meza E, Gonzalez-Aragon MC, Ramirez-Bermudez J, Corona T. Epilepsy and multiple sclerosis: Increased risk among progressive forms. Epilepsy Res 2009; 84: 250-253.

focusing on relative bioavailability of various oral formulations; pharmacokinetic characterization in healthy volunteers, MS patients and special populations; elucidation of the drug-drug interaction potential both *in vitro* and *in vivo* with commonly used concomitant medications; population pharmacokinetic and exposure-response analyses using data from various Phase I, II studies and the pivotal clinical trials.

The proposed commercial dosage form is extended release film coated tablet and the strength is 10 mg. The proposed dose for fampridine is 10 mg bd.

Clinical aspects

Pharmacokinetics

Fampridine is rapidly and completely absorbed from the gastrointestinal tract. It is largely unbound to plasma proteins and has a volume of distribution of 2.6 L/kg. Some fampridine is metabolised via CYP2E1 to its 2 main metabolites (3-OH-4-AP and 3-OH-4-AP sulfate). Its main metabolites are inactive. The major route of excretion is renal with approximately 90% of the dose recovered in urine within 24 hours. The elimination half-life is approximately 6 hours. C_{max} and to a lesser extent AUC increase proportionally and steady plasma concentrations are achieved with 4 days of bd dosing with the slow release formulation.

In particular, the evaluator advised extreme caution in patients with renal impairment. Safety data on patients with mild renal impairment is too limited to allow specific recommendations for fampridine's use in this population. A daily dosage could be justified in patients with mild to moderate impairment but there are no or limited pharmacokinetic, efficacy or safety data to guide recommendations. Patients with severe renal impairment should not receive fampridine SR on the basis of currently available data.

Pharmacodynamics

A role for aminopyridines in reducing conduction block in multiple sclerosis was first proposed in 1978 long after their epileptogenic properties were described.[33] Pilot studies using biologically plausible biomarkers showed encouraging responses but investigators found it difficult to translate these effects into clinically meaningful endpoints – such as the widely used EDSS. This was partly due to the narrow therapeutic window of the immediate release formulation. In the early 1990s, observations linking clinical toxicity of fampridine to peak serum levels led to the development of a slow release formulation with good stability and better pharmacokinetic properties.[17,26] Subsequent studies with fampridine SR using a range of neurologic measures suggested that improvements in timed walking may be a useful therapeutic effect.[34] This effect was further refined to dichotomise patients into responders and nonresponders based on consistently faster walking during treatment.[28] Clinical meaningfulness was proposed on the basis of group differences between responders and nonresponders (including fampridine and placebo treated subjects in each group). Criticisms of this methodology include its proneness to bias and the conceptual similarity between the T25FWT and the MSWS-12. In the evaluator's opinion, it is biologically plausible that a subgroup of MS patients with established disease could consistently respond to fampridine and show improved timed walking and lower limb strength while on treatment. Therefore, a responder analysis in this case is appropriate.

Dose response analysis for efficacy indicates that the lowest effective dose of fampridine has not been identified by the development program.

Clinical efficacy

The conclusions of the evaluator are described under Evaluator's overall conclusions on clinical efficacy.

Dose-response studies and main clinical studies

Exposure-response relationship looks within the observed exposure ranges tested in the development program. At 10 mg bd dosing, exposure of fampridine for most of the patients appeared to be above 200 µg·hr/mL and few below 200 µg·hr/mL. The probability of having at least one CNS related AE was steeply increased for patients with fampridine exposure above 200 µg·hr/mL. A lower dose than 10 mg bid may be studied if the current safety profile including seizure incidence at 10 mg bid is not acceptable.

Clinical studies in special populations

Renal impairment

The mean C_{max} and $AUC_{0-\infty}$ of fampridine increased by 67% and 75% in mildly impaired subjects, by 60% and 105% in moderately impaired subjects, and by 100% and 299% in severely impaired subjects, respectively, when compared to normal subjects.

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

"Timed Walk Responder" was the primary efficacy endpoint in the 2 pivotal studies; MS-F203 and MS-F204. Timed Walk responders, were defined as a patient with a faster walking speed on timed 25-foot walk test for at least three of the four visits during the double blind treatment period, as compared to the maximum walking speed for any of the four pre-treatment visits and the first post-treatment visit.

1. On the basis of pooled analysis the Timed Walk responder rate was 37.3% in the fampridine arm versus 8.9% in placebo groups ($p<0.001$). The clinical meaningfulness of this result was tested by comparing MSWS-12 disability scores in Timed Walk responders (from both the fampridine and placebo arms) to the Timed Walk nonresponders. The change from baseline score was -7.19 vs -0.06 respectively ($p<0.006$).
2. In addition, in comparison between treatment groups, fampridine SR Timed-Walk responders showed a statistically significant greater percentage of improvement in MSWS-12 score than that for the fampridine SR Timed-Walk nonresponders and placebo treated patients. Results from analyses of SGI and CGI data lead to the same conclusion.
3. Maintenance of treatment effect was assessed by the change from baseline in walking speed at the end of the double blind treatment period. Fampridine SR Timed-Walk responders had a statistically significantly greater increase in walking speed than fampridine SR Timed-Walk nonresponders and placebo ($p<0.001$ for both comparisons in all three studies). The results suggest that the effect of fampridine SR was sustained while on treatment; there was no evidence of the development of tolerance.
4. In all three placebo controlled studies, fampridine SR Timed Walk responders had statistically significant greater average increases (improvement) in LEMMT scores than the placebo group. The magnitude of the average increase in LEMMT score for the fampridine SR Timed Walk responders (0.16 units compared to 0.03 units for the placebo group) appeared small; however, considering the maximum possible mean improvement was 1.0 (from a baseline mean score of 4.00 on the 0 to 5 point scale), the increase is relatively substantial.

5. The pooled fampridine SR Timed Walk nonresponder group also had statistically significantly improved leg strength compared to the placebo group (0.09 units versus 0.03 units, p=0.006).
6. The pooled results indicate that the average reduction (improvement) in Ashworth Score for spasticity for the fampridine SR Timed Walk responders during the double blind period was 0.15 units compared to 0.07 units for the placebo group (p = 0.003).
7. The fampridine SR Timed-Walk nonresponder group also had significantly reduced spasticity (mean reduction of 0.16 units) compared to the placebo group (p=0.009), indicating that improvements in walking speed and spasticity seen with fampridine SR treatment are somewhat independent.
8. Comparison between treatment groups (disregarding responder status) showed similar results. The pooled fampridine SR-treated patients showed a statistically significant greater reduction in Ashworth Score compared to placebo (0.16 versus 0.07, p<0.001).
9. Maintenance of benefit from extension studies.

Clinical safety

The conclusions of the evaluator are described under Evaluator's overall conclusions on clinical safety.

Benefit risk assessment

Benefits

Key efficacy findings:

The MS patients included in the trials were able to walk 25 feet over 8-45 seconds.

Statistical significance was achieved in the primary outcome in both pivotal studies (MS-F203 and MS-F204). In pooled analysis, 37.3% in the fampridine arm were responders versus 8.9% in placebo groups (p<0.001). Responders were defined as patients who demonstrated improved walking speed in at least 3 of 4 visits during double blind treatment compared with the fastest walking speed measured during any of the 5 visits during the placebo phase.

The average magnitude of improvement in walking speed among Timed Walk responders across the three studies ranged from 25.1% to 26.1% (compared to 1.3% to 6.1% for Timed Walk nonresponders).

In pooled analysis, responders showed greater improvements in the 12 item MS Walking Scale, SGI and CGI ratings than nonresponders.

In pooled analysis, fampridine treated patients (irrespective of responder status) showed:

- significant improvements in average percentage change in walking speed, greater lower limb strength and reduced spasticity compared to placebo patients.
- significant reductions in MSWS-12 score, improved SCI and CGI scores at the end of the double blind treatment period

The evaluator agreed with the primary findings that fampridine treatment is associated with a significant improvement in walking speed in a subgroup of patients with MS. The evaluator concurred that treatment response is linked to improved subjective ratings of walking and the response is maintained through the treatment period without evidence of tolerance. On balance, the long term efficacy of fampridine to improve walking speed is

likely. However, this hasn't been demonstrated convincingly on the available data – the fampridine responders in the extension studies may have been going to improve anyway.

The evidence for efficacy comes from three adequate and well-controlled studies: MS-F202, MS-F203 and MS-F204. MS-F203 and MS-F204 form the basis of the application and both were positive for their primary outcome measures demonstrating a treatment effect for fampridine SR. Consistent effects on treatment response were found in each of the studies and the primary outcome was highly statistically significant in the two pivotal studies. Long term controlled data is lacking: the double blind treatment periods were relatively short (14 and 9 weeks).

The primary end point for the pivotal studies is unusual and was chosen in discussion with the FDA after *post hoc* analysis of the results of MS-F202. A 3 step sequential analysis was proposed for the primary endpoint to demonstrate:

a. There was a difference in Timed Walk responder rates between treatment groups,
b. Responders had clinically meaningful improvements (as measured by the MSWS-12) and
c. The response was maintained during the treatment period.

The TGA-adopted EU guideline which considered issues of multiplicity has a section as follows: [45]

"Two or more primary variables are needed to describe clinically relevant treatment benefits.

Here, interpretation of the results is most clear-cut because, in order to provide sufficient evidence of the clinically relevant treatment benefit, each null hypotheses on every primary variable has to be rejected at the same significance level (for example 0.05). (Examples of this clinical situation include in the treatment of Alzheimer's disease and in the chronic treatment of patients with chronic obstructive pulmonary disease.) In these situations, there is no intention or opportunity to select the most favourable result and, consequently, the individual type I error levels are set equal to the overall type I error level a, that is, no reduction is necessary. This procedure inflates the relevant type II error (here: falsely accepting that at least one null hypothesis is true), which in the worst case scenario is the sum of the type II errors connected with the individual hypotheses. This inflation must be taken into account for a proper estimation of the sample size for the trial.

Statistical significance is needed for all primary variables. Therefore, no formal adjustment is necessary. Each of the steps in the primary outcome was highly statistically significant."

The use of a responder analysis in the 2 pivotal studies is appropriate based on:

1. The biological plausibility of a subgroup of patients with a significant degree of disability due to demyelination as opposed to axonal loss.
2. The pre-specification and appropriate statistical analysis strategies used.
3. The treatment effect seems to be significant but the proportion of responders is relatively small

The clinical meaningfulness of improved walking speed has to be considered. An improvement in time to walk 25 feet in the fampridine group by an average 0.88 seconds

[45] EMEA, Committee for Proprietary Medicinal Products (CPMP), 19 September 2002. Points to Consider on Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99).

cannot be considered clinically meaningful even though the percentage change in walking speed was significant between fampridine and placebo groups.

An improvement in time to walk 25 feet in the responder group (largely fampridine) of 2.3 seconds is likely clinically meaningful. However, the evaluator noted that the method with which the clinical meaningfulness of the Timed Walk was demonstrated could be improved; a conceptually aligned scale, the 12 item MS Walking Scale was used to demonstrate meaningful differences in treatment responders. Therefore a broader impact on health related quality of life has not clearly been demonstrated. Quality of life measures may be considered an important part of evaluating symptomatic (non-disease modifying) therapies.

Risks

The efficacy of fampridine must be considered against a widely acknowledged safety signal: seizures

The current evidence supports a dose related risk of seizure with fampridine, with modest experience at the dose intended for treatment and some evidence of increasing risk above the therapeutic dose.

Seizures were rigorously documented in the database. Overall, the incidence rate observed during the long term, open-label treatment with fampridine SR 10 mg bd was also consistent with the rates reported for placebo groups in long-term studies of other MS drugs (0.0 to 1.1 per 100 patient-years). This incidence rate also aligns with the findings in a prospective study of first seizure onset among 255 Swedish MS patients.[42]

However, comparing the seizure risk in the fampridine SR clinical trial population with background data must be viewed with caution. Patients in the fampridine trials were carefully screened to exclude a personal history of seizures or concerning EEGs. This screening in the fampridine trials may lead to important differences between the fampridine SR population and the general MS background population with regards to seizure risk.

If the seizure risk is born out in the general MS population, then the benefit/risk profile is acceptable.

Balance

MS is an often devastating, progressive disease that affects millions of adults worldwide. The primary goals of therapy in patients with MS are to prevent relapse and to delay the progressive worsening of the disease by limiting disability progression and reducing cognitive dysfunction. Three broad categories of medications have a role in the management of MS. Disease-modifying drugs, corticosteroids and other treatment modalities that target specific symptoms, such as implantable baclofen pumps to control spasticity, also have a role in the management of MS.

Fampridine offers patients with MS the potential for the first treatment for walking impairment, an important unmet need in this disease.

In the evaluator's opinion, a benefit in walking speed has been demonstrated in a subgroup of heterogeneous MS patients. Important inclusion criteria were ability to walk 25 feet (10 metres) in 8-45 seconds. Patients were screened with EEGs and past seizures were important exclusions. However, only 37.3% of patients treated with fampridine had a response to the treatment. On balance of available evidence, the response is likely to be useful to the patient which was reflected in improved walking score ratings and SGI changes.

The main risks that were identified in the development program are the risks of increased seizure, which relates closely to serum fampridine levels. From studies using the recommended dose of fampridine SR (10 mg bd), the seizure risk would appear to be comparable to the seizure rate from prospective MS studies. Current observational extension data with fampridine SR for MS disability puts the incidence of new seizures at 0.4 per 100 patient years. However, one patient taking the recommended dose had status epilepticus requiring prolonged intensive care treatment.

The MS patients in the fampridine studies MS-F203 and MS-F204 and extension studies were carefully screened, more likely to be compliant and are not likely represent the general MS population. Therefore, although the reported seizure risk is within acceptable limits, the seizure rate may well turn out to be higher with wider use of fampridine. The proposed Consumer Medicines Information (CMI) and PI highlight this potential risk and a risk mitigation strategy has been proposed.

From a patient perspective, it would therefore be reasonable to assume that the potential risk of drug-induced epilepsy would be unacceptable if the patient themselves was a nonresponder.

Conclusions

The overall benefit risk balance of fampridine SR is positive to improve walking in MS patients with walking impairment who also demonstrate responsiveness to fampridine. Conditions for registration should include:

- An evaluation of a 7.5 mg bd dose (as per FDA recommendation)
- An evaluation of serum levels in patients with mild or moderate renal impairment.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR). The sponsor identified the following safety concerns (Table 14):

Table 14: Safety concerns for fampridine

Important potential risks	1. Seizures
Important missing information	1. Pregnancy 2. Special populations • Adolescents • Patients > 65 years of age • Interaction with renally secreted drugs

The sponsor proposed routine and additional Pharmacovigilance (PhV) activities, and routine risk minimisation activities (Table 15).[46,47]

Table 15: Proposed pharmacovigilance and risk minimisation activities

Safety concern	Proposed Pharmacovigilance activities	Proposed risk minimization activities
Seizures	Routine Pharmacovigilance Observational Study	Routine risk minimization by referencing safety concerns and in SmPC and PIL.
Missing information: Special population groups (Pregnancy, adolescents, patients >65 years) Interaction with renally secreted drugs	Routine Pharmacovigilance Pregnancy Registry Observational Study Preclinical renal drug-interaction study	Routine risk minimization by referencing safety concerns and in SmPC and PIL.

SmPC: Summary of Product Characteristics
PIL: Patient Information Leaflet

The additional PhV activities are 2 post marketing studies:

- Fampridine-PR Observational Study
- Fampridine-PR Pregnancy Registry

It was also proposed to undertake a preclinical renal drug interaction study.

The safety specification was reviewed by the clinical and nonclinical evaluators. The clinical evaluator assessed the safety specification as satisfactory. The nonclinical evaluator agreed with the conclusions in the Risk Management Plan (RMP) that:

- Fampridine PR is not thought to represent a concern for the occurrence of torsades de pointes with clinical use.
- the effects in these [rat and dog repeat dose and rat and rabbit reproductive toxicity] studies were therefore observed only at exposures considered in excess of the maximum human therapeutic exposures
- In these studies fampridine (4-AP) did not show any potential to be mutagenic, clastogenic or carcinogenic. Additionally, no reduction in fertility or developmental toxicity was observed in either rats or rabbits.' (although effects on fertility were assessed only in rats)
- No other [apart from CNS] specific organ toxic effects considered of relevance to humans were seen.

[46] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[47] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Nonclinical data revealed that convulsions are the main risk associated with the use of fampridine. The RMP notes that the CNS effects seen in the toxicology studies have been extensively investigated in human studies.

The OPR evaluator considered that overall the RMP was acceptable. Post marketing surveillance and studies will be of particular importance give the relatively small numbers of subjects (400 MS patients) who have received the recommended dose of 4-AP.

A number of issues were noted and it was recommended to the Delegate that the sponsor should:

- Provide information on predicted usage in Australia and the basis on which this is derived;
- Specify use in patients with CVS disease as missing information as an additional safety concern.
- Revise the PhV plan to address missing information in patients with CVS disease;
- Provide comprehensive information on the proposed pregnancy register including duration of data collection, data to be collected, the analysis plan and reporting processes and timelines;
- Include other AEs such as UTI, and use in special populations such as those with CVS disease in the objectives for the observational study; and
- Provide TGA with the final protocol (including the statistical analysis plan) for the observational study or if not yet complete advise on when this will occur.
- Consider the nonproprietary name for Australia taking into account the potential for confusion between 4-AP and medicines with similar spelling, and the changes made in the US; and
- Implement a communication plan for prescribers and pharmacists in Australia as is occurring in the US as an additional risk minimisation activity.

The OPR evaluator also made a number of recommendations with respect to the PI and the Consumer Medicines Information (CMI) which are beyond the scope of this AusPAR.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The absolute bioavailability of fampridine immediate release and enteric coated tablets has been reported in the literature as 95%. An absolute bioavailability study has not been performed using the prolonged release tablet because of poor tolerance to intravenous administration.

The 10 mg prolonged release tablet was shown to be bioequivalent to an oral solution of fampridine in terms of AUC. As expected, T_{max} was longer (3.7 h compared to 1.1 h) and C_{max} lower (by 57%) for the tablet compared to the solution.

A high fat meal had no significant effect on the extent of absorption of fampridine from the 10 mg prolonged release tablet, although the mean C_{max} was increased by 23%. The highest individual C_{max} result in the fed state was 51 ng/mL (compared to 42 ng/mL fasted), which is still well below the 100 ng/mL level at which serious adverse events occur. The PI indicates that the tablets may be taken without regard to meals.

There was no objection in terms of chemistry, manufacturing and controls to registration of this product.

Nonclinical

Adequate toxicity studies were submitted. These studies revealed that the main safety issue for fampridine is its pro-convulsive activity. The threshold plasma concentration for induction of convulsions was about 110 ng/mL in rats and dogs (> 4 fold the human C_{max} at the MRHD). There was no evidence of target organ toxicity, genotoxicity, carcinogenicity or cardiovascular safety issues and safety margins were adequate. Reproductive toxicity was observed in neonates of dams administered fampridine (reduced viability and body weight gain) but fampridine was not embryotoxic or teratogenic.

There were no nonclinical reasons that would preclude the registration of fampridine for the proposed indication at a dose of 10 mg twice daily.

Nonclinical data did not predict clinical efficacy, which will need to be adequately demonstrated by the clinical data.

Clinical

Pharmacology

On the overall outcome of the biopharmaceutical studies, the clinical evaluator stated that:

- The pharmacokinetic methods were rigorous and that the statistical methodology was appropriate.
- In humans, fampridine is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration.
- The plasma C_{max} and AUC values of fampridine increased in a dose proportional manner following single dose administration of 5-25 mg. Dose proportionality was also observed with 5-20 mg administered bd as a tablet in the fasted state and further confirmed with fampridine SR 12.5 mg tablet following multiple doses.
- The relative bioavailability of fampridine SR 10 mg dose used in the pivotal Phase III studies MS-F203 and MS-F204 as compared to a 10 mg buffered aqueous oral solution (0.83 mg/mL) was 96% under fasting conditions. The sustained release tablet delays absorption of fampridine relative to the solution formulation, characterized by lower C_{max} concentration (approximately 40% of those achieved with the oral solution) and delayed T_{max} (from 3.2 hours for the oral solution versus 5.4 to 5.5 hours on average for the sustained release tablets).
- The fampridine SR 10 mg tablet commercial formulation utilizes hydroxypropyl methylcellulose as the release rate controlling polymer. With food, absorption is delayed, with the median peak concentration occurring 3.0 hours post dose in the fasted state and 5.0 hours post dose in the fed state. Therefore, food had relatively small impact on C_{max} and AUC (a slight increase of approximately 17% and approximately 5%, respectively under fed conditions). Since fampridine is indicated for chronic dosing, the delay in T_{max} is not considered clinically significant. The results justify administration of fampridine SR tablets with or without regard to food.
- The apparent volume of distribution of fampridine is 2.6 L/kg. The mean protein binding was 1-3%, evaluated over a range of concentrations and pH. Fampridine was largely unbound and had a high free drug fraction at all three concentrations tested.
- The elimination half-life of fampridine following administration of SR tablet formulation was 5.2 to 6.5 hours. The plasma half-life of the sulfate conjugate is approximately 7.6 hours and the half-life of 3-hydroxy-4-aminopyridine was not

determined as concentrations for most subjects were close to or below the limit of quantitation.

- Overall renal clearance of fampridine was 22.2 L/hour (370 mL/min) and suggests active tubular secretion since it is much higher than the glomerular filtration rate.
- Fampridine is not extensively metabolized and mainly eliminated as unchanged drug in urine. Radiolabelled mass balance and metabolism studies indicates that fampridine and metabolites are eliminated nearly completely after 24 hours with 96% of the dose recovered in the urine and 0.5% recovery in faeces. Most of the excreted radioactivity in the 0-4 hour pooled urine was parent drug (90.3%). Two metabolites were identified: 3-hydroxy-4-aminopyridine (4.3%) and 3-hydroxy-4-aminopyridine sulfate (2.6%). These metabolites have been shown to have no pharmacologic activity on potassium channels.
- Analysis of serum fampridine levels in patients with steady state levels of fampridine tested a week apart showed no significant differences in C_{max} and AUC levels.
- In a population pharmacokinetic and pharmacokinetic-pharmacodynamic analysis of fampridine SR tablets, body mass index, race, subject status (healthy controls vs MS patients) and the most commonly used concomitant medications did not appear to affect the pharmacokinetics.
- Fampridine has not been studied in patients with hepatic impairment. Since fampridine is primarily excreted unchanged in the urine, hepatic insufficiency may not significantly affect fampridine pharmacokinetics or recommended dosing.
- A population pharmacokinetic analysis showed that fampridine clearance decreases with increasing age (49L/hr to 39L/hr over 20 years to 80 years).
- A population pharmacokinetic analysis showed that fampridine clearance was approximately 14.5% lower for females (36 L/hr) at the same age and CrCL. Also, the volume of distribution was found to be significantly lower in females as compared to males.
- The effects of renal impairment on the pharmacokinetic profile were studied in single dose administration of fampridine SR in subjects with normal renal function, mild, moderate or severe renal impairment. The mean C_{max} and $AUC_{0-\infty}$ of fampridine increased by 67% and 75% in mildly impaired subjects, by 60% and 105% in moderately impaired subjects, and by 100% and 299% in severely impaired subjects, respectively, when compared to normal subjects. The mean C_{max} and $AUC_{0-\infty}$ of 3-hydroxy-4-aminopyridine sulfate increased by 35% and 80% in mildly impaired subjects, by 123% and 216% in moderately impaired subjects, and by 8 fold and 26 fold in severely impaired subjects, respectively, when compared to normal subjects. The CL/F and CLr of fampridine showed significant relationship ($p < 0.0001$ for CL/F and $p = 0.0001$ for CLr) with creatinine clearance. No studies of the effect of renal impairment on steady state pharmacokinetics have been done.

  The evaluator advised extreme caution in patients with renal impairment. Safety data on patients with mild renal impairment is too limited to allow specific recommendations for fampridine's use in this population. A daily dosage could be justified in patients with mild to moderate impairment but there are no or limited pharmacokinetic, efficacy or safety data to guide recommendations. Patients with severe renal impairment should not receive fampridine SR on the basis of currently available data.

- Population PK analysis evaluating the effect of most commonly used concomitant medications in MS patients indicated no change in fampridine plasma levels as a result of co-administration of these concomitantly used medications. Common concomitant medications included baclofen, glatiramer acetate, interferon beta, tizanidine, renal transport inhibitors (including ACE inhibitors, nitrofurantoin, trimethoprim-sulfamethoxazole, amoxicillin, and trimethoprim) and diuretics (including hydrochlorothiazides and potassium sparing drugs). The evaluator agreed that there are not likely to be any clinically relevant pharmacokinetic interactions with this drug.

In the opinion of the evaluator, the pharmacokinetic program has satisfactorily characterised the key variables for fampridine in MS. However, there are little or no PK data for patients with hepatic or in particular renal impairment; or in children, adolescents, the elderly; or in different racial groups. These issues are adequately reflected in the PI.

The clinical evaluator reached the following conclusions on pharmacodynamics:

A role for aminopyridines in reducing conduction block in multiple sclerosis was first proposed in 1978 long after their epileptogenic properties were described.[33] Pilot studies using biologically plausible biomarkers showed encouraging responses but investigators found it difficult to translate these effects into clinically meaningful endpoints, such as the widely used EDSS. This was partly due to the narrow therapeutic window of the immediate release formulation. In the early 1990's, observations linking clinical toxicity of fampridine to peak serum levels led to the development of a slow release formulation with good stability and better pharmacokinetic properties.[17,26] Subsequent studies with fampridine SR using a range of neurologic measures suggested that improvements in timed walking may be a useful therapeutic effect.[34] This effect was further refined to dichotomise patients into responders and nonresponders based on consistently faster walking during treatment.[28] Clinical meaningfulness was proposed on the basis of group differences between responders and nonresponders (including fampridine and placebo treated subjects in each group). Criticisms of this methodology include its proneness to bias and the conceptual similarity between the T25FWT and the MSWS-12. In the evaluator's opinion, it is biologically plausible that a subgroup of MS patients with established disease could consistently respond to fampridine and show improved timed walking and lower limb strength while on treatment. Therefore, a responder analysis in this case is appropriate.

Dose response analysis for efficacy indicates that the lowest effective dose of fampridine has not been identified by the development program.

Efficacy

The clinical evaluator identified 11 efficacy and safety studies on multiple sclerosis (MS). Of particular relevance were the pivotal studies MS-F203 and MS-F204.

MS-F203 was a Phase III, double blind, placebo-controlled, parallel group, 21-week study (one week post screening, two weeks of single-blinded placebo run-in, 14 weeks of double blind treatment, and four weeks of no treatment as follow-up) in patients diagnosed with MS, able to complete 2 trials of the T25FW in an average time of 8-45 s at screening, no exacerbations within 60 days of screening and no history of seizures or evidence of epileptiform activity on a screening ECG.

The primary efficacy end points included:

1. Changes in walking speed (in feed per second) as measured by the T25FW from the MSFC: a response analysis will be performed to determine the numbers of subjects

who show a consistent improvement while on drug. A responder defined as a subject with a faster walking speed for at least three visits during the double blind treatment period (Visits 3 through 6) as compared to the maximum speed for any of the pre-treatment visits (Screening Visit, Visits 0, 1 and 2) and the first post treatment visit (Visit 7).

2. The clinical significance of this improvement as examined by comparison of changes from baseline in average score on the MSWS-12 for those subjects who show consistent improvement compared to those who do not.
3. The maintenance of improvement over the course of treatment as examined by comparing the walking speed at the last on drug visit with the baseline walking speed for those subjects who show a consistent improvement while on fampridine SR compared to subjects on placebo treatment.

The related secondary efficacy endpoints included:

- Percent change from baseline in walking speed at each double blind visit.
- Change from baseline in LEMMT at each double blind visit.
- Change from baseline in the Average Ashworth Score at each double blind visit Subjective Variables.
- Average SGI score during the double blind period.
- The CGI score, recorded at the end of the double blind period.

Regarding the efficacy outcome for the study, the CE stated that:

- The proportion of Timed Walk responders was higher in the fampridine group (78/224 or 35%) than in the placebo group (6/72 or 8%; p<0.0001).
- Improvement in walking speed in fampridine treated Timed Walk responders, which was maintained throughout the treatment period, was 25.2% (95% CI 21.5% to 28.8%) and 4.7% (1.0% to 8.4%) in the placebo group.
- Compared to Timed Walk nonresponders, Timed Walk responders showed a

1. Greater improvement in 12-item multiple sclerosis walking scale scores (-6.84, 95% CI-9.65 to -4.02) than Timed Walk nonresponders (0.05, -1.48 to 1.57; p=0.0002).
2. Significant improvements in the SGI and CGI (p <0.001 for each).

Also,

1. Significant increases in LEMMT score were seen in both the fampridine SR Timed Walk responders (p< 0.001) and the fampridine SR Timed Walk nonresponders (p=0.046) compared to placebo.

- Despite achieving significance for the primary outcome measures, the average walking speed during double blind treatment was not significantly different between fampridine and placebo (Table 5).

MS-F204 was a Phase III, double blind, placebo controlled, parallel group, 14 week study (one week post screening, two weeks of single blind placebo run-in, 9 weeks of double blind treatment, and two weeks of no treatment follow up) in patients diagnosed with MS and able to complete the T25FW in an average of 8-45 secs at the screening visit.

The primary efficacy endpoints were:

1. To demonstrate that more patients treated with fampridine SR 10 mg bd experience consistent increase in walking speed while on drug versus patients

treated with placebo. Walking speed at each visit was based on the average of two T25FW assessments made within 5 minutes of each other.

For the analysis of efficacy, the primary efficacy variable was responder status, based on consistency of response in walking speed on the T25FW. A Timed Walk responder was defined as a patient with a faster walking speed for at least three of the first four double blind visits (Visits 3 through 6) as compared to the maximum walking speed for any of the pretreatment visits (Screening Visit, Visits 0, 1 and 2) and the post treatment visit (Visit 8). As mentioned, the purpose of the last double blind visit (Visit 7) was to obtain data on efficacy and drug plasma concentration from near the end of the normal 12 hour dosing interval; therefore, Visit 7 was not part of the responder criterion.

The secondary efficacy endpoints were:

1. To demonstrate improved leg strength in:
    a. Fampridine SR 10 mg bd patients who experience consistent improvements in walking speed versus placebo; and
    b. Fampridine SR 10 mg bd patients who do not experience consistent improvements in walking speed versus placebo.
2. To measure the maintenance of efficacy towards the end of the dosing interval (10-12 hours post dose at steady-state) as measured by walking speed and leg strength.

For the analysis of efficacy, the secondary efficacy variable was the average change from baseline in LEMMT during the 8 week, double blind treatment period, considered separately and sequentially for fampridine SR-treated Time Walk responders and Time Walk non responders vs placebo treated patients. Additional variables were the average change from baseline in the Ashworth Score and the MSWS-12, the average SGI score during the double blind period and the CGI score at the end of the double blind period.

Additional efficacy measurements were additional measurements, Ashworth Assessment of Spasticity, MSWS-12, SGI and CGI.

Regarding the efficacy outcome for the study, the clinical evaluator stated that:

- The primary efficacy endpoint for the study was met: the percentage of patients who met the Timed Walk responder criterion was 42.9% in the fampridine SR treated group compared with 9.3% in the placebo treated group. This difference was highly statistically significant ($p<0.001$), and consistent with the results of study MS-F203.
- The increased response rate in the fampridine SR group was observed across all four major types of MS disease course.
- The average improvement in walking speed for the fampridine SR responders during the double blind period was 25% compared to 6% for the fampridine SR non responders and 8% for the placebo group (the *post hoc* statistical comparison between the fampridine SR responders and placebo group was significant, $p<0.001$).
- There was a small decrease in the magnitude of walking speed improvement in the fampridine SR responder group at the end of the normal dosing interval from hours 10-12, the response at hour>12 of about 20% walking speed improvement for the Timed Walk responders, is still considered a meaningful level of change.
- The secondary efficacy endpoint of greater leg strength improvement in the fampridine SR Timed Walk responders compared with placebo treated patients was also met ($p=0.028$). However, the change in leg strength for fampridine SR Timed Walk

nonresponders was not statistically significantly different from either placebo treated patients or fampridine SR Timed Walk responders (Figure 9).

- Fampridine ST Timed Walk responders showed a numerically greater mean improvement than the placebo group in average change from baseline in the Ashworth score, a measure of spasticity.
- In post hoc statistical comparisons, Timed Walk responders (independent of treatment) showed a greater improvement than Timed Walk nonresponders (independent of treatment) for the three summary subjective outcomes in this study: average change from baseline in the MSWS-12 (responders -6.04 [SD 13.9], nonresponders 0.8 [SD 10.5]; p<0.001), average SCI score over the double blind period (responders 4.8 [SD 1.0], nonresponders 4.2 [SD 1.0]; p<0.001), and CGI at end of the double blind period (responders 3.4 [SD 0.8], nonresponders 3.8 [SD 0.6]; p<0.001).
- However, the average walking speed and average change in LEMMT on drug vs Baseline during the double blind treatment were not different between fampridine and placebo (Table 6).

On the pooled analyses and meta-analysis of efficacy for studies F202, F203 and F204, the clinical evaluator stated that:

- Timed Walk response rates were 37.3% in the fampridine SR 10 mg bd group and 8.9% in the placebo group (P<0.001). The effect of fampridine SR on Timed Walk response was highly consistent across subgroups.
- For clinical characterisation of Timed Walk responders (irrespective of treatment allocation), the mean (a) change in MSWS-12 was -7.19 in Timed Walk responders vs -0.006 in Timed Walk nonresponders (P<0.001), (b) CGI rated significantly better in Timed Walk responders vs Timed Walk nonresponders (P<0.001) and (c) SCI significantly better in Timed Walk responders vs Timed Walk nonresponders (P<0.001).
- Maintenance of treatment effect was assessed by the change from baseline in walking speed at the end of the double blind treatment period. Fampridine SR Timed Walk responders had a statistically significantly greater increase in walking speed than fampridine SR Timed Walk nonresponders and placebo (p<0.001 for both comparisons in all three studies). The results suggest that the effect of fampridine SR was sustained while on treatment; there was no evidence of the development of tolerance.
- In all three placebo controlled studies, fampridine SR Timed Walk responders had statistically significant greater average increases (improvement) in LEMMT scores than the placebo group. The magnitude of the average increase in LEMMT score for the fampridine SR Timed Walk responders (0.16 units compared to 0.03 units for the placebo group) appeared small; however, considering the maximum possible mean improvement was 1.0 (from a baseline mean score of 4.00 on the 0 to 5 point scale), the increase is relatively substantial.
- The pooled fampridine SR Timed Walk nonresponder group also had statistically significantly improved leg strength compared to the placebo group (0.09 units versus 0.03 units, p=0.006).
- The pooled results indicate that the average reduction (improvement) in Ashworth Score for spasticity for the fampridine SR Timed Walk responders during the double blind period was 0.15 units compared to 0.07 units for the placebo group (p=0.003).

- The fampridine SR Timed Walk nonresponder group also had significantly reduced spasticity (mean reduction of 0.16 units) compared to the placebo group (p=0.009), indicating that improvements in walking speed and spasticity seen with fampridine SR treatment are somewhat independent.
- Comparison between treatment groups (disregarding responder status) showed similar results. The pooled fampridine SR treated patients showed a statistically significant greater reduction in Ashworth Score compared to placebo (0.16 versus 0.07, p<0.001).
- Maintenance of benefit from extension studies was established but lost after discontinuation.

The clinical evaluator's summarised efficacy in the Evaluator's overall conclusions on clinical efficacy

Safety

The clinical evaluator summarised that:

In terms of safety, adequately controlled studies on 10 mg fampridine SR bd have demonstrated that the majority of side effects are mild or moderate in severity and usually self-limiting. Nervous system disorders (balance disturbance, dizziness, headache, paraesthesia, and tremor), psychiatric disorders (insomnia and anxiety), minor cardiac symptoms, constipation, dyspepsia, nausea and vomiting, asthenia, flu-like symptoms, nasophyaryngitis, urine infections, back pain and pruritis occur ≥1% more frequently compared to placebo arm. In the MS controlled trials, 3.4% of 507 fampridine treated subjects had one or more AEs leading to discontinuation compared to 2.1% of 238 placebo subjects. Many AE's are dose dependent. Relatively high retention rates are reported in long term extension studies with fampridine.

Fampridine has been shown to potentiate seizures in a dose dependant fashion in preclinical and clinical studies. In the early development phase of fampridine, higher doses (>10 mg bd) and immediate release forms (which produced higher plasma C_{max} levels) that were associated with plasma fampridine levels >100 ng/mL were associated with increased risk of seizure. Although the number of subjects receiving these higher doses was relatively small, 2.4% of MS patients treated with fampridine SR 20 mg bd had seizures as did approximately 4% of patients at 30 and 35 mg bd. This dose dependence was also observed for CNS events in general in the dose ranging MS-F202 study. The narrow therapeutic window of fampridine in this regard is reflected in the observation that some seizures were triggered by patients inadvertently doubling up on dosing during earlier clinical studies.

It has been estimated that seizures occur in 2-3% of all MS patients and may be more common in progressive disease. Fampridine may potentiate the risk of seizure even at doses of 10 mg bd. The data of extension studies suggest that seizures occurred at exposure levels within the range expected for the 10 mg bd dose, as the maximum fampridine concentration observed for the 10 mg bd dosing regimen was 87.3 ng/mL. More than 333 patients have been followed for a period of more than 2 years in open labelled extension studies using 10 mg fampridine SR bd but there are no data available from controlled studies with this dose beyond 14 weeks. Moreover, the population studied in long term extension studies has been carefully screened for EEG abnormalities and past seizure, closely observed and their follow up has been relatively short given the potential for long term symptomatic treatment. Therefore a significant effect on seizure risk with fampridine cannot be ruled out. Current observational extension data with fampridine for

MS disability puts the incidence of new seizures at 0.4 per 100 patient years – which puts it on a par with rather limited prospective studies.

In MS controlled trials, 3.4% of 507 fampridine treated subjects had one or more AE's leading to discontinuation compared to 2.1% of 238 placebo subjects.

More post marketing experience is required to assess whether there is a possible association between fampridine and other potentially serious effects such as suicidality.

Benefit Risk Assessment of the Evaluator

The clinical evaluator stated that:

MS is an often devastating, progressive disease that affects millions of adults worldwide. The primary goals of therapy in patients with MS are to prevent relapse and to delay the progressive worsening of the disease by limiting disability progression and reducing cognitive dysfunction. Three broad categories of medications have a role in the management of MS. Disease-modifying drugs, corticosteroids and other treatment modalities that target specific symptoms, such as implantable baclofen pumps to control spasticity, also have a role in the management of MS.

Fampridine offers patients with MS the potential for the first treatment for walking impairment, an important unmet need in this disease.

In the evaluator's opinion, a benefit in walking speed has been demonstrated in a subgroup of heterogeneous MS patients. Important inclusion criteria were ability to walk 25 feet (10 meters) in 8-45 seconds. Patients were screened with EEGs and past seizures were important exclusions. However, only 37.3% of patients treated with fampridine had a response to the treatment. On balance of available evidence, the response is likely to be useful to the patient which was reflected in improved walking score ratings and SGI changes.

The main risks that were identified in the development program are the risks of increased seizure which relates closely to serum fampridine levels. From studies using the recommended dose of fampridine SR (10 mg bd), the seizure risk would appear to be comparable to the seizure rate from prospective MS studies. Current observational extension data with fampridine SR for MS disability puts the incidence of new seizures at 0.4 per 100 patient years. However, one patient taking the recommended dose had status epilepticus requiring prolonged intensive care treatment.

The MS patients in the fampridine studies MS-F203 and MS-F204 and extension studies were carefully screened, more likely to be compliant and not likely to be representative of the general MS population. Therefore, although the reported seizure risk is within acceptable limits, the seizure rate may well turn out to be higher with wider use of fampridine. The CMI and PI highlight this potential risk and a risk mitigation strategy has been proposed.

From a patient perspective, it would therefore be reasonable to assume that the potential risk of drug induced epilepsy would be unacceptable if the patient was a nonresponder.

In conclusion, the clinical evaluator has recommended an amended indication. The clinical evaluator stated that the overall benefit /risk balance of fampridine SR is positive to improved walking in MS patients with walking impairment who also demonstrate responsiveness to fampridine. The clinical evaluator also suggested the following conditions for registration:

1. Evaluation of a 7.5 mg bd dose (as per FDA recommendation)
2. Evaluation of serum levels in patients with mild or moderate renal impairment.

Risk Management Plan

The sponsor provided a comprehensive and clear response to the recommendations from evaluation of the EU RMP and provided an updated and Australian specific AU RMP version 1 dated October 2010.

The key changes in the AU RMP were:

- Inclusion of seizures as an identified safety concern;
- Use of fampridine in patients with a history of seizures is contraindicated;
- The additions of seizure incidence in patients using fampridine and its long term safety as missing information; and
- Recognition of pre existing cardiovascular disease as a potential risk

However, the OPR identified a number of issues as detailed below:

- Patients with CVS risk factors and with established CVS disease are referred to as a potential risk; these are different populations and there needs to be clarification of whether the concern is for patients with risk factors and / or established disease.
- The lack of a communication plan about fampridine for prescribers and pharmacists as recommended in the EU RMP evaluation and occurring in the US.
- The lack of information on the proposed preclinical study regarding fampridine's effect on seizure threshold.
- The question of Australian participation in the post marketing observational study and pregnancy register.
- The need for contingency plans to undertake the post marketing observational study and implement the pregnancy register if fampridine is not registered in the EU.
- The need for the therapeutic Goods Administration (TGA) to receive the final protocol of the observation study and information on the proposed pre clinical study investigating fampridine's effect on seizure threshold.
- It is not stated how MS nurses and the MS Society will be educated to enable them to be sources of information about fampridine for patients.

It was recommended that the sponsor should:

1. Clarify whether patients with CVS risk factors and / or established CVS disease are considered to be a potential safety concern;
2. Develop an education and communication plan about fampridine for prescribers, pharmacists, MS nurses and the MS Society, and, provide the plan and methods to assess its effectiveness to the TGA prior to its implementation.
3. Provide information on the preclinical study regarding the fampridine effect on seizure threshold and the final protocol for the post marketing observational study.
4. Provide reasons for the non inclusion of Australian patients in the post marketing observational study and pregnancy register.
5. Present contingency plans for undertaking the post marketing observational study and implementing the pregnancy register if fampridine is not registered in the EU.

The sponsor's response was reviewed with the conclusions that:

- The responses to questions one, three and four were considered satisfactory.
- In regards to the response to question two, the sponsor should be specifically requested to provide the materials to be used with Multiple Sclerosis nurses and have these approved by the OPR prior to marketing.
- In response to question five, the sponsor has indicated that should the product not be approved in the European Union (EU) that the patient groups could be included in other planned studies of the developmental program. These have not been identified. The sponsor also suggests that this could be undertaken through passive surveillance reporting in the United States where fampridine is already registered.
- Should fampridine not be approved in the EU the sponsor should be required to add these groups to the planned studies and provide information as to the studies and a timeline of the significant milestones including start and complication dates and timing of interim and final reports. At this stage routine spontaneous adverse event reporting is not considered adequate.

Risk-Benefit Analysis

Delegate Considerations

The findings and conclusions of the clinical evaluator were noted. In particular, the modest efficacy of fampridine in combating the debilitating effects of MS rather than attenuating the demyelinating process of MS was noted. There is definitely a clinical role for an agent capable of improving walking (hence quality of life), albeit of modest proportions, in MS patients with walking impairment. The oral availability of fampridine is convenient for MS patients and also promotes compliance.

Due to its somewhat narrow therapeutic window, the sponsor was strongly encouraged to pursue clinical trial studies establishing a lower effective dose regimen than the 10 mg bd currently recommended as per the submitted data. The latter is in line with the FDA recommendation. The serum level should be closely monitored so as to minimise the occurrence of seizures in fampridine responsive patients, more so if there is any underlying renal dysfunction. The PI needs to include a reference to the latter. The use of fampridine in seizure prone patients is already contraindicated in the PI. In addition, it is also necessary to limit the use of fampridine only to fampridine responders because of the potential risk of seizures in a nonresponder MS patient persisting on protracted usage, in the hope of some eventual response. To this end, the Delegate agreed to a modification of the proposed indication:

Fampyra prolonged release tablets are indicated for the treatment of adult patients with multiple sclerosis who have shown improvement of walking ability after 8 to 14 weeks of treatment.

The 8 to 14 weeks duration represent the duration of exposure in the pivotal double blind placebo controlled trials and there were no paediatric studies in the data submitted.

It was suggested that the sponsor's proposed statement "As with all medicines, physicians should review the benefit / risk of Fampyra treatment with the individual patient to ensure continuing positive benefit / risk" be included under the "Dosage and Administration" section of the PI immediately below the dosage regimen. To put it otherwise in the Precautions section of the PI under the heading "Maintenance / Extended treatment" is to inadvertently approve or endorse maintenance / extended use of fampridine when there are no properly conducted clinical trial data on efficacy / safety towards that effect.

The RMP assessment has led to some conclusions and the sponsor would be required to comply with these before registration if approval is granted.

The Delegate proposed that consideration be given to the approval of the application for a modified version of the proposed indication as above.

Response from Sponsor

The sponsor agreed with the revised indication as proposed by the Delegate with "prolonged" replaced by "modified" as recommended by the quality evaluator. The sponsor also agreed to include the following statement in the Dosage and Administration section of the PI:

"As with all medicines, physicians should review the benefit / risk of Fampyra treatment with the individual patient to ensure continuing positive benefit / risk."

Fampridine Serum Monitoring

The sponsor noted that the Delegate and the clinical evaluator advised extreme caution in patients with renal impairment on the basis that safety data was considered too limited to allow specific recommendations on patients with mild renal impairment.

The sponsor carefully considered the Delegate's recommendation to closely monitor serum fampridine levels but considered this would be difficult to implement, create additional burden for prescribers and patients and would create a delay for the marketing of Fampyra.

The sponsor questioned the clinical value of such monitoring as there are no absolute thresholds of fampridine serum levels that are associated with increased risk of particular CNS adverse reactions. It was considered that this could be seen as an extremely tight condition of registration and may seem unreasonable to clinicians considering Fampyra for this unmet clinical need. Furthermore, no standard monitoring has been developed for commercial roll out.

The sponsor proposed to contraindicate Fampyra in patients with moderate to severe renal impairment and place a statement on renal impairment in the Precautions section of the PI.

Risk Management Plan

The sponsor provided details of its proposed Education Plan component of the RMP. The plan consists of a two step mail-out, one at launch and one following Pharmaceutical Benefits Scheme listing. The sponsor acknowledged the importance of the evaluation of a lower dose and indicated that a protocol for a study to support the 7.5 mg bd dose had been finalised. The sponsor also discussed the approach to mitigate the risk of CNS adverse reactions.

The sponsor disagreed with the need for educational materials to be approved by the OPR prior to marketing as this was considered to be over regulation. However, on further discussions with TGA agreed to provide educational materials for use with Multiple Sclerosis nurses within the RMP for evaluation by the Office of Product Review.

The sponsor also discussed the inclusion of Australian patients in observational trials and a pregnancy register. It noted that in the event of fampridine not gaining approval in the EU, the usefulness of conducting such an observational study would be considerably limited. In addition, some of the identified safety concerns do not readily lend themselves to quantification in further Phase III studies. Moreover, routine pharmacovigilance in the US has already generated substantial data and these data were providing some

quantification on the incidence of seizure and the use in elderly, adolescent and pregnant patients.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission for the indication:

For the symptomatic improvement of walking ability in adult patients with Multiple Sclerosis who have shown improvement after 8 weeks of treatment.

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy, considered there is a marginal benefit-risk profile for this product.

In making this recommendation, the ACPM noted the clear clinical need for a product in this treatment area. The Committee considered that the clinical trials demonstrated a small clinical benefit, however, the response may be difficult to reproduce in the standard clinical setting. It was noted that although the primary efficacy endpoint of the pivotal trial has been validated, it was only a component of the standard clinical scale and this was of questionable scientific application. Data on maintenance of effect was limited. Short term reporting on Quality of Life measures was positive but the long term significance to patients was unclear as there was no long term Quality of Life data.

The safety profile of fampridine was a cause for concern as there is a significant risk of seizures. It was noted that this risk was only partially mitigated by the modified release compared to the immediate release formulation and is increased in patients with renal impairment. The ACPM noted the clear relationship between renal impairment and safety issues, in particular seizures. The proposal by the sponsor to adopt the Kidney Health Australia (KHA) guideline in categorising renal impairment and use eGFR is an appropriate approach to assessing the risk associated with diminished renal function in the use of fampridine regarding safety. The Committee considered that there should be a strict exclusion for anyone who had any history of seizures.

Given the reports of limited efficacy, the potential for placebo effect was real. Overall, a small clinical benefit was demonstrated for one particular aspect (walking) but with safety issues. Therefore the Committee considered it important that administration should be limited to the 8 weeks required to show response and that a walk test be used to demonstrate response in each patient. Those not responding must be withdrawn from treatment. Also, as this product is for symptom relief rather than a disease modifying agent studies on lower doses would be appropriate.

The ACPM considered the specific conditions of registration should include:

- Provision to the TGA of the questions and answers subsequent to the consideration of the application by the EMA
- Provision to the TGA of the findings of the studies undertaken and the direction of the FDA on safety.

The ACPM also recommended a number of changes to be considered to the PI and CMI but these are beyond the scope of this AusPAR.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Fampyra modified release tablets containing fampridine, indicated for:

The symptomatic improvement of walking ability in adult patients with Multiple Sclerosis who have shown improvement after 8 weeks of treatment.

Included among the specific conditions of registration were the following:

- The implementation in Australia of the fampridine Risk Management Plan (RMP), dated December 2010 and any subsequent revisions, as agreed with the TGA and its Office of Product Review.
- The sponsor is required to provide the TGA with the questions and answers subsequent to the consideration of the submission to the EMA and the findings of the studies undertaken and the direction of the FDA on safety as described by the sponsor.

Attachment 1. Product Information

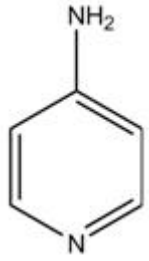
The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

FAMPYRA® (fampridine) 10 mg Modified Release (MR) tablet

NAME OF THE MEDICINE

FAMPYRA® (fampridine) is a 10 mg modified release white to off-white, film coated, oval shaped, biconvex, non-scored tablet with flat edge, debossed with "A10" on one side. Fampridine is also known by its chemical name, 4-aminopyridine with the following structure:



Fampridine is a fine white powder with a molecular weight of 94.1, CAS 504-24-5 a molecular formula of $C_5H_6N_2$, an octanol/water partition coefficient (log P) of -0.76 and pKa of 9.17. At ambient conditions, fampridine is soluble in water (unbuffered ≥ 49 mg/mL, pH 7.0 buffered ≥ 57 mg/mL), methanol ≥ 53 mg/mL, acetone ≥ 52 mg/mL, tetrahydrofuran ≥ 52 mg/mL, isopropanol ≥ 52 mg/mL, acetonitrile ≥ 62 mg/mL, N, N-dimethylformamide ≥ 83 mg/mL, dimethylsulfoxide ≥ 78 mg/mL, and ethanol ≥ 77 mg/mL.

DESCRIPTION

FAMPYRA is a potassium channel blocker, available in a 10 mg tablet strength. Each tablet contains 10 mg fampridine, formulated as a modified release tablet for twice-daily oral administration. Each tablet also contains hypromellose, microcrystalline cellulose, silicon dioxide, magnesium stearate and the film coat (Opadry White Y-1-7000 E171) contains hypromellose, titanium dioxide and macrogol 400.

PHARMACOLOGY

Pharmacodynamics

Fampridine is a non-selective potassium channel blocker and is a lipid-soluble drug which readily crosses the blood-brain barrier. Multiple Sclerosis (MS) is characterised by demyelination, and although the exact mechanism of action of fampridine is not known, fampridine is believed to act mainly by blocking the potassium channels in demyelinated nerves, which reduces the leakage of current from the axons, restoring neuronal conduction and action potential formation.

FAMPYRA does not prolong the QTc interval and does not have a clinically important effect on QRS duration.

Pharmacokinetics

Absorption:
Orally administered fampridine is rapidly and completely absorbed from the gastrointestinal tract. Absolute bioavailability of FAMPYRA has not been assessed, but relative bioavailability (as compared to an aqueous oral solution) is 95%. FAMPYRA tablets have a prolonged release of fampridine characterized by a slower rise to and a lower peak concentration when compared to an immediate release formulation, without any effect on the extent of absorption.

When FAMPYRA is taken with food, the reduction in the area under the plasma concentration-time curve (AUC0-∞) of fampridine is approximately 2-7% (10 mg dose). The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy.

Distribution:
Fampridine is largely unbound to plasma proteins (greater than 90%) and has a volume of distribution of 2.6 L/kg.

Metabolism:
Fampridine is metabolised by oxidation to 3-hydroxy-4-aminopyridine and further conjugated to the 3- hydroxy-4-aminopyridine sulfate. Negligible pharmacological activity was found for these fampridine metabolites against selected potassium channels *in vitro*.

The 3-hydroxylation of fampridine to 3-hydroxy-4-aminopyridine by human liver microsomes appeared to be catalyzed by two or more kinetically distinct enzymes. CYP2E1 appeared to be the major enzyme responsible for the 3-hydroxylation of fampridine, based on correlation analysis, chemical inhibition studies and incubations with recombinant human CYP enzymes.

Elimination:
The major route of elimination for fampridine is renal excretion, with approximately 90% of the dose recovered in urine as parent drug within 24 hours. Renal clearance (CLR 370 mL/min) is substantially greater than glomerular filtration rate. Faecal excretion accounts for less than 1% of the administered dose.

FAMPYRA is characterized by linear (dose-proportional) pharmacokinetics with a terminal elimination half-life of approximately 6 hours. The maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) increase proportionately over a dose range of 5 to 40 mg. There is no evidence of clinically relevant accumulation of fampridine taken at the recommended dose in patients with full renal function. In patients with increasing amounts of renal impairment accumulation occurs in line with the degree of impairment.

CLINICAL TRIALS

Two phase III, randomised, double-blind, placebo controlled confirmatory studies, (MS-F203 and MS-F204) demonstrated the efficacy of FAMPYRA, (10mg b.i.d) in improving walking ability in patients with relapsing remitting, secondary progressive and primary progressive MS. The majority of patients in these trials were using immunomodulatory drugs, (including interferons, glatiramer acetate and natalizumab), however the magnitude of improvement in walking ability was independent of concomitant therapy.

No differences in effectiveness based on degree of impairment, age, gender or body mass index were detected.

The primary endpoint was the responder rate in walking speed as measured by the Timed 25-foot Walk (T25FW), a quantitative test of walking ability that has been demonstrated to be a useful and reliable measure of the complex neurological process of walking. This responder rate analysis was performed to determine the number of patients who showed consistent improvement in walking speed during double-blind treatment, i.e Timed Walk Responders. A responder was defined as a patient who consistently had a faster walking speed for at least three visits out of a possible four during the double blind period as compared to the maximum value among five non-double blind off-treatment visits. The clinical meaningfulness of the primary endpoint (timed walk response) was validated by demonstrating significant association between improvements in walking speed with improvements on a patient self-assessment of walking disability, the 12-item Multiple Sclerosis Walking Scale (MSWS12). The MSWS12 questionnaire measures the patient's impression of the effect of their MS related walking disability over the previous two weeks on their ability to perform a range of activities of daily life, such as standing, climbing stairs, moving around the home and walking distances outside.

A significantly greater proportion of patients taking FAMPYRA 10 mg b.i.d had a consistent improvement in walking speed compared to patients taking placebo as measured by the T25FW, (MS-F203: 34.8% vs 8.3%, $p<0.001$; MS-F204: 42.9% vs 9.3%, $p<0.001$). The increased responder rate in the FAMPYRA cohort was observed across all types of MS disease included in the studies, independent of whether they were on DMT treatment or not. The Timed Walk Responders also demonstrated statistically significant mean improvement in walking speed (i.e., magnitude of timed walk response) compared to placebo (pooled results: 25.3% vs. 5.8%; $p<0.001$) as reported by % change from baseline T25FW score. The improvement appeared rapidly (within weeks) after starting treatment.

Based on change from baseline MSWS-12 scores, Timed Walk Responders taking FAMPYRA also demonstrated statistically and clinically significant, improvement in their ability to perform a range of activities of daily life, such as standing, climbing stairs, moving around the home and walking distances outside. Similarly, the SGI (Subject Global Impression) and CGI (Clinician Global Impression) scores showed FAMPYRA timed walk responders had significantly greater improvement than timed walk non-responders.

FAMPYRA also demonstrated significant improvements in leg strength, as measured by the Lower Extremity Manual Muscle Test (LEMMT), seen in the FAMPYRA 10mg b.i.d treatment group compared to placebo ($p<0.003$) (MS-F203). Also, pooled results indicated a significant reduction in the Ashworth Score ($p<0.001$), which measures the degree of muscle spasticity, in the FAMPYRA treatment compared to placebo group.

INDICATIONS

FAMPYRA modified release tablets are indicated for the symptomatic improvement of walking ability in adult patients with Multiple Sclerosis who have shown improvement after 8 weeks of treatment.

CONTRAINDICATIONS

FAMPYRA is contraindicated in patients with known hypersensitivity to fampridine or any excipients in this product.

FAMPYRA should not be administered to patients with moderate or severe renal impairment (Creatinine clearance <50 mL/min or eGFR less than 59 mL/min/1.73m^2).

FAMPYRA should not be administered to patients with prior history of seizure.

Prior to starting FAMPYRA all patients should be assessed for their risk of seizure, by taking a full patient history. Patients who are considered by the physician to be at high risk of seizure should be excluded from treatment.

FAMPYRA should not be administered to patients currently on treatment with other forms of fampridine / 4-aminopyridine.

PRECAUTIONS

FAMPYRA should not be administered at doses higher than the recommended dose of 10 mg, twice daily, 12 hours apart.

Renal Impairment

Fampridine is primarily excreted unchanged through the kidneys. Patients with renal impairment may have higher plasma concentrations, which are associated with increased adverse drug reactions, in particular, neurological effects. Therefore, FAMPYRA should be used with caution, and monitoring of renal function considered in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min or eGFR 60-89 mL/min/1.73m^2).

Particular caution is required when FAMPYRA is prescribed concurrently with drugs or medicinal products that can significantly impact renal function.

Seizures

A dose-dependent increase in risk of seizures has been observed in clinical studies with FAMPYRA at doses above the recommended 10mg taken twice daily. The recommended daily dose of FAMPYRA, 10mg, twice daily, taken 12 hours apart should not be exceeded.

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

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

Effects on fertility

No adverse effects on fertility were observed in rats following oral doses of fampridine up to 9 mg/kg/day in males and females treated prior to and during mating, continuing in females to late gestation or weaning. Exposure at this dose was equivalent to 8 fold the

human exposure at the maximum recommended human dose (MRHD), based on plasma AUC, and maternal toxicity was observed.

Use in Pregnancy (Category C)

Adequate and well-controlled studies in pregnant women have not been conducted. FAMPYRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive studies in rats and rabbits, when fampridine was administered orally at doses up to 10 mg/kg/day and 5 mg/kg/day, respectively, during the period of organogenesis, there was no evidence of embryotoxicity or teratogenicity, even at doses that were maternally toxic. In a study in which rats were dosed from early gestation to weaning, there were no effects on the offspring at a dose of 1mg/kg/day, giving a systemic exposure (plasma AUC) about 1.5 fold human exposure at the MRHD. Pup survival and weight gains were reduced at higher doses.

Use in lactation

It is not known whether fampridine is excreted in human milk and the excretion of fampridine in milk has not been studied in animals. Lipophilic drugs pass easily into milk because of the high percentage of fat content in milk. Fampridine, being a lipophilic drug, may be excreted in human milk. Because of the potential for serious adverse reactions from fampridine in the breast-fed infant, a decision on whether to discontinue breast-feeding or to discontinue therapy with FAMPYRA should be made, taking into account the importance of FAMPYRA to the woman.

Paediatric use

Safety and effectiveness of FAMPYRA in patients younger than 18 years of age have not been established.

Use in the elderly

Clinical studies of FAMPYRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients. Population pharmacokinetics showed that fampridine clearance modestly decreased with increased age, but not sufficiently to necessitate a dose adjustment with increasing age.

Carcinogenicity

Fampridine did not cause any increase in tumours in lifetime dietary carcinogenicity studies in mice and rats. The highest dose used in mice was approximately 80 mg/kg/day, which produced an exposure (based on plasma AUC) that was 11 fold human exposure at the MRHD. The highest dose in rats was approximately 18 mg/kg/day, which produced an exposure (based on plasma AUC) that was 10 fold human exposure at the MRHD. There was a significant increase in uterine polyps in high dose female rats.

Genotoxicity

Fampridine was not genotoxic in *in vitro* assays (bacterial reverse mutation assay, mouse lymphoma *tk* assay, and chromosomal aberration test in Chinese Hamster Ovary cells), or in *in vivo* mouse and rat micronucleus tests.

Interactions with other medicines

Fampridine is actively secreted unchanged by the kidneys; there is a theoretical possibility of an interaction with other drugs that are renally secreted (see PHARMACOLOGY, Pharmacokinetics).

In human liver microsomes *in vitro*, there was little evidence of a direct or metabolism-dependent inhibition of activities of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 by fampridine at concentrations up to 30µM (approximately 100 times the C_{max} at the MRHD). Fampridine is therefore unlikely to inhibit CYP enzymes, or affect the pharmacokinetics of drugs that are substrates of these enzymes, at therapeutic concentrations.

Treatment of cultured human hepatocytes with fampridine at concentrations up to 25µM (nearly 100 times the C_{max} at the MRHD) for 3 days had little or no effect on CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2E1 or CYP3A4/5 enzyme activities. Thus, there is little potential for induction of these enzymes at therapeutic concentrations. Fampridine is not a substrate or an inhibitor for the p-glycoprotein transporter in vitro. Thus, fampridine is unlikely to affect the pharmacokinetics of drugs that are substrates of p-glycoprotein and the pharmacokinetics of fampridine are unlikely to be affected by drugs that inhibit p-glycoprotein.

Interferon: Fampridine has been administered concomitantly with interferon-beta and no pharmacokinetic drug interactions were observed.

Baclofen: Fampridine has been administered concomitantly with baclofen and no pharmacokinetic drug interactions were observed.

Use in Renal or Hepatic Impairment

FAMPYRA is eliminated through the kidneys primarily as unchanged drug and therefore, caution should be taken in prescribing FAMPYRA in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min or eGFR 60-89 mL/min/1.73m^2). Renal function in these patients should be closely monitored as the clinical situation warrants.

Patients with moderate to severe renal impairment (Creatinine clearance <50 mL/min or eGFR less than 59 mL/min/1.73m^2) should be excluded from treatment (see, CONTRAINDICATIONS).

FAMPYRA has not been studied in patients with hepatic impairment in clinical trials. Since fampridine is primarily excreted unchanged in the urine, hepatic insufficiency is not expected to significantly affect fampridine pharmacokinetics. No dose adjustment is required for patients with hepatic impairment.

Effects on Ability to Drive or Use Machines
No studies have been conducted.

ADVERSE EFFECTS

Clinical Trial Data

Adverse drug reactions are defined as those adverse events occurring at ≥1% higher frequency in the active treatment period with FAMPYRA than with placebo and considered with other fampridine data.

The highest incidence of adverse reactions identified from placebo-controlled trials in MS patients with FAMPYRA given at the recommended dose relate to nervous system excitation, as expected with the mechanism of action of FAMPYRA. These include insomnia, balance disorder, dizziness, headache and asthenia. Urinary Tract Infection (UTI) is also reported more frequently, although infection was often not proven. It is thought that this effect may be in part due to an effect of FAMPYRA to produce neuronal stimulation in the bladder mimicking symptoms of UTI.

MedDRA SOC	Preferred Term	Frequency category
Infections and infestations	Urinary tract infection	Very Common
Psychiatric disorders	Insomnia	Common
	Anxiety	Common
Nervous system disorders	Balance disorder	Common
	Dizziness	Common
	Headache	Common
	Paraesthesia	Common
	Tremor	Common
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	Common
	Dyspnoea	Common
Gastrointestinal disorders	Nausea	Common
	Vomiting	Common
	Constipation	Common
	Dyspepsia	Common
Musculoskeletal and connective tissue disorders	Back pain	Common
General disorders and administration site conditions	Asthenia	Common

Post-Marketing Data

Suspected adverse reactions reported in post-marketing experience that are not already included under “Clinical Trial Data” are described below.

<u>Seizure</u>

In post-marketing experience, there have been reports of seizure. Confounding factors may have contributed to the occurrence of seizure in some patients.

DOSAGE AND ADMINISTRATION

The recommended dosage of FAMPYRA for adults is one 10 mg tablet, twice daily, taken approximately 12 hours apart.

Tablets must be swallowed whole. As the tablets are modified release tablets, doses cannot be divided, crushed, dissolved, sucked or chewed. The tablets can be taken with or without food.

The usual dosing regime of one tablet in the morning and one tablet in the evening taken 12 hours apart should always be followed. A double dose should not be taken if a dose is missed.

Patients with moderate to severe renal impairment (Creatinine clearance <50 mL/min or eGFR less than 59 mL/min/1.73m^2) should be excluded from treatment (see, CONTRAINDICATIONS).

As with all medicines, physicians should review the individual benefit/risk of FAMPYRA treatment with the individual patient to ensure continuing positive benefit/risk. Prescribers should reevaluate the patient 8 weeks after the first treatment. Continued therapy should not be considered unless a walk test demonstrates response.

OVERDOSAGE

Symptoms

Acute symptoms of overdose were consistent with central nervous system excitation and included confusion, tremulousness, diaphoresis, seizure, and amnesia. The severity of symptoms is usually closely related to the pharmacokinetic exposure.

Treatment

Patients should be provided supportive care. Repeated seizure activity should be treated with benzodiazepine, phenytoin, or other appropriate acute anti-seizure therapy.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

FAMPYRA (fampridine) 10 mg Modified Release Tablets are off white, oval bi-convex, film coated, modified release tablets with a flat edge, debossed with A10 on one side and plain on the other, each containing fampridine 10 mg.

Each pack contains 4 HDPE bottles with a polypropylene child-resistant closure. Each bottle contains 14 tablets and a silica gel desiccant (in total there are 56 tablets in each pack).

Do not store above 25°C. Store the tablets in the original bottle.

Do not use after the expiry date printed on the pack. After first opening a bottle, use within 7 days.

NAME AND ADDRESS OF THE SPONSOR.

Biogen Idec Australia Pty Ltd
ABN 30 095 760 115
Suite 1, Level 5, 123 Epping Road
North Ryde NSW 2113

POISON SCHEDULE OF THE MEDICINE
S4

DATE OF APPROVAL
13/May/2011

DATE OF AMENDMENT
23/May/2011

FAMPYRA® is marketed by Biogen Idec International, GmbH under license from Acorda Therapeutics, Inc. and is manufactured for Acorda under license from Elan Pharma International Ltd. (EPIL), Ireland, utilizing EPIL's MatriX Drug Absorption System (MXDAS™) technology. MXDAS™ is a trademark of Elan Pharma International Ltd. (EPIL).
FAMPYRA® is a registered trademark of Acorda Therapeutics, Inc.

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Reference/Publication #